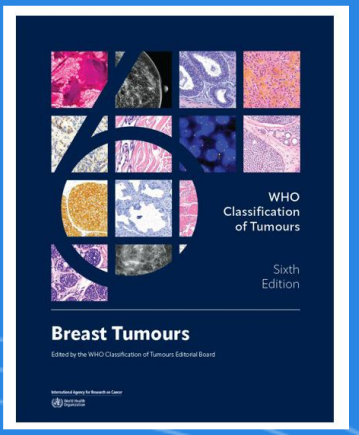
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WHO 6th Breast Tumors Classification 2026 What is new and noteworthy?

Edi Brogi MD PhD

Director of Breast Pathology- Memorial Sloan Kettering Cancer Center

Professor of Clinical Pathology and Laboratory Medicine- Weill Cornell Medical College

The International Academy of Pathology
Hong Kong Division

Scientific Congress November 6-8, 2026

WHO Classification of Tumours

1st Editorial Board Meeting
Breast Tumours

2 October 2024
Lyon, France



WHO Classification of Tumours

1st Editorial Board Meeting
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Lyon, France



WHO Classification of tumours - Why is it important?

- Uniform nomenclature - adopted worldwide
- Standardized framework for categorization of tumours
  - Facilitate accurate diagnosis
  - Guide therapeutic strategies
  - Inform research
  - Enable precise epidemiological data collections by cancer registries

- 6th series includes
  - oncology, radiology and molecular genetics experts
  - pathologists practicing in low- and middle-income country settings

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WHO 6th ed. Classification of Tumours of the Breast

Breast Tumours (6th ed.)

1. Front matter and Introduction

- **Website beta version**
- **How to cite this volume**
- **Copyright**
- **The WHO Classification of Tumours Editorial Board**
- **IARC/WHO Committee for ICD-O**
- **Subcommittees**
  - Computational Pathology
  - Genetics and Genomics
  - Grey zone and rare tumours
  - Imaging and Radiology
  - Tumour clarification and refining
  - Tumour harmonization
  - WCT–LMIC liaison
- **Production**
- **List of abbreviations**
- **Foreword**
- **ICD-O coding**
- **TNM staging tables**
- **Contributors**
- **Declaration of interests**

Suggestions from subcommittees

- Evidence-based

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Suggestions from subcommittees

2. Introduction to tumours of the breast

3. Epithelial tumours of the breast: Part 1

4. Epithelial tumours of the breast: Part 2

5. Fibroepithelial tumours and hamartomas of the breast

6. Tumours of the nipple

7. Mesenchymal tumours of the breast

8. Haematolymphoid tumours of the breast

9. Tumours of the male breast

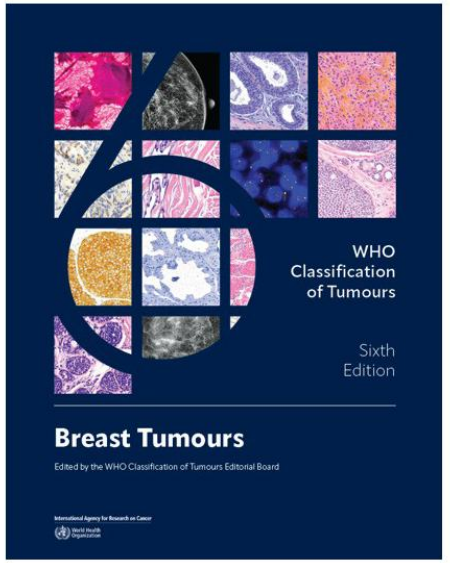
10. Genetic tumour syndromes of the breast

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Lecture Overview

BR5th ed. compared to BR6th ed.





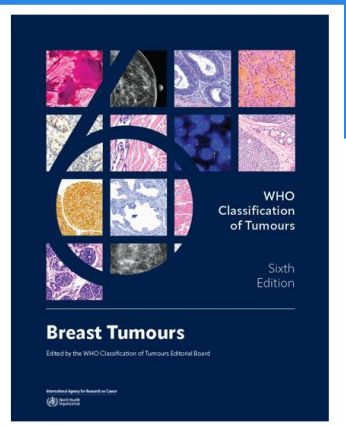
Focus on most significant changes

Neuroendocrine tumors and Fibroepithelial tumors mentioned only briefly

(see Prof. Gary Tse's lectures on Sunday Nov 8, 2026)

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BR 6th Introduction to tumours of the breast



General introduction

- Shorter than in 5th edition
- **Information pertaining to specific tumors is included in the tumors specific chapters**

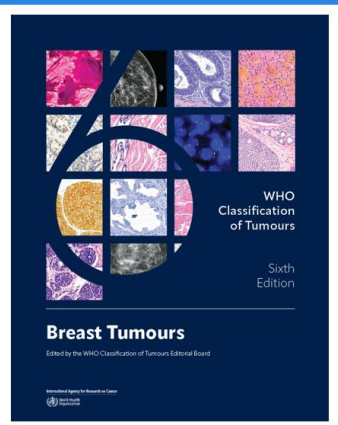
Small diagnostic samples

- Fine needle aspiration biopsy (FNAB) and Core needle biopsy (CNB)
- Imaging modalities and standardized reporting
- **B coding system for categorizing breast CNB findings**
- Triple assessment

Digital pathology and artificial intelligence

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Epithelial Tumours of the breast: split into two parts



2.0: Epithelial tumours of the breast: Part 1

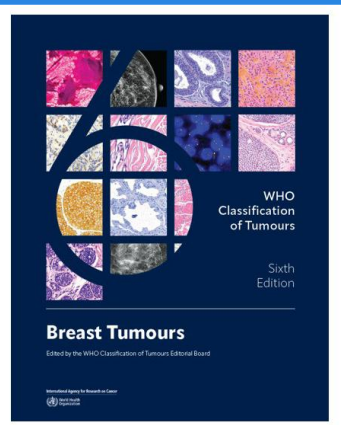
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  - 2.2.2: Sclerosing adenosis
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- **2.3: Adenomas**
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  - 2.7.1: Ductal carcinoma in situ

3.0: Epithelial tumours of the breast: Part 2

- **3.1: Epithelial tumours of the breast: Part 2: Introduction**
- **3.1.6: Molecular classification**
- **3.1.9: Prognosis and prediction**
- **3.2: Invasive breast carcinoma**
  - 3.2.2: Invasive breast carcinoma of no special type
  - 3.2.3: Microinvasive carcinoma
  - 3.2.4: Invasive lobular carcinoma
  - 3.2.5: Tubular carcinoma
  - 3.2.6: Invasive cribriform carcinoma
  - 3.2.7: Mucinous carcinoma
  - 3.2.8: Invasive micropapillary carcinoma
  - 3.2.9: Invasive apocrine carcinoma
  - 3.2.10: Metaplastic carcinoma
- **3.3: Rare and salivary gland–type tumours**
  - 3.3.1: Rare and salivary gland–type tumours: Introduction
  - 3.3.2: Acinic cell–like carcinoma
  - 3.3.3: Adenoid cystic carcinoma
  - 3.3.4: Secretory carcinoma
  - 3.3.5: Mucoepidermoid carcinoma
  - 3.3.7: Mucinous cystadenocarcinoma
  - 3.3.8: Tall cell carcinoma with reversed polarity
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  - 3.4.4: Neuroendocrine carcinoma

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BR 6th Sections 2: Epithelial Tumours part #1



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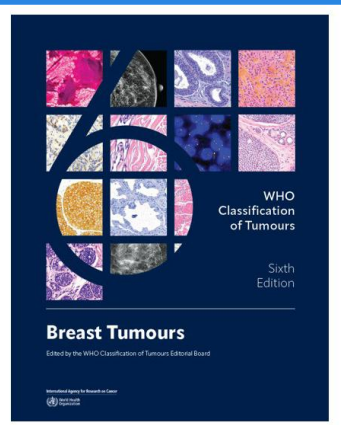
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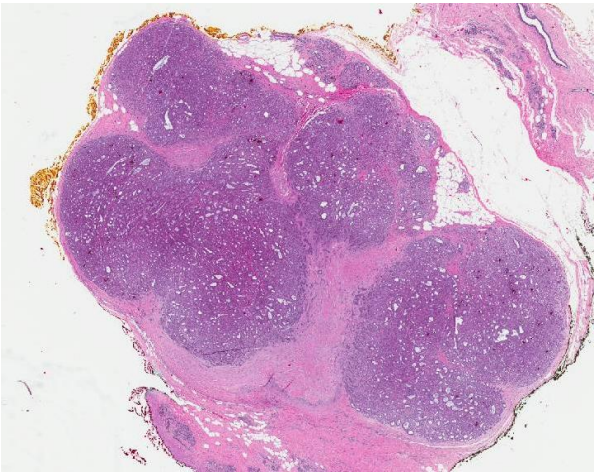
Adenoid Cystic Carcinoma is discussed under Rare and Salivary Gland-type Tumors

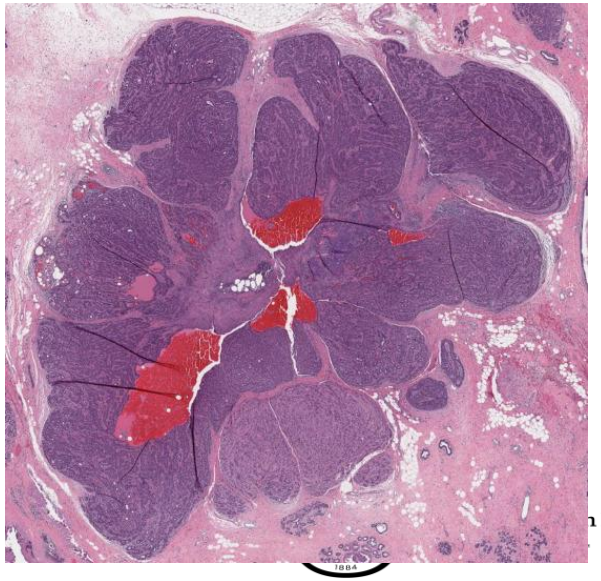
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Adenomyoepithelioma (AME) Histopathology

- At low-power magnification, AME typically has a multilobulated contour with a central sclerotic area and fibrous septae

- **6th ed. "Small satellite nodules at the periphery of the main tumor should not be necessarily considered indicative of malignancy."**



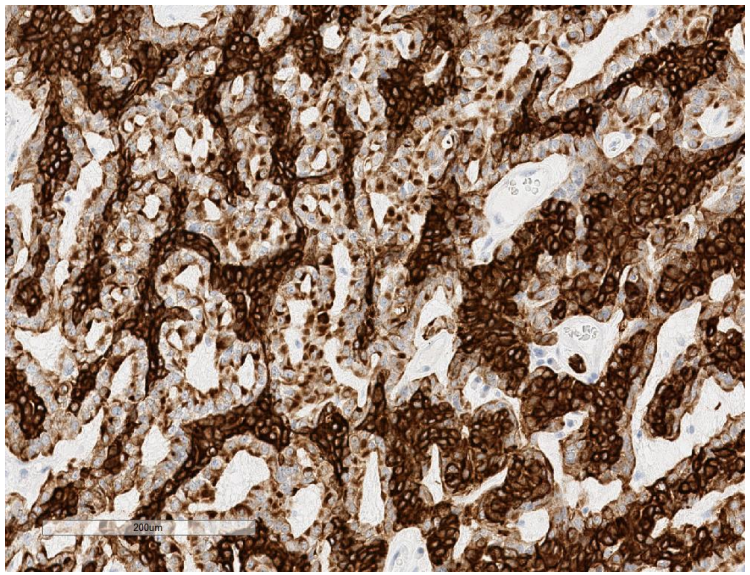


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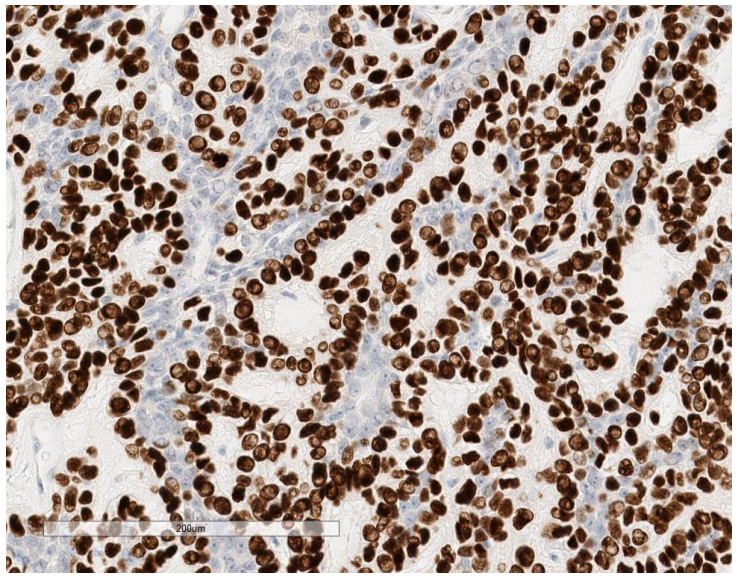
AME Histopathology

AME consists of closely juxtaposed glands and tubules with a double cell layer

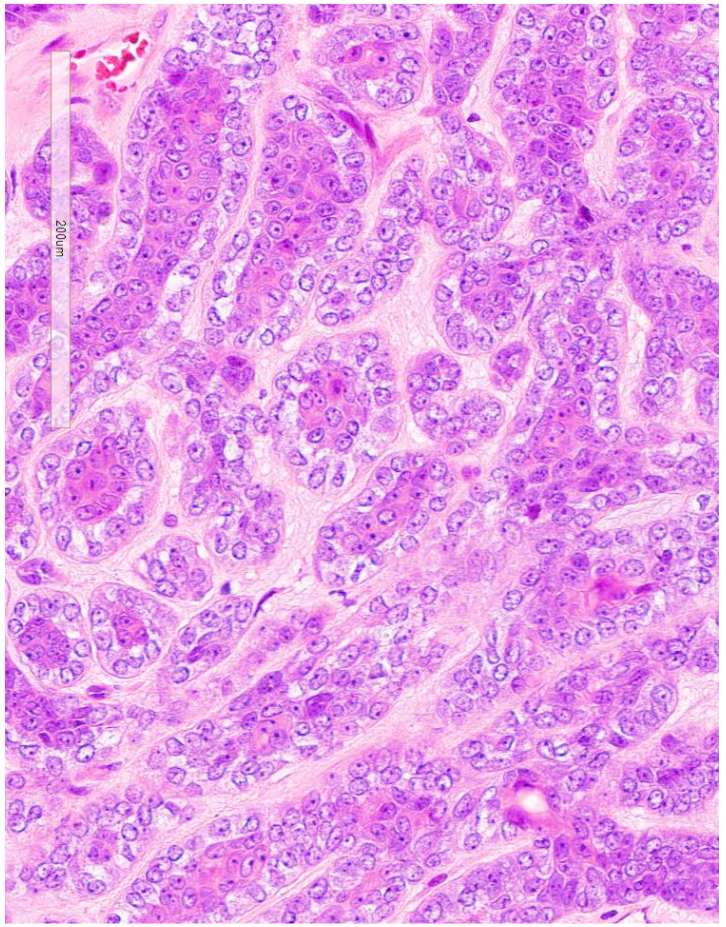
- **epithelial cells** form the glandular lumen
- **myoepithelial cells** form the outer cell layer



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p63

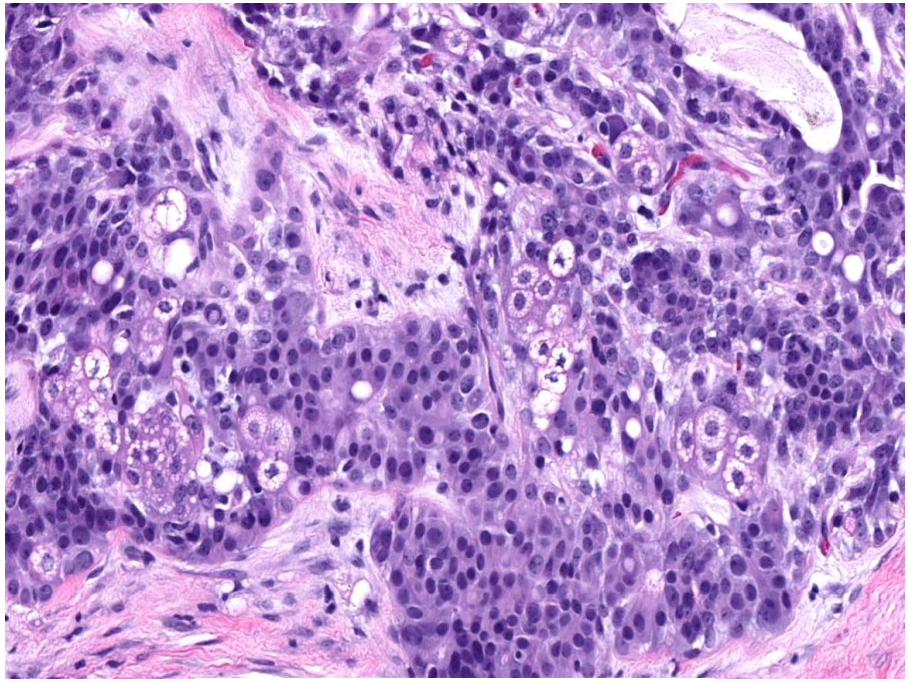


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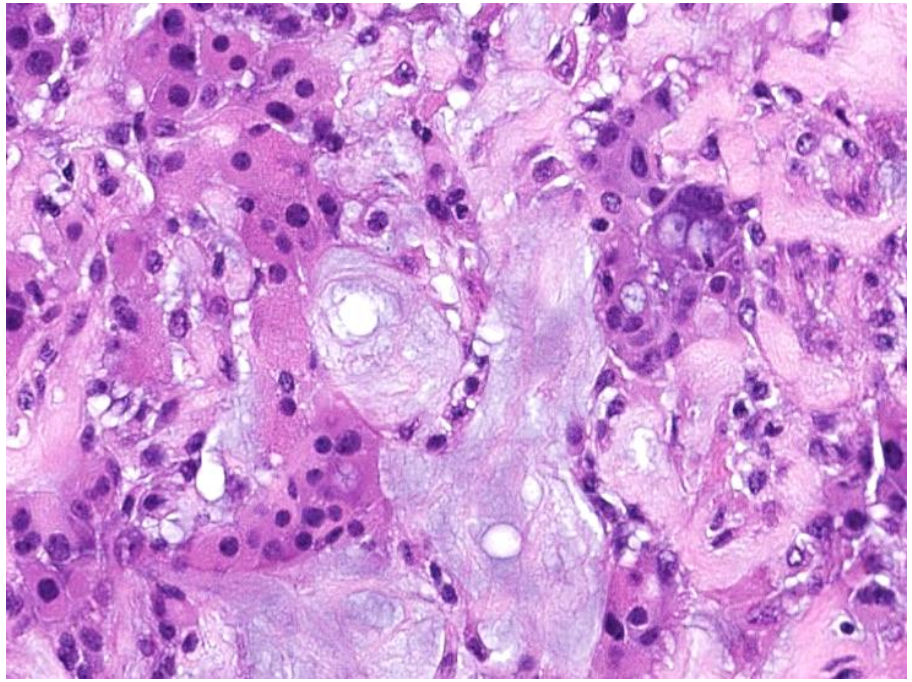
AME Histopathology

Epithelium often has apocrine features, and may show focal sebaceous or squamous metaplasia

Focal myxoid stroma possible (ddx pleomorphic adenoma)



sebaceous metaplasia

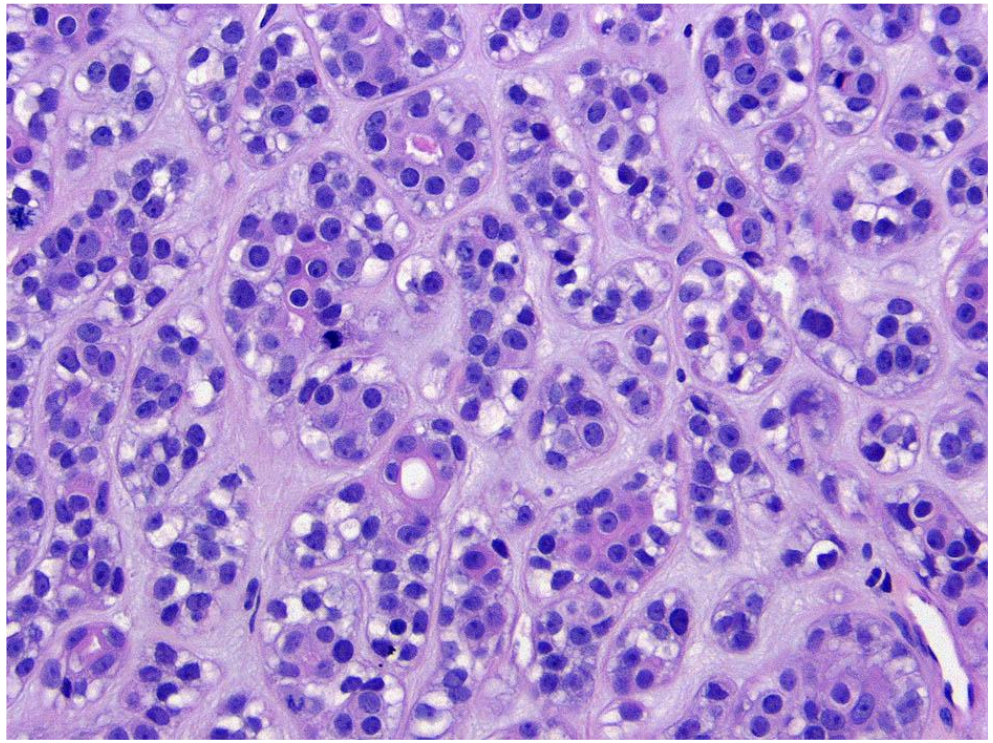


myxoid stroma

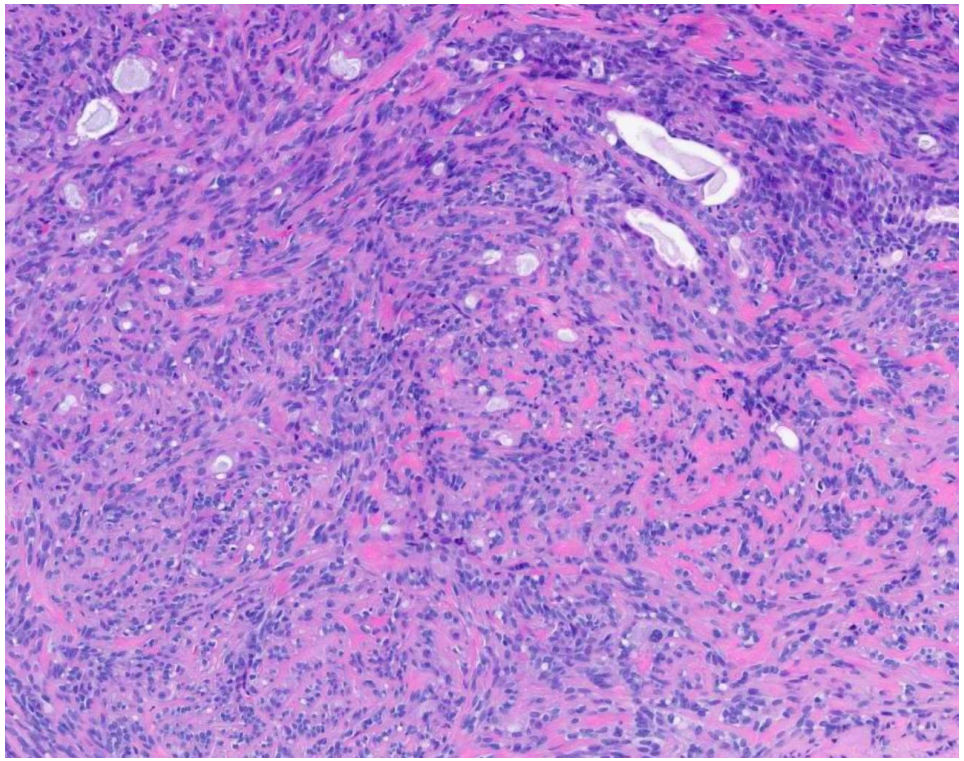
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Myoepithelial cells in AME

May have clear glycogen-rich cytoplasm or spindle, myoid, or plasmacytoid morphology



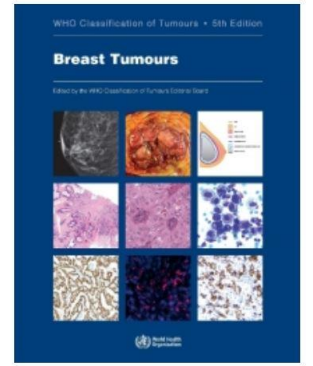
Clear MECs



spindle MECs

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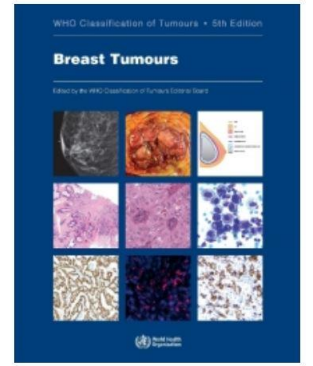
WHO 5th ed 2019



	AME	Malignant AME
Terminology and definition	Classic AME	AME with carcinoma (AME-M) • the malignancy may arise from either luminal epithelial or myoepithelial components, or from both cell types. • When both epithelial and myoepithelial components are malignant, the term "epithelial-myoepithelial carcinoma" is used.
Morphology comments	"Mitotically active classic AME can be difficult to distinguish from AME-M."	Wide spectrum of morphological features "Epithelial-myoepithelial carcinoma shows malignant changes in both the luminal and myoepithelial components."
Molecular alterations	Most studies done on Malignant AMEs	HRAS and PIK3CA genes Genetic subtypes of AME vary depending on ER status
Limited info on prognosis	Some reports of metastatic classic AME→ suggestion that "AME may be best regarded as neoplasm of low malignant potential"	Staging according to invasive component

ering

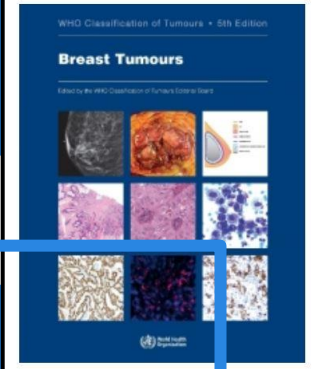
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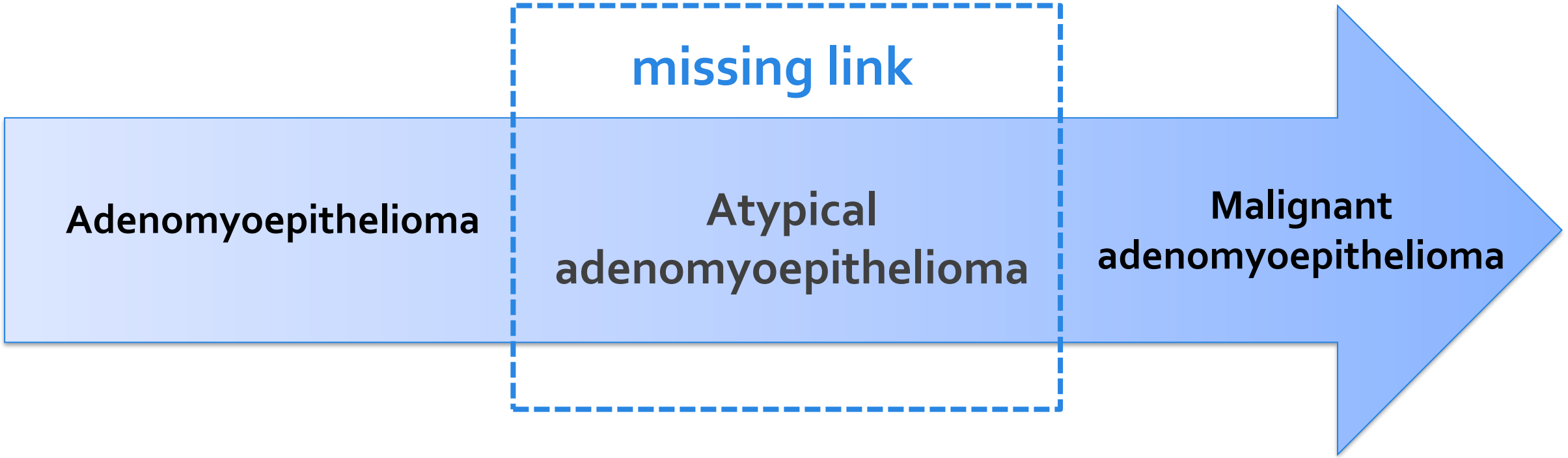
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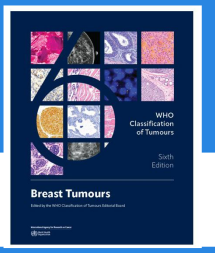
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Limited info on prognosis	Some reports of metastatic classic AME→ suggestion that "AME may be best regarded as neoplasm of low malignant potential"	**Staging according to invasive component**

Diagnostic criteria were not specified precisely



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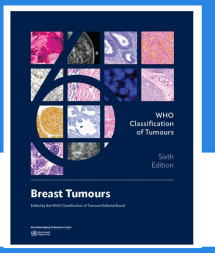
Classic AME (WHO 6th ed)



Subtype	Atypia	Mitoses	Epithelial atypia	necrosis	LN mets
Benign AME	absent	up to 1.5/ mm^2 (3/10 HPF of 0.5 mm in diameter and 0.2 mm^2 in area)	absent	absent	none
Atypical AME	mild to moderate atypia in • epithelium • myoepithelium • both	up to 2.5 /mm^2 (5/10 HPF of 0.5 mm in diameter and 0.2 mm^2)	extent & degree of epithelial atypia may warrant the Dx of DCIS arising in AME *Report DCIS in AME and manage as DCIS*	may be present focally	Rare reports *No routine SLN biopsy recommended for atypical AME*

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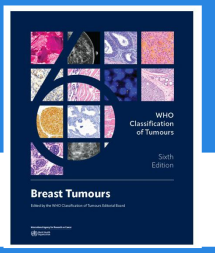
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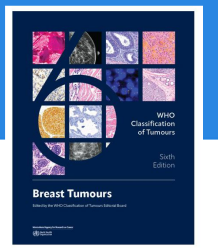
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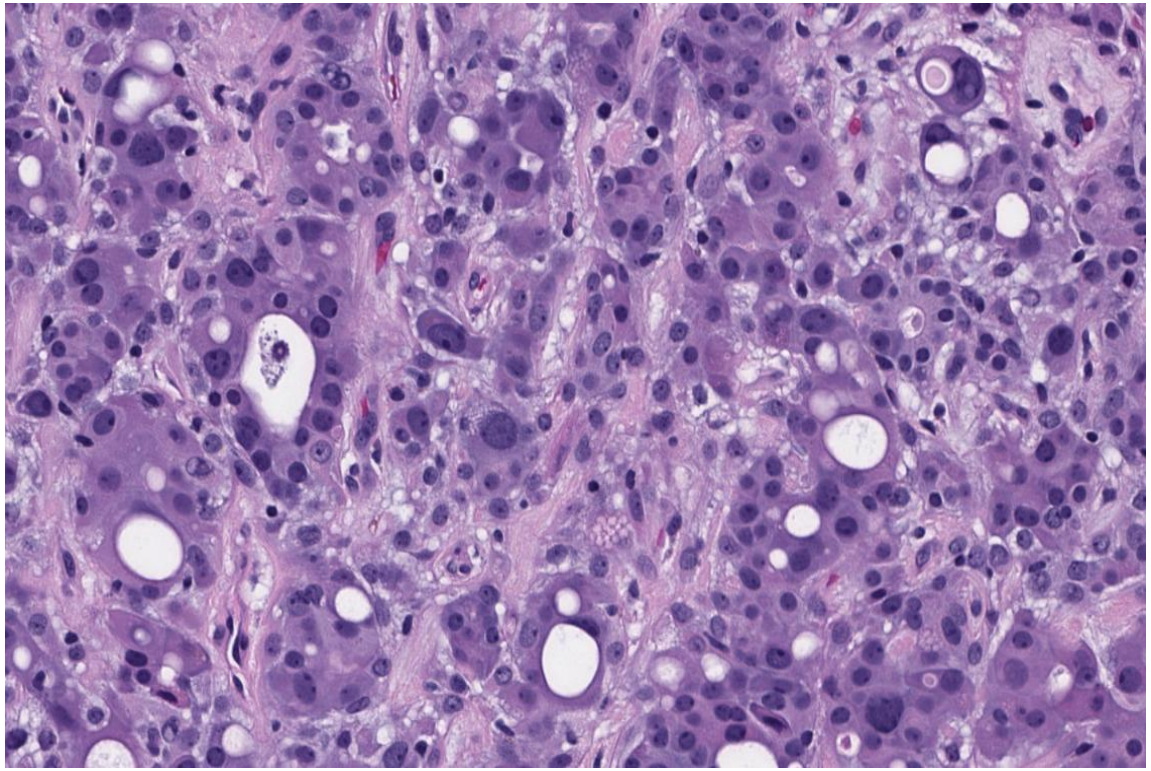
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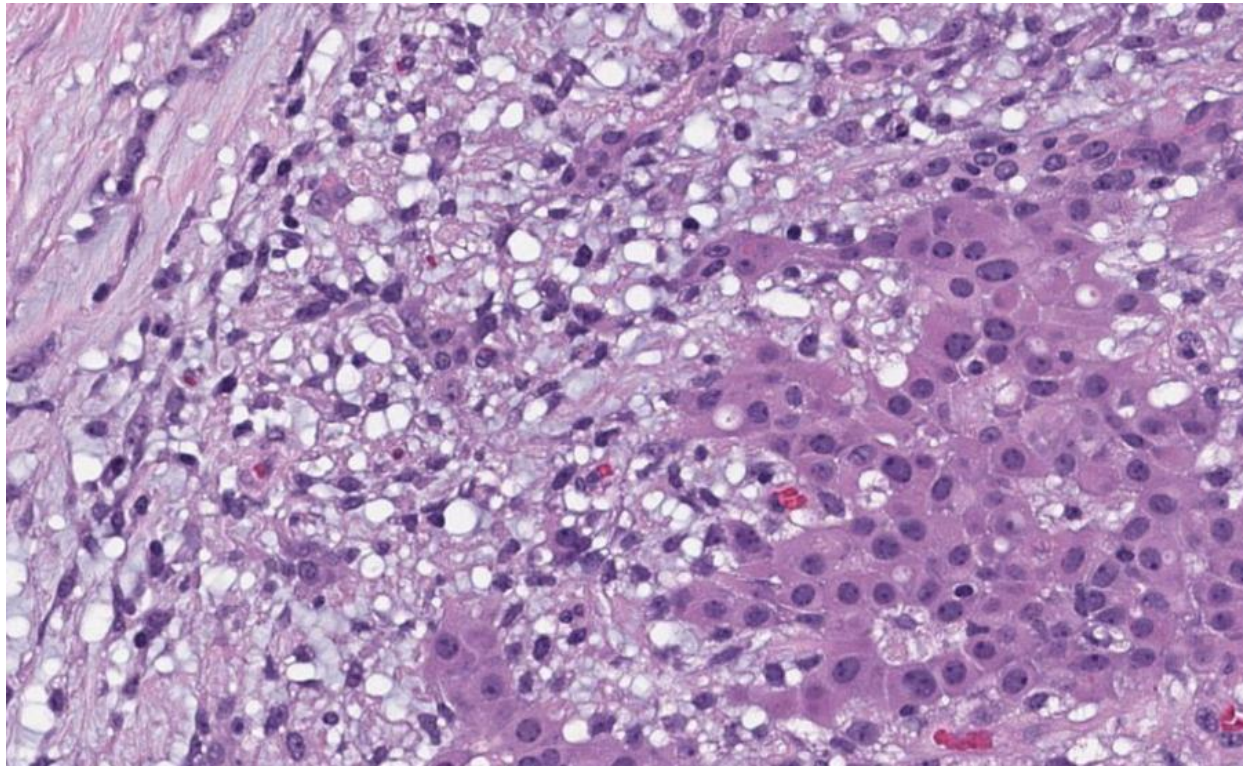
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Atypical AME



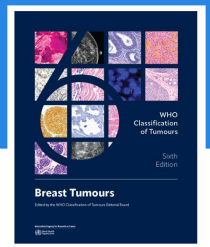
Mild to moderate atypia in epithelium, myoepithelium or both





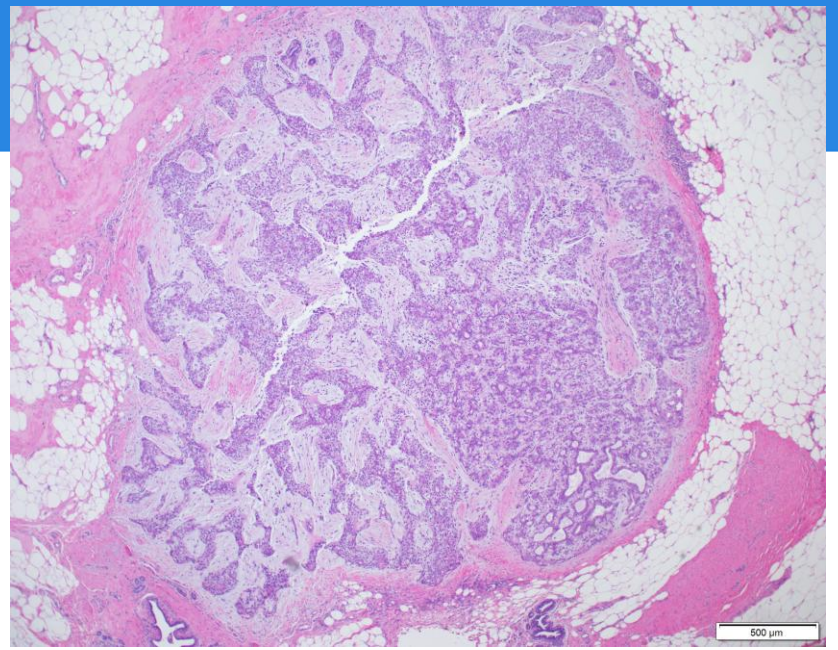
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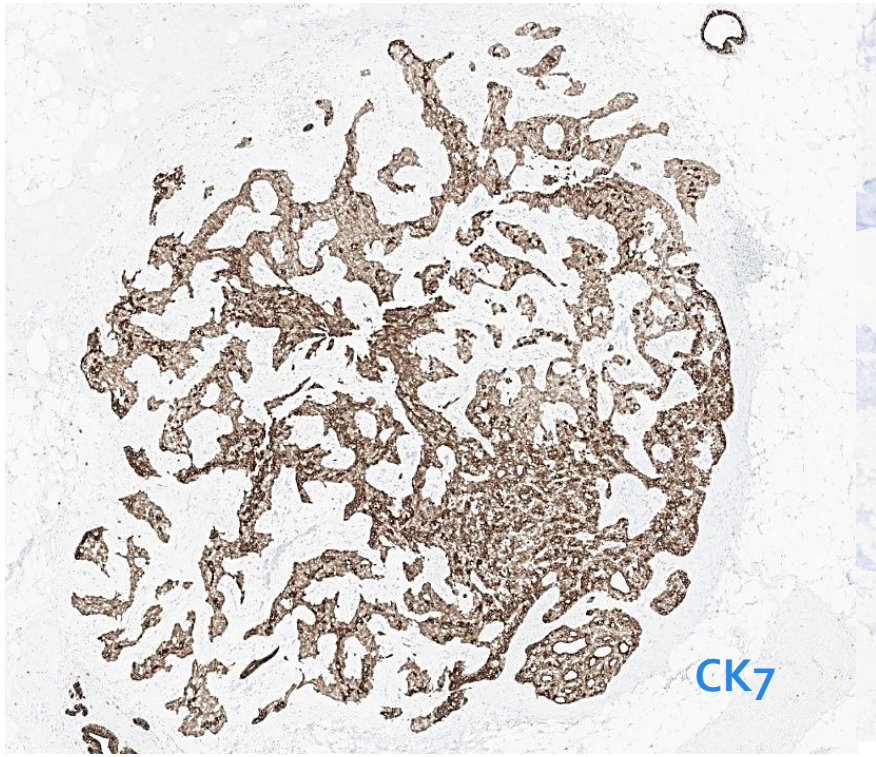
AME immunohistochemistry

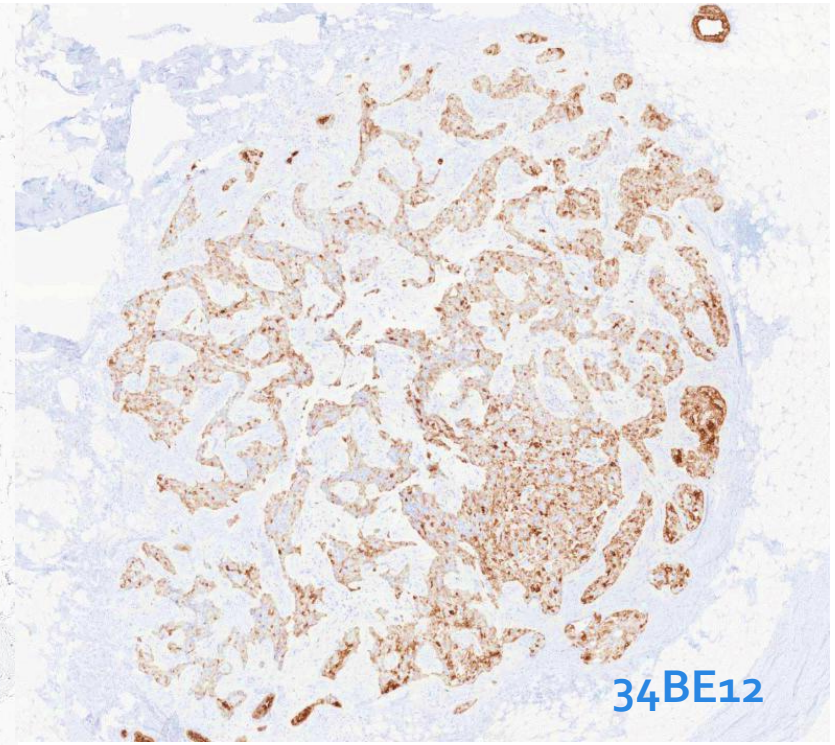


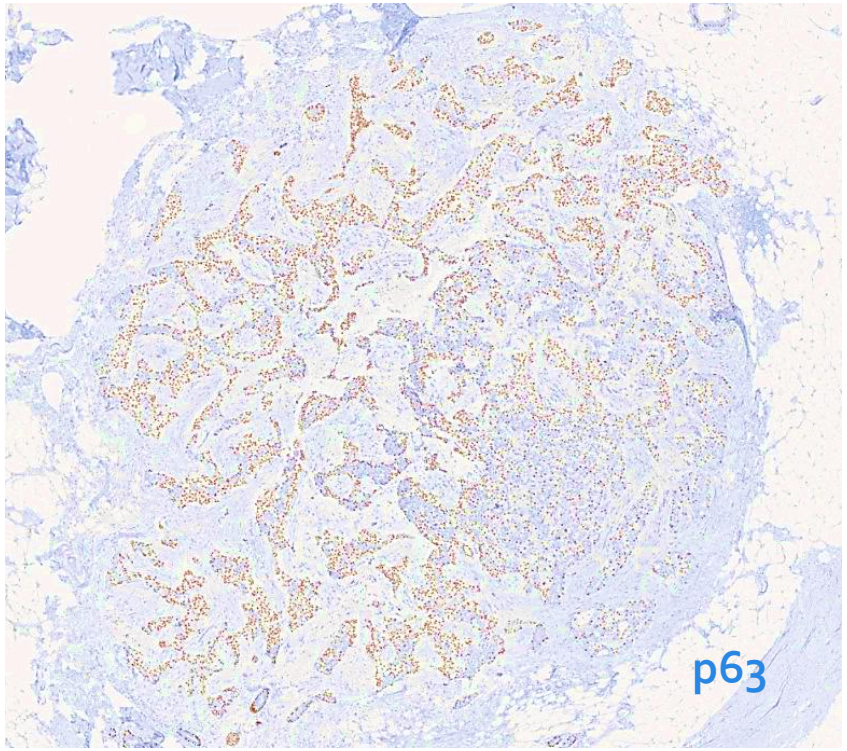
Aberrant staining patterns (in atypical AME)

- **High Molecular Weight CKs may show paradoxical staining pattern: Epithelium positive, MECs negative**
- **MECs tend to stain in a variable and unpredictable pattern for the entire range of IHC MEC markers**

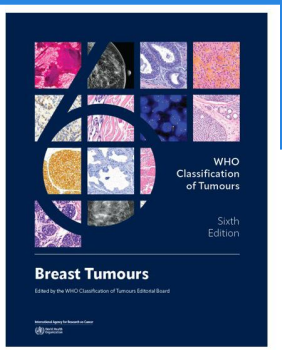






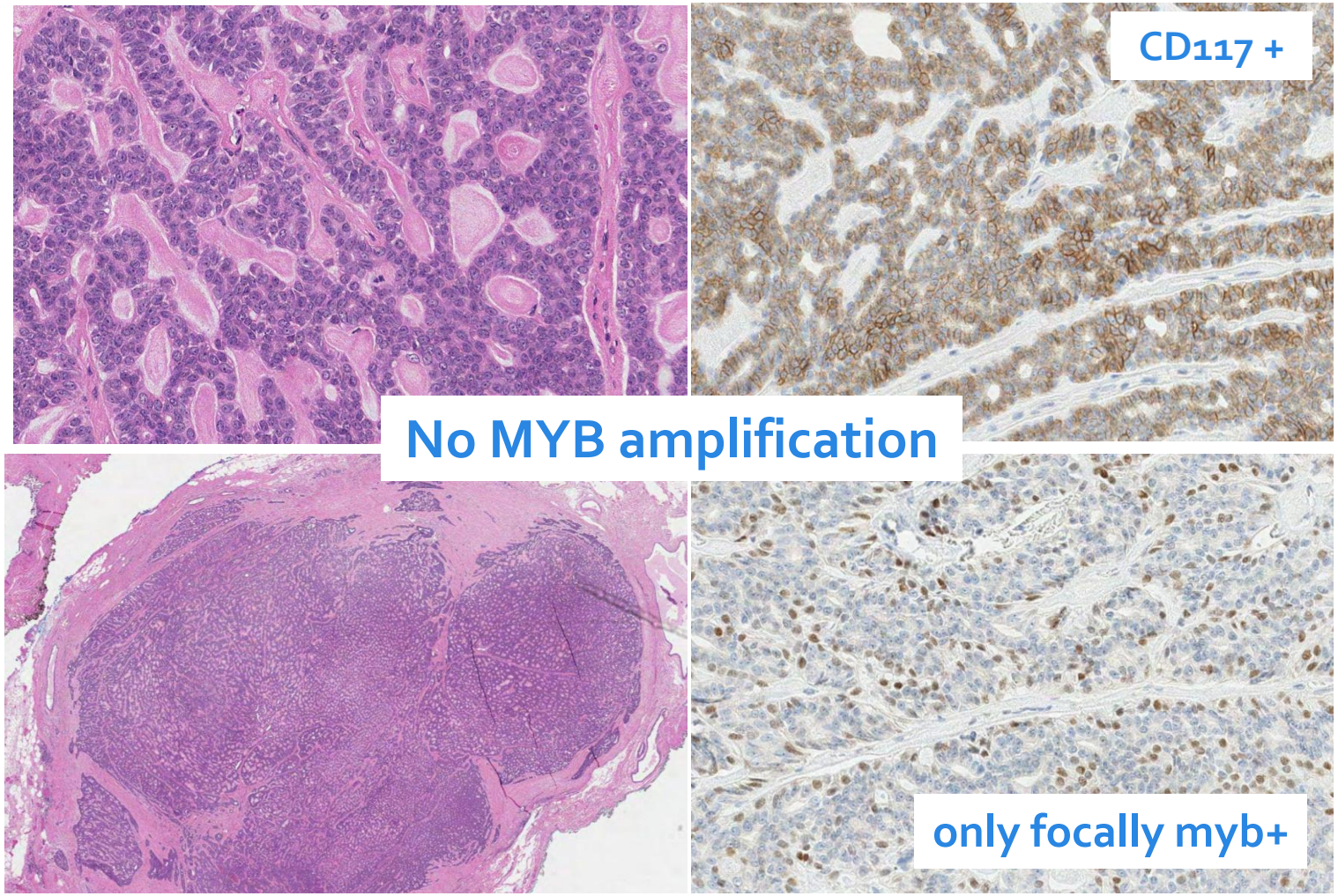


Atypical AME versus Malignant-AME



- Atypical mitoses in an atypical AME should raise suspicion for malignant transformation.
- Mitotically active AME with cytological atypia can be difficult to distinguish from Malignant AME.
- AME exhibiting mild to moderate cytological atypia or as many as 2.5 mitoses/mm^2 (5 mitoses/10 HPF of 0.5 mm in diameter and 0.2 mm^2 in area) but lacking other features of malignancy can be classified as atypical AME.

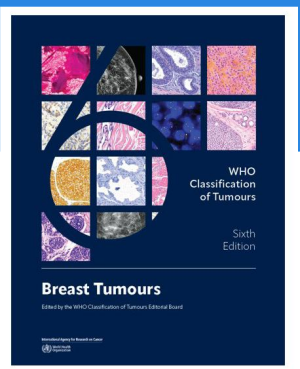
Atypical AME may mimic AdCC (conventional type)



This tumor harbored *HRAS Q61R* mutation diagnostic of AME/ M-AME

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Classic AME - clinical behavior



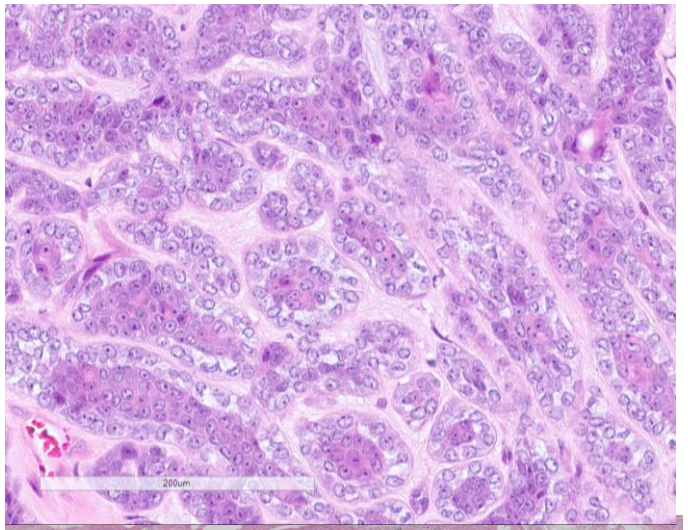
- Most breast AMEs pursue a benign clinical course.
- Complete surgical excision is curative.
- AMEs with an extensive intraductal papillary component or satellite nodules are more likely to recur.
- Distant metastases from benign AMEs (=lacking significant cytological atypia or increased cell proliferation) have been reported.
- Considering these rare metastatic cases and the potential for malignant transformation, classic AME may be better regarded as a neoplasm of uncertain malignant potential.

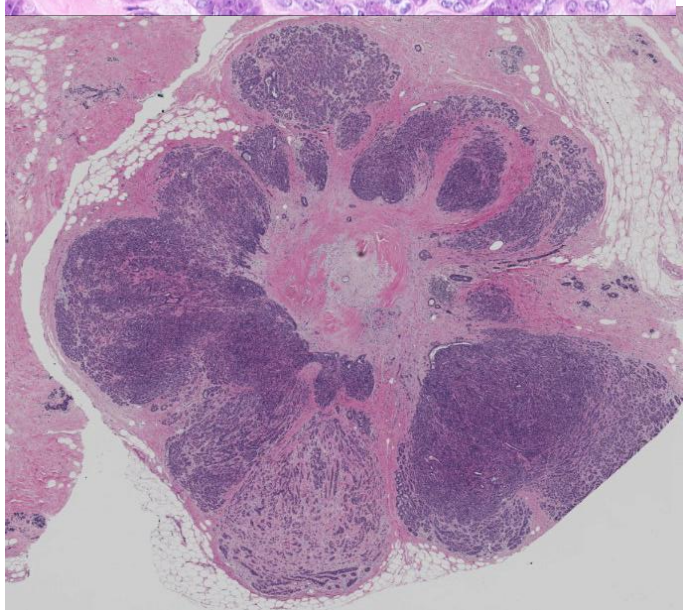
CNB Dx of Classic AME (Benign and atypical) warrants excision

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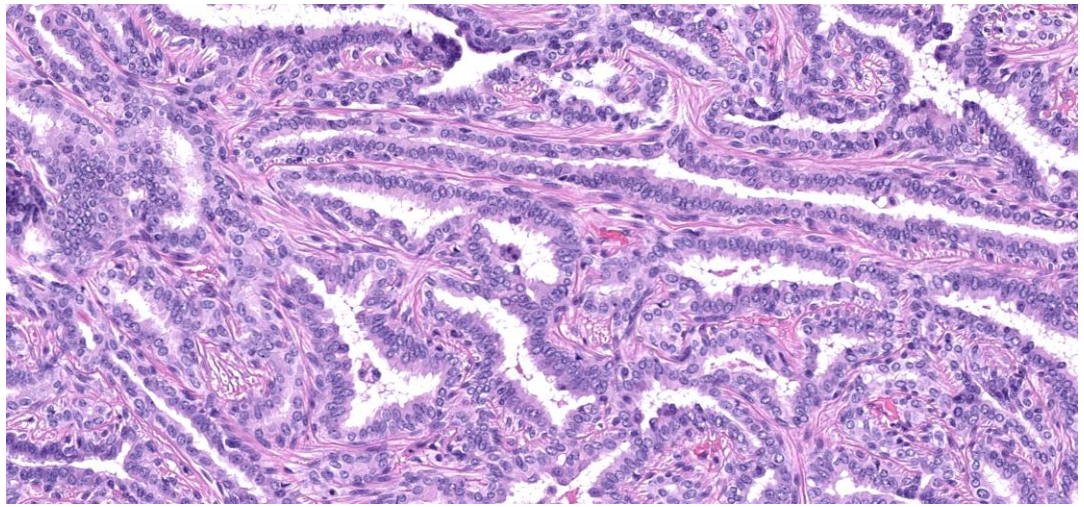
Differential diagnosis: Benign AME versus Intraductal papilloma

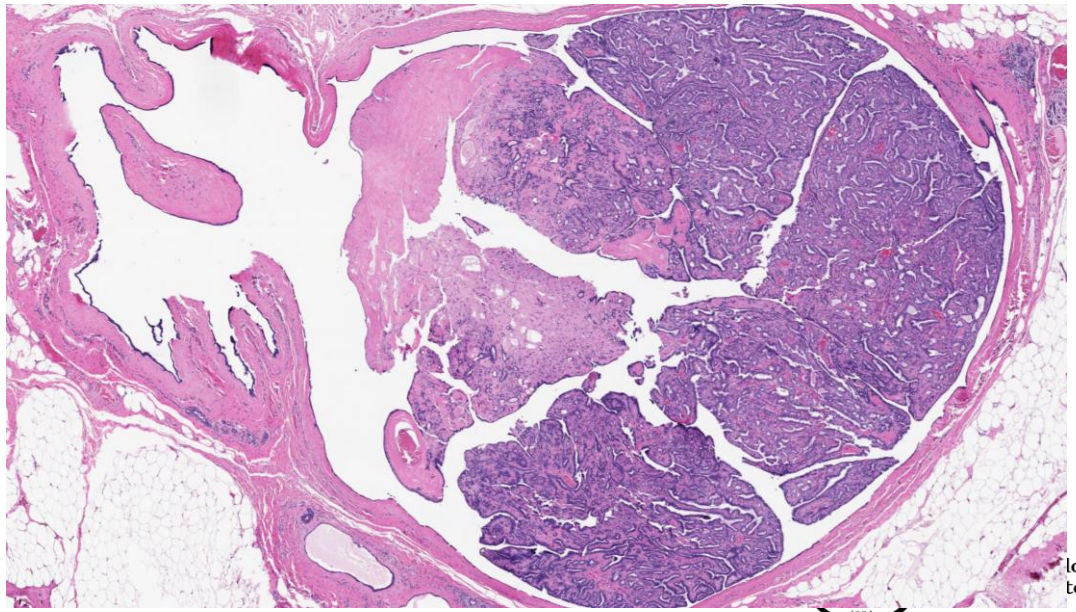
AME





Intraductal Papilloma

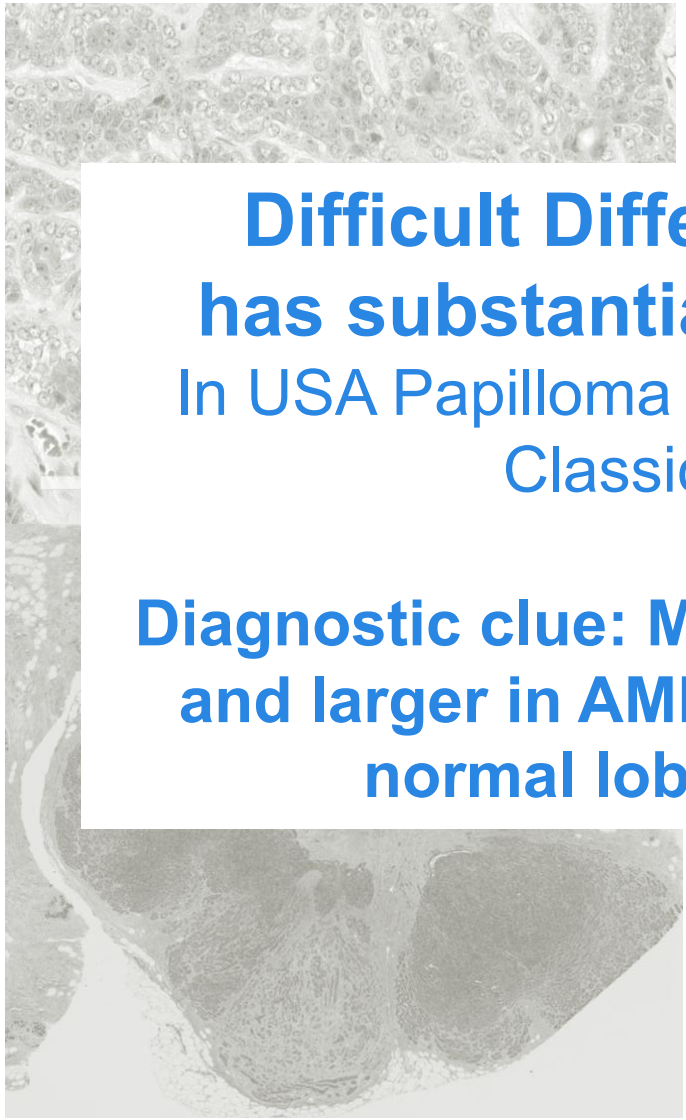




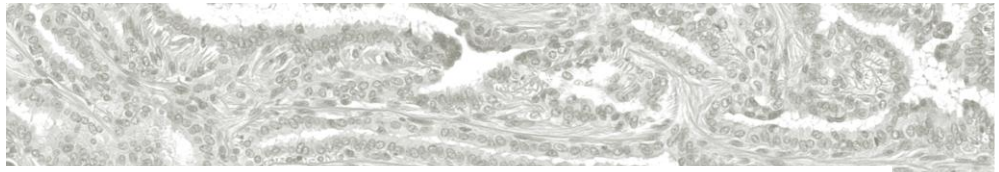
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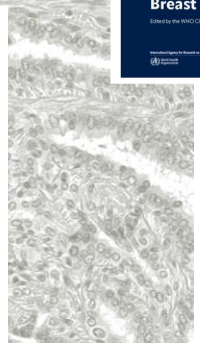
Differential diagnosis: Benign AME versus Intraductal papilloma

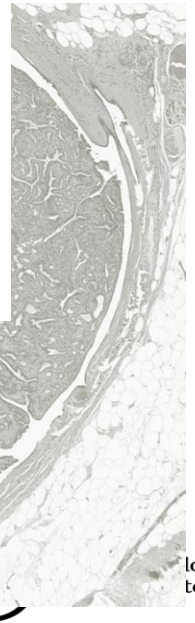
AME

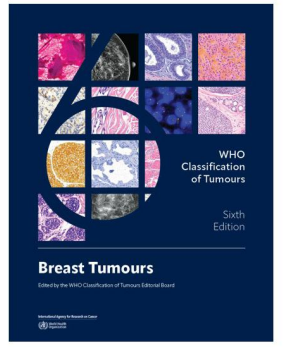


Intraductal Papilloma







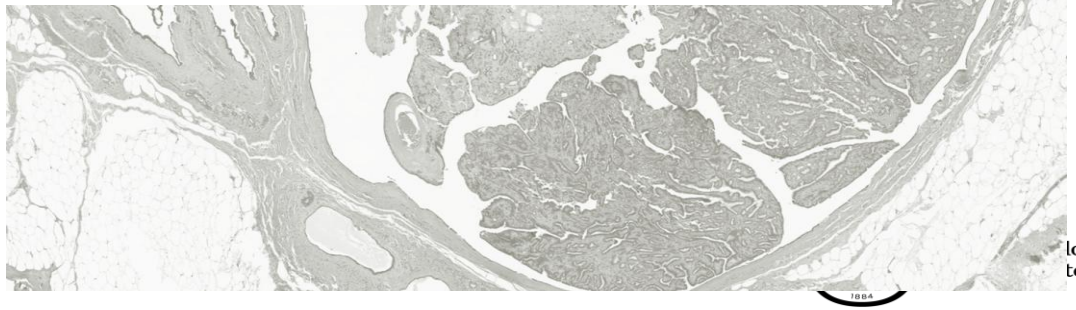


Difficult Differential DX in CNB material has substantial management implications

In USA Papilloma without atypia is not always excised

Classic AME warrants excision

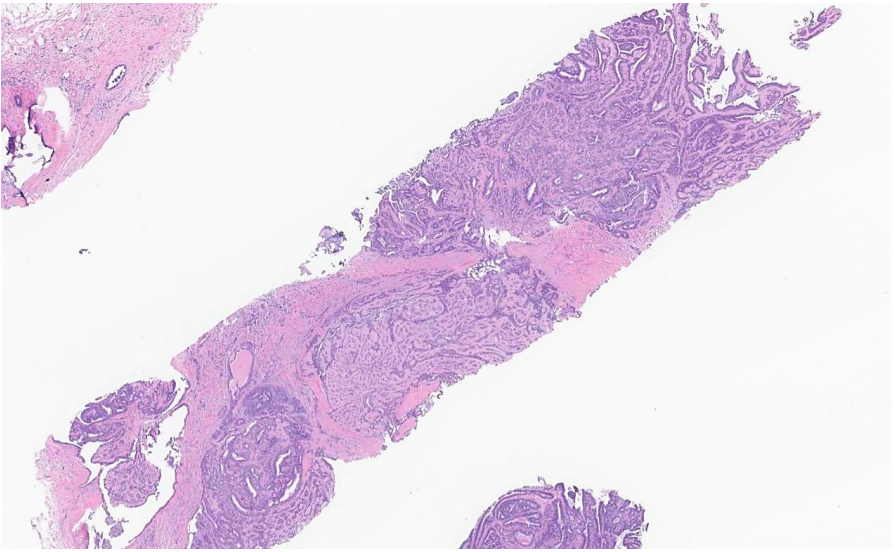
Diagnostic clue: MECs are more numerous, plumper, and larger in AMEs than in intraductal papillomas, normal lobules, and nodular adenosis

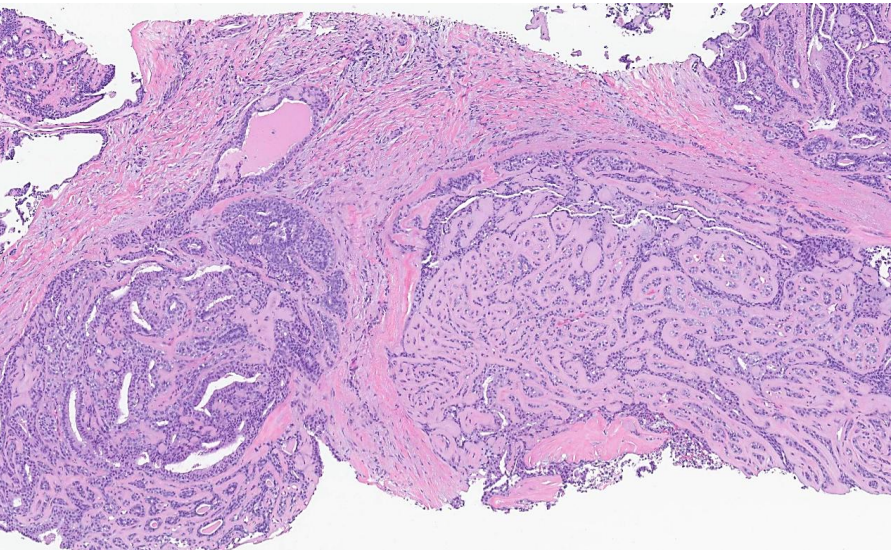


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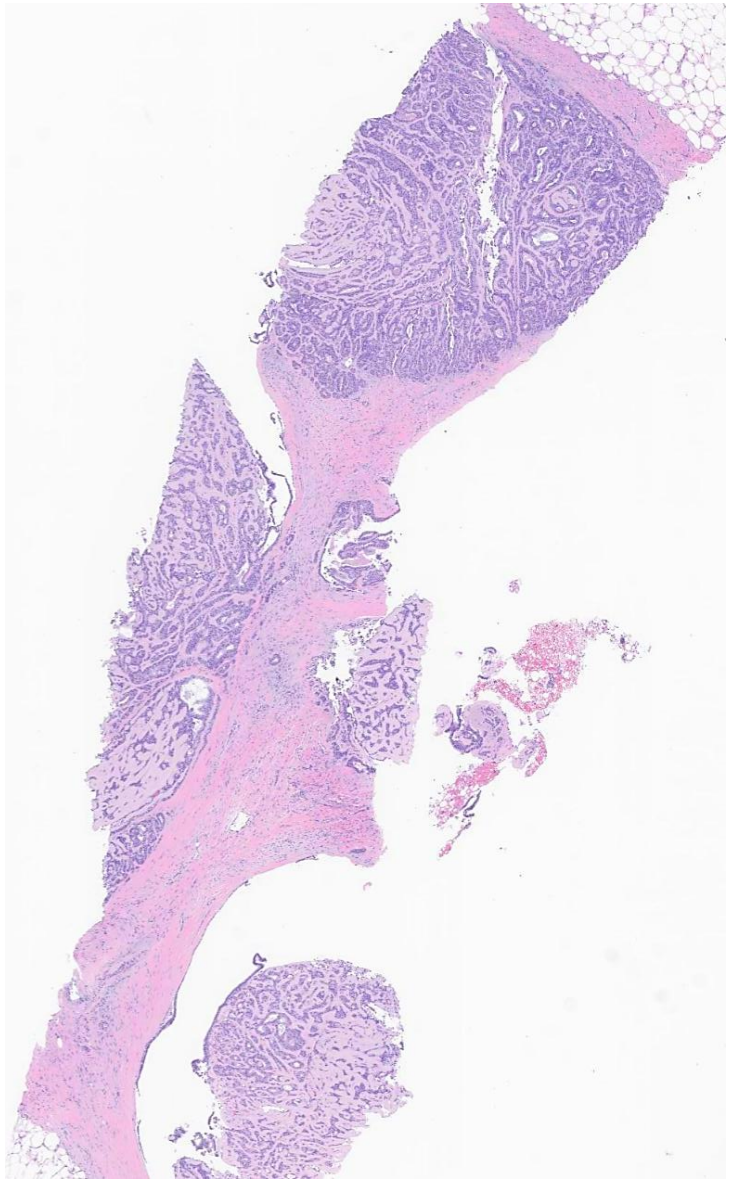
AME misdiagnosed as IDP in CNB (real case example)

2024: 0.7 cm mass CNB Dx IDP

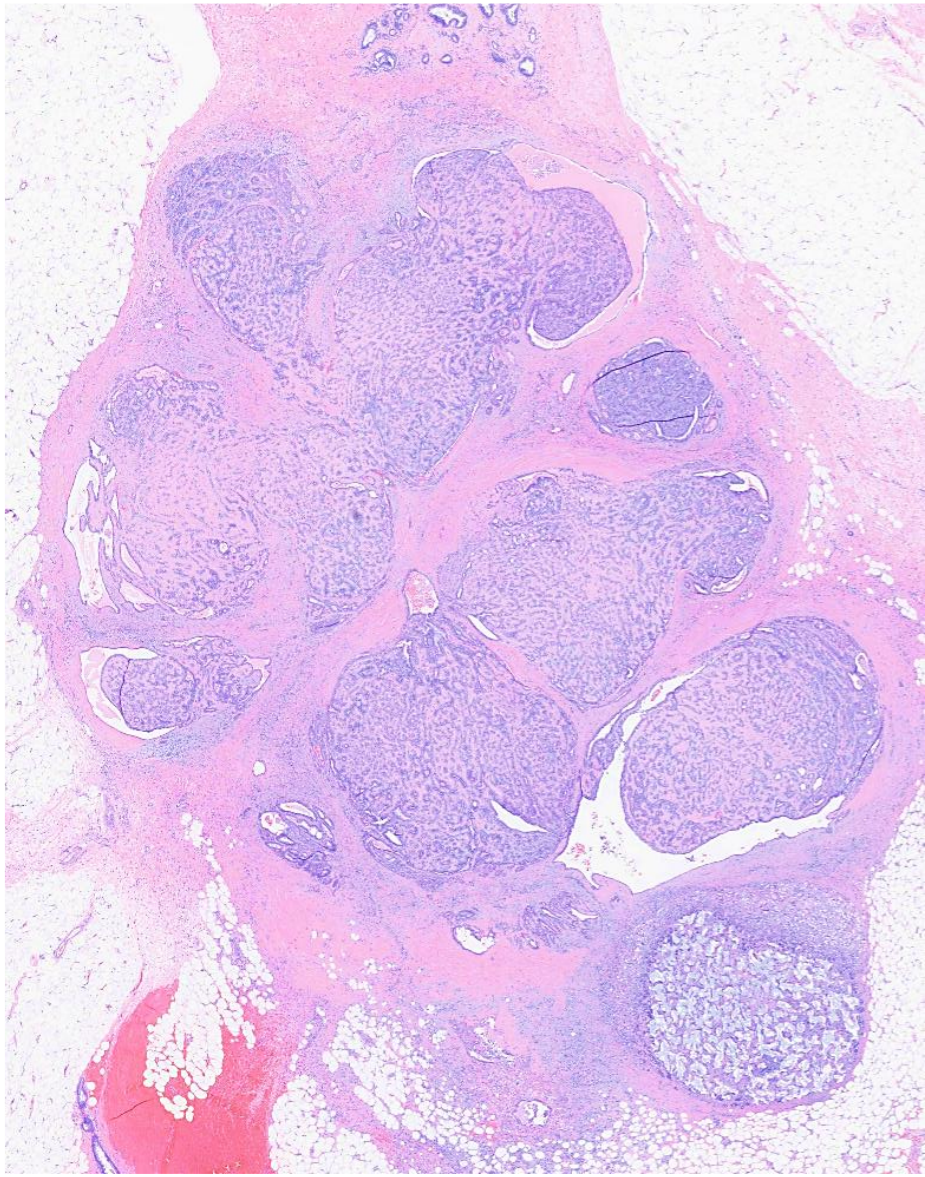




2026: 1.6 cm mass CNB Dx AME



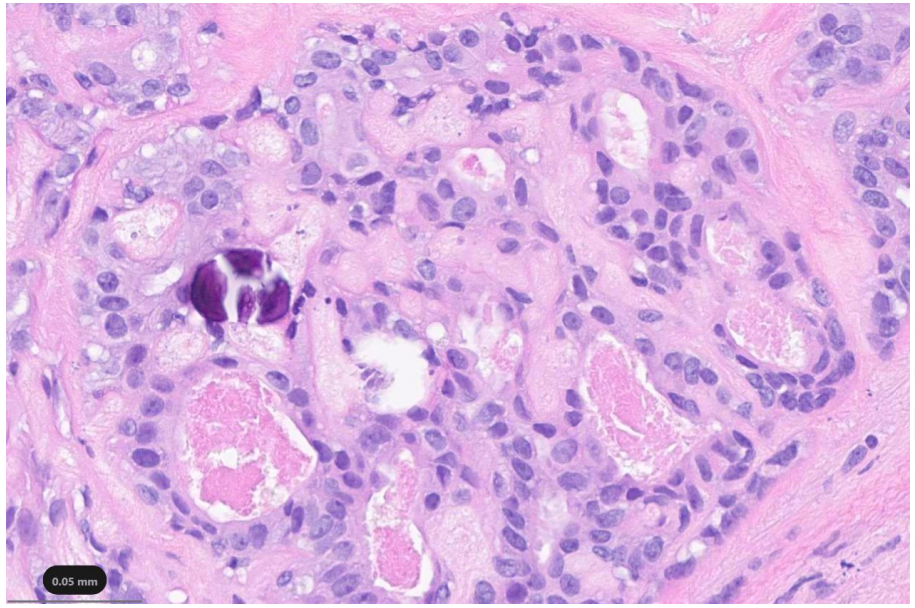
2026: excision AME

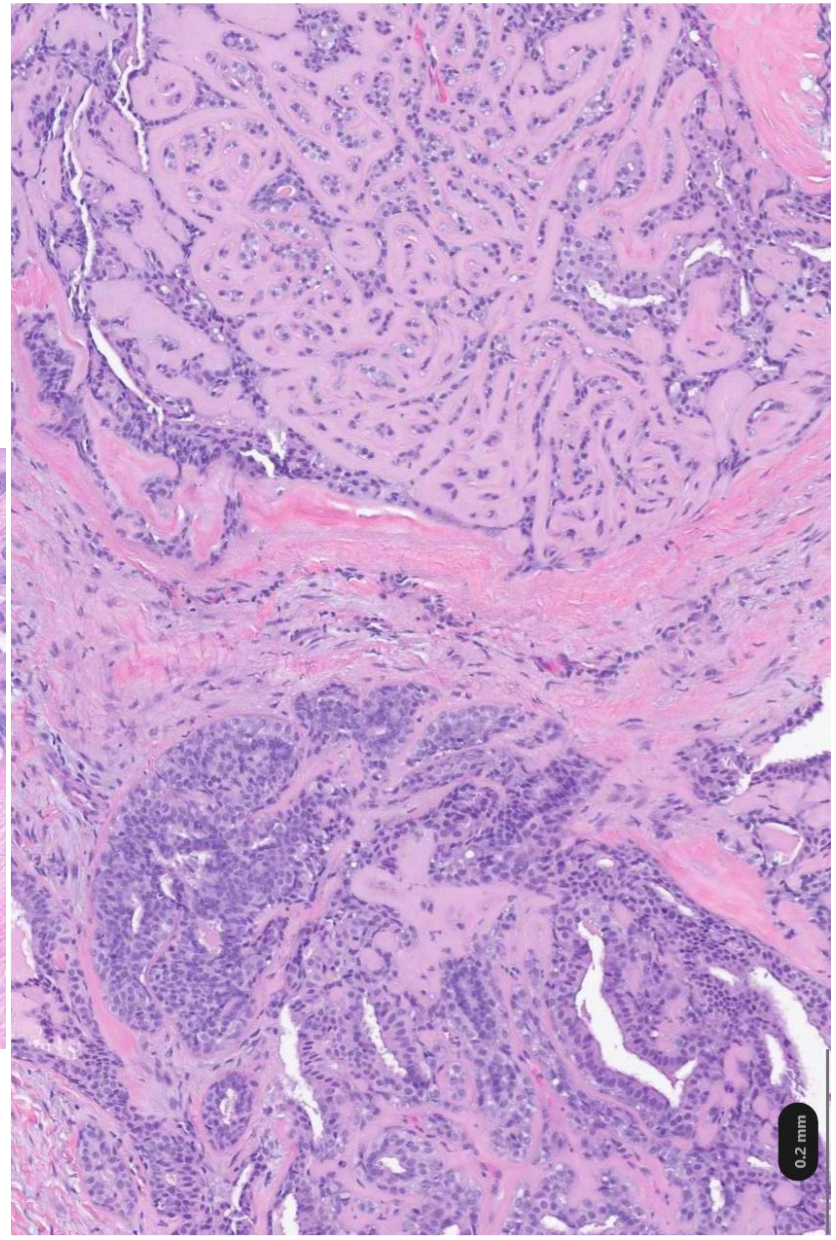


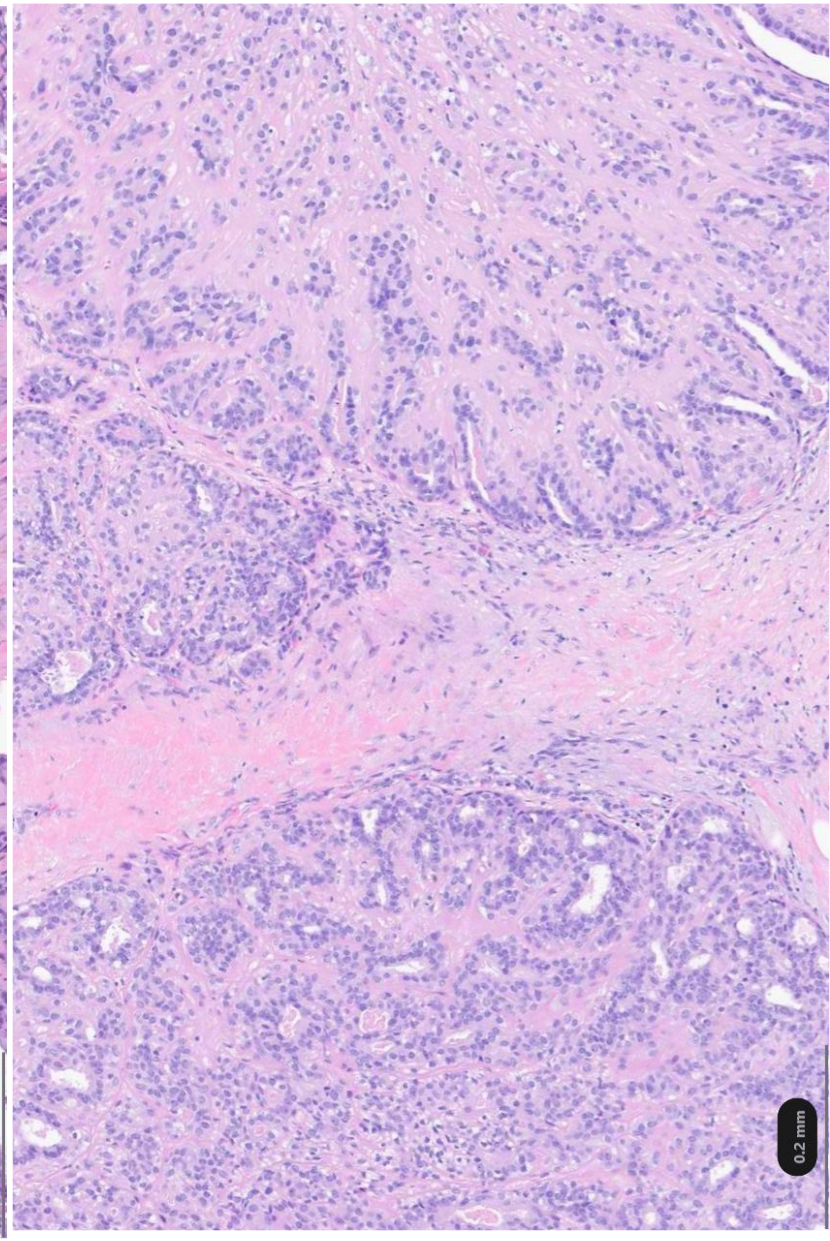
Useful for AME diagnosis (based on my personal experience)

Thick hyaline basement membrane

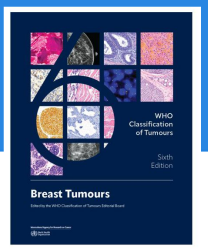
Foci of collagenous spherulosis







Malignant AME (M-AME)

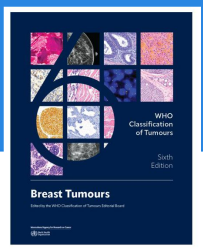


- **M-AME is an AME with carcinoma, in which the malignancy may arise from either the luminal epithelial or myoepithelial component, or from both cell types.**
- *Other acceptable terminology:* AME with invasive carcinoma
- ***Not recommended:*** ~~**epithelial-myoepithelial carcinoma**~~ ~~**adenomyoepithelial carcinoma**~~

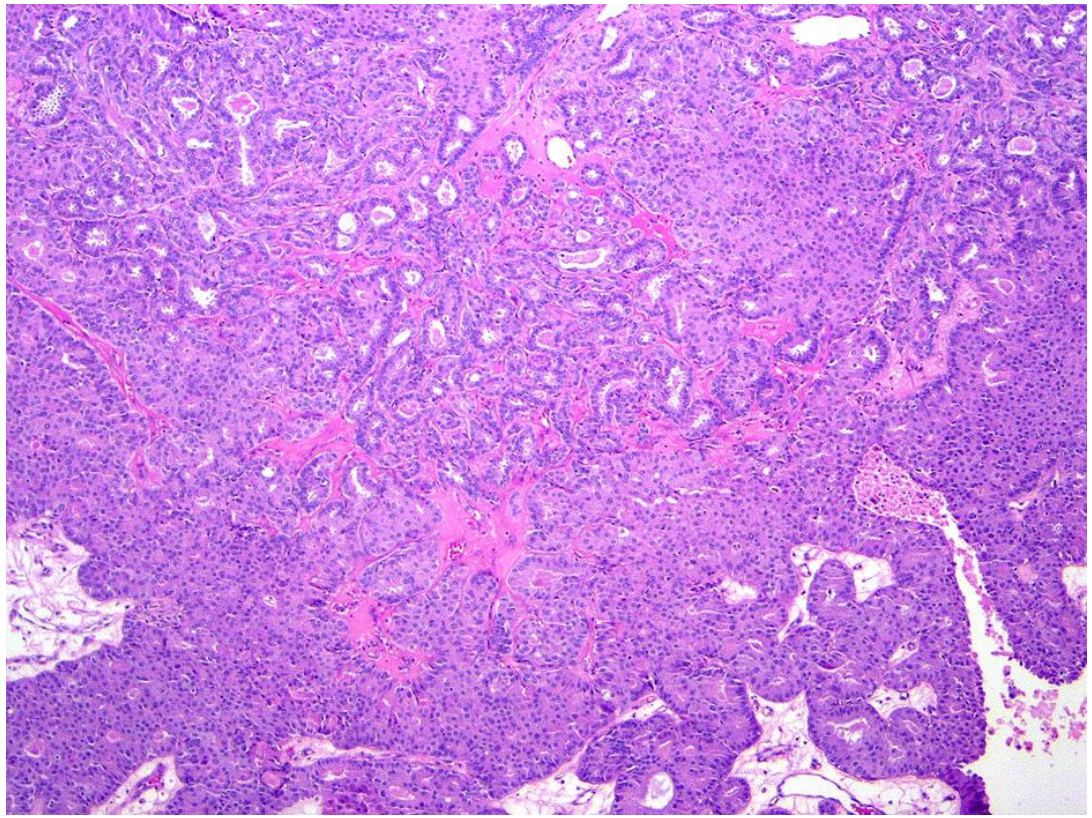
In AME with malignant change of the luminal and/or myoepithelial component, the underlying AME is recognized, with cytological atypia, increased mitoses, and necrosis in the malignant component

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Malignant AME

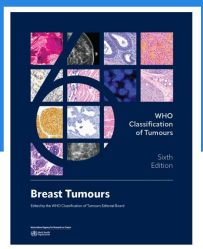


If **malignant transformation affects mainly the epithelial component**, the tumor morphology is that of invasive breast carcinoma NST and carcinomas of special types, including lobular carcinoma

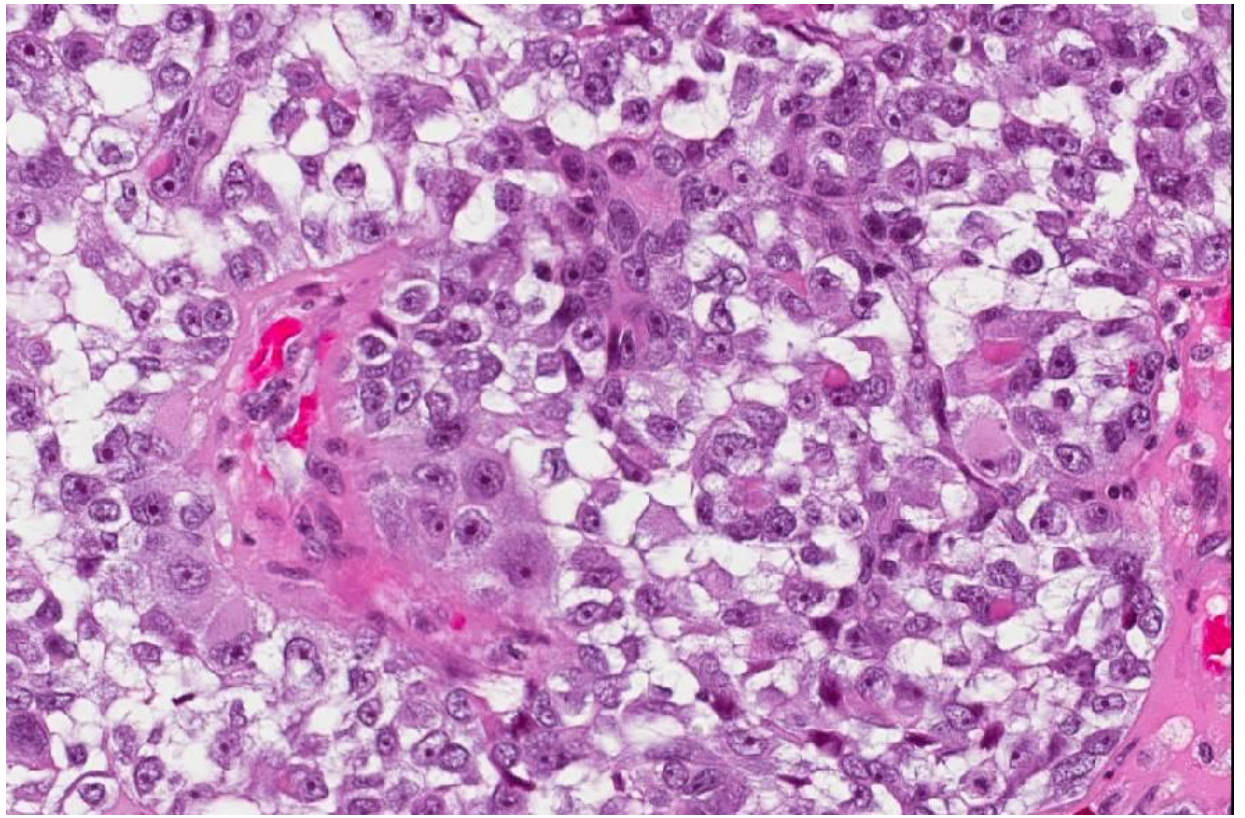


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Malignant AME

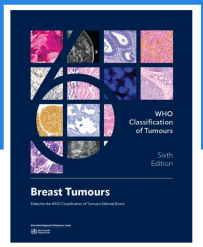


If **malignant transformation affects mainly the myoepithelial component**, overgrowth of spindle or epithelioid MECs predominates, with clear or eosinophilic cytoplasm, nuclear atypia, and frequent mitoses



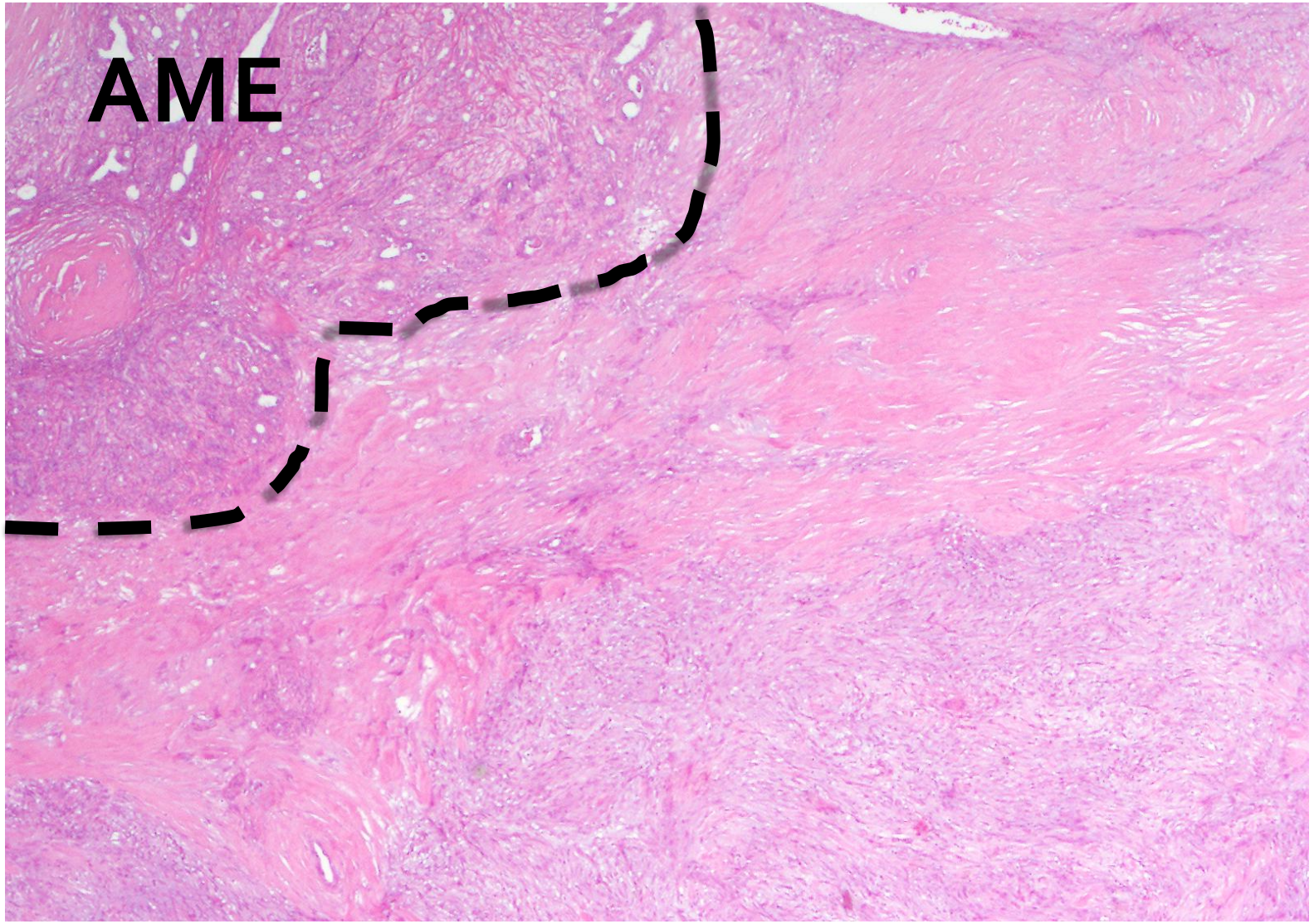
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Malignant AME



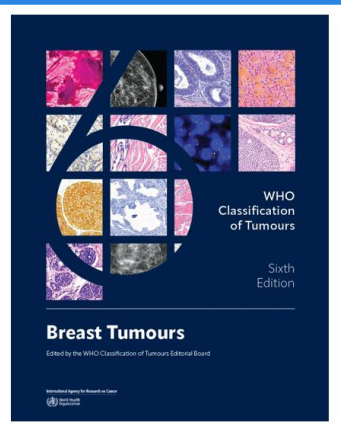
- Not uncommonly, the invasive carcinoma component is of the metaplastic subtype:
  - spindle cell
  - squamous cell
  - (low-grade) adenosquamous
  - matrix-producing
- *Rarely, tumors with an adenoid cystic carcinoma component have been reported*
- Size of the invasive component is used for staging

M-AME: Fibromatosis-like carcinoma arising in AME



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BR 6th Sections 2: Epithelial Tumours part #1



2.0: Epithelial tumours of the breast: Part 1

2.1: Benign epithelial proliferations and precursors
- 2.1.1: Benign epithelial proliferations and precursors: Introduction
- 2.1.2: Usual ductal hyperplasia
- 2.1.3: Columnar cell lesions, including flat epithelial atypia
- 2.1.4: Atypical ductal hyperplasia

2.2: Adenosis and sclerosing lesions
- 2.2.1: Adenosis and sclerosing lesions: Introduction
- 2.2.2: Sclerosing adenosis
- 2.2.3: Apocrine adenosis and apocrine adenoma
- 2.2.4: Microglandular adenosis
- 2.2.5: Radial scar / complex sclerosing lesion

2.3: Adenomas
- 2.3.0: Adenomas: Introduction
- 2.3.1: Tubular adenoma
- 2.3.2: Lactating adenoma
- 2.3.3: Ductal adenoma

2.4: Epithelial-myoepithelial tumours
- 2.4.1: Epithelial-myoepithelial tumours: Introduction
- 2.4.2: Pleomorphic adenoma
- 2.4.3: Classic adenomyoepithelioma
- 2.4.4: Malignant adenomyoepithelioma

2.5: Papillary neoplasms
- 2.5.1: Papillary neoplasms: Introduction
- 2.5.2: Intraductal papilloma
- 2.5.3: Papillary ductal carcinoma in situ
- 2.5.4: Encapsulated papillary carcinoma
- 2.5.5: Solid papillary carcinoma (in situ and invasive)
- 2.5.6: Invasive papillary carcinoma

2.6: Non-invasive lobular neoplasia
- 2.6.1: Non-invasive lobular neoplasia: Introduction
- 2.6.2: Atypical lobular hyperplasia
- 2.6.3: Lobular carcinoma in situ

2.7: Ductal carcinoma in situ
- 2.7.0: Ductal carcinoma in situ: Introduction
- 2.7.1: Ductal carcinoma in situ

- **Encapsulated Papillary Carcinoma (EPC)**
- **Invasive Papillary Carcinoma (IPC)**

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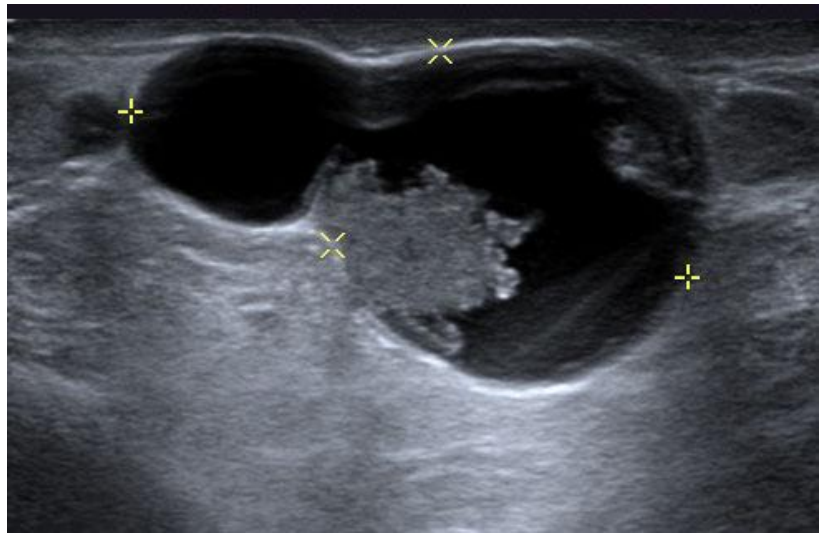
Encapsulated Papillary Carcinoma

Postmenopausal women (usually 7th decade)

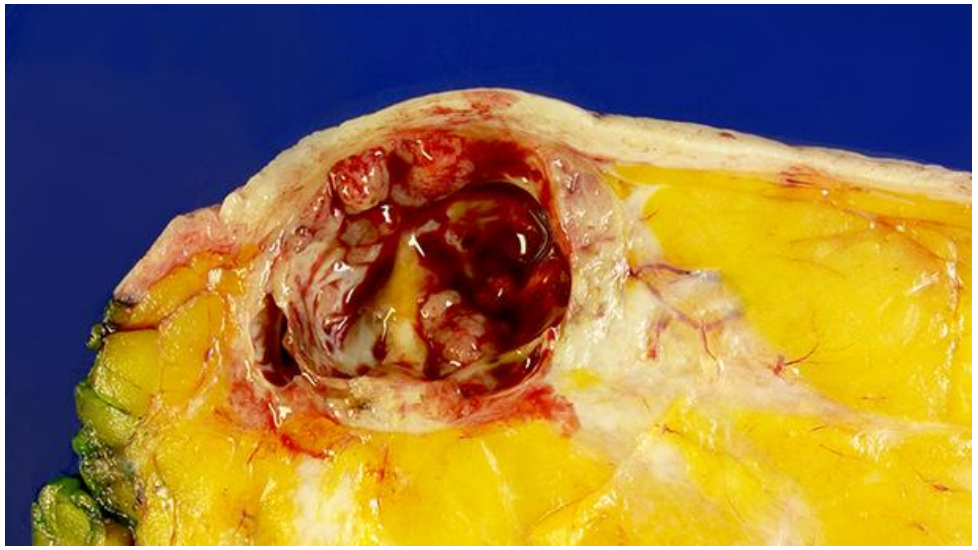
- may occur in younger women and in men

Clinical presentation

- +/- bloody nipple discharge
- circumscribed retro-/ sub-areolar mass
- round to oval, solid and cystic by U/S



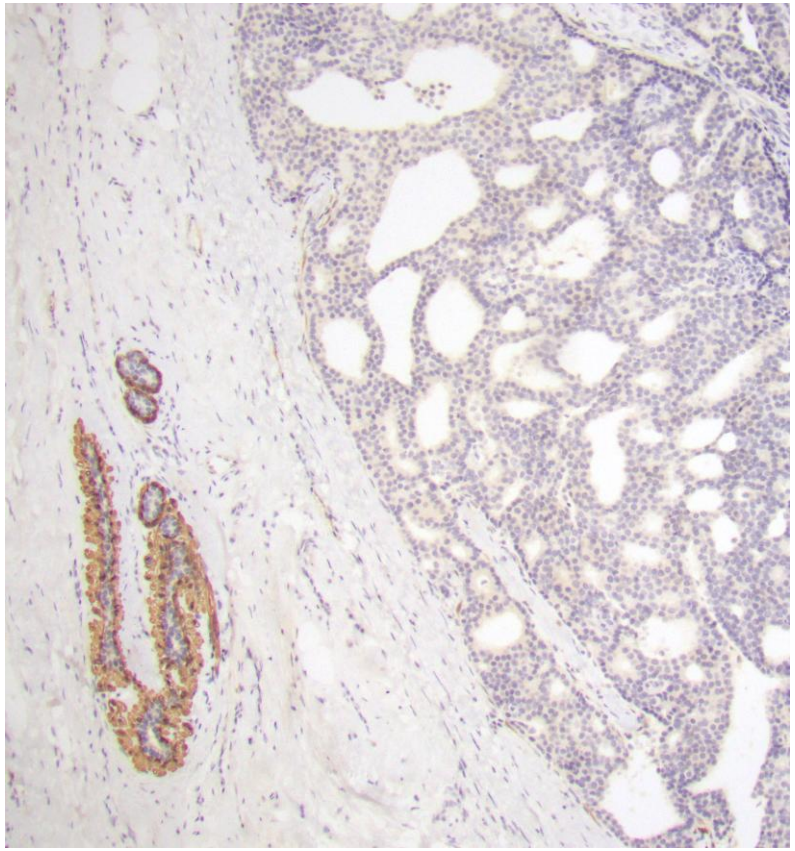




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EPC has no (or only a few rare) myoepithelial cells

calponin

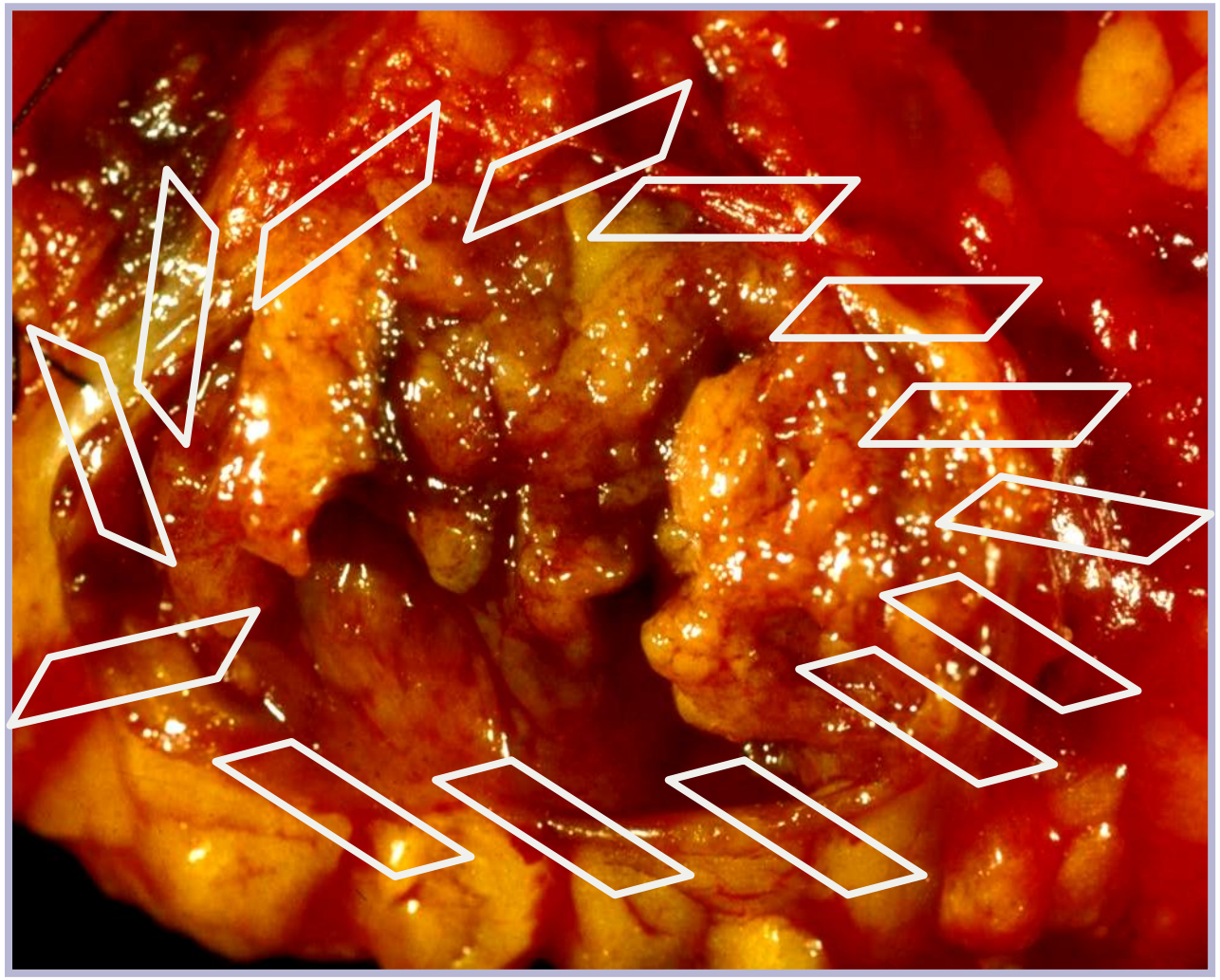


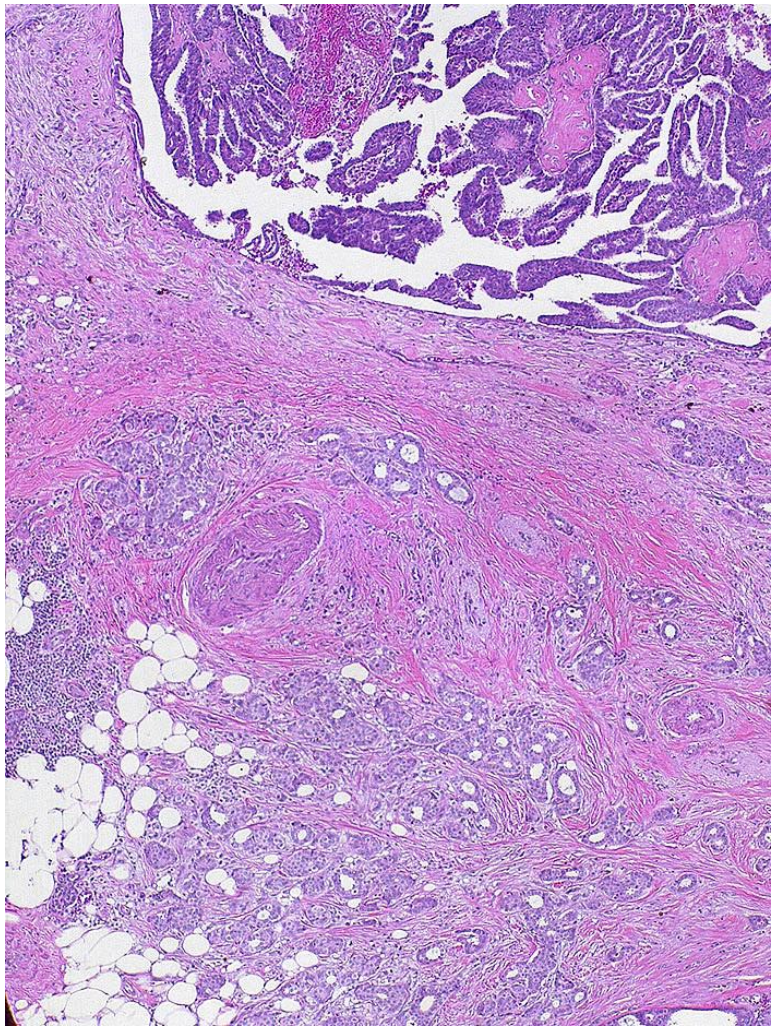
EPC is characterized by absence of MECs along the papillae *and* around the tumor → "invasive" carcinoma with blunt invasion

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

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Sample EPC +capsule+ adjacent tissue to rule out frank invasion





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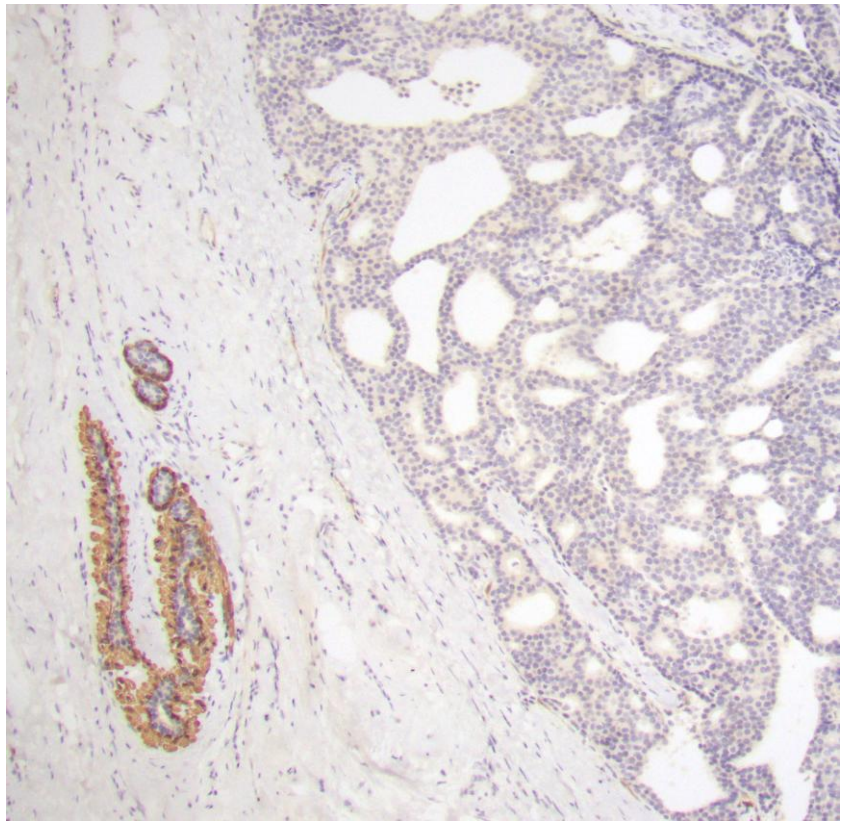
EPC

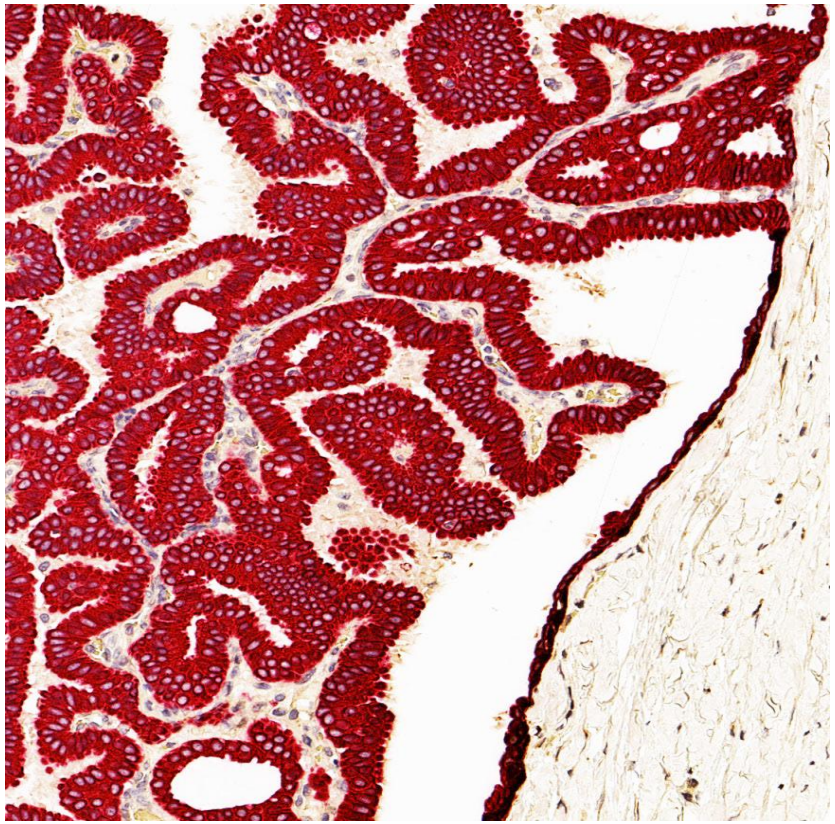
papillary DCIS

No MECs along the papillae
and around the tumor

MECs around the tumor
NOT along the papillae

calponin



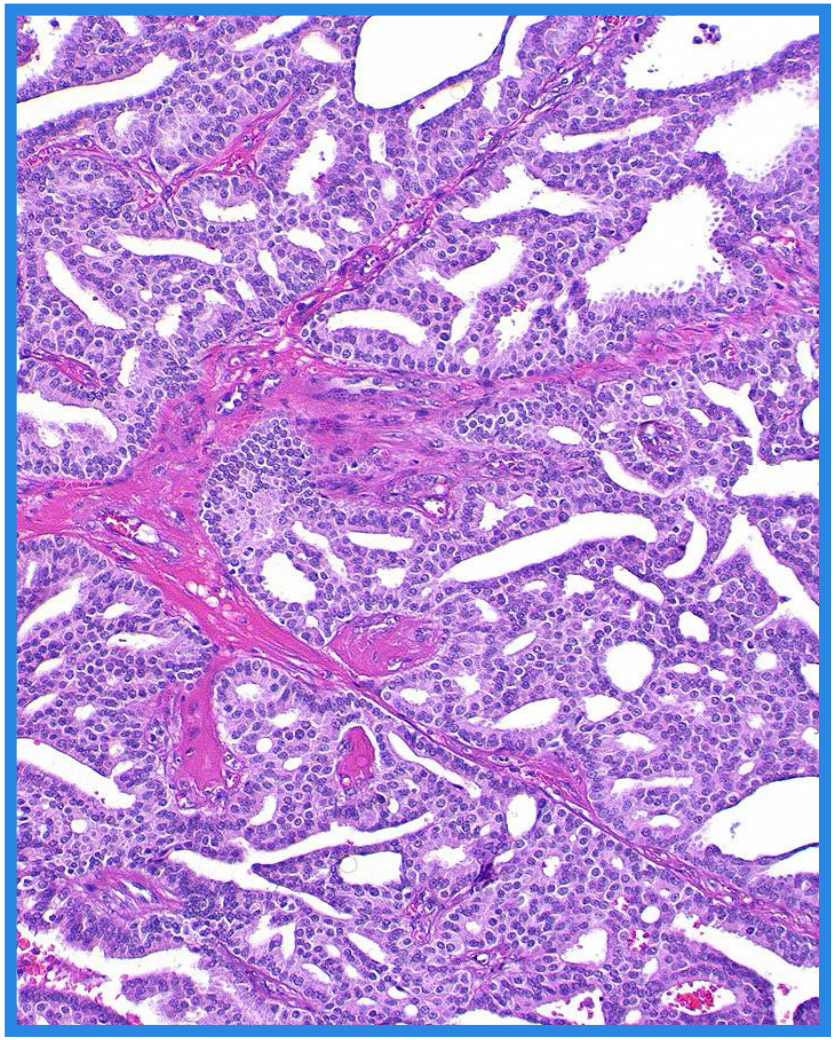


ADH5

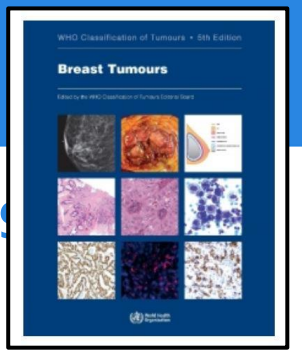
EPC with no associated conventional invasive carcinoma is staged as pTis clinical behavior similar to that of DCIS

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Encapsulated Papillary Carcinoma (EPC)



WHO 5th ed. 201



- One series of 12 EPC-like carcinomas of high NG w/o frank invasion
  1 of 10 patients with F/U died of disease

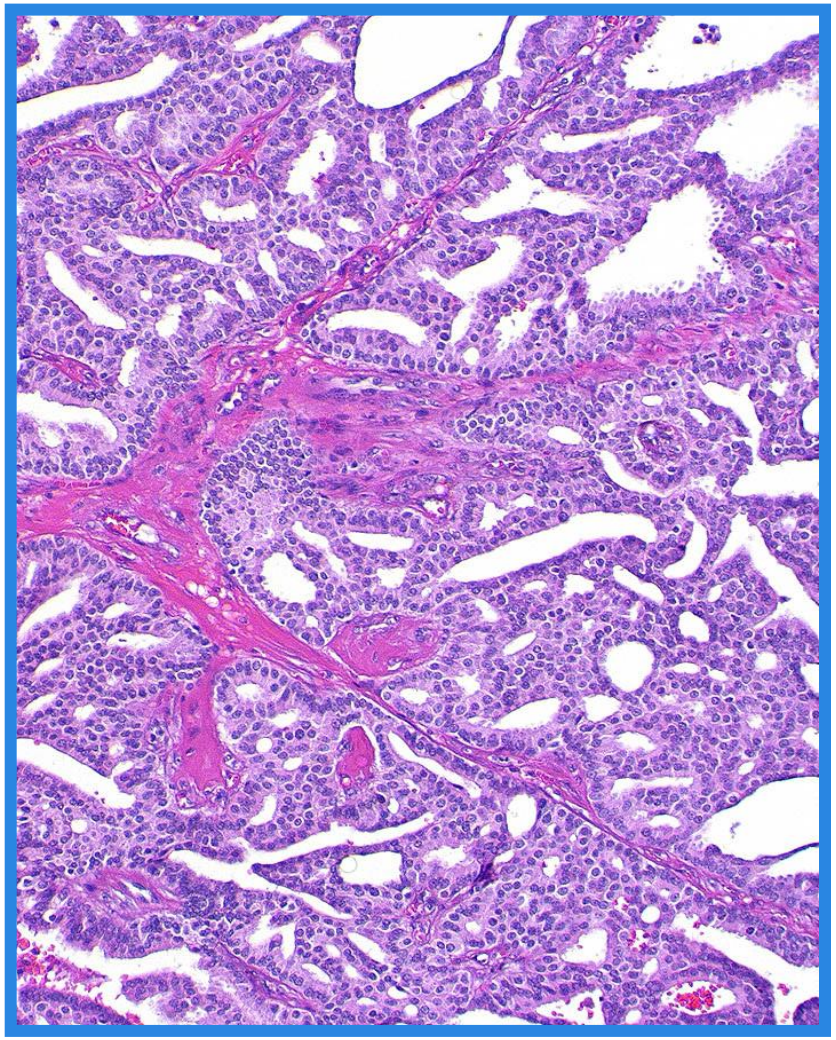
Rakha EA, et al. Histopathology. 2015 Apr;66(5):740-6. PMID: 25382726

- In the WHO 5th ed. EPC Dx was restricted to tumors of Low-Intermediate NG
- EPC-Like carcinoma of High NG or HER2(+) were to be classified as Invasive Papillary Carcinoma (IPC)

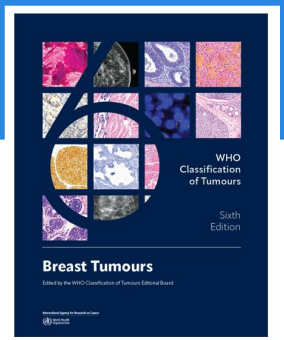
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Encapsulated Papillary Carcinoma (EPC)



WHO 6th ed. 2026



- One series of 12 EPC-like carcinomas of high NG w/o frank invasion
  1 of 10 patients with F/U died of disease

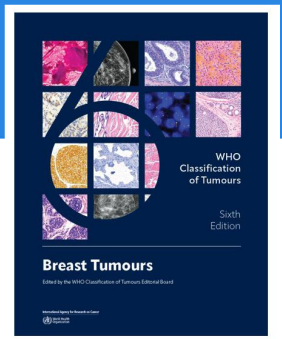
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- ~~In the WHO 5th ed. EPC Dx was restricted to tumors of Low-Intermediate NG~~
- ~~EPC-Like carcinoma of High NG or HER2(+) were to be classified as Invasive Papillary Carcinoma (IPC)~~

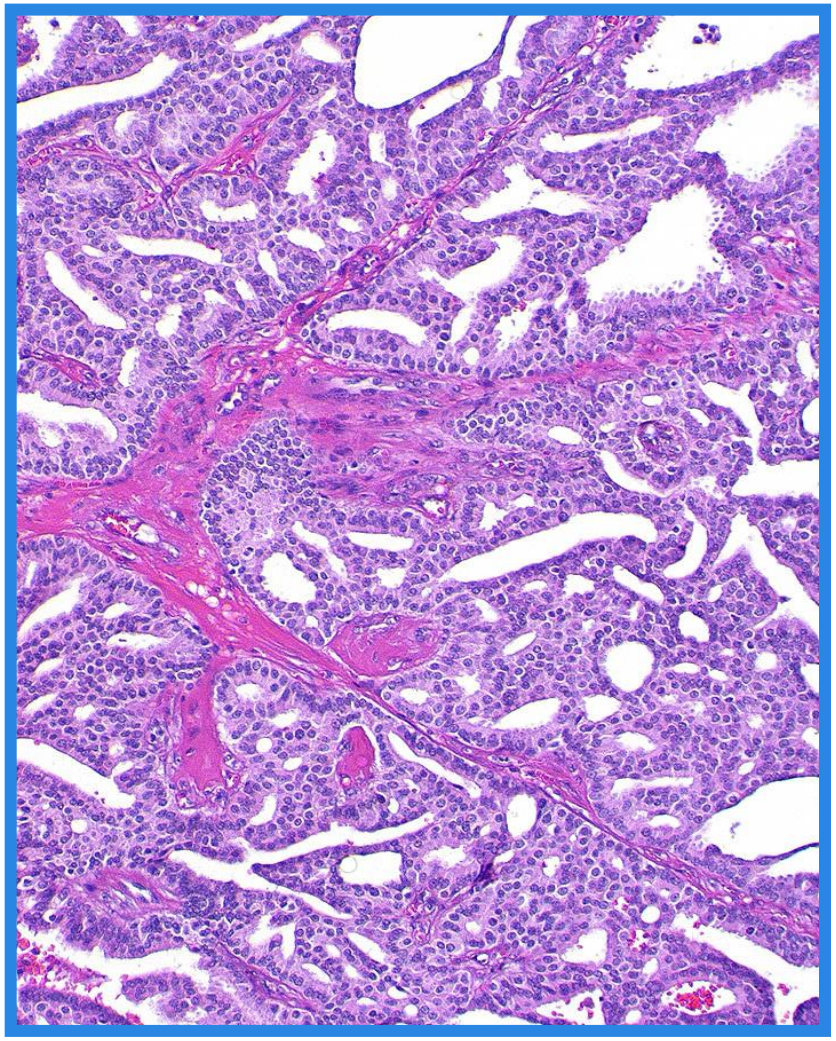
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Encapsulated Papillary Carcinoma (EPC)



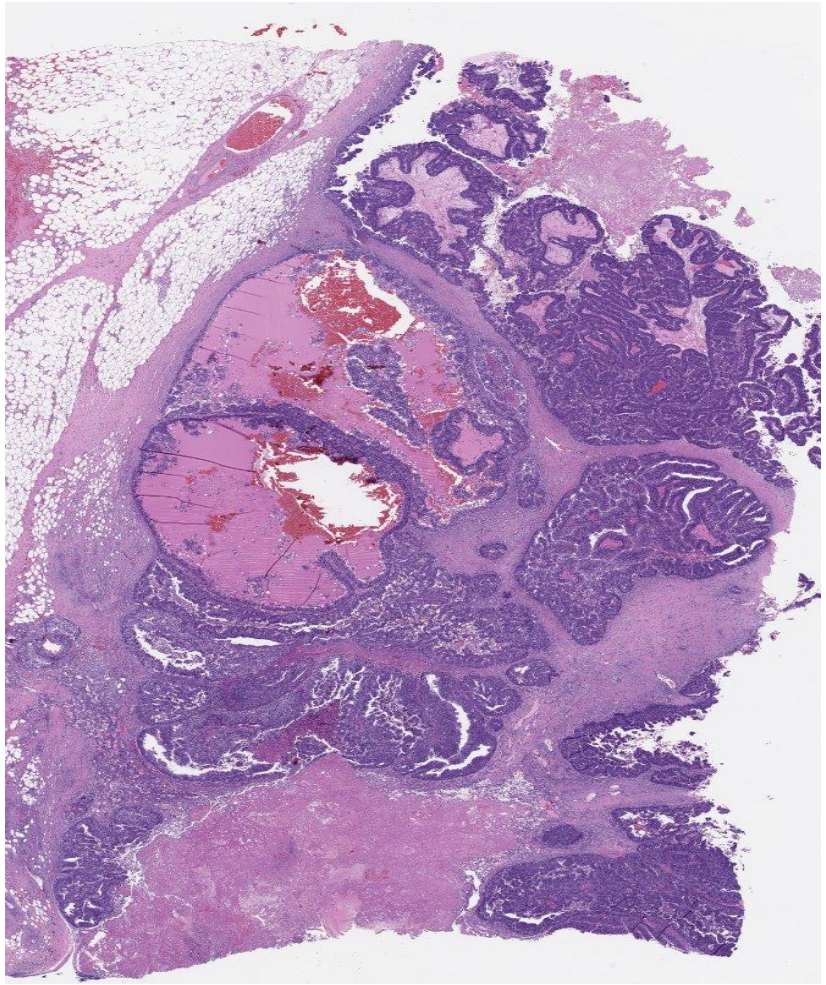
WHO 6th ed. 2026



"In the absence of frank invasion, the editorial board recommends that EPC-like carcinoma of High NG or HER2+ be categorized as EPC (staged as DCIS), with a comment enumerating the unusual features.

In these cases, thorough histological examination of the surgical excision specimen is advised to exclude the possibility of a high-grade invasive carcinoma with pseudopapillary growth secondary to central necrosis."

Example: pseudopapillary invasive carcinoma with necrosis

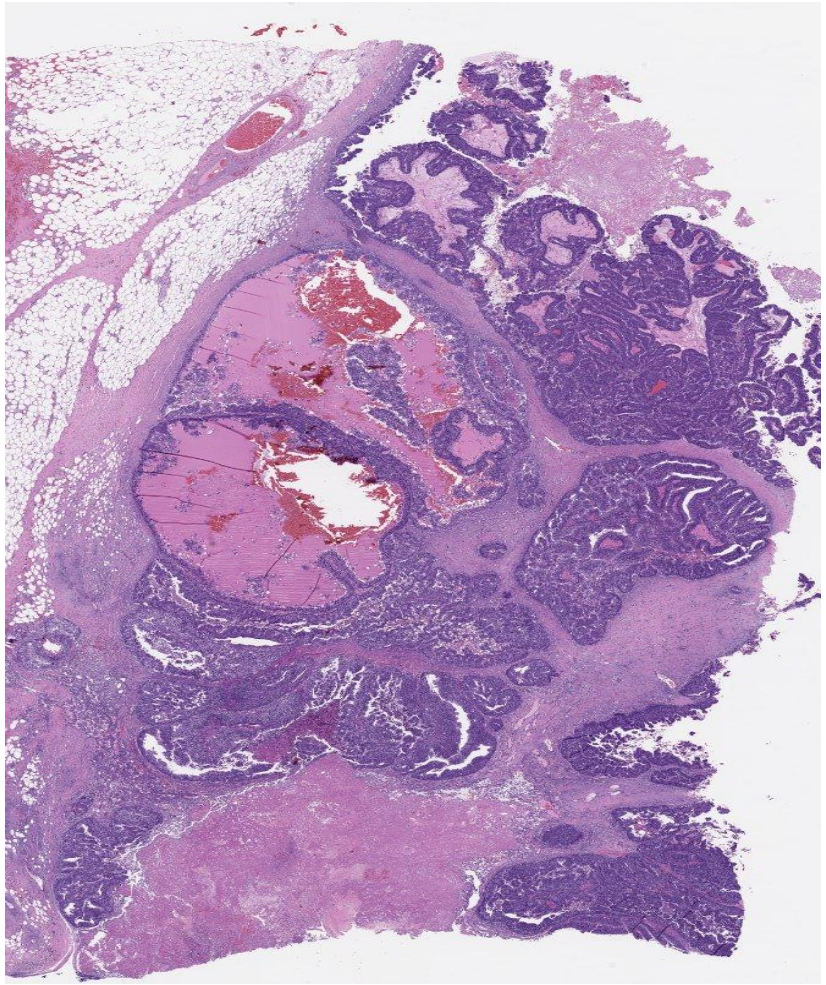


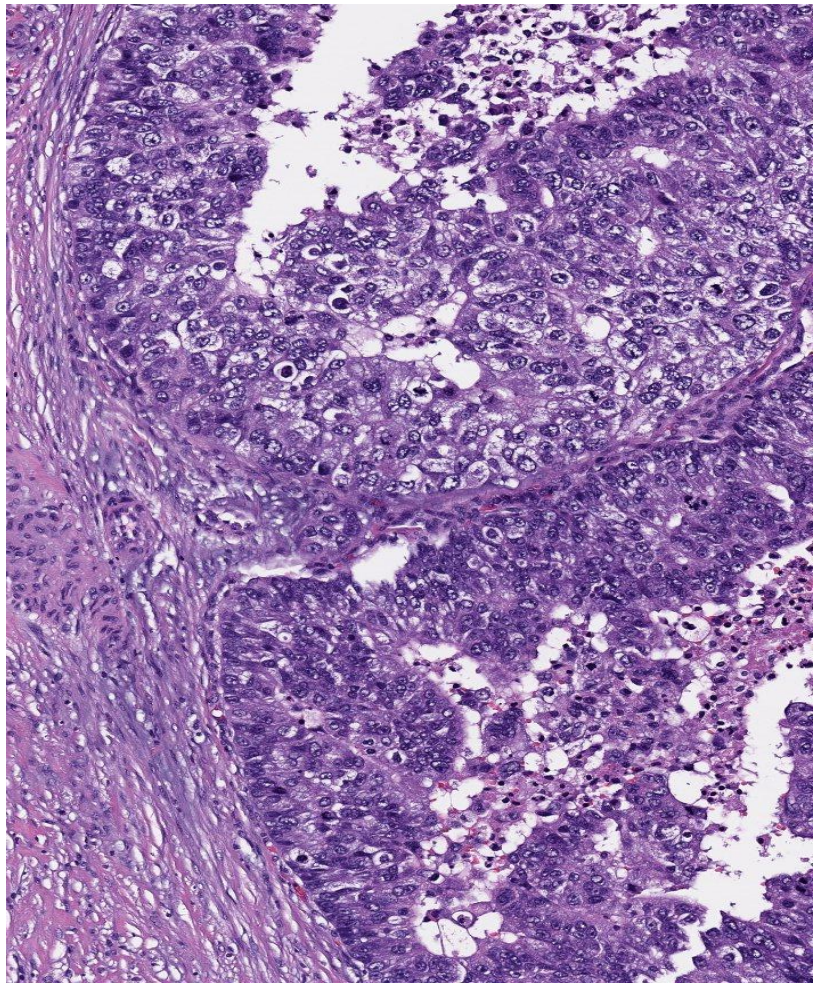
Invasive carcinoma of high nuclear grade
with pseudopapillary pattern
secondary to necrosis

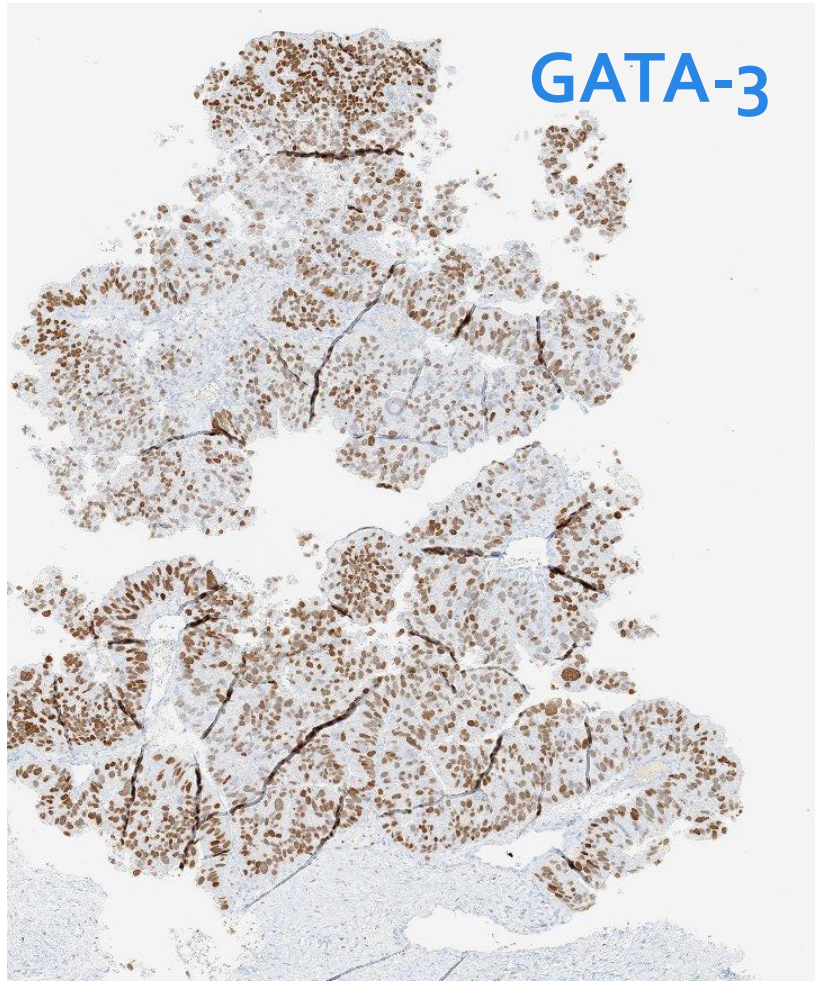
This invasive carcinoma
is apparently circumscribed
and may mimic EPC of high NG

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No definite DCIS → Rule out metastatic carcinoma



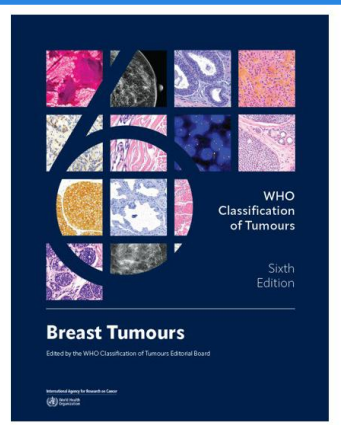




Markers of breast origin: GATA3, Sox10 *and TRPS1*

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Epithelial Tumours of the breast Part #2

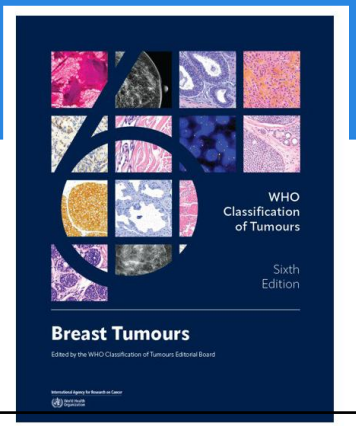


3.0: Epithelial tumours of the breast: Part 2

- **3.1: Epithelial tumours of the breast: Part 2: Introduction**
- **3.1.6: Molecular classification**
- **3.1.9: Prognosis and prediction**
- **3.2: Invasive breast carcinoma**
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  - 3.2.5: Tubular carcinoma
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  - 3.2.10: Metaplastic carcinoma
- **3.3: Rare and salivary gland–type tumours**
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- **3.4: Neuroendocrine neoplasms**
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  - 3.4.4: Neuroendocrine carcinoma

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Epithelial Tumours of the breast Part #2



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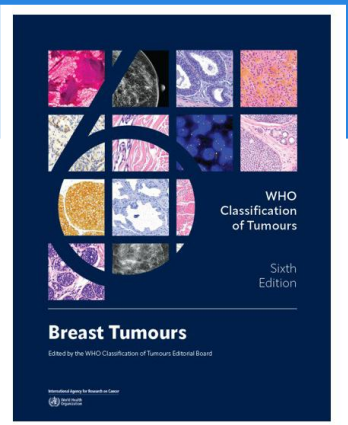
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- **Nuclear pleomorphism: assess in the area with the highest degree of pleomorphism** in comparison with the regularity of the nuclear size and shape of normal epithelial cells in adjacent breast tissue.
- Preferred magnification for nuclear scoring: **40× objective.**
- **Score 1…. Score 2 … Score 3…**
- **The minimum proportion of tumour nuclei which should show marked nuclear atypia/ pleomorphism before a score of 3 is allocated has not been well defined.**
- **An occasional enlarged or bizarre nucleus should not be used to give a score of 2 rather than a score of 2.**

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Epithelial Tumours of the breast Part #2



3.0: Epithelial tumours of the breast: Part 2

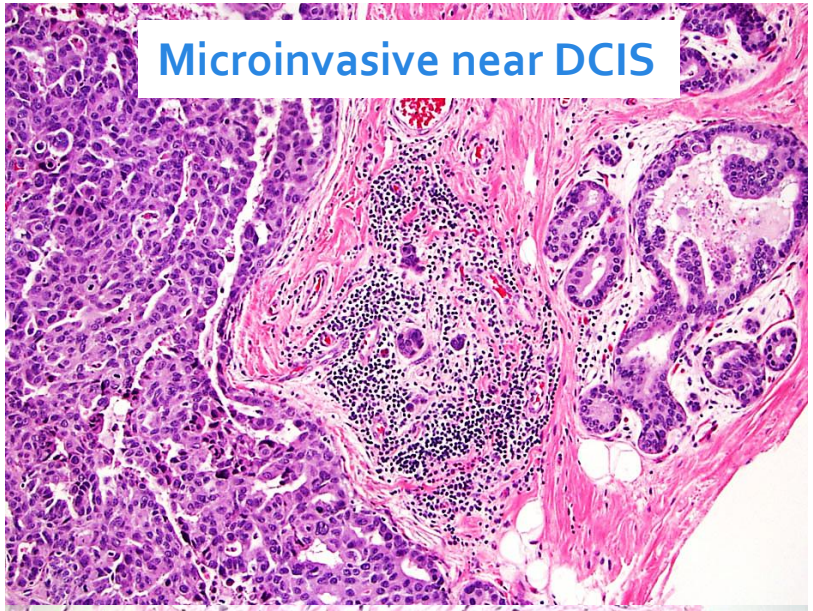
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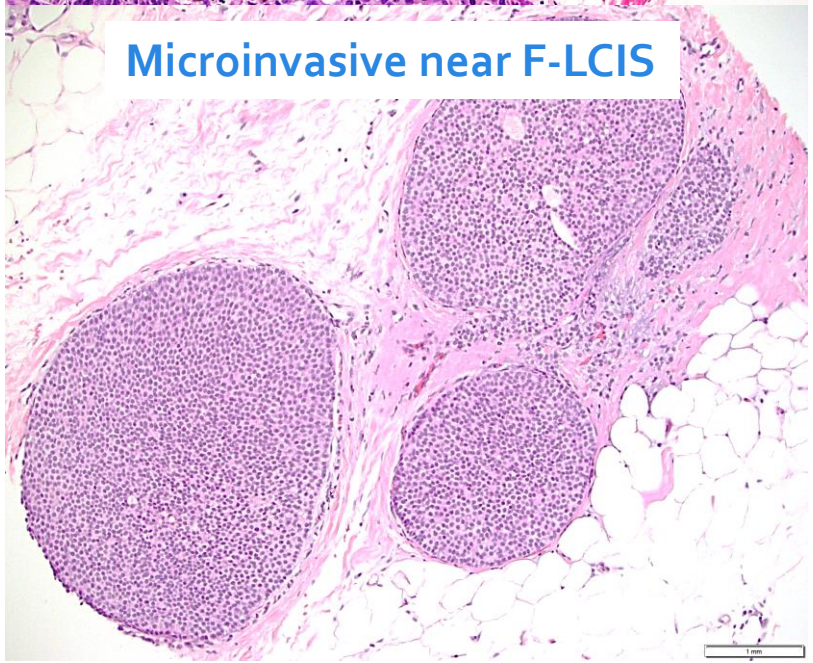
3.2.3 Microinvasive carcinoma

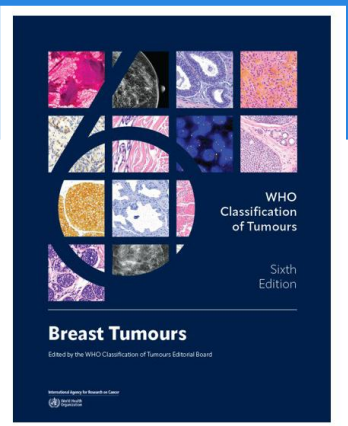
Microinvasive carcinoma of the breast is an invasive breast carcinoma ≤ 1 mm.

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Epithelial Tumours of the breast Part #2







3.2.3 Microinvasive carcinoma

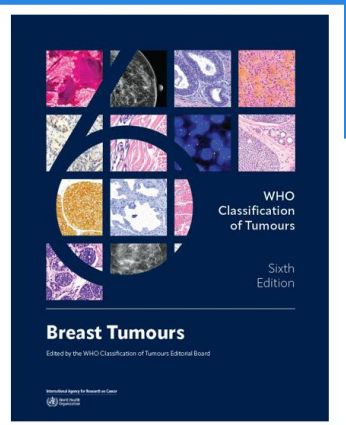
It is the earliest morphologically recognized form of invasive carcinoma with a dominant CIS component, most commonly high-grade DCIS.

Less commonly observed in association with classic, florid, and pleomorphic LCIS, rarely with Paget disease of the nipple

No need to specify if ductal, lobular, or other types

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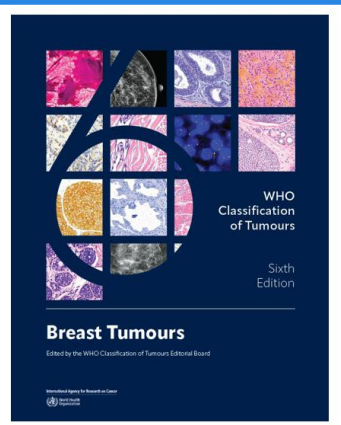
3.2.3 Microinvasive carcinoma



- May carry a low risk of metastatic spread
- Assess hormone receptor and HER2 status if possible.

- Microinvasive carcinoma in association with DCIS may be multifocal.
- Indicate if the microinvasive carcinoma is multifocal
  - may be associated with worse disease-free survival
  - may influence adjuvant therapy recommendations.
- In some centers, the number of foci of microinvasion is recorded as an indication of microinvasive lesion burden.

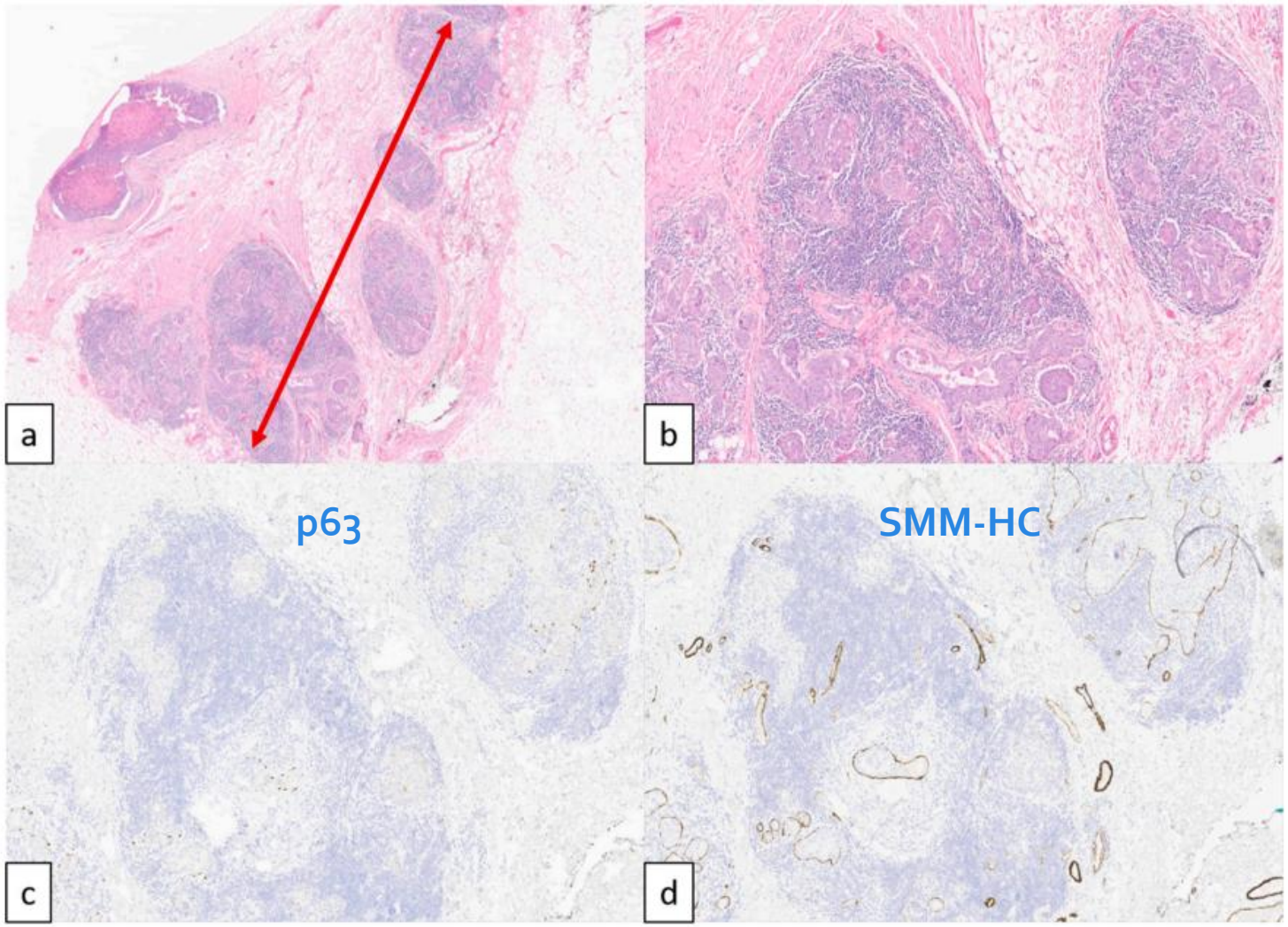
3.2.3 Microinvasive carcinoma



Multiple foci of microinvasion in close proximity

- "**A pragmatic approach** would be to apply the same recommendation used for staging multifocal established invasive carcinomas and **regard deposits <5 mm apart as part of a single invasive tumour deposit.**
- This is a **practical approach which would classify close proximity multifocal microinvasion (<5 mm apart) as an established invasive carcinoma, base the invasive tumour size measurement on the maximum dimension of the region with two or more microinvasive foci, and stage accordingly.**
- There should be **caution in applying this rule** if there is very minimal infiltration, and examination of further deeper sections should be considered.

Example: 4 foci of microinvasion or 4 mm Invasive carcinoma?



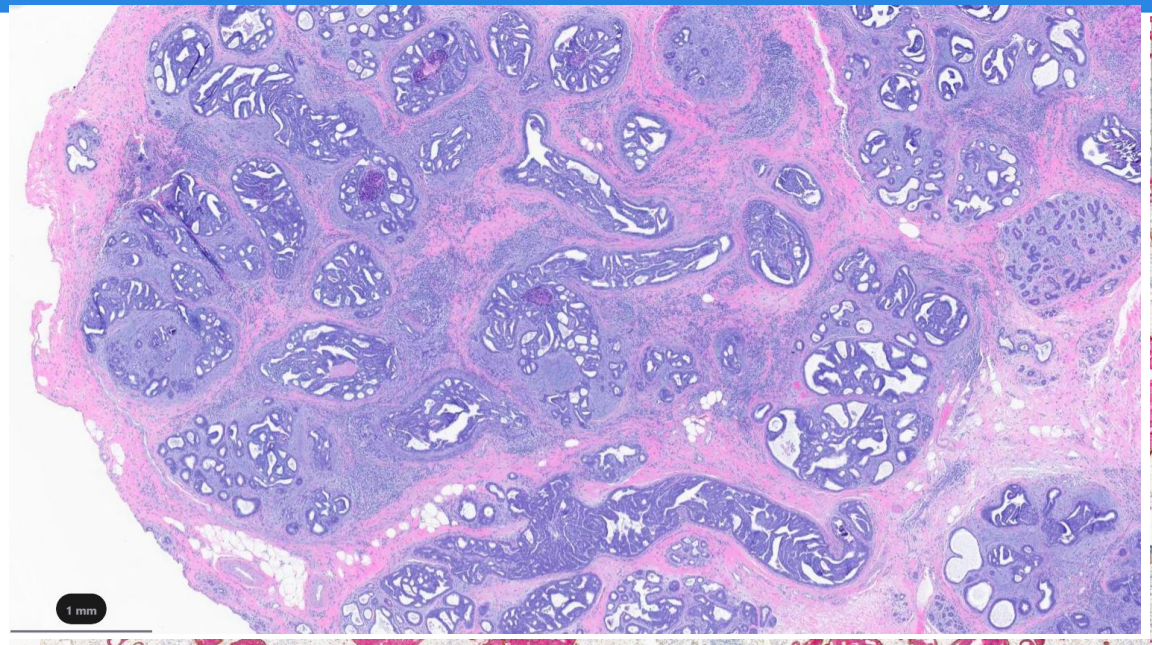
Closely associated foci of microinvasive carcinoma (≤5 mm apart) summated and staged according to overall size.

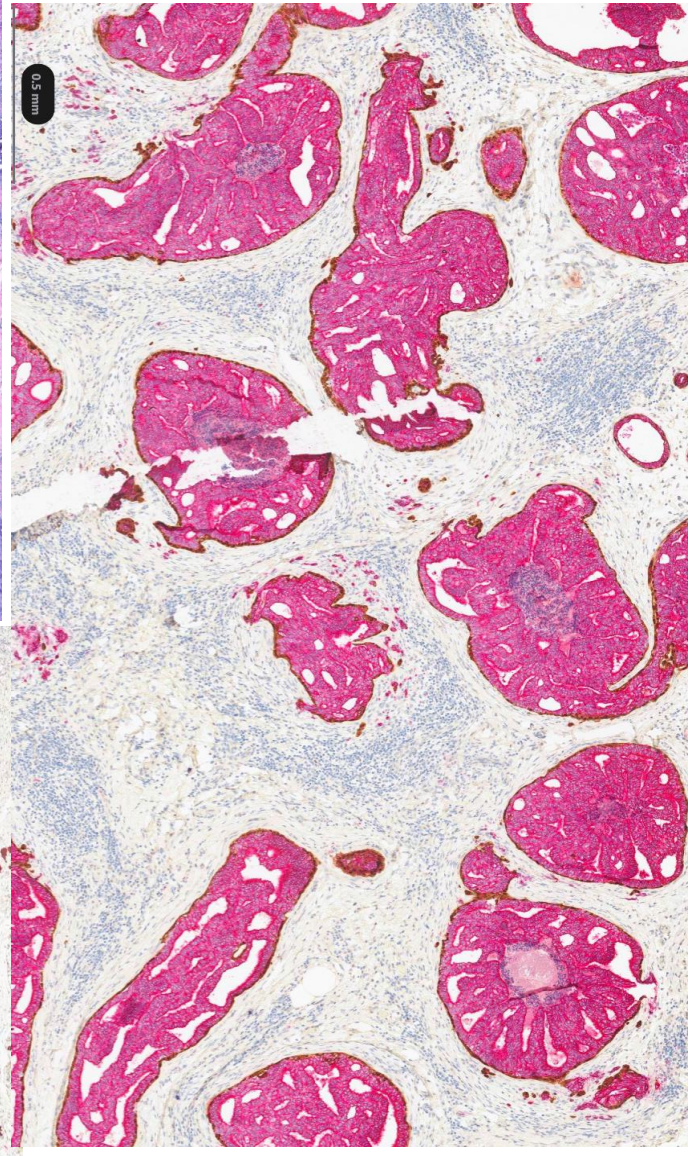
The case shown here had been interpreted initially as 4 separate microinvasive foci.

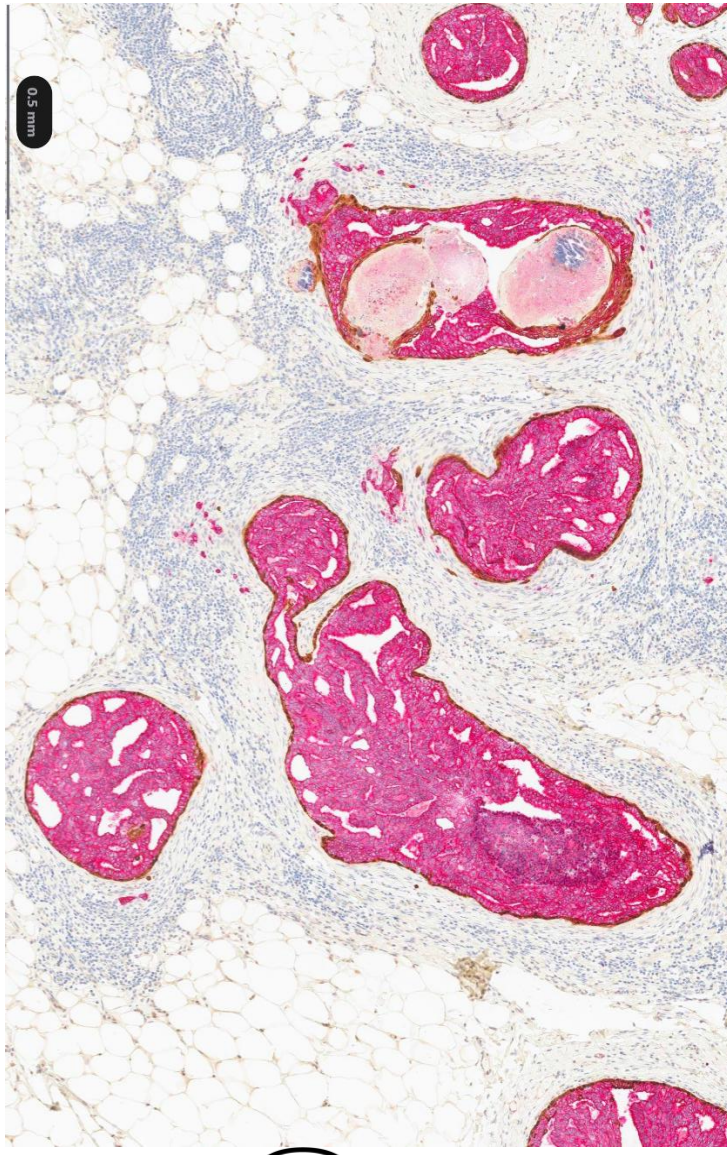
Han R, Brogi E. Microinvasive carcinoma of the breast. *Hum Pathol*. 2025;162:105856.

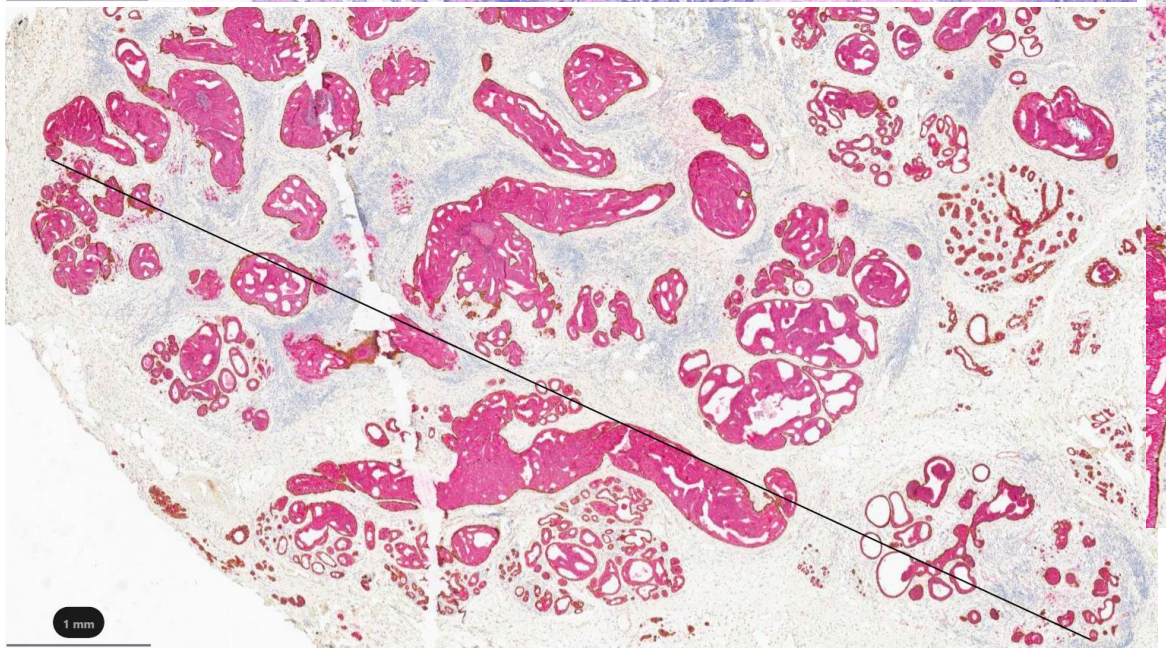
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Diagnosed as multiple foci of microinvasion distributed over a 7 mm span



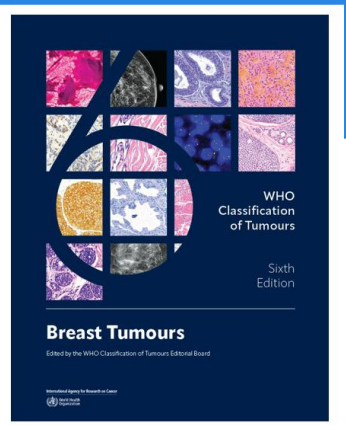






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Epithelial Tumours of the breast Part #2



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3.2.4 Invasive Lobular Carcinoma

Grade ILC using Nottingham grading system

Cytomorphology

classic, signet-ring, apocrine, histiocytoid, pleomorphic

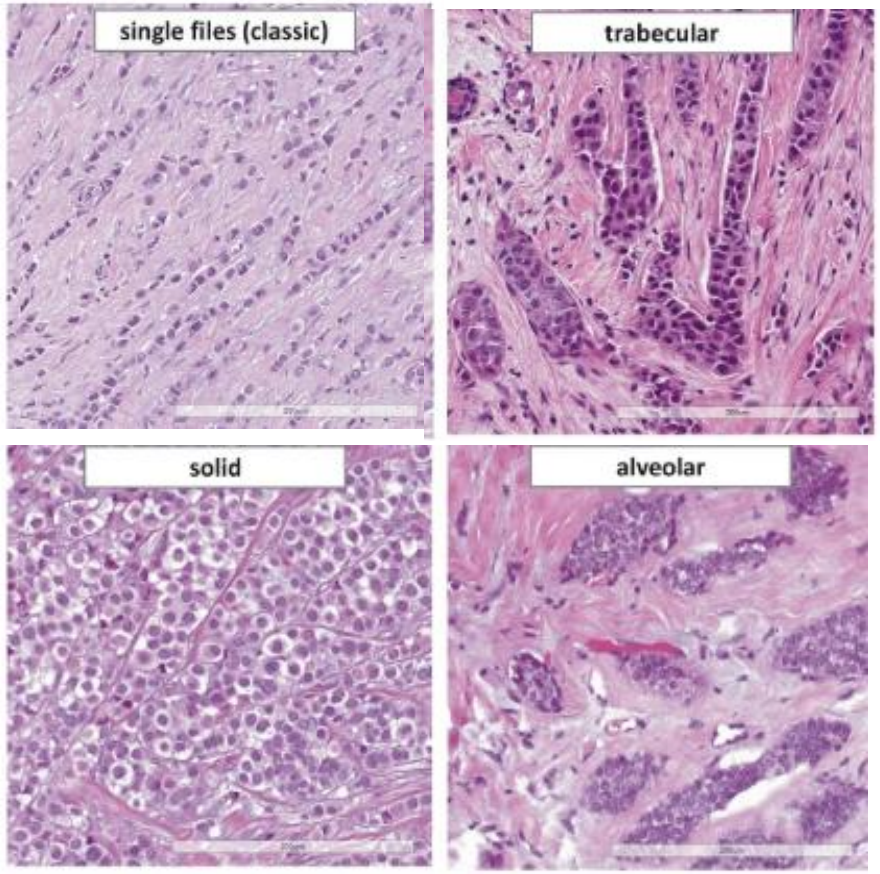
Architectural pattern

classic, trabecular, solid, alveolar, solid-papillary

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ILC patterns

- **Classic**: single file, concentric
- **Trabecular:** typical ILC cells form in cords, two to three cells thick, may mimic IBC-NST.
- **Solid:** sheets of dyscohesive cells of lobular morphology
- **Alveolar:** aggregates of ≥20 cells … separated by thick or thin collagenous septa. …Alveoli separated by thin and incomplete septa…, the distinction from the solid pattern may be difficult and the term "solid/alveolar" could be used in such situations.



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ILC Patterns

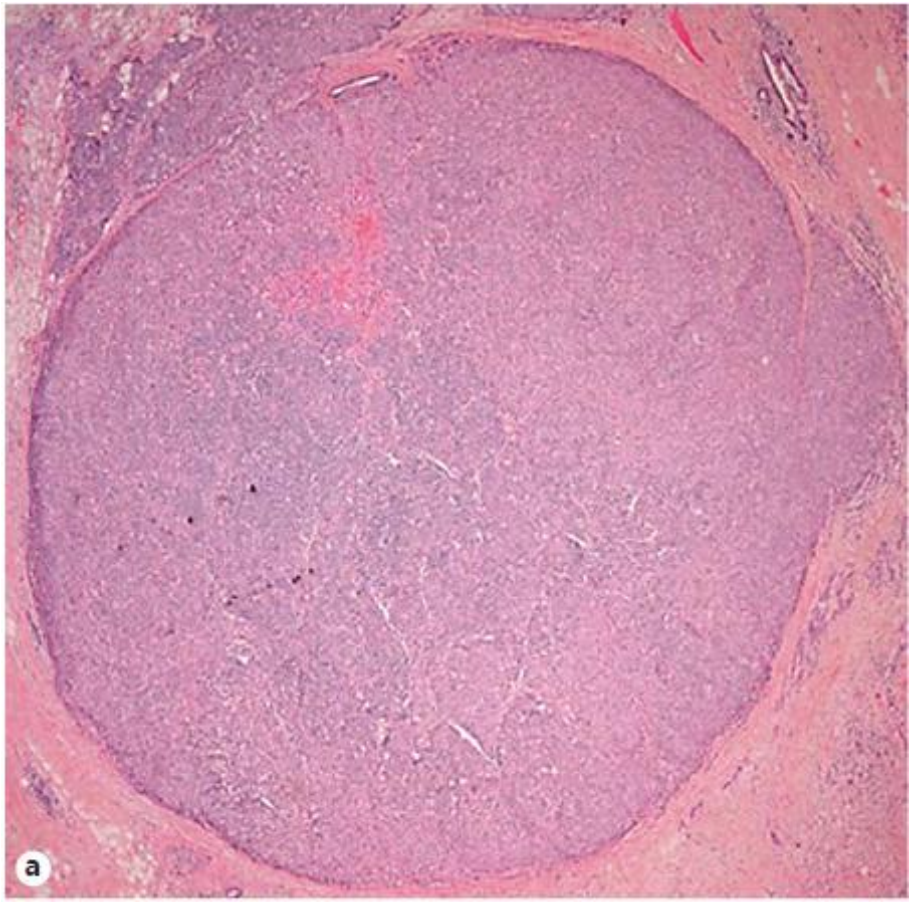
Solid papillary (variation of solid pattern): … well delimited peripherally with a pseudocapsule, often satellite foci of ILC at the periphery of the tumour.

Avoid confusion with other papillary lesions (i.e solid papillary carcinoma or EPC), particularly in small biopsies.

Invasive Lobular Carcinoma Mimicking Papillary Carcinoma: A Report of Three Cases

Pathobiology 2016;83:221–227

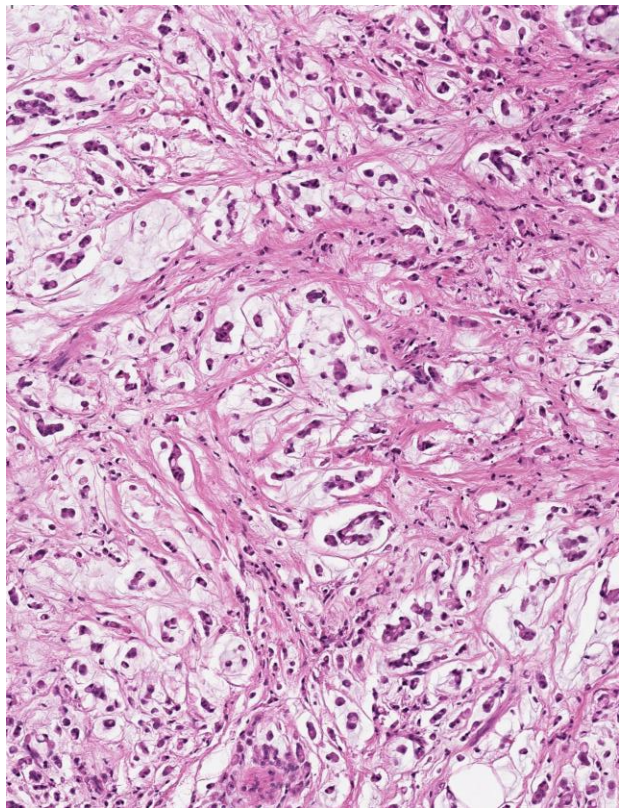
Emad A. Rakha Areeg Abbas Rachael Sheeran

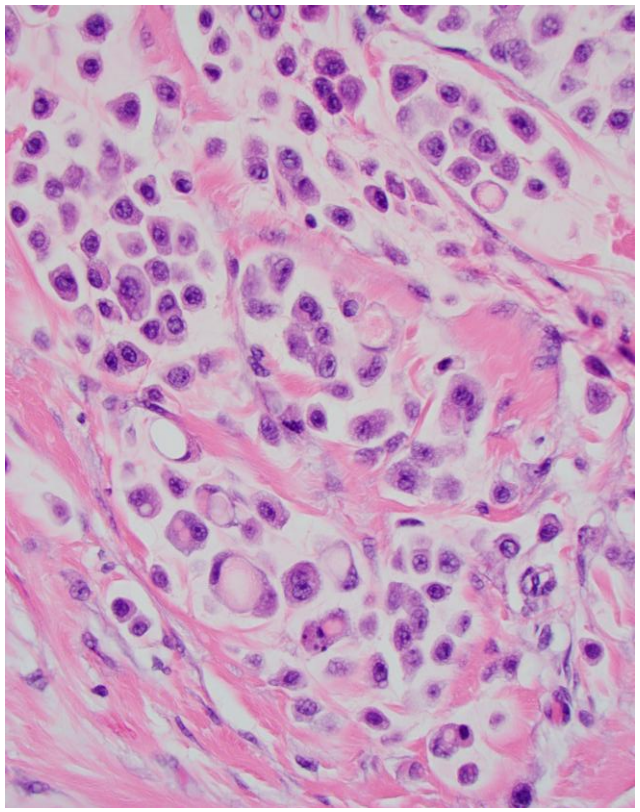


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ILC with extracellular mucin (ILC-EM)

- Recently described
- Associated with LN mets in >50% cases
- Has features unusual for ILC
  - grade 3
  - tumour necrosis
  - sometimes HER2 3+
- Extracellular mucin may be focal
- **ILC with extracellular mucin (poor prognosis) is not to be confused with mucinous carcinoma (usually favorable prognosis).**





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"Tubulolobular" carcinoma and E-cadherin

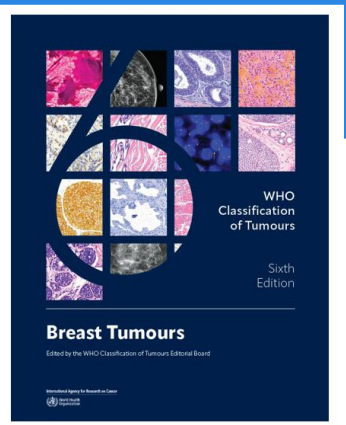
"Tubulolobular carcinoma" used in the past for **tumors with combined ILC and small well-formed glands morphology.**

At present, it is recommended that **tumors with combined ILC and small well-formed glands morphology** be classified as

- **Tubulolobular carcinoma: if there is no E-cadherin expression**
- **Mixed ILC and tubular carcinoma:**
  - **ILC component is E-cadherin–negative**
  - **Tubular component is E-cadherin–positive**

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Epithelial Tumours of the breast Part #2



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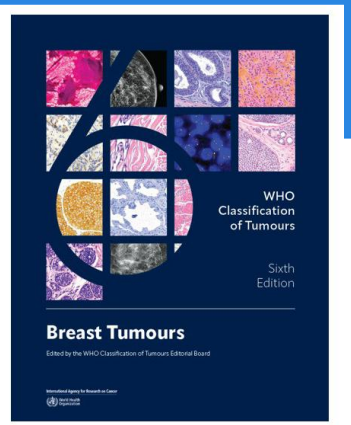
3.4.1: Neuroendocrine neoplasms: Introduction
3.4.3: Neuroendocrine tumour
3.4.4: Neuroendocrine carcinoma

3.2.6 Invasive cribriform carcinoma

"Invasive" added to avoid confusion with cribriform DCIS

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Epithelial Tumours of the breast Part #2



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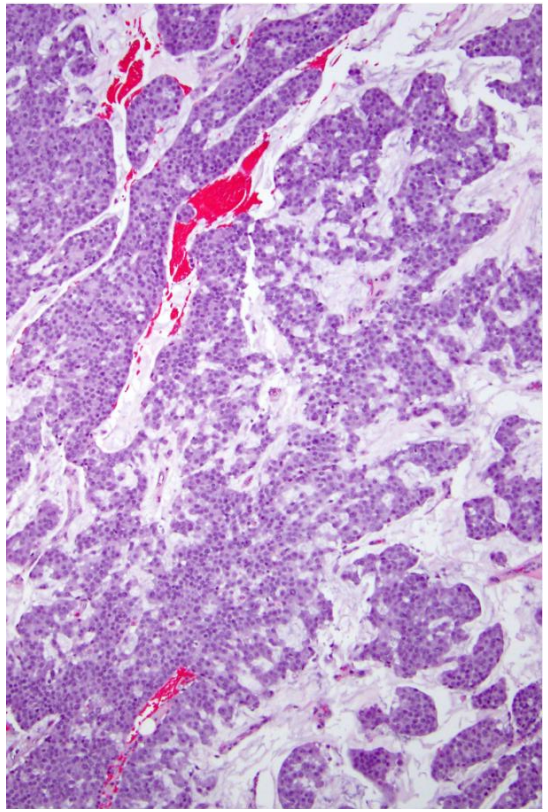
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3.2.7 Mucinous Carcinoma

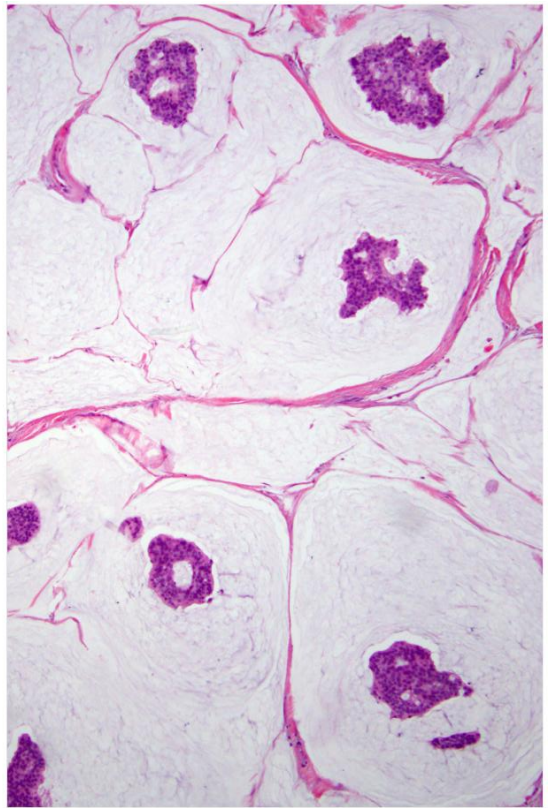
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3.2.7 Mucinous carcinoma (MC)

Clusters of epithelia with **low to intermediate NG, ER-positive and HER2-negative, floating in mucin.**



Hypercellular



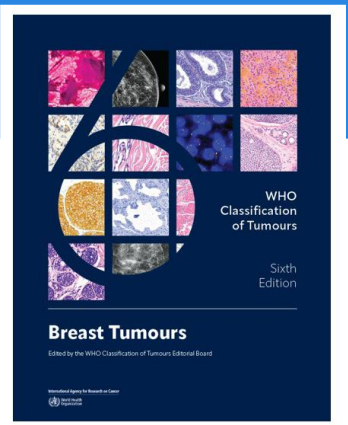
Hypocellular

NOT mucinous carcinoma

- **High NG or HER2(+): classify as IBC-NST with mucin production**
  worse prognosis than MC
- **ILC with extracellular mucin**
  worse prognosis than MC
- **Metaplastic carcinoma with chondromyxoid matrix**
  ER-negative
  worse prognosis than MC

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Epithelial Tumours of the breast Part #2



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  - 3.4.4: Neuroendocrine carcinoma

Acinic cell carcinoma → acinic cell–<u>like</u> carcinoma

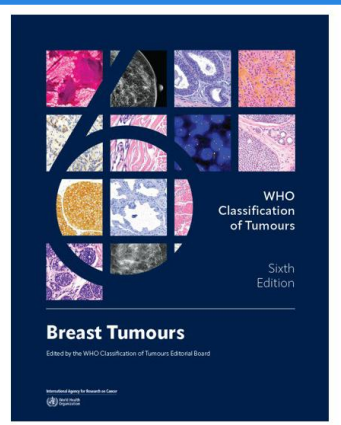
- No gene rearrangement and NR4A3 protein overexpression characteristic of acinic cell carcinoma (of salivary glands or pancreas)
- Molecular profile similar to conventional triple-negative BC and to carcinomas arising in association with MGA.

Polymorphous adenocarcinoma has been removed

- only rare case reports (considered as a low level of evidence)

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Epithelial Tumours of the breast Part #2



3.0: Epithelial tumours of the breast: Part 2

3.1: Epithelial tumours of the breast: Part 2: Introduction

3.1.6: Molecular classification

3.1.9: Prognosis and prediction

3.2: Invasive breast carcinoma

- 3.2.2: Invasive breast carcinoma of no special type
- 3.2.3: Microinvasive carcinoma
- 3.2.4: Invasive lobular carcinoma
- 3.2.5: Tubular carcinoma
- 3.2.6: Invasive cribriform carcinoma
- 3.2.7: Mucinous carcinoma
- 3.2.8: Invasive micropapillary carcinoma
- 3.2.9: Invasive apocrine carcinoma
- 3.2.10: Metaplastic carcinoma

3.3: Rare and salivary gland–type tumours

- 3.3.1: Rare and salivary gland–type tumours: Introduction
- 3.3.2: Acinic cell–like carcinoma
- 3.3.3: Adenoid cystic carcinoma
- 3.3.4: Secretory carcinoma
- 3.3.5: Mucoepidermoid carcinoma
- 3.3.7: Mucinous cystadenocarcinoma
- 3.3.8: Tall cell carcinoma with reversed polarity

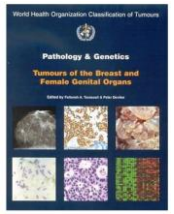
3.4: Neuroendocrine neoplasms

- 3.4.1: Neuroendocrine neoplasms: Introduction
- 3.4.3: Neuroendocrine tumour
- 3.4.4: Neuroendocrine carcinoma

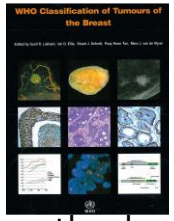
3.4 Neuroendocrine Neoplasms

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Breast cancer and neuroendocrine differentiation



3rd ed.



4th ed.

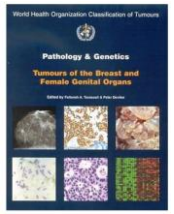


5th ed.

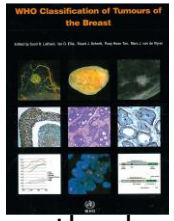
WHO	Terminology	Definition	Subtypes	NE marker profile
2003	Neuroendocrine tumor	• Morphological features similar to those of NE tumors of both GI tract and lung • Express NE marker of 50% of cell population • IBC-NOS with focal NED revealed by NE markers in scattered cells were excluded.	• Solid neuroendocrine carcinoma • Small cell/oat cell carcinoma • Large cell carcinoma	• CG and/or SYN • NSE described in poorly-differentiated/small cell carcinoma
2012	Carcinoma with neuroendocrine features	• Morphological features similar to those of NE tumors of GI tract and lung • Express NE marker to a greater or a lesser degree • IBC-NST and special subtypes with NED were included.	• Neuroendocrine tumor, well differentiated • Neuroendocrine tumor, poorly-differentiated/small cell carcinoma • IBC with neuroendocrine differentiation (included mucinous carcinoma and solid papillary carcinoma with NED)	• CG and/or SYN • NSE described in poorly-differentiated/small cell carcinoma
2019	Neuroendocrine neoplasm	• Tumor with predominant (>90%) NED • Solid papillary carcinoma and hypercellular subtype of mucinous carcinoma were excluded	• NET • NEC (small cell NEC; large cell NEC)	• CG and/or SYN expression is characteristic in NET, Some also express CD56 • CG and/or SYN in 2/3 of NEC and expression of PGP9.5, CD56 and NSE in majority of NEC
	Invasive breast cancer NST with neuroendocrine features	• ≤90% NE histological features or NE marker expression ➢ 10–90%: mixed invasive NST and NET/NEC ➢ <10%: invasive NST commented on the focal NE pattern		

Tsang JY, Tse GM. Breast cancer with neuroendocrine differentiation. Mod Pathol. 2021;34(6):1062-1073. PMID: 33531618.

Breast cancer and neuroendocrine differentiation



3rd ed.



4th ed.

WHO	Terminology	Definition	Subtypes	NE marker profile
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2012	Carcinoma with neuroendocrine features	• Morphological features similar to those of NE tumors of GI tract and lung • Express NE marker to a greater or a lesser degree • IBC-NST and special subtypes with NED were included.	• Neuroendocrine tumor, well differentiated • Neuroendocrine tumor, poorly-differentiated/small cell carcinoma • IBC with neuroendocrine differentiation (included mucinous carcinoma and solid papillary carcinoma with NED)	• CG and/or SYN • NSE described in poorly-differentiated/small cell carcinoma
2019				

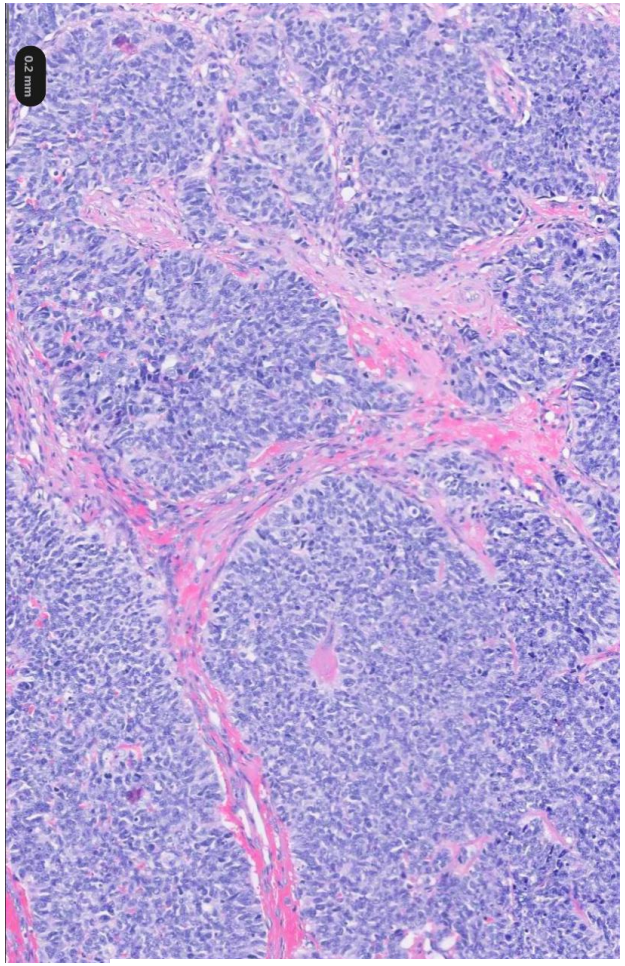


5th ed.

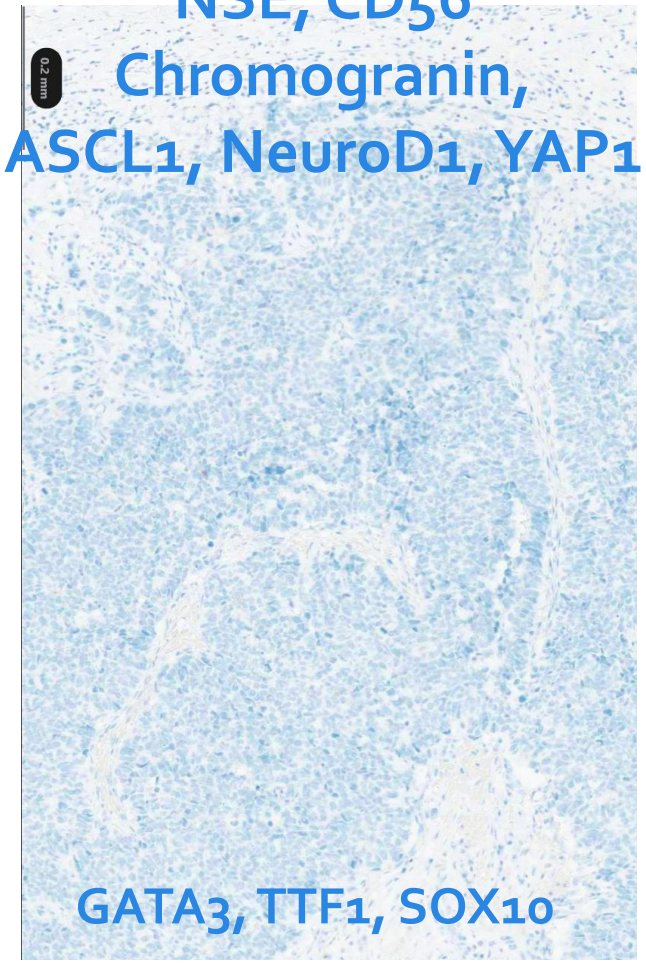
Limitations of 5th ed. classification

- Benign NE cells not demonstrated in the breast
- Many new NE markers
- Clinical significance of NE differentiation in breast tumors unknown/ debated
  - Breast NETs are usually strongly ER-positive
  - Unknown prognostic and treatment implications of NE breast carcinomas

Novel Neuroendocrine Markers, including ASCL1, NeuroD1, POU2F3

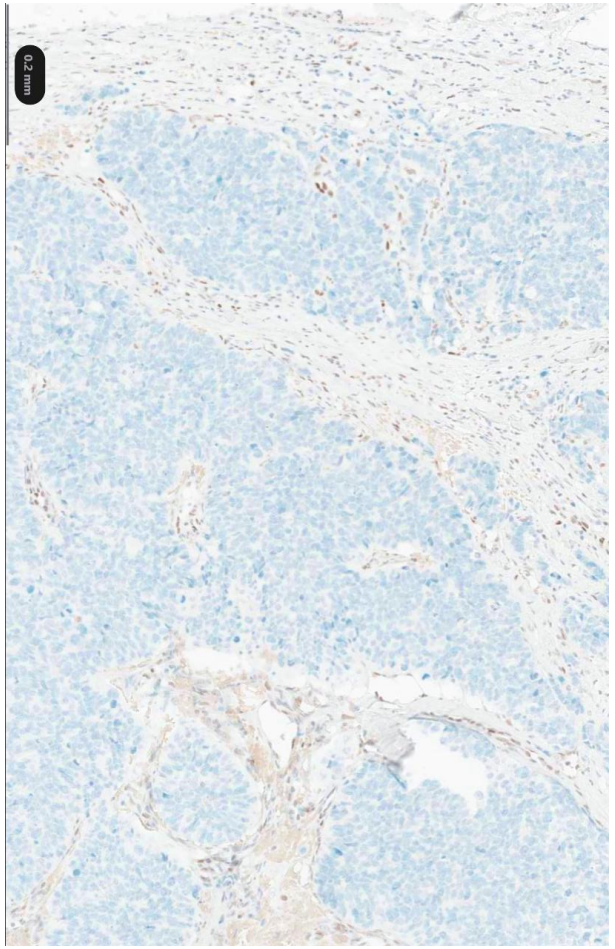


Synaptophysin,
NSE, CD56
Chromogranin,
ASCL1, NeuroD1, YAP1

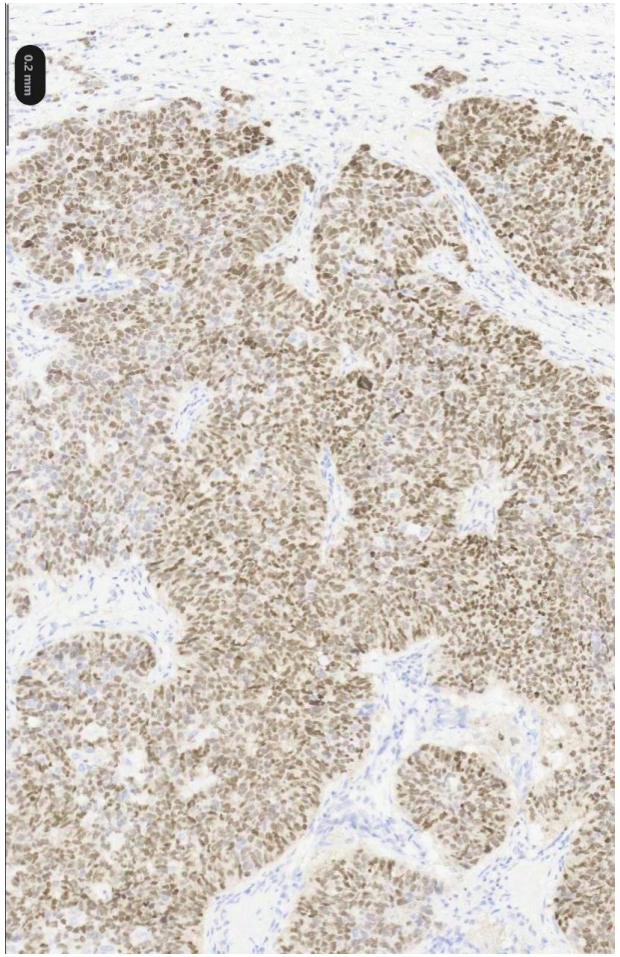


GATA3, TTF1, SOX10

RB1



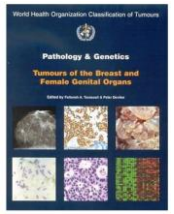
POU2F3



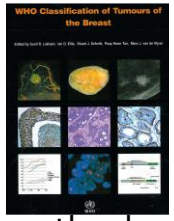
Breast mass: Final DX: Small cell carcinoma neuroendocrine low, origin undetermined

See Baine MK, et al. SCLC Subtypes Defined by ASCL1, NEUROD1, POU2F3, and YAP1. J Thorac Oncol. 2020;15(12):1823-1835.

Breast cancer and neuroendocrine differentiation



3rd ed.



4th ed.

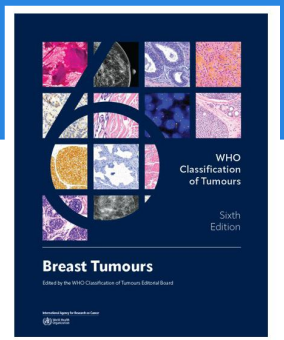
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2012	Carcinoma with neuroendocrine features	• Morphological features similar to those of NE tumors of GI tract and lung • Express NE marker to a greater or a lesser degree • IBC-NST and special subtypes with NED were included.	• Neuroendocrine tumor, well differentiated • Neuroendocrine tumor, poorly-differentiated/small cell carcinoma • IBC with neuroendocrine differentiation (included mucinous carcinoma and solid papillary carcinoma with NED)	• CG and/or SYN • NSE described in poorly-differentiated/small cell carcinoma
2019				



5th ed.

WHO 6th ed.
addresses the limitations
of 5th ed. classification of NE neoplasms of the breast

Diagnostic algorithm for IBC with neuroendocrine morphology



INVASIVE BREAST CARCINOMA (IBC) WITH NEUROENDOCRINE (NE) MORPHOLOGY ON H&E

Mucinous Carcinoma*
Solid Papillary Carcinoma*
IBC negative for NE markers

NE differentiation confirmed by IHC expression of NE marker

Small cell carcinoma

Typical NE tumour morphology
- NE marker expression strong and diffuse

Diagnosed as
- Mucinous Carcinoma
- Solid Papillary Carcinoma
- IBC-NST

Diagnosed as
IBC-NST
(NE marker expression focal and weak**)**

Diagnosed as
IBC-NST with NE differentiation**
(NE marker expression moderate to strong or diffuse weak, but unequivocal**)**

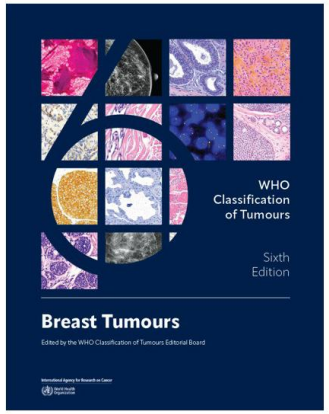
Diagnosed as
Breast Primary NET
(exceptionally rare) - diagnosis should only be made after metastatic NET, solid papillary carcinoma and IBC-NST with NE differentiation have been considered and excluded

Diagnosed as
Breast Small Cell Carcinoma
(exceptionally rare as a pure entity in which metastasis to the breast needs to be ruled out, but can co-exist with IBC)

IHC: immunohistochemistry
*IHC may be used for confirmation although not necessary
** Large cell neuroendocrine carcinoma is likely to belong to this group.

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5. Fibroepithelial tumours and hamartomas of the breast



Fibroepithelial tumours and hamartomas of the breast: Introduction

- Hamartoma
- Fibroadenoma
- Phyllodes tumour

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WHO 5th ed (2019)

Feature	Benign PT	Borderline PT	Malignant PT
Tumor border	Well-defined	Well-defined, may be focally permeative	Permeative
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	Usually few; <2.5 mitoses/ mm^2 (< 5 mitoses/10 HPFs)	Usually frequent; 2 to <5 mitoses/mm^2 (5-9 /10 HPFs)	Usually abundant; ≥5 mitoses/ mm^2 (≥10/ 10 HPFs)
Stromal overgrowth	Absent	Absent (or very focal)	Often present
Malignant heterologous elements	Absent	Absent	May be present

In the absence of malignant heterologous elements (except well diff liposarcoma), the diagnosis of Malignant PT required all 5 malignant criteria

World Health Organization Classification of Tumours of the Breast. 5th ed. Lyon: IARC Press, 2019.

WHO 5th ed. criteria for Dx of Malignant PT did not identify all PTs that caused patients death

TABLE 8. Morphologic Features of 7 Patients That Died of Disease

No	Age, y	Tumor size, cm	Tumor borders	Stromal cellularity	Stromal atypia	Mitoses per 10 HPF	Stromal overgrowth	Necrosis	Malignant heterologous elements	Adjuvant treatment at diagnosis	Distant metastases	Time to metastasis, mo	Metastasis site	Last follow-up, mo
1	43	17	Permeative	Marked	Marked	≥10	Yes	Yes	No	None	Yes	24	Lung	30
2	57	22	Permeative	Marked	Marked	≥10	Yes	Yes	No	None	Yes	25	Lung and abdomen	57
3	58	8	Permeative	Marked	Marked	≥10	Yes	No	No	None	Yes	47	Lung	54
4	56	25	Permeative	Moderate	Marked	≥10	Yes	Yes	No	None	Yes	2	Lung	11
5	63	8	Focally permeative	Marked	Marked	≥10	Yes	No	No	None	Yes	19	Pelvis/ abdomen	43
6	89	8	Focally permeative	Marked	Marked	<10	No	No	No	None	Yes	15	Bone	26
7	60	5	Focally permeative	Moderate	Moderate	≥10	Yes	No	No	None	Yes	61	Bone	82

HPF indicates high-power field.

Conclusion: WHO 5th ed. criteria for Dx of Malignant PT are too strict and need to be refined

Turashvili G, et al. Comprehensive Clinical-Pathologic Assessment of Malignant Phyllodes Tumors: Proposing Refined Diagnostic Criteria. Am J Surg Pathol. 2023;47(11):1195-1206.



Histopathology

Histopathology 2025, 87, 169–182. DOI: 10.1111/his.15455

REVIEW

Malignant phyllodes tumours of the breast: the case for revising WHO's 'full house' diagnostic criteria

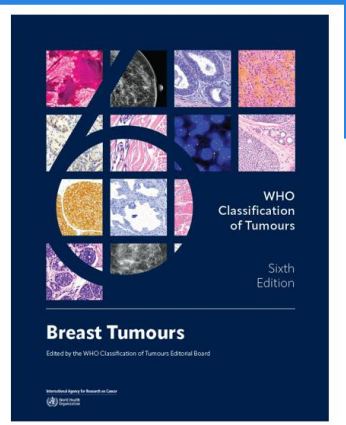
Puay Hoon Tan,[1] Ian O Ellis,[2] Kimberly H Allison,[3] Sunil S Badve,[4] Edi Brogi,[5] Grace Callagy,[6] Emmanuelle Charafe-Jauffret,[7] Chih-Jung Chen,[8] Yunn-Yi Chen,[9] Laura C Collins,[10] Gábor Cserni,[11] Lounes Djerroudi,[12] Maria Pia Foschini,[13] Stephen B Fox,[14] Helenice Gobbi,[15] Mihir Gudi,[16] Oi Harada,[17] Shabnam Jaffer,[18] Janina Kulka,[19] Hajime Kuroda,[20] Sunil R Lakhani,[21] Xiaoxian Li,[4] Takuya Moriya,[22] Sandra O'Toole,[23] Sarah E Pinder,[24] Elena Provenzano,[25] Cecily Quinn,[26] Wendy Raymond,[27] Aysegul A Sahin,[28] Fernando Schmitt,[29] Abeer M Shaaban,[30] Tanuja Shet,[31] Kalliopi P Siziopikou,[32] Ping Tang,[33] Gary M Tse,[34] Zsuzsanna Varga,[35] Anne Vincent-Salomon,[12] Hannah Wen,[5] Rin Yamaguchi,[36] Wentao Yang,[37] Stuart J Schnitt[38] & Emad A Rakha[39,40]

[1]Luma Medical Centre, Singapore, Singapore, [2]Department of Histopathology, City Hospital Campus, Nottingham University Hospitals, Nottingham, UK, [3]Department of Pathology, Stanford Medicine, Stanford, CA, [4]Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, [5]Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [6]Discipline of Pathology, School of Medicine, University of Galway, Galway, Ireland, [7]Centre de Recherche en Cancérologie de Marseille, ICEP Platform, CRCM Inserm UMR1068, Institut Paoli-Calmettes, Aix Marseille Université U105, Marseille, France, [8]Department of Pathology and Laboratory Medicine, Taichung Veterans General Hospital, and School of Medicine, Chung Shan Medical University, Taichung, Taiwan, [9]Department of Pathology, UCSF Medical Center, San Francisco, CA, [10]Department of Pathology, Beth Israel Deaconess Medical Center and, Harvard Medical School, Boston, MA, USA, [11]Department of Pathology, Bács-Kiskun County Teaching Hospital, Kecskemét, and Department of Pathology, University of Szeged, Albert Szent-Györgyi Medical Faculty, Szeged, Hungary, [12]Institut Curie, Institute of Women's Cancers, Department of Pathology, Paris, France, [13]Department of Biomedical and Neuromotor Sciences, University of Bologna, Anatomic Pathology at Bellaria Hospital, Bologna, Italy, [14]Department of Pathology, University of Melbourne, Melbourne, Victoria, Australia, [15]Discipline of Special Pathology, Institute of Health Sciences, Federal University of Triangulo Mineiro, Uberaba, MG, Brazil, [16]Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore, [17]Department of Clinical Pathology, Hokuto Hospital Obihiro, Hokkaido, Japan, [18]Northwell Health Lenox Hill Hospital, New York, NY, USA, [19]Department of Pathology, Forensic and Insurance Medicine, Semmelweis University Budapest and Eurofins Medserv Ltd, Budapest, Hungary, [20]Department of Diagnostic Pathology, Tokyo Women's Medical University Adachi Medical Center, Tokyo, Japan, [21]University of Queensland and Pathology Queensland, Brisbane, Australia, [22]Department of Pathology, Kawasaki Medical School, Kurashiki, Japan, [23]Royal Prince Alfred Hospital and NSW Health Pathology, School of Medical Sciences, University of Sydney, Sydney, NSW, Australia, [24]School of Cancer and Pharmaceutical Sciences, King's College London and Guy's and St Thomas's Hospitals, London, [25]Department of Histopathology, Addenbrookes Hospital and NIH Cambridge Biomedical Research Centre, Cambridge, UK, [26]Irish National Breast Screening Programme and Department of Histopathology, St Vincent's

- Emerging evidence suggests that strict criteria for malignant PTs may underdiagnose tumors with metastatic potential and histological features that would otherwise be considered malignant in soft tissue tumors.
- **We recommend redefining malignant PTs to include cases meeting at least four of the five WHO criteria, supplemented by comprehensive sampling and clinical context.**
- This cautious approach balances the risk of under- and over-diagnosis with the need for standardized, reproducible diagnostic practices.

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WHO 6th ed (2026)



Revised criteria for MALIGNANT PT Diagnosis

At least 4 of 5 malignant criteria

OR

Malignant heterologous elements

(except well differentiated liposarcoma)

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WHO 6th (2026)

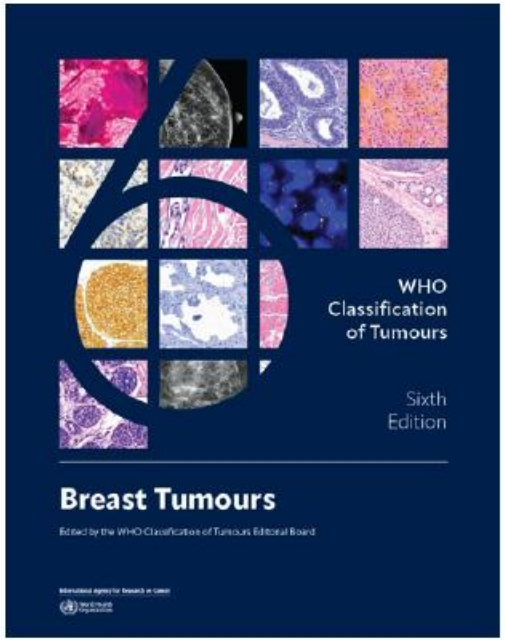
Feature	Fibroadenoma	Benign PT	Borderline PT	Malignant PT[a]
Tumor border	Well-defined [b]	Well-defined [c]	Well-defined, may be focally permeative	Permeative
Stromal cellularity	Variable, scant to uncommonly cellular[d], usually uniform	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal atypia	none	Mild or none	Mild or moderate	Marked
Mitotic activity	Usually none, rarely low[d]	Usually few; <2.5 mitoses/ mm^2 < 5 mitoses/10 HPF	Usually frequent; 2-5 mitoses/mm^2 5-9 /10 HPF	Usually abundant; >5 mitoses/ mm^2 $\geq$10 per 10 HPF
Stromal overgrowth	absent	Absent	Absent, or very focal	Often present
Malignant heterologous elements	absent	Absent	Absent	May be present[e]

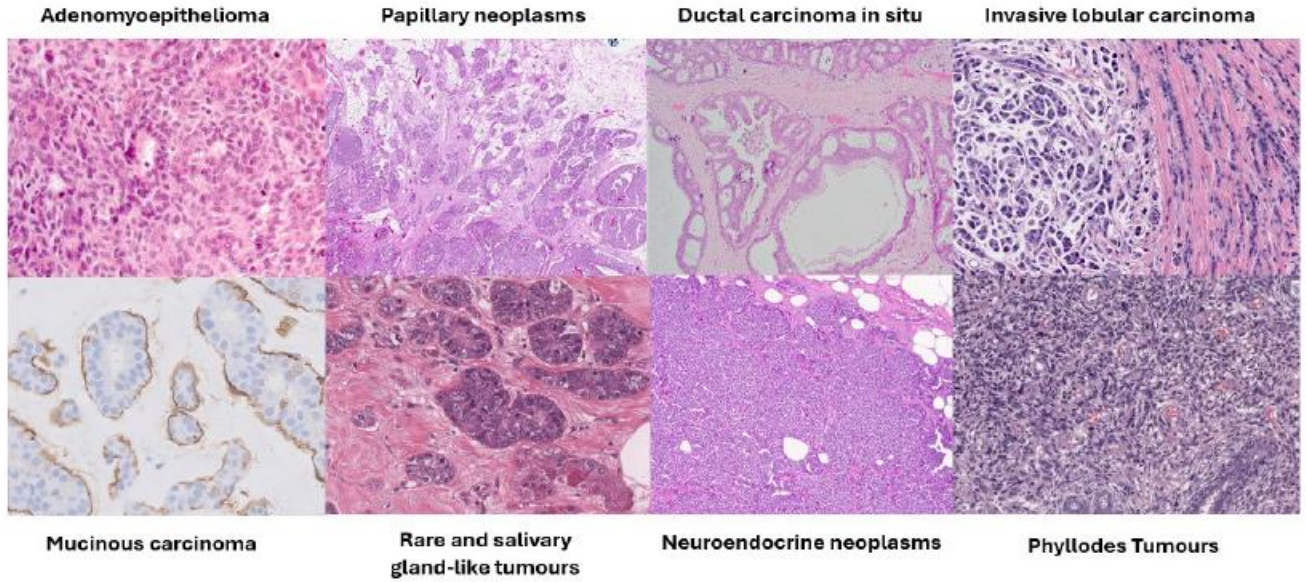
[a]Diagnosis of malignant PT requires at least four of the five malignant histological features. [b]Occasional FAs may have a slightly irregular interphase with adjacent stroma. [c]Occasional benign PTs may possess slightly irregular borders, other features are benign grade. [d]FAs in young people may have increased stromal cellularity and increased mitoses. [e]The presence of malignant heterologous elements (except well-diff liposarcoma) in a PT allows a malignant categorization.

WHO6th ed review article

World Health Organization Classification of Tumours of the Breast 6th edition 2026

This review summarises the main changes introduced in the 6th edition of the World Health Organization Classification of Breast Tumours, with emphasis on accurate diagnosis and clinical implications





Quinn C, Tan PH, et al. World Health Organization classification of tumours of the breast 6th edition 2026. Histopathology. 2026;89(2):199-218. PMID: 42011085

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Thank you for your attention



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