keeping abreast of BREAST PATHOLOGY

Journal Club | Apr 2021

Content

1. Latest WHO 2019 updates
2. Review of papillary lesions
3. Handling of post-neoadjuvant therapy specimens

latest WHO 2019 UPDATES & other updates

Table 1. Major changes within the new classification of tumours of the breast

Topic	Status in WHO 2012	Change in WHO 2019
Mitotic counts	Expressed per 10 HPFs	Given per mm^2
Carcinoma with medullary features	Separate entity	Now regarded as TIL-rich IBC-NST
Oncocytic, lipid-rich, glycogen-rich clear cell, sebaceous, pleomorphic, melanotic, oncocytic and choriocarcinomatous carcinomas, carcinoma with osteoclast-like giant stromal giant cells	Separate entities	Now regarded as rare variants of carcinoma NST
Inflammatory, bilateral and non-synchronous breast carcinomas	Separate entities	Now recognised as distinct clinical presentations rather than special subtypes
Lobular carcinoma *in situ*	Classic, pleomorphic types	Classic, pleomorphic and florid types
Neuroendocrine neoplasms	–	True primary neuroendocrine neoplasms are typed as NET, SCNEC, or LCNEC
Neuroendocrine differentiation	–	Overridden by morphological tumour type (NST, mucinous, solid papillary)
Well-differentiated liposarcoma in phyllodes tumours	Histological criterion of malignancy by itself	No longer a histological criterion of malignancy by itself
Mucinous cystadenocarcinoma	Not recognised	Recognised as a new entity
Breast tumour resembling the tall cell variant of papillary thyroid carcinoma; solid papillary carcinoma with reverse polarity	–	Now grouped as tall cell carcinoma with reversed polarity
Periductal stromal tumour	Separate fibroepithelial entity	Variant of phyllodes tumour
Mesenchymal tumours, haematolymphoid tumours, and genetic tumour syndromes	–	Covered in dedicated chapters

IBC-NST, invasive breast carcinoma no special type; HPF, high-power field; LCNEC, large-cell neuroendocrine carcinoma; NET, neuroendocrine tumour; NST, no special type; SCNEC, small-cell neuroendocrine carcinoma; TIL, tumour-infiltrating lymphocyte; WHO, World Health Organization.

PH Tan et al. Histopathology (2020), 77, 181–185.

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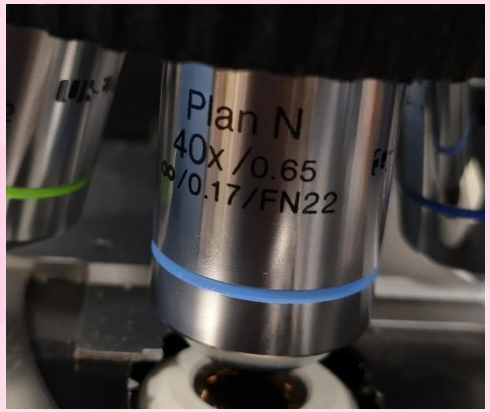
PH Tan et al. Histopathology (2020), 77, 181–185.

General Changes

- **Reorganisation of content**
  - By tumour type / systems (e.g. epithelial, mesenchymal, haemtolymphoid)
  - Progression from benign to malignant entities
  - New genetic tumour syndromes chapter

- **Mitotic count** change from per 10 HPF to per mm^2
  - Cut off for field diameter of 0.55 mm provided in department micro template; for others, refer to conversion table in WHO book / CAP protocol 2020

How to calculate field diameter:
Field number (FN) on objective lens divided by magnification



Example:
Field diameter
= 22 / 40
= 0.55

PH Tan et al. Histopathology (2020), 77, 181–185.

Nomenclature / Classification Changes

- **Reclassification of some entities**, with IBC-NST encompassing more morphologic variants
  - Carcinoma with medullary features → TIL-rich variant of IBC-NST
  - Other rare variants of IBC-NST: oncocytic, lipid-rich, glycogen-rich, clear cell etc

- **Neuroendocrine neoplasms** to follow nomenclature as per other organ sites (i.e. NET, small cell NEC, large cell NEC)
  - Excludes specific breast cancer subtypes which can show neuroendocrine differentiation (e.g. mucinous carcinoma, solid papillary carcinoma)

- **Lobular neoplasia** – new florid type LCIS

PH Tan et al. Histopathology (2020), 77, 181–185.

Mixed IBC NST and special subtype carcinoma may be used when special subtype makes up **10-90%** of the tumour

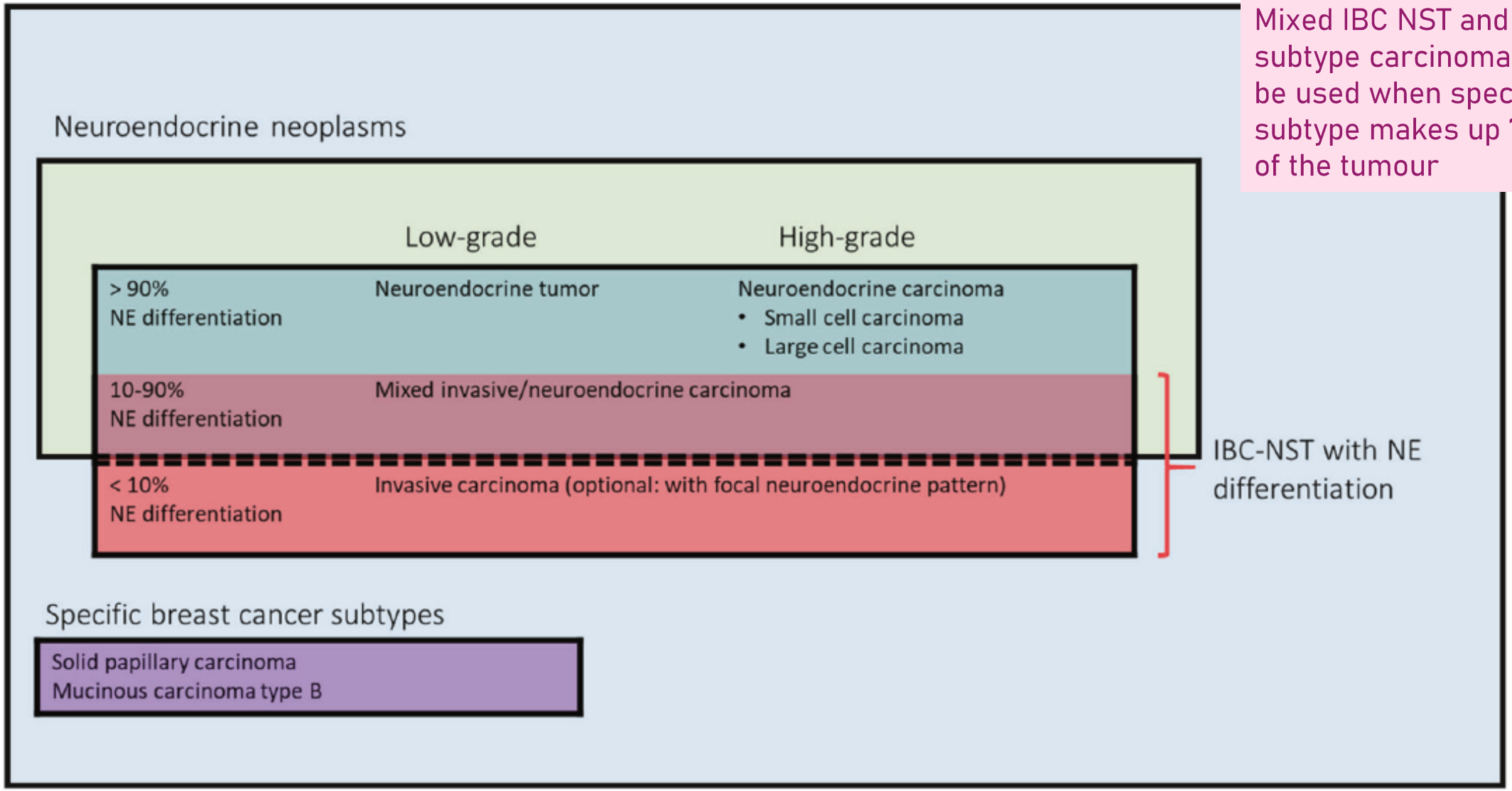


Fig. 1 WHO classification (2019) of NE cancers. Breast neoplasms with predominant neuroendocrine differentiation were classified as neuroendocrine neoplasm while those with less NE differentiation were labeled based on the non-NEN component.

JY Tsang, GM Tse. Mod Pathol (2021).

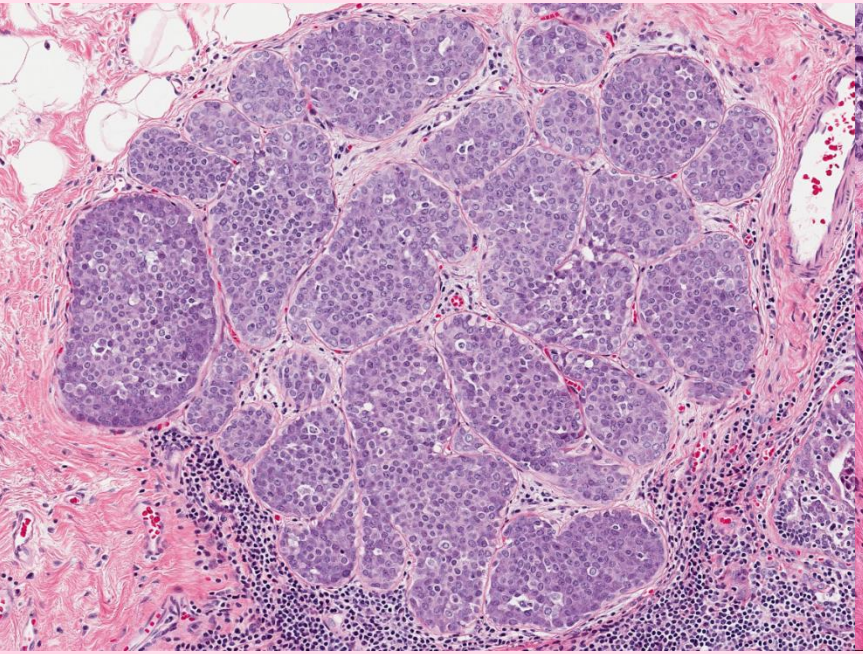
Lobular Neoplasia

- **Atypical lobular neoplasia (ALH)**: Less than 50% of the acini in a TDLU involved
- **Lobular carcinoma in-situ (LCIS)**: More than 50% of the acini
  - **Classic type**
  - **Pleomorphic type**: More marked nuclear pleomorphism (looks like high grade DCIS)
  - **Florid type**: Cytologic features of classic LCIS, but with marked distension of TDLUs/ducts; little or no intervening stroma between distended acini, and/or size of distended acinus or duct approx 40-50 cells in diameter

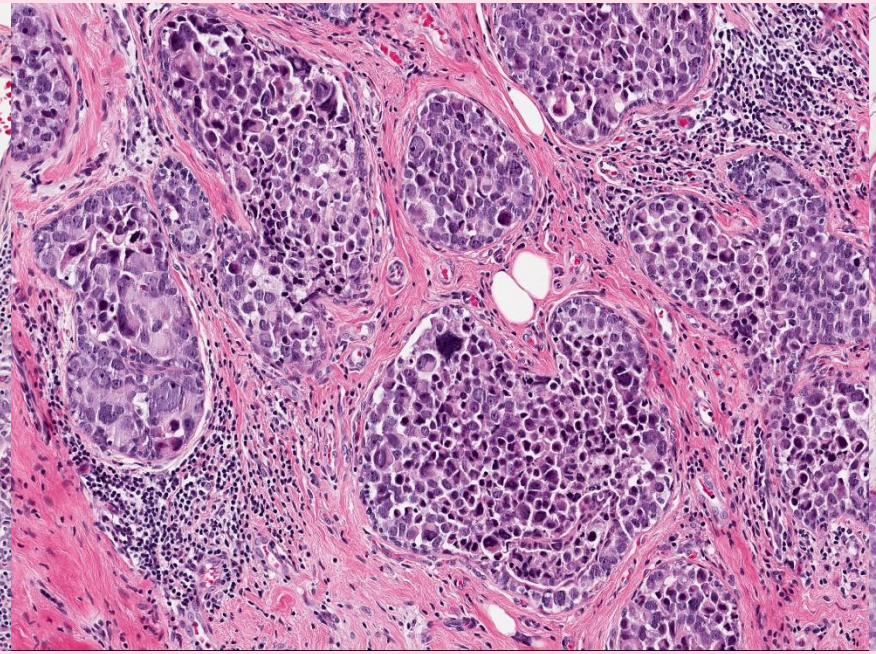
* If features borderline between classic type and pleomorphic or florid type, should be designated as classic LCIS

* WHO recommends excision for pleomorphic and florid LCIS diagnosed on core biopsy

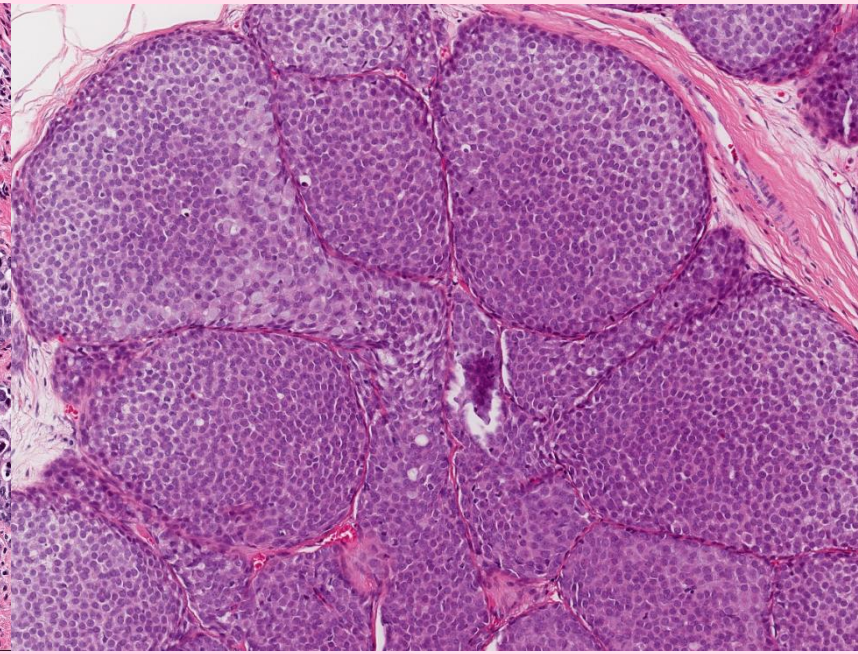
LCIS



Classic type



Pleomorphic type

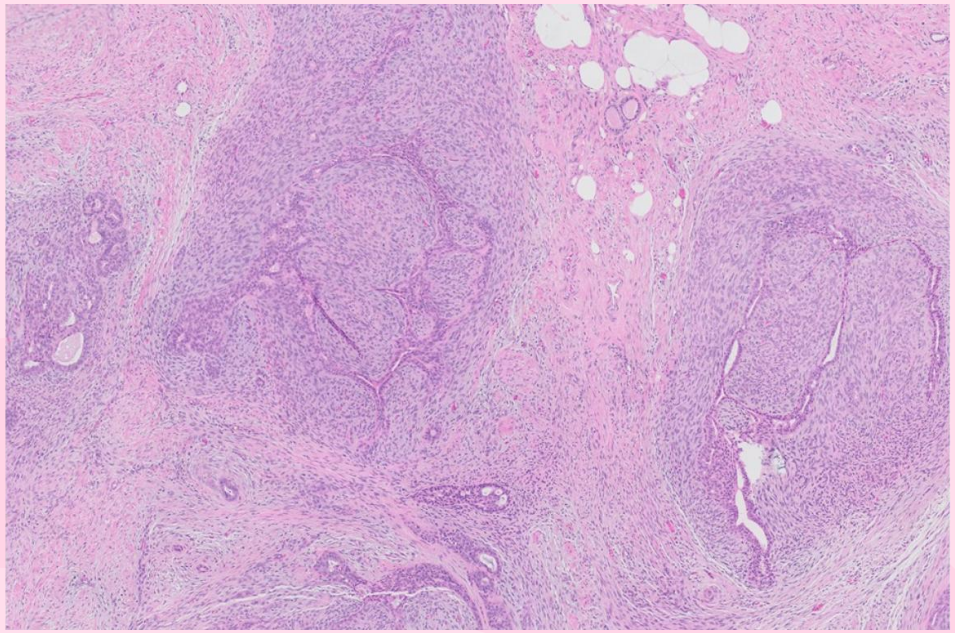


Florid type

Phyllodes Tumour

- Well-differentiated liposarcoma NO LONGER a histologic criterion for malignancy
  - Metastatic risk is low when well-differentiated liposarcoma occurs as the only heterologous element in a phyllodes tumour

- Periductal stromal tumour – now considered a variant of Phyllodes tumour
  - Some co-exist morphologically with phyllodes tumour, and focal phyllodes features were found in their recurrences



WHO Classification of Tumours of the Breast (5th Edition)

New Entities

- **Mucinous cystadenocarcinoma**
  - Invasive carcinoma with good prognosis
  - Resembles pancreatobiliary or ovarian mucinous cystadenocarcinoma

- **Tall cell carcinoma with reversed polarity**
  - Under section of rare and salivary gland type tumours
  - Resembles tall cell variant of papillary thyroid carcinoma
  - Harbour *IDH2* and *PIK3CA* mutations

PH Tan et al. Histopathology (2020), 77, 181–185.

Mucinous cystadenocarcinoma – new entity?

Human Pathology (2010) **41**, 910–913

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

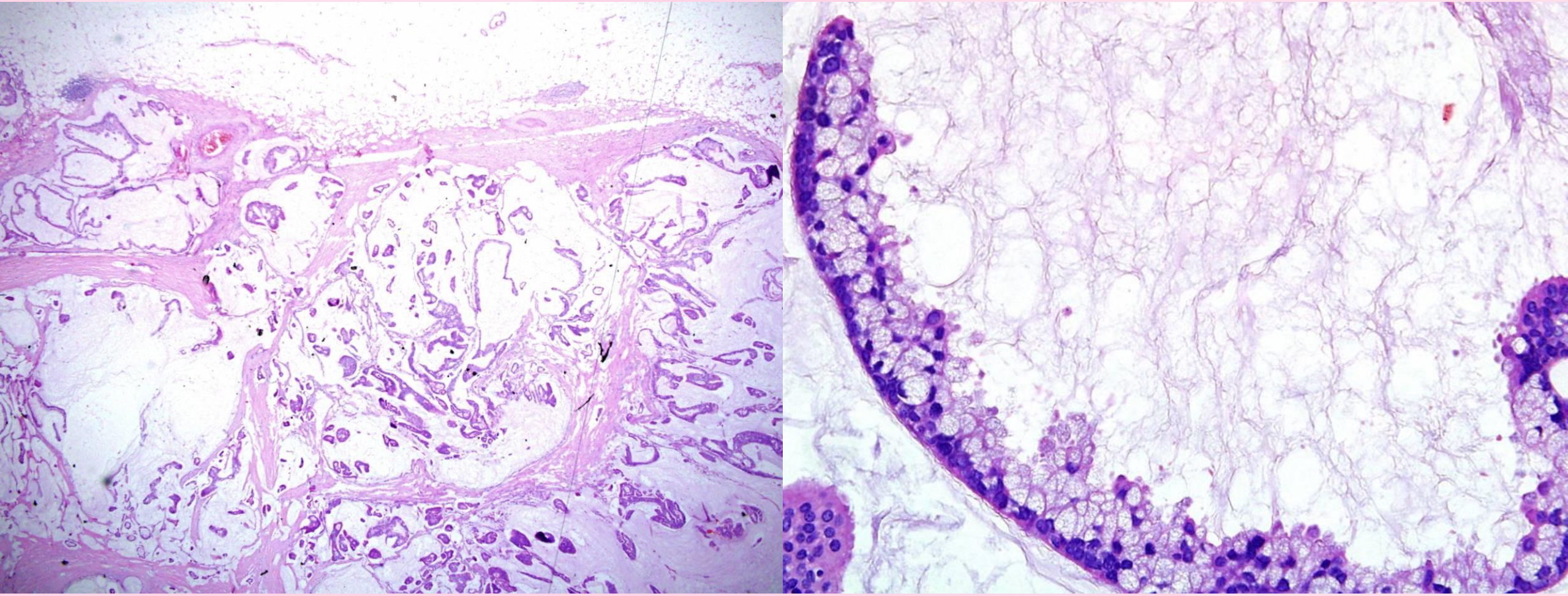
Case study

Mucinous cystadenocarcinoma of the breast with amplification of the HER2-gene confirmed by FISH: The first case reported

Fredrik Petersson MD PhD*, Brendan Pang MD, Thomas P. Thamboo MD, Thomas Choudary Putti MD

Department of Pathology, National University Health System, Singapore 119074, Singapore

Mucinous cystadenocarcinoma



Tall cell carcinoma with reversed polarity

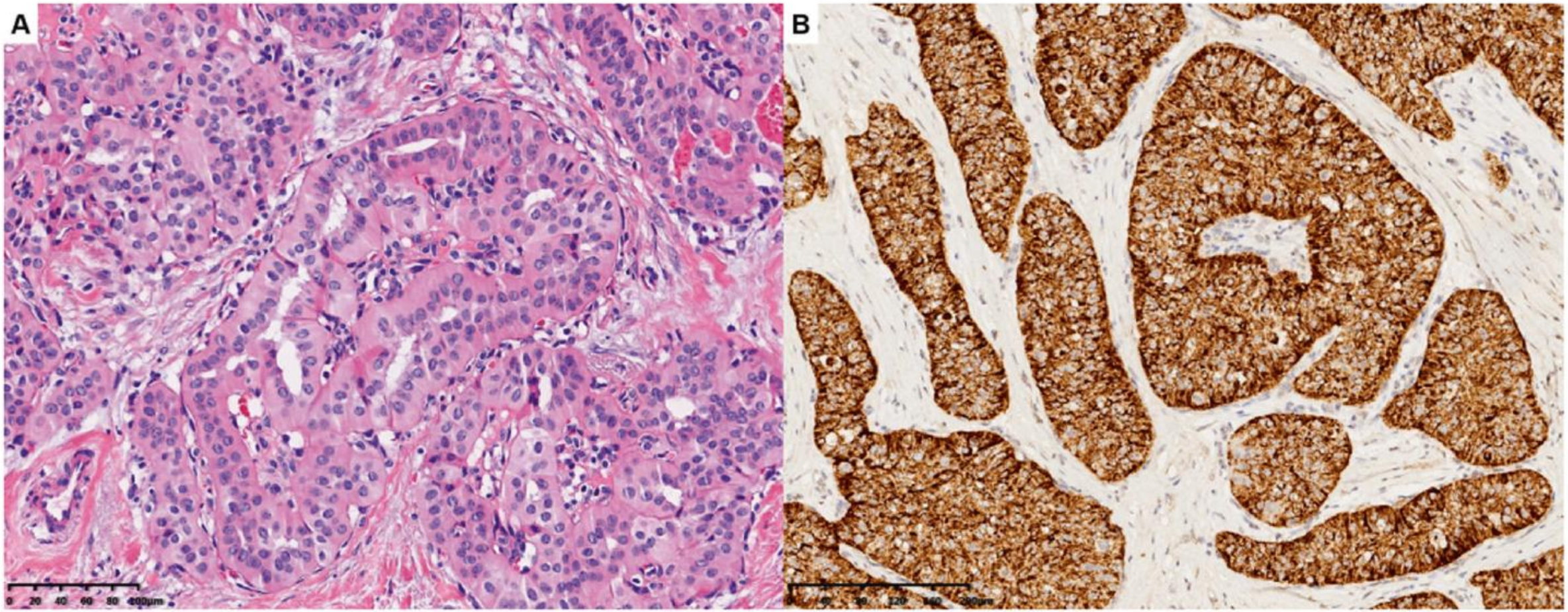


Fig. 21 Tall cell carcinoma with reversed polarity (courtesy of Dr. Wentao Yang). This tumor shows tubulo- to solid-papillary structures lined by columnar cells with vesicular nuclei, small nucleoli and occasional nuclear grooves. The nuclei of many tumor cells are aligned towards the apical/luminal aspect ("reversed polarity") (**A**). Immunohistochemistry for IDH2 R172S shows positive staining in tumor cells (**B**).

TKY Tay, PH Tan. Mod Pathol (2021).

ASCO 2020 Guidelines (ER/PR Reporting)

- New category of **ER low positive** for 1-10% immunoreactivity
  - Additional comment recommended to be included for ER low positive case
  - See updated micro reporting templates in shared drive (updated Feb 2021)

- ER testing recommended for DCIS cases
  - Already part of department protocol to perform **ER and PR on resection specimens with DCIS** only
  - Reminder that HER2 is NOT required for cases with DCIS only

- Other recommendations mostly already being practised by our lab

Have you ever wondered…

When do surgeons do sentinel lymph node biopsy (be it for frozen or for paraffin sections) for non invasive CA cases?

For DCIS, SLNB is done when

- Palpable lump
- Mastectomy case – because if final histology is invasive carcinoma, they cannot do SLNB anymore after mastectomy

Some surgeons also do pre-emptive SLNB if

- Lesion is in UOQ – postop distortion of the parenchyma may affect lymphatic flow and render subsequent SLNB inaccurate

Disclaimer: Anecdotal opinion from a breast surgeon; may not represent prevalent practice

review of PAPILLARY LESIONS

Modern Pathology
https://doi.org/10.1038/s41379-020-00732-3

REVIEW ARTICLE

Papillary neoplasms of the breast—reviewing the spectrum

Timothy Kwang Yong Tay[1] · Puay Hoon Tan[2]

Received: 12 October 2020 / Revised: 15 November 2020 / Accepted: 24 November 2020

Papillary Lesions

1. Intraductal papilloma
2. Encapsulated papillary carcinoma
3. Solid papillary carcinoma
4. Adenomyoepithelioma

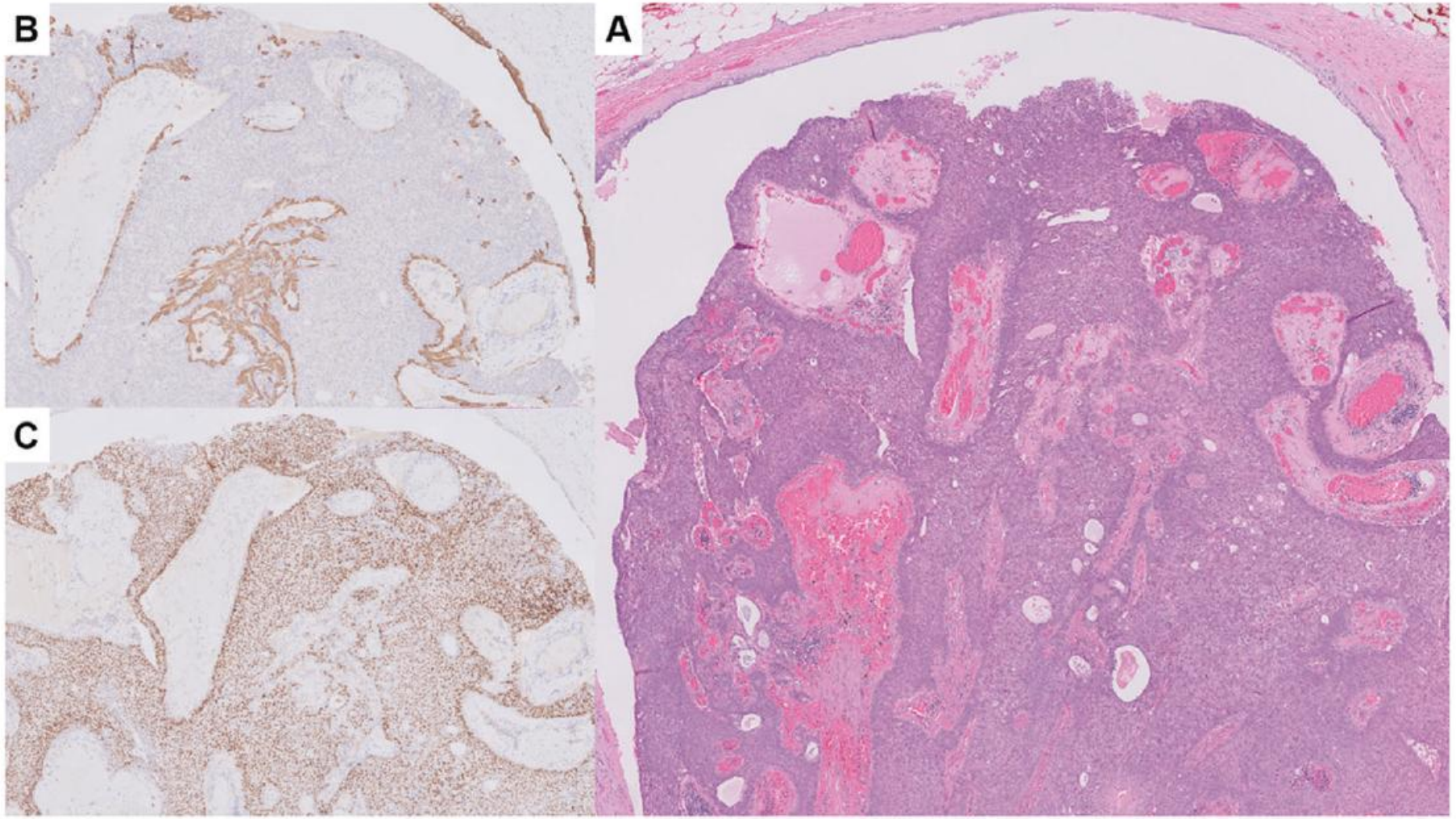
1. Intraductal Papilloma (IDP)

When is it more than just an intraductal papilloma?

- With ADH – low grade atypical epithelial proliferation measuring less than 3 mm
- With DCIS – low grade atypical epithelial proliferation measuring 3 mm or larger; or atypical epithelial proliferation of intermediate to high nuclear grade (regardless of size)

TKY Tay, PH Tan. Mod Pathol (2021).

Fig. 4 Intraductal papilloma with DCIS. A solid area of proliferation within the papilloma (16 mm in extent; >3 mm) in keeping with DCIS (**A**). Unlike usual ductal hyperplasia, DCIS stains negative for high molecular weight cytokeratins like CK14 (**B**) and shows uniformly positive staining for ER (**C**).



TKY Tay, PH Tan. Mod Pathol (2021).

2. Encapsulated Papillary Carcinoma (EPC)

- Usually seen in elderly / postmenopausal women
- Centrally located mass
- Delicate papillary fronds lined by epithelial cells with low to intermediate grade nuclear atypia
- Low mitotic activity (mean of 3 per 10 HPF)
- **Can have cribriform / solid areas**
- Typically ER and PR positive, HER2 negative

TKY Tay, PH Tan. Mod Pathol (2021).

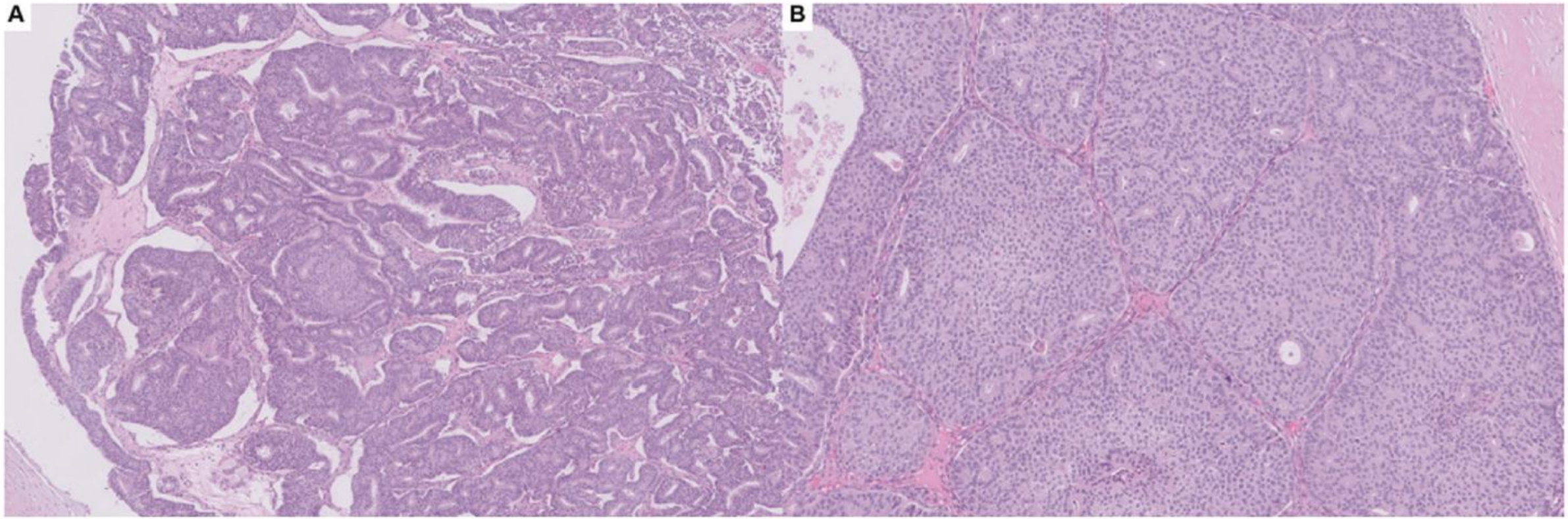
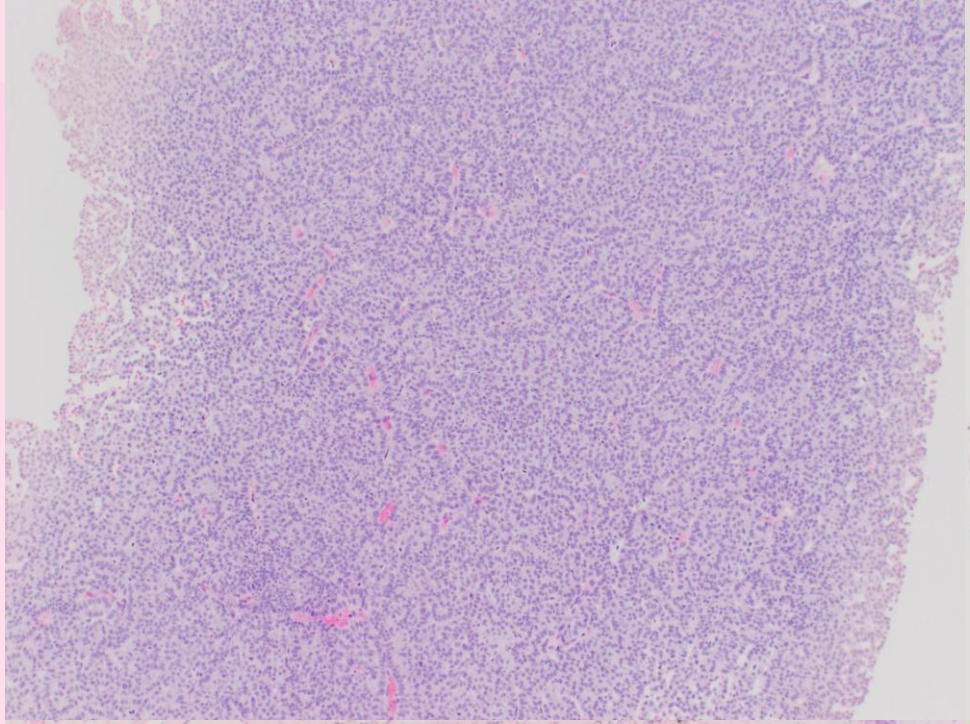
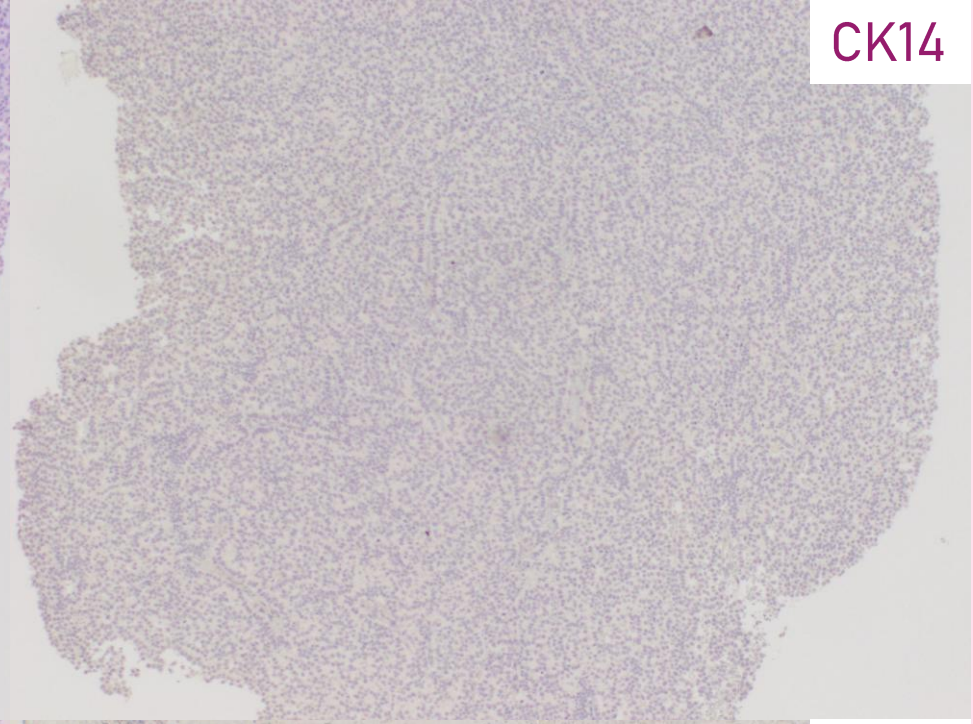


Fig. 9 Encapsulated papillary carcinoma. Papillary to cribriform architecture (**A**) and focal solid areas can be present (**B**).

TKY Tay, PH Tan. Mod Pathol (2021).

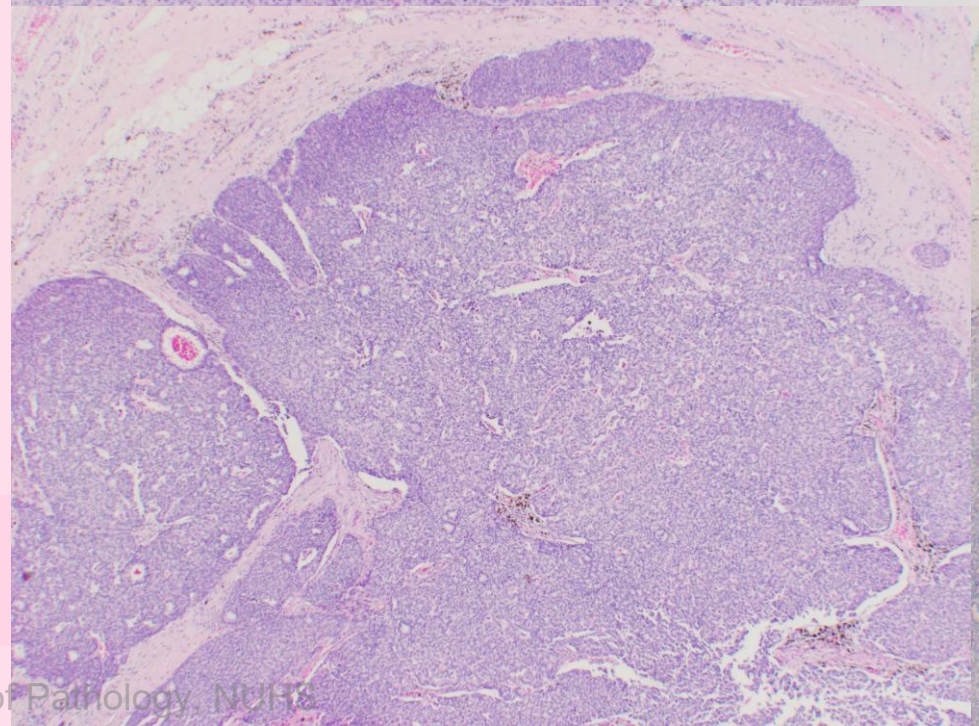
Biopsy

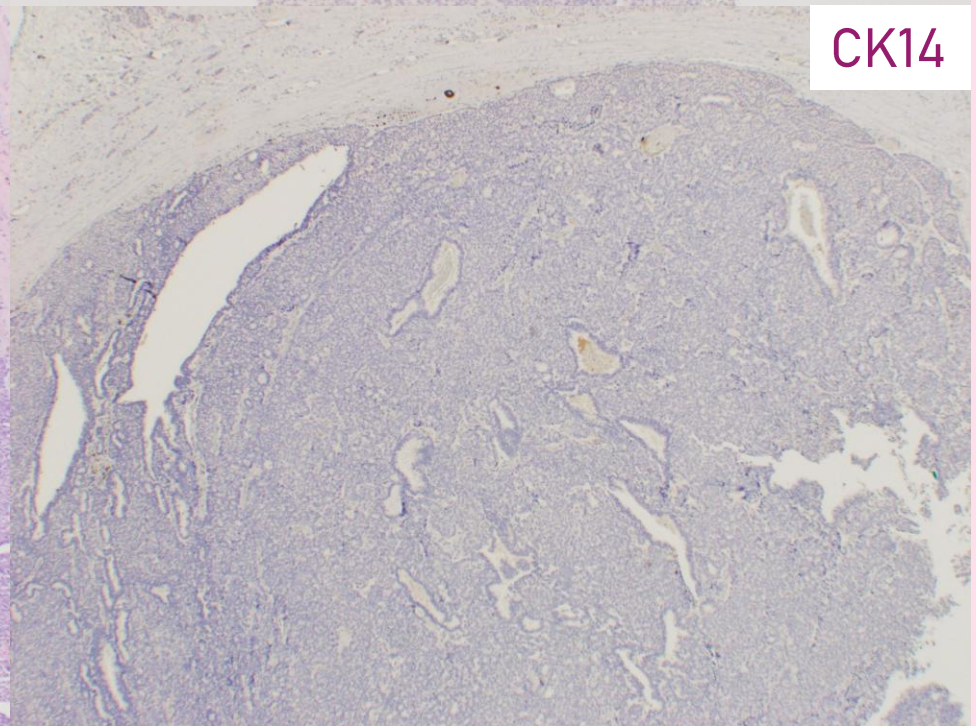




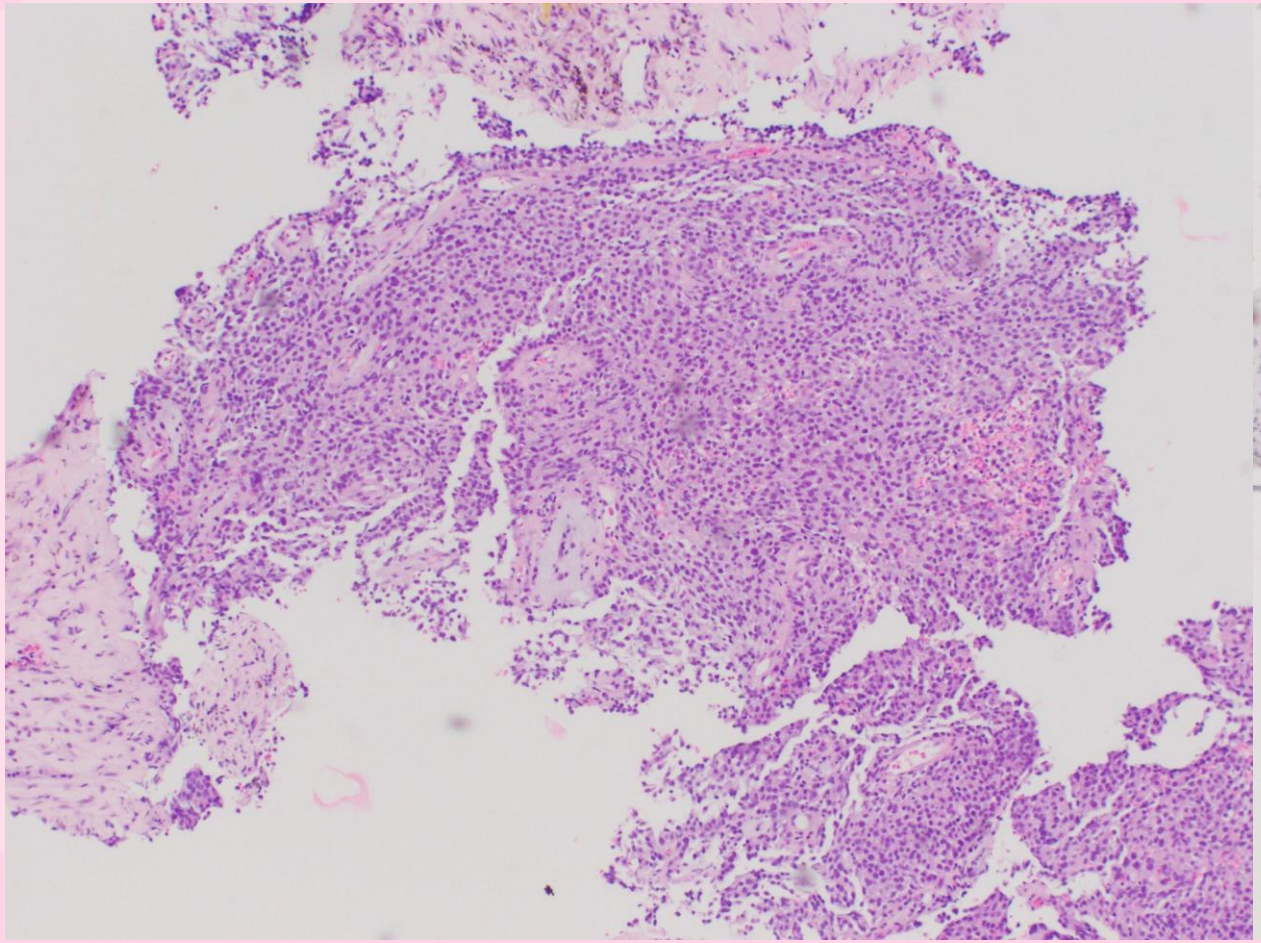
CK14

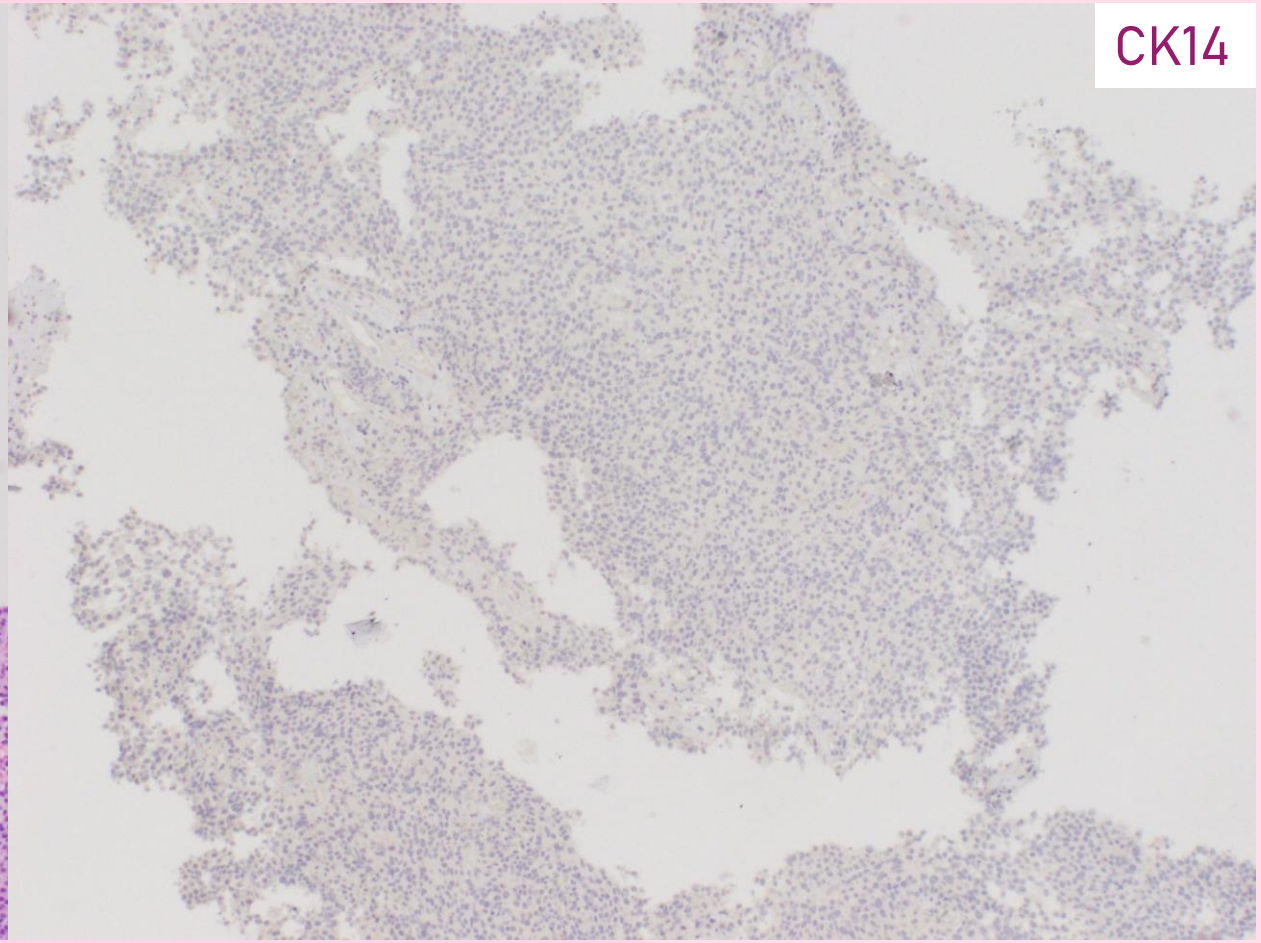
Resection





CK14




CK14

2. Encapsulated Papillary Carcinoma (EPC)

- Ongoing debate as to whether it is an in-situ or invasive carcinoma
- In a review, 3% of pure EPCs were found to have LN metastases; 2.2% had distant metastases
- General consensus – pure EPC should be staged and managed as in-situ carcinoma, to avoid over-treatment

TKY Tay, PH Tan. Mod Pathol (2021).

3. Solid Papillary Carcinoma (SPC)

- Usually seen in elderly / postmenopausal women
- Presents with a mass +/- nipple discharge
- Expansile solid nodules with interspersed delicate fibrovascular cores, monotonous proliferation of round to spindled epithelial cells
- Cells can be plasmacytoid or contain mucin
- Low mitotic rate (<5 per 10 HPF)
- ER positive, HER2 negative, shows neuroendocrine differentiation

TKY Tay, PH Tan. Mod Pathol (2021).

3. Solid Papillary Carcinoma (SPC)

1. **In-situ**: Well-circumscribed nodules, pushing borders, +/- myoepithelial cells at periphery
2. **Invasive**: Absent myoepithelial cell layer, irregular/jagged outlines of nodules, desmoplastic stroma
3. **With invasive carcinoma**: Can range from IBC-NST to other special subtypes (e.g. mucinous, tubular, lobular)

* Remember to specify this information in your report

TKY Tay, PH Tan. Mod Pathol (2021).

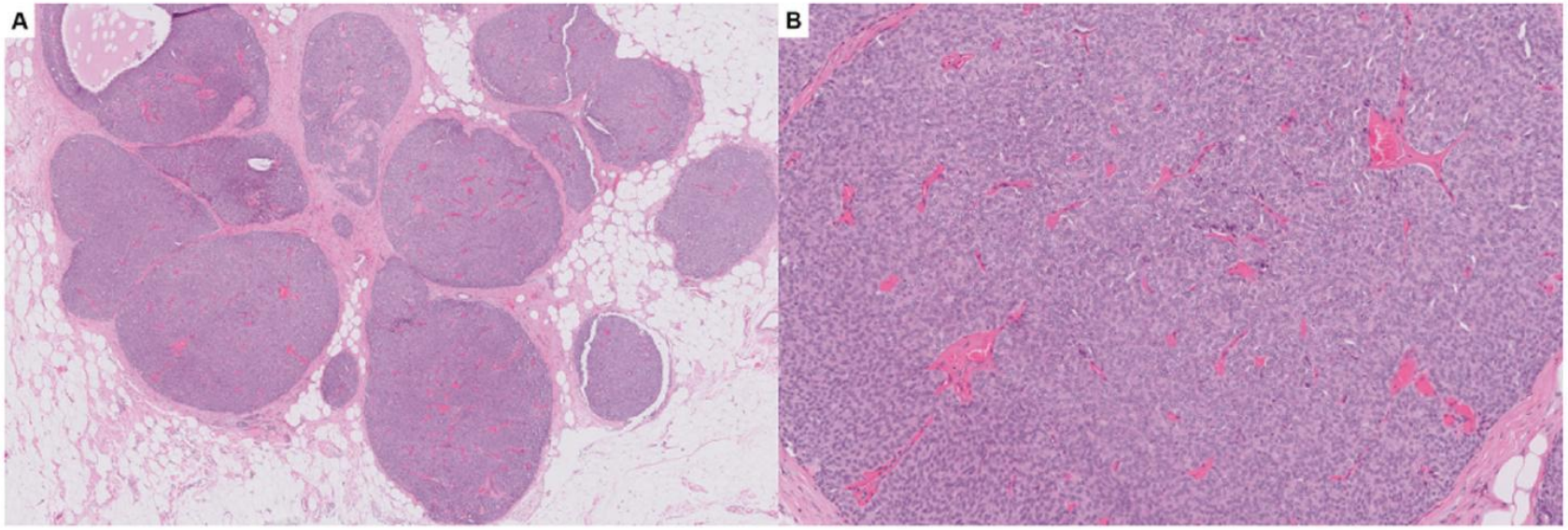


Fig. 14 Solid-papillary carcinoma in situ. An often multinodular lesion resembling a cluster of ducts that are filled and expanded by a solid-papillary proliferation of tumor cells. The lesion has well-circumscribed, pushing borders without evidence of stromal invasion (**A**). Closer examination of the nodules shows intervening delicate fibrovascular cores compressed by a solid proliferation of tumor cells of low nuclear grade (**B**).

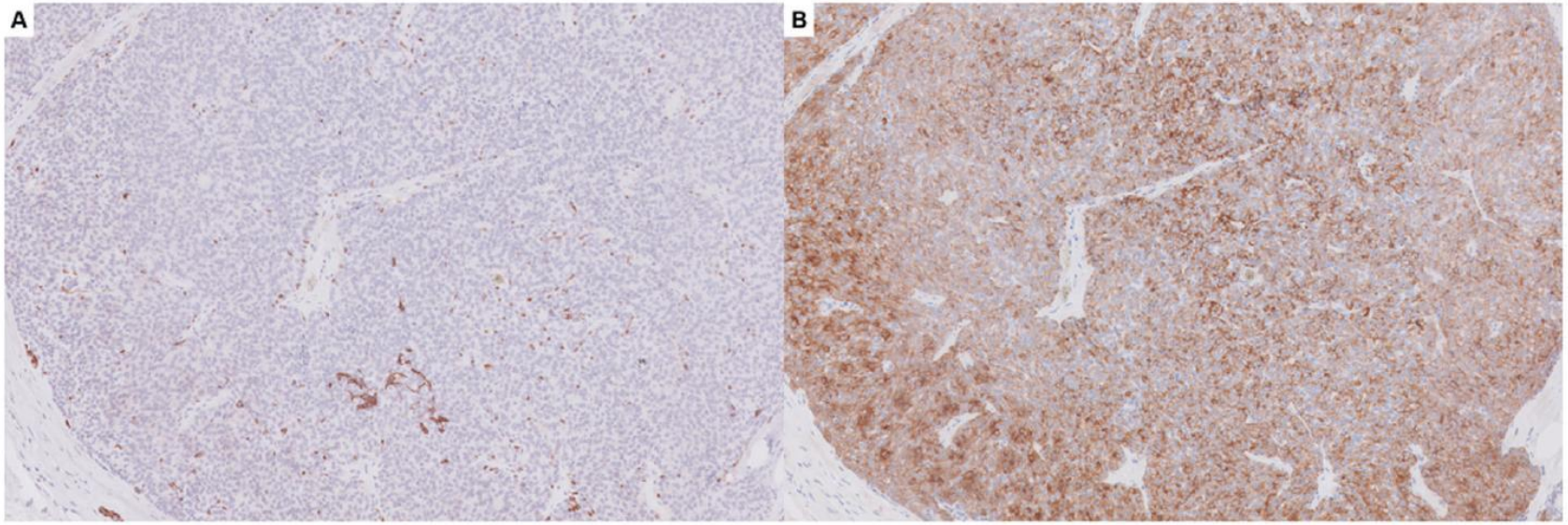


Fig. 15 Solid-papillary carcinoma in situ. While myoepithelial cells are usually absent within the nodules, focal staining for myoepithelial markers such as p63/CK5-6 in this case has been reported (**A**). Neuroendocrine expression with positivity for synaptophysin is often seen (**B**).

TKY Tay, PH Tan.
Mod Pathol (2021).

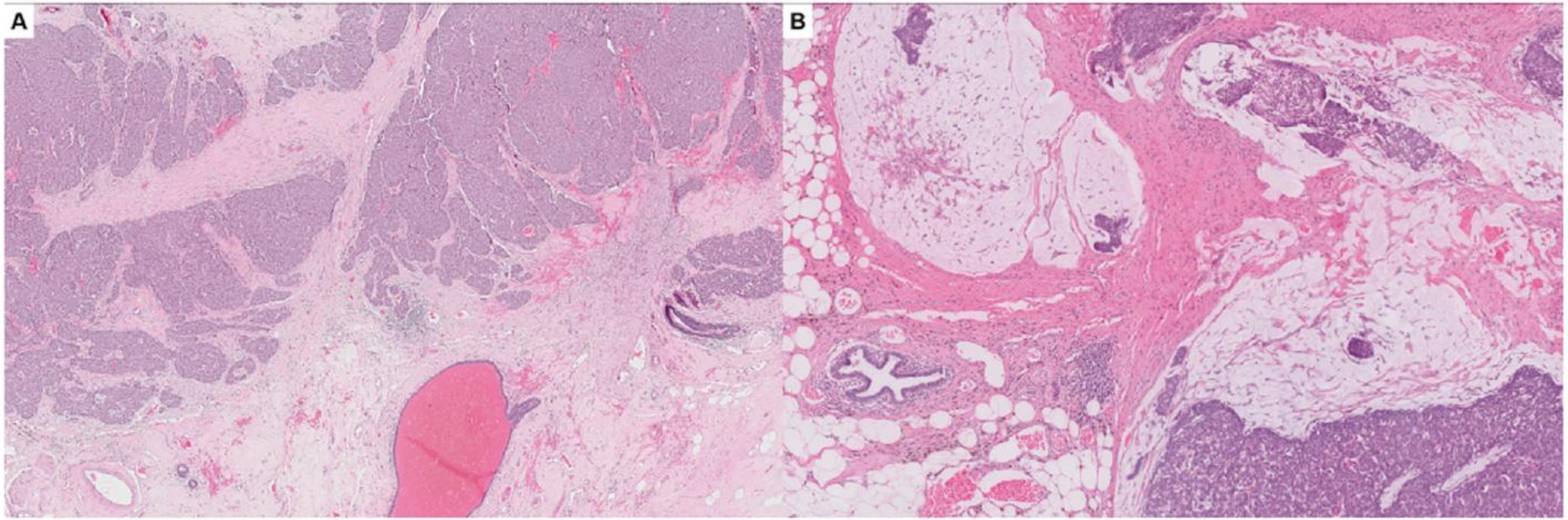


Fig. 17 Solid-papillary carcinoma with invasive disease. Invasive solid-papillary carcinoma is diagnosed when the tumor nodules do not have the rounded, pushing borders of in situ disease, but rather, have irregular, jagged contours that may resemble pieces of a jigsaw puzzle when closely apposed, with an infiltrative pattern in the stroma (**A**). Solid-papillary carcinoma with an invasive carcinoma component, on the other hand, refers to an in situ solid-papillary carcinoma with an area of invasive carcinoma which may be of various histological types including mucinous carcinoma (**B**; solid-papillary carcinoma component not shown).

TKY Tay, PH Tan. Mod Pathol (2021).

4. Adenomyoepithelioma (AME)

- Biphasic proliferation of epithelial and myoepithelial cells
- Variety of architectural patterns, including papillary pattern → when this predominates, it becomes difficult to differentiate from IDP
- Clues to AME
  - More conspicuous myoepithelial component (>50%)

    Pitfall with IHC: Luminal cells may show paradoxical staining for HMWCK instead of the myoepithelial cells
  - ER expression can be positive or negative

    Negative ER expression would be unusual for IDP → favour AME

TKY Tay, PH Tan. Mod Pathol (2021).

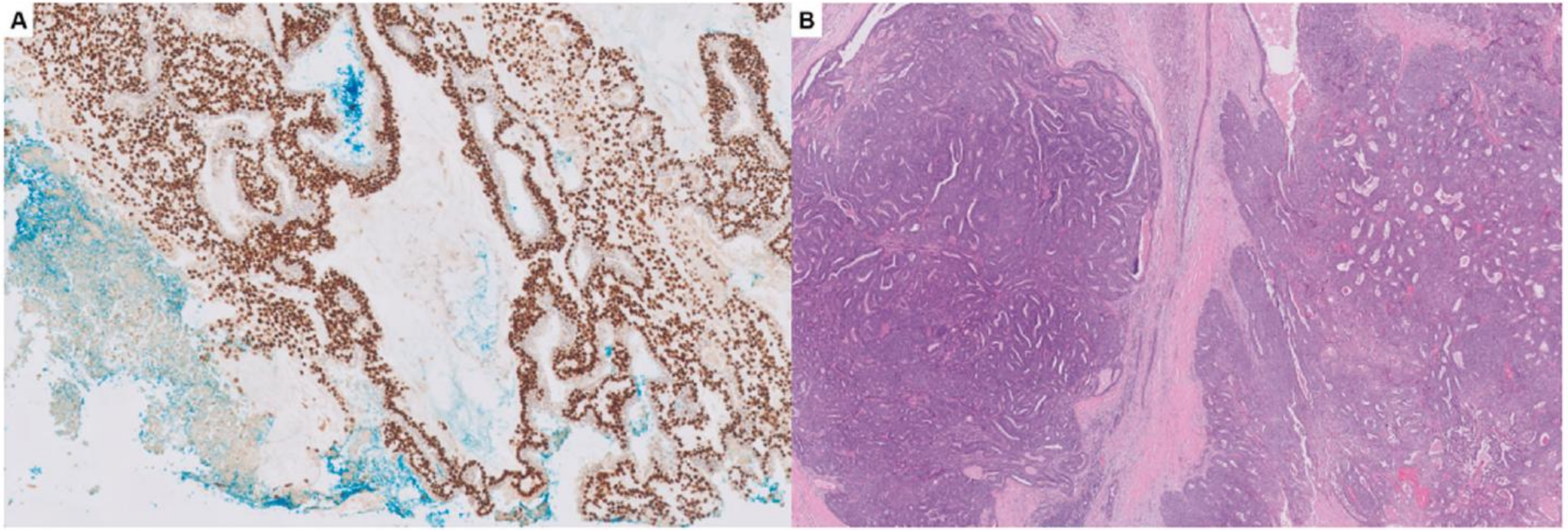


Fig. 19 Malignant adenomyoepithelioma. P63 stain of the tumor in Fig. 18 highlights the increased number of myoepithelial cells (**A**). This tumor was also negative for ER which is unusual for a papilloma. Subsequent resection again showed a papillary tumor (**B**).

TKY Tay, PH Tan. Mod Pathol (2021).

Histopathology

Histopathology 2016, **68**, 22–32. DOI: 10.1111/his.12866

REVIEW

Pathological criteria and practical issues in papillary lesions of the breast – a review

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Practical Issues with Papillary Lesions

1. **Invasion or not?**
   Diagnosis of invasive malignancy should not be based on the apparently infiltrative pattern only; we also need to take into account the cytological and architectural features of the papillary lesion itself

Table 1. Features that are helpful in differentiating benign glandular entrapment and invasive foci

Features	Benign glandular entrapment	Invasive foci
Arrangement of epithelial cells	Irregular but smoothly contoured clusters, flow in the direction of the fibroblasts and bundles of collagen	Traversing the normal stroma in different directions
Architectures of epithelial cell clusters	Polygonal shape compressed into long and slender cords	Open and sometimes angulated lumen
Myoepithelial cells	Present	Absent

YB Ni, GM Tse. Histopathology (2016), 68, 22–32.

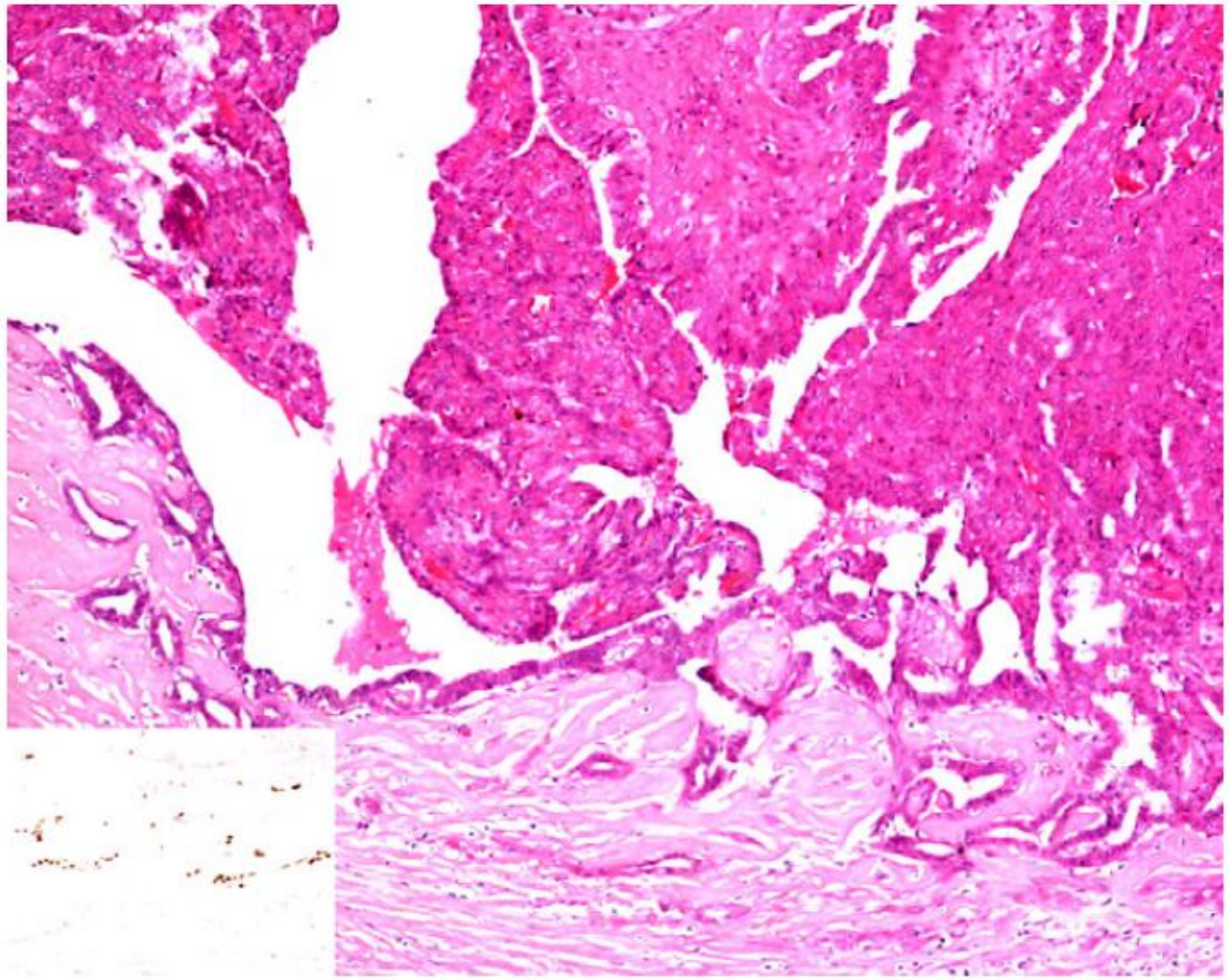


Figure 7. Benign glandular entrapment in intraductal papilloma. The epithelial cells are arranged in irregular but smoothly contoured clusters, and are compressed by the collagenized stroma. They tend to flow in the direction of bundles of collagen. The inset shows that p63 highlights myoepithelial cells surrounding the entrapped epithelial cells.

Mechanical displacement due to prior biopsy

- IHC for myoepithelial cells will not be helpful
- Look for features of prior biopsy – hemorrhage, haemosiderin-laden macrophages, fat necrosis, inflammation, granulation tissue, needle tract reaction
- Note – it is also possible to have invasion adjacent to needle tract (by chance)!

YB Ni, GM Tse. Histopathology (2016), 68, 22–32.

Practical Issues with Papillary Lesions

2. **IHC general rules and exceptions**

Most frequently used markers: p63, HMWCK, ER

General rules:

Benign papillary lesions – p63 and HMWCK positive
Malignant papillary lesions – p63 and HMWCK negative, ER homogeneous

Exceptions:

IDPs with columnar cell change – can show homogeneous ER staining
HMWCK expression should be assessed in solid areas, not papillary areas
Lack of myoepithelial layer does not always imply invasion (e.g. EPC, SPC)

YB Ni, GM Tse. Histopathology (2016), 68, 22–32.

Have you ever wondered…

What is the margin clearance that surgeons expect for WLE specimens? Are all margins "equal" (in terms of their significance)?

Invasive carcinoma – as long as not involved
DCIS – 2 mm clearance preferred

Whether surgeons go back for re-excision depends on the site of involvement, extent and other patient factors → usually the anterior and posterior margins are less of a concern

Note: Do indicate in the report the extent of margin involvement (e.g. focal, extensive, or even exact measurement of the length of involvement if possible) – commonly asked question by surgeons at tumour board

handling of POST CHEMOTHERAPY specimens

Premise

- No strict protocol for grossing and reporting post chemotherapy specimens in our institution so far

- Several classifications systems exist for evaluation of post chemotherapy breast specimens
  E.g. The Residual Cancer Burden (online tool), Residual Proliferative Cancer Burden etc

- Different definitions of pathological complete response (pCR)
  Residual disease in LN portends worse prognosis
  pCR should include absence of disease in BOTH the breast and axillary LNs

Note: Majority of the issues that will be discussed are pertaining to cases with no grossly visible residual tumour

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

Residual Cancer Burden Calculator

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area: 13 (mm) X 13 (mm)

Overall Cancer Cellularity (as percentage of area): 5 (%)

Percentage of Cancer That Is *in situ* Disease: 0 (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes: 0

Diameter of Largest Metastasis: 0 (mm)

Reset Calculate

Residual Cancer Burden: 1.301

Residual Cancer Burden Class: RCB-I

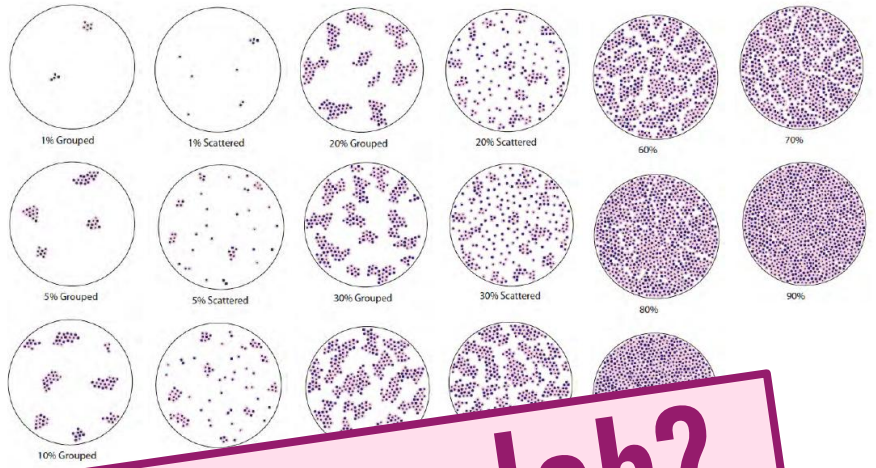
- RCB 0:
  - cPR; no residual disease
- RCB I:
  - Minimal residual disease
  - RCB index <1.36
- RCB II- moderate residual disease
- RCB III
  - Extensive residual

Google terms: residual cancer burden breast

www.mdanderson.org/breastcancer_RCB

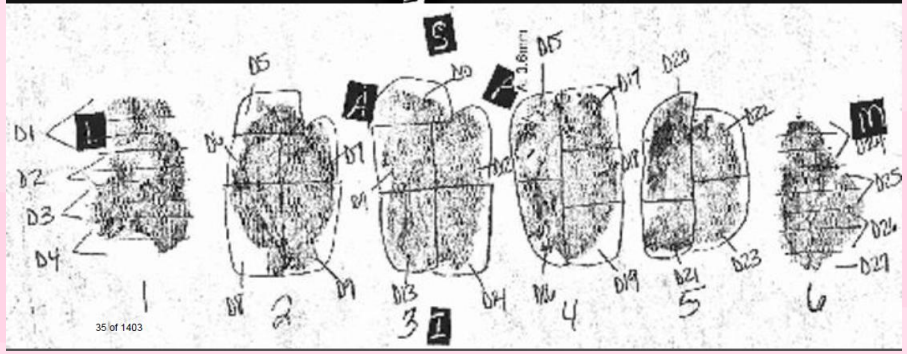
13 of 1403

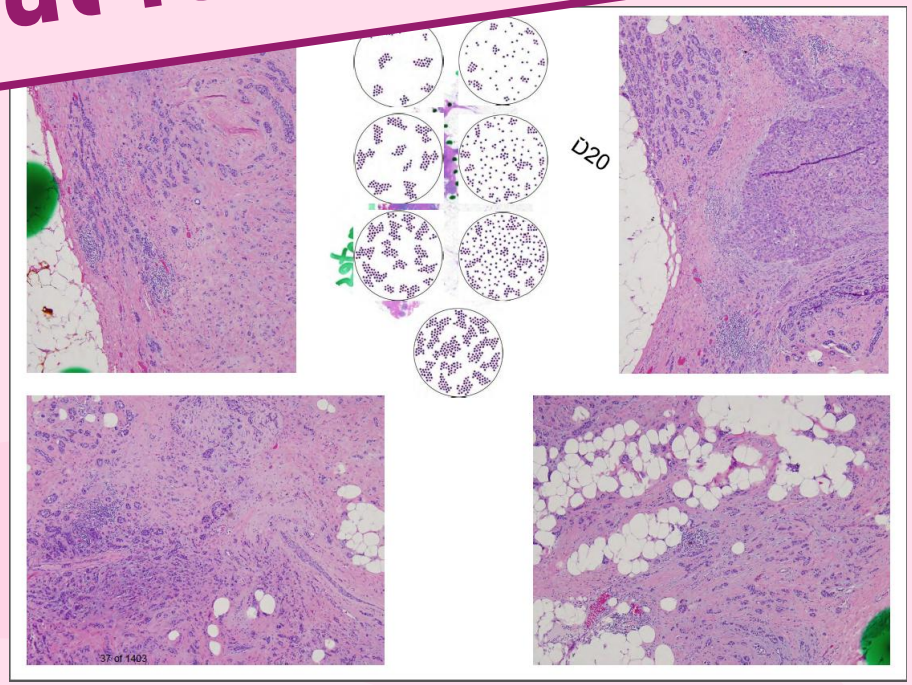
Graphical Illustration of Percentage Cancer Cellularity



mm2
mm 2
1% cellularity
cellularity

Is this practical for our lab?





MODERN PATHOLOGY (2015) 28, 1185–1201

Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group

Elena Provenzano[1], Veerle Bossuyt[2], Giuseppe Viale[3], David Cameron[4], Sunil Badve[5], Carsten Denkert[6], Gaëtan MacGrogan[7], Frédérique Penault-Llorca[8], Judy Boughey[9], Giuseppe Curigliano[10], J Michael Dixon[11], Laura Esserman[12], Gerd Fastner[13], Thorsten Kuehn[14], Florentia Peintinger[15,16], Gunter von Minckwitz[17], Julia White[18], Wei Yang[19] and W Fraser Symmans[20] on behalf of the Residual Disease Characterization Working Group of the Breast International Group-North American Breast Cancer Group (BIG-NABCG) collaboration

BIG-NABCG* Study

- Standard operating procedures collected from 28 trials and 25 sites

- Significant variability of practice was found, including:
  - Extent of sampling (4 to 40 blocks)
  - Thickness of primary tumour sectioning (2 to 10 mm)
  - Routine use of IHC when no tumour was identified
  - Measurement of residual tumour
  - System of grading response

* Breast International Group-North American Breast Cancer Group
E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

BIG-NABCG Recommendations – Specimen Handling

1. **General advice**

   Record image of sliced specimen (be it radiograph, photograph, photocopy or drawing) → used as a map for sections taken

2. **Small lumpectomy specimens**

   Submit in entirety if <5 cm or <30 g

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

BIG-NABCG Recommendations – Specimen Handling

3. **Large lumpectomy specimens / mastectomy**

Sample grossly seen tumour bed and/or location of marker clip and immediately adjacent tissue

Degree of sampling depends on: pre-treatment size, presence of grossly visible tumour, grossly visible tumour bed

Full face of pre-treatment area of involvement per every 1 cm slice; or
(if tumour is large) 5 representative blocks of a cross section of pre-treatment area of involvement per 1-2 cm of pre-treatment size (max ~25 blocks)

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

BIG-NABCG Recommendations – Reporting

1. **Breast specimen**

   Histologic appearance of tumour bed:

   - Loose oedematous reactive stroma
   - Variable inflammatory infiltrate – lipid-laden or haemosiderin-laden macrophages, lymphocytes, plasma cells
   - Background breast lobules – hyalinised, atrophic, perilobular lymphocytic infiltrate

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

BIG-NABCG Recommendations – Reporting

1. **Breast specimen**

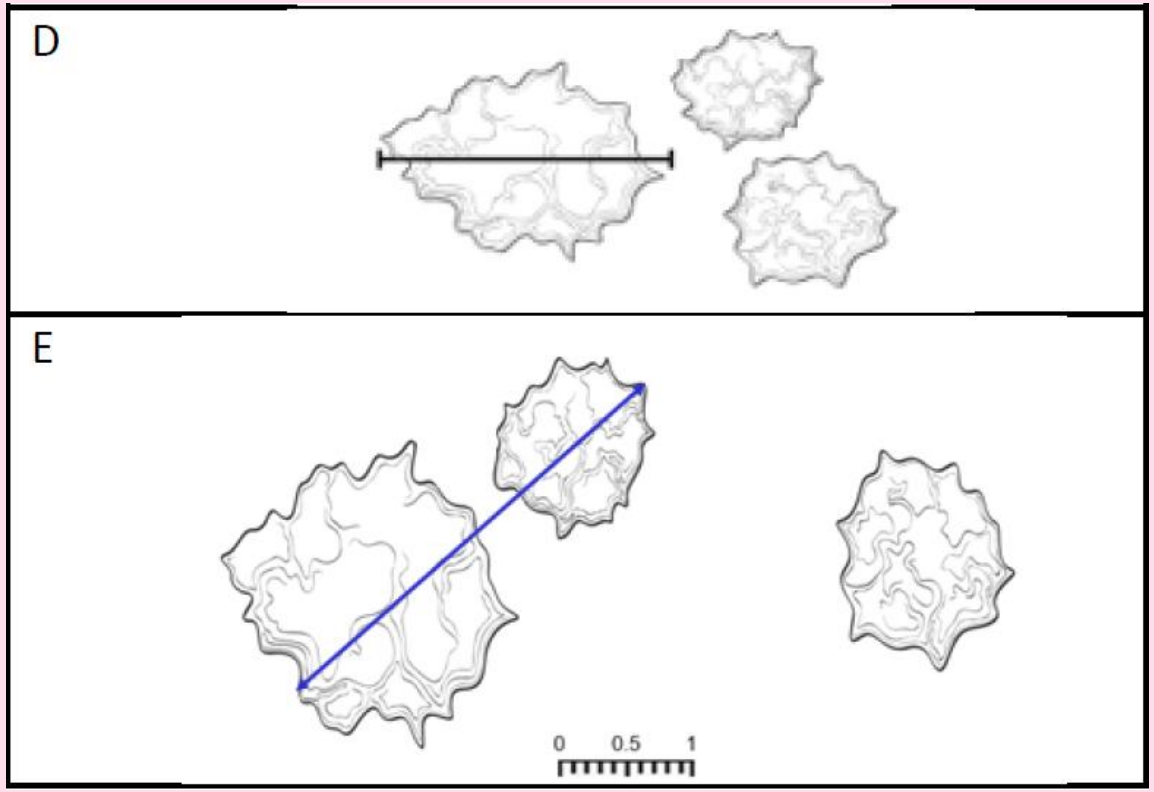
   2 main patterns of response to NACT: concentric shrinking vs scatter pattern

   i. If **single** tumour pre-operatively – regard residual disease as single tumour (esp if scattered tumour cells/nests are present within reactive stromal background)

   ii. If **multiple** tumours pre-operatively, or tumour foci separated by normal breast tissue – regard as multiple lesions and measure each independently

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

General guidelines for measurement of tumour size (AJCC 8th Edition)

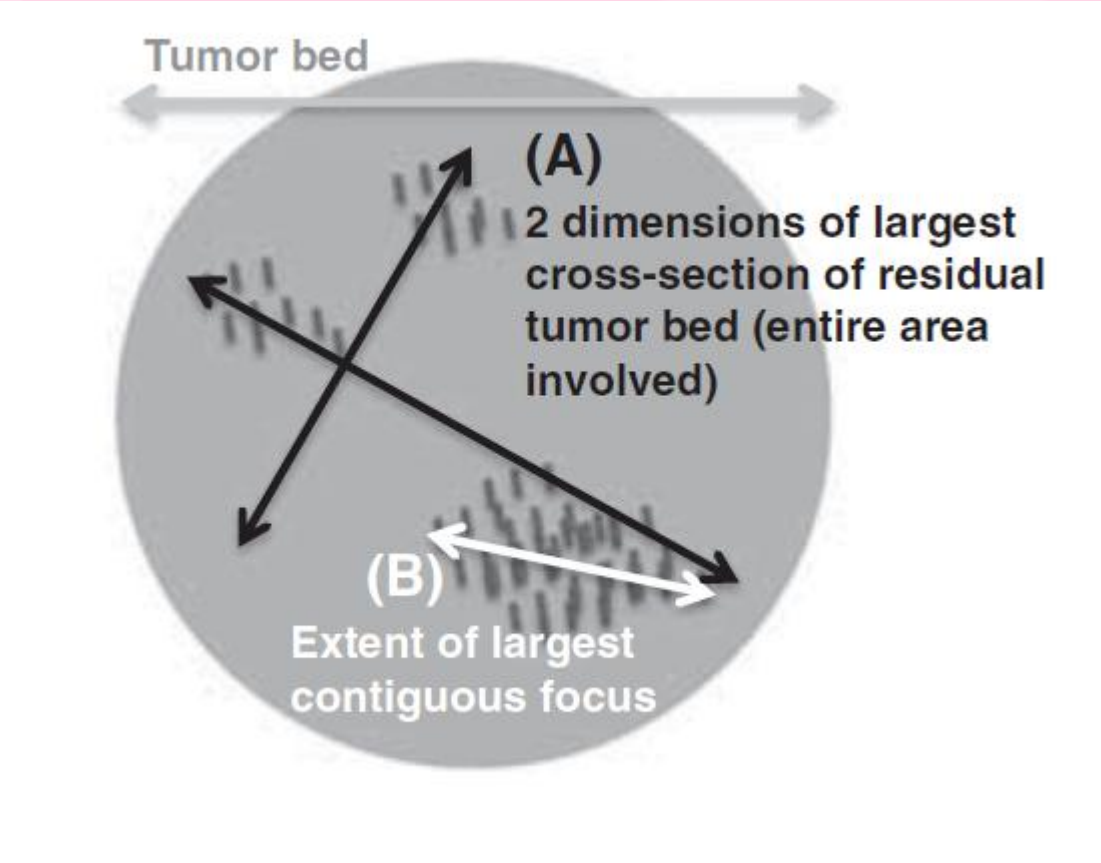


If multiple carcinomas – size of largest invasive carcinoma focus used for T staging

If multiple carcinomas in close proximity – if two histologically similar carcinomas are within 5 mm of each other, measure from outer edges of the two

If carcinoma with multiple satellite foci within 1-5 mm of main carcinoma – only measure the size of the main carcinoma

CAP Protocol for Resection Specimens From Patients with Invasive Carcinoma of the Breast Version 4.4.0.0 (Feb 2020)



(B) Measurement guidelines as per AJCC 8th edition
→ this may underestimate the tumour extent

(A) Measurement to include tumour cell clusters and intervening fibrous tissue – correlates with survival and is a better indicator of response
→ authors suggest to give BOTH measurements in the report

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

Microscopy

Size/extent of residual tumor: _ mm

Largest cross-section of residual tumor bed (entire area involved) _ x _ mm represented in cassettes (….)

Posttreatment histological grade

Residual cellularity:__%

DCIS: present/absent

Total lesion size including DCIS: _ x _ mm

Percentage of residual cellularity that is CIS:__%

Lymphovascular space invasion: present/absent/indeterminate/extensive

In the absence of residual tumor, is the previous tumor site identified (clip site/area of fibrosis): yes/no

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

BIG-NABCG Recommendations – Reporting

1. **Breast specimen**

    iii. Residual LVI only – NOT pCR; can quantify as focal or extensive (≥1 foci in >1 block)

    iv. Margins – tumour bed extending to margins should be documented

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

BIG-NABCG Recommendations – Reporting

2. **Axillary lymph nodes**

   Any residual disease in LNs, including ITCs and micrometastases, should NOT be considered as pCR

   Size of largest metastasis was strongest predictor of overall survival

   If residual metastatic tumour occurs as scattered tumours cells/nests within area of fibrosis, size of entire area (including tumour cells and intervening stroma) should be measured, instead of largest cell cluster

E Provenzano et al. Mod Pathol (2015), 28, 1185–1201.

Summary

- Be aware of the latest nomenclature, definition changes and updates
  - Do use the latest WHO 2019 nomenclature (e.g. invasive carcinoma of no special type)
- Be aware of the pitfalls in papillary lesions
- Be aware of the challenges and unique histologic changes in the grossing and reporting of post-chemotherapy specimens

Thank You!

References and Credits

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2. JY Tsang, GM Tse. Breast cancer with neuroendocrine differentiation: an update based on the latest WHO classification. Modern Pathology. 2021. https://doi.org/10.1038/s41379-021-00736-7
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5. E Provenzano et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Modern Pathology. 2015; 28: 1185-1201.
6. AJCC 8th Edition Breast Cancer Staging System
7. WHO Classification of Tumours of the Breast (5th edition) [online]
8. Presentation slides design from Slidesgo, including icons by Flaticon and infographics and images by Freepik