The Spectrum of Papillary Lesions

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Outline

• Clinico-radiological presentation

• WHO 2003 *versus* 2012: the spectrum of papillary lesions

• Handling of papillary lesions
Papillary lesions in the breast

Lesions that share a typical architectural pattern, being defined as epithelial proliferations supported by fibrovascular stalks with or without a layer of myoepithelial cells occurring anywhere in the ductal system (from the large retroareolar ducts to the TDLU).

Papillary morphogenesis is not a feature of normal breast tissue.
Papillary lesions in the breast

Lesions that share a typical architectural pattern, being defined as epithelial proliferations supported by fibrovascular stalks with or without a layer of myoepithelial cells occurring anywhere in the ductal system (from the large retroareolar ducts to the TDLU)

- **Number**: -Solitary - Multiple

- **Location**: -Central (Q5) - Peripheral (TDLU)
Nipple discharge
• clear or bloodstained, sticky
• unilateral
• from a single duct
• spontaneous
• persistent

Drawing adapted from Gaëtan MACGROGAN, Institut Bergognié, Bordeaux
Nipple discharge
• clear or bloodstained, sticky
• unilateral
• from a single duct
• spontaneous
• persistent

Smear cytology suggestive for Papilloma

Description and suggestion of a papillomatous lesion with atypia
Nipple discharge
• clear or bloodstained, sticky
• unilateral
• from a single duct
• spontaneous
• persistent,

Smear cytology suggestive for Papilloma

versus

Degenerative artifacts
• foamy cytoplasm
• poorly preserved nuclei
Opacity
Microcalcifications

Drawing adapted from Gaëtan MACGROGAN, Institut Bergognié, Bordeaux
Radiological appearances of papillary breast lesions  
*Clinical Radiology* 2008

M.J. Brookes*, A.G. Bourke

well-defined, ovoid mass, predominantly solid appearance, but with a cystic component marked posterior acoustic enhancement

well-defined margins and a surrounding lucent “halo”

Opacity
Microcalcifications

*Drawing adapted from Gaëtan MACGROGAN, Institut Bergognié, Bordeaux*
Peripheral or intraparechymal
Intraductal Papilloma

• Palpable mass (60%)
• Abnormal mammogram
  - Opacity (70%)
  - Asymmetry (13%)
  - Calcification (10%)
• Radiologic risk of malignancy
  - R2: 14%
  - R3-4a: 62%
  - R5: 24%
• Ultrasound:
  - Normal (20%)
  - Complex cyst (23%)
  - Solid lesion (50%)

FNA
Core biopsy

FNA Papillary Lesion

Background: debris +; histiocytes+; blood+

Cellularity: +++ (poor if sclerotic)

Large 3D sheets: ++

Fibrovascular cores: ++

Cell clusters: ++

Single cells: ++

Myoepithelial cells: +
Large 3D sheets elk-horn folding
Fibrous sheets (dense or mixoid, poorly cellular or hypercellular)

Large 3D sheets, “origami-like” folding
Fibrovascular cores: thin and convoluted

fibroadenoma  papillary lesion
Fine needle aspiration cytology of papillary lesions of the breast: how accurate is the diagnosis?

G M K Tse, T K F Ma, P C W Lui, D C H Ng, A M C Yu, J S L Vong, Y Niu, B Chaiwun, W W M Lam and P H Tan

*J Clin Pathol* 2008;61:945–949

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**Take-home messages**

- Cytological diagnosis of papillary lesions of the breast is difficult, with **low sensitivity and specificity**.
- If a papillary lesion is suspected in the fine needle aspiration cytology, prompt histological evaluation is warranted for **accurate diagnosis**.
Core biopsy Papillary Lesion
Outline

- Clinico-radiological presentation
- WHO 2003 *versus* 2012: the spectrum of papillary lesions
- Handling of papillary lesions
WHO 2003

- Central Intraductal papilloma
- Peripheral intraductal papilloma
- Atypical intraductal papilloma
- Intraductal papillary carcinoma
- Encapsulated papillary carcinoma
- Invasive Papillary Carcinoma

WHO 2012

- Intraductal papilloma (central or peripheral)
  - With ADH or DCIS
- Intraductal papillary carcinoma
- Encapsulated papillary carcinoma
- Solid papillary carcinoma
- Invasive Papillary Carcinoma
Intraductal papilloma

• Proliferation of epithelial and myoepithelial cells overlying fibrovascular stalks, thus creating an arborescent structure within the lumen of a duct

Images: courtesy of Anne Vincent-Salomon, Institut Curie, Paris
Intraductal papilloma

- **Central**—large ducts involved

  - Unilateral sanguineous nipple discharge, while palpable masses are less frequent.
  - MX: possible circumscribed retroareolar mass with dilated duct, small lesions can be occult.
  - Calcifications: rare

- **Peripheral**—terminal ducts and TDLU

  - Often clinically occult and multiple, nipple discharge less frequent
Intraductal Papilloma

**Changes**: inflammation, necrosis, and metaplasia (apocrine, squamous, chondroid, osseous, mucinous)
Sclero-calcific papilloma (involution)
The whole range of atypical/neoplastic proliferations may arise in a papilloma or secondarily involve it.

Changes: inflammation, necrosis, and metaplasia (apocrine, squamous, chondroid, osseous, mucinous)

Intraductal Papilloma
Intraductal Papilloma

- Central
  - Same architectural patterns
- Peripheral
  - Concomitant sclerosing adenosis, radial scars, UDH, ADH, and *in situ* carcinoma
Low magnification:

• Solid areas of epithelial proliferation within a papilloma

High magnification:

- Ovoid or spindle epithelial cells; inconspicuous cytoplasmic margins,
- Frequently overlapping bland nuclei
- Arranged in streaming or whirling patterns
- Slit-like clear spaces punctuated the epithelial proliferation
Intraductal papilloma with usual type hyperplasia: mosaic-like expression of basal cell CKs
Intraductal papilloma with usual type hyperplasia: mosaic-like expression of basal cell CKs

Apocrine metaplasia involving the epithelium of acini may be present and extensive.
Papilloma with atypical apocrine metaplasia, e.g., apocrine cells with a three fold variation in nuclear size (quite difficult to be differentiated from normal apocrine cells)

Atypical apocrine hyperplasia, e.g., an apocrine cell population organized in a solid or cribriform pattern
Papillary lesions of the breast: selected diagnostic and management issues

L C Collins & S J Schnitt

Histopathology 2008, 52, 20–29

Papilloma with atypia (atypical papilloma) or papilloma with ductal carcinoma in situ?

There are no universally accepted criteria for distinguishing atypical papilloma and papilloma with DCIS from each other.
Atypical papilloma  Papilloma with ADH or DCIS
2012 WHO Working Group recommends relying on size as a criterion, with 3 mm being the cutoff.
It is acknowledged that scientific evidence for this size criterion is lacking, but the WHO Working Group has adopted this as a pragmatic guideline that allows broad application to routine diagnostic practice.
• **A LOW NUCLEAR GRADE** atypical epithelial proliferation measuring <3 mm within an intraductal papilloma is diagnosed as **ADH**, 
• whereas a similar cytoarchitecturally abnormal epithelial population measuring ≥3 mm is regarded as **DCIS** within an intraductal papilloma.
When the abnormal epithelial proliferation shows intermediate or high nuclear grade, DCIS should be diagnosed regardless of extent.
Conventional forms of DCIS existing within or partially effacing an intraductal papilloma are not diagnosed as intraductal papillary carcinoma, but as DCIS within an intraductal papilloma.

A diagnosis of an intraductal papillary carcinoma requires the malignant process to recapitulate a papillary architecture.
Papillary DCIS/Intraductal papillary carcinoma

• Intraductal proliferation featuring fibrovascular cores covered by neoplastic epithelium

Tan PH et al, Histopathology 2015
Papillary DCIS/Intraductal papillary carcinoma

- A monotonous epithelial cell population
- Often seen with other morphological patterns of DCIS

=> Classification based on nuclear grade
Myoepithelial cells in Papillary DCIS

- Myoep cells **preserved** at the epithelium–stroma interface at the periphery of the ducts
- Myoep cells **absent** in fibrovascular stalks

Rakha EA. J Clin Pathol 2016
Papillary carcinomas

• Papillary DCIS
• Encapsulated Papillary Carcinoma (EPC)
• Solid Papillary Carcinoma (SPC)
• Invasive papillary carcinoma
Encapsulated Papillary Carcinoma

- Aka:
  intracystic papillary carcinoma
  encysted papillary carcinoma

- Solitary, circumscribed tumor, arborizing papillary fronds surrounded by a fibrotic rim

Rakha EA et al, Histopathology 2016
Encapsulated Papillary Carcinoma

• Fibrous capsule
• Myoep cells absent

➢ Staged as *In situ* disease

*Rakha EA et al, Histopathology 2016*
Encapsulated Papillary Carcinoma

• Fibrous capsule
• Myoep cells absent

➢ Staged as *In situ* disease

➢ A diagnosis of *frank invasion* should only be made when malignant cells infiltrate beyond the fibrous capsule, and not according to the presence of entrapped malignant tissue within the capsule

*Images: courtesy of Anne Vincent-Salomon*
When frankly invasive carcinoma is present ..... it is most prudent to report only the size of the frankly invasive component as the tumour size for staging purposes in order to avoid overtreatment.

We do not take the size of the encapsulated papillary carcinoma itself into consideration in determination of the T stage.

Pseudoinvasion

The tubules are within the sclerotic rim
Signs of hemorrhagy are present
Colesterol clefts may be seen
Displaced epithelium within the core needle biopsy site

- epithelial fragments or clusters are confined to the organizing haemorrhage, granulation tissue, or scar of the needle biopsy site

- epithelium that shows varying degrees of degenerative changes and, not infrequently, squamoid features may be seen in the stroma

Absence of myoepithelial cells MUST NOT be used as evidence of an invasive process.
Approximately 3% of pure EPCs

High-grade encapsulated papillary carcinoma of the breast: an under-recognized entity

Emad A Rakha, Zsuzsanna Varga, Somalia Elsheik & Ian O Ellis

EPC/High-grade features:
- nuclear pleomorphism
- increased mitotic activity
High-grade encapsulated papillary carcinoma of the breast: an under-recognized entity

Emad A Rakha, Zsuzsanna Varga,¹ Somaia Elsheik & Ian O Ellis

EPC/High-grade features:
- nuclear pleomorphism
- increased mitotic activity

➢ These tumours not only showed histological features associated with aggressive behaviour, but were also often hormone receptor-negative, tended to be of larger size, and were more frequently associated with stromal invasion.

➢ Of the 10 patients with follow-up data, one with pure high-grade EPC developed recurrence and died of her disease.
Solid Papillary Carcinoma

• In WHO 2003:
  - *not a discrete section*
  - Briefly alluded to in the chapter on ‘intracystic papillary carcinoma’ as a solid variant.
  - solid neuroendocrine carcinoma
Solid Papillary Carcinoma

• In WHO 2012:

Expansive lesion, with a solid growth pattern at low magnification:

>> cellular nodules/solid sheets and festoons, lined by delicate fibro-vascular stroma
FREQUENTLY

- Spindle cell morphology
- Mucin production

Rabban JT

*Hum Pathol. 2006;37:787-93.*
FREQUENTLY

- Spindle cell morphology
- Mucin production
- Neuroendocrine differentiation

UK NHSBSP breast histopathology EQA scheme: circulation of one H&E-stained slide prepared at 70 levels with no IHC data available, no clinical details, and no consultation with colleagues
LOW concordance rate

- Both cases were reported as an invasive carcinoma in 75% (425/564) and 77% (466/603) of responses, respectively.

- Of the coordinators, 64% and 55%, respectively, diagnosed them as invasive disease, and the remainder diagnosed them as *in situ* disease.
Solid Papillary Carcinoma

- Myoep cells present or absent

- Whenever in doubt:
  - Staged as *in situ* disease

- Staged as *invasive SPC* when:
  - presence of a geographical jigsaw pattern with more ragged and irregular margins (often associated stromal reaction)

*Rakha EA, Histopathology 2016, 69, 862–870*
Solid Papillary Carcinoma

- Myoep cells present or absent

- Staged as *in situ* disease

- Staging:

  It can be accompanied by conventional invasive carcinoma, which is separately graded and staged
Invasive papillary carcinoma

Rare in its pure form

A carcinoma showing papillary architecture in >90% of its invasive component

Metastasis (predominantly papillary growth pattern) from other organ sites to be considered

Rakha EA, Histopathology 2016, 69, 862–870

Tan PH et al, Histopathology 2015, 66, 761–770
Molecular pathology of papillary carcinomas

Genetic landscape
- Low level of CNAs, few amps
- 1q+/16q-/16p+
- At lower frequency than grade matched ER+ IC-NST
- PIK3CA mutations: 43%

Transcriptome
- No recurrent fusion gene
- ECP, SPC, IPC: lower expression of genes connected to proliferation and migration
- EPC: lowest levels overall

Duprez R et al, J Pathol 2012; Piscuoglio S et al, Mol Oncology 2014
Papillary carcinomas

- Papillary DCIS
- Encapsulated Papillary Carcinoma (EPC)
- Solid Papillary Carcinoma (SPC)
- Invasive papillary carcinoma
- +1?
Neoplastic cells arranged in aggregates showing a solid to papillary architecture

- Papillae can be so closely packed as to result in a solid or trabecular configuration
- Some areas may feature a follicular pattern

Amorphous, eosinophilic material, reminiscent of colloid

Columnar to cuboidal cells with eosinophilic granular cytoplasm and moderately pleomorphic nuclei
• Morphologic overlap with other papillary lesions of the breast

• Lack of immunohistochemical and genetic evidence of an association with PTC
  – NO TTF-1 and thyroglobulin expression
  – NO RET rearrangements
  – NO BRAF exon 15 mutations

=> They should be considered morphologic variants of papillary breast carcinoma
Solid Papillary Carcinoma with Reverse Polarity (SPCRP)
A discrete subtype of invasive breast carcinoma (a tumor with unique histologic and genetic properties

13 cases, WES

10/13 (77%): R172 IDH2 mutations
Co-occurrence of PIK3CA or PIK3R1 mutations in 8/10

PRUNE2 mutations: 67% de mutations (6/9 cases) + calretininin expression
Outline

• Clinico-radiological presentation

• WHO 2003 versus 2012: the spectrum of papillary lesions

• Handling of papillary lesions & Take Home messages
Papillary lesions on CORE BIOPSY

PL may show intralesional heterogeneity and the limited sampling achieved with NCB may miss areas of *in situ* cancer.

The majority of these lesions should, therefore, be designated **B3** of uncertain malignant potential.

*(Excision)*

On rare occasions when a **small lesion has been very widely sampled** and submitted for pathological examination a benign **B2 classification** may be considered.

*(Mammographic Follow-up)*

Conversely, when a sample of a PL in a NCB shows **atypia**, for example **strongly suspicious of papillary carcinoma in situ**, a **B4** designation may occasionally be more appropriate.

*European Guidelines for quality assurance in breast cancer screening*
Handling of papillary lesions on cb

• The presence of atypical features or carcinoma in a papillary neoplasm on core biopsy necessitates surgical excision

• Whether a papillary lesion with benign appearances observed on core biopsy also requires excision is less clear

Histopathology 2015, 66, 761–770
<table>
<thead>
<tr>
<th>References</th>
<th>Preoperative diagnosis</th>
<th>Risk of malignancy on surgical specimens</th>
</tr>
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<tbody>
<tr>
<td>The Breast Journal (2012)</td>
<td>• Papilloma without atypia</td>
<td>4.6%</td>
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<tr>
<td></td>
<td>• Papilloma with atypia</td>
<td>13.0%</td>
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<tr>
<td>EJSO 38 (2012)</td>
<td>• Papilloma</td>
<td>5.9%</td>
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<tr>
<td></td>
<td>• Atypical papilloma</td>
<td>15.4%</td>
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<tr>
<td>Clin Radiol. (2011)</td>
<td>• Benign papillomas</td>
<td>10.2%</td>
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<tr>
<td>AJR Am J Roentgenol. (2011)</td>
<td>• Benign papilloma</td>
<td>10.9% papilloma with atypia</td>
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<tr>
<td></td>
<td></td>
<td>3.1% carcinoma</td>
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<tr>
<td>The Breast Journal (2016)</td>
<td>• Papilloma without atypia</td>
<td>7.5%</td>
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<tr>
<td></td>
<td>• Papilloma with ADH</td>
<td>33.3%</td>
</tr>
</tbody>
</table>
Benign papillary lesions

• An approach adopted in many institutions and screening programmes is for partially sampled benign papillary lesions to be completely excised, owing to the risk of undersampling a worse lesion

  => *This may be accomplished through a mammotome procedure*

• Some studies however, suggest that papillary lesions with benign findings on core biopsy may be followed up

*Histopathology 2015, 66, 761–770*

*BCRT 2016, 159:203-213*
Recommended criteria for excision

• The presence of a mass lesion

• Discrepancy between core biopsy features and radiological findings

• Unusual histological findings

• Uncertainty on the part of the pathologist

• Discussion in a multidisciplinary team is valuable and application of immunohistochemistry may also be useful
Papillary lesions in the breast

**Proposed classification**

- solitary
- multiple

\[\text{Rx/US findings}\]

- Benign papilloma
- Papilloma with ADH
- *In situ* papillary carcinoma
- EPC
- SPC
- Invasive papillary carcinoma

**Suggested management**

- Excision (altern.: follow up?)
- Wide excision
- Wide excision
- Wide excision (+SN?)
- Wide excision (+SN?)
- Wide excision+SN
Milestone in Papillary lesions

- **STRAIGHTFORWARD**: identification and classification of papillary DCIS as *in situ* and invasive PC into invasive disease

- **CONTROVERSIAL**: diagnosis and classification of encapsulated and solid PCs:
  - Overlapping histological features
  - Uncertain clinical behaviour

*Rakha EA, Histopathology 2016, 69, 862–870*
Take home messages

• Recommended:
  1. thorough sampling of these lesions and making the diagnosis on the basis of examination of the whole lesion
  2. the use of IHC
  3. consultation with colleagues before final diagnosis

Rakha EA, Histopathology 2016, 69, 862–870
Take home messages

• IHC:
  – myoepithelial cells
  – ER and high molecular weight CKs

=> helpful when there is doubt regarding the neoplastic nature of a papillary lesion, and can differentiate between benign papilloma, papillary DCIS, and PC

Rakha EA, Histopathology 2016, 69, 862–870
Take home messages

• **A panel approach:** The WHO Working Group recommends using a panel of two to three antibodies to demonstrate myoepithelial cells on immunohistochemistry

*Tan PH et al, Histopathology 2015, 66, 761–770*
Take home messages

- IHC:
  
  *it may have limited value in differentiating encapsulated and solid PC from invasive PC*

Rakha EA, Histopathology 2016, 69, 862–870
Take home messages

• SPC/Invasion:
  An approach to these challenging cases is consultation with colleagues, seeking expert opinion
    
=> in borderline cases, reporting them as encapsulated or solid PC with a comment on the uncertain behaviour of these indolent potential invasive lesions

Rakha EA, Histopathology 2016, 69, 862–870
Take home messages

• Clinicians should be aware of the diagnostic difficulty and the uncertainty regarding the behaviour of these lesions

MDT meetings
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