Memorial Sloan Kettering Cancer Center

Papillary Neoplasms of the Breast

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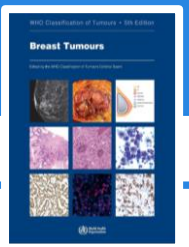
Pezcoller Seminar - Trento, September 15, 2022

Papillary Breast Lesions: Overview

- Morphology and diagnostic criteria
- Upgrades and management of papilloma at CNB
- What's NEW according to WHO 5th ed.

BR 5th Edition - Epithelial Tumours of the Breast



1. Benign epithelial proliferations and precursors
2. Adenosis and benign sclerosing lesion
3. Adenomas
4. Epithelial-myoepithelial tumors
5. **Papillary neoplasms**
6. Non-invasive lobular neoplasia
7. DCIS
8. Invasive Breast Carcinoma
9. Rare and salivary gland-type tumors
10. Neuroendocrine neoplasms

- **Intraductal papilloma (IDP)**
  - **Without atypia**
  - **With ADH**
  - **With DCIS**
- **Papillary DCIS**
- **Encapsulated Papillary Carcinoma (EPC)**
- **Solid Papillary Carcinoma (SPC)**
  - **In situ**
  - **Invasive**
- **Invasive Papillary Carcinoma (IPC)**

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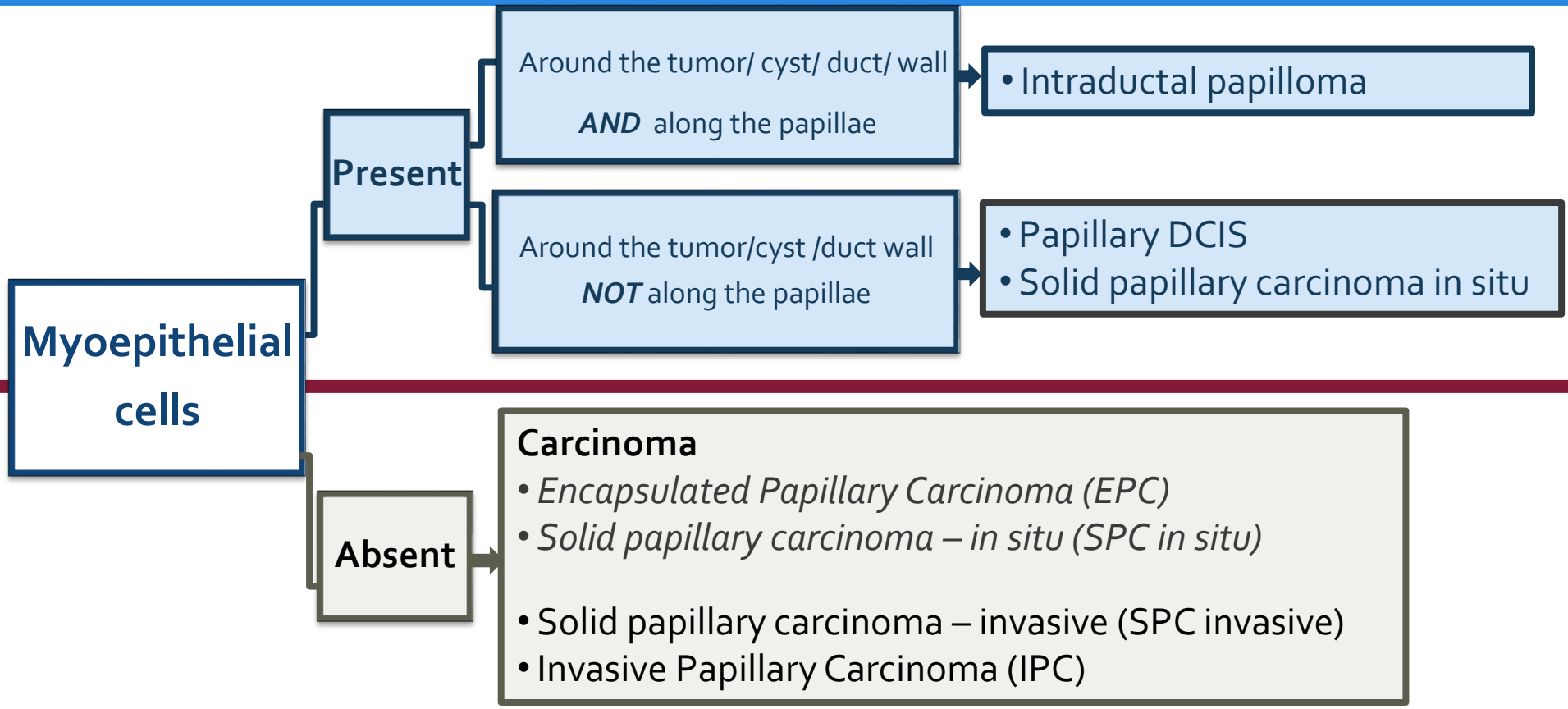
What's a papillary neoplasm? How is it diagnosed?

A papillary neoplasm is composed predominantly of papillae, each consisting of a fibrovascular core covered by epithelium with or without a myoepithelial layer, depending on the type of papillary neoplasm.

WHO Breast Tumours 5th ed. (2019)

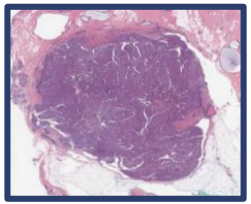
The diagnosis of a papillary neoplasm requires
evaluation of epithelium *and* myoepithelium

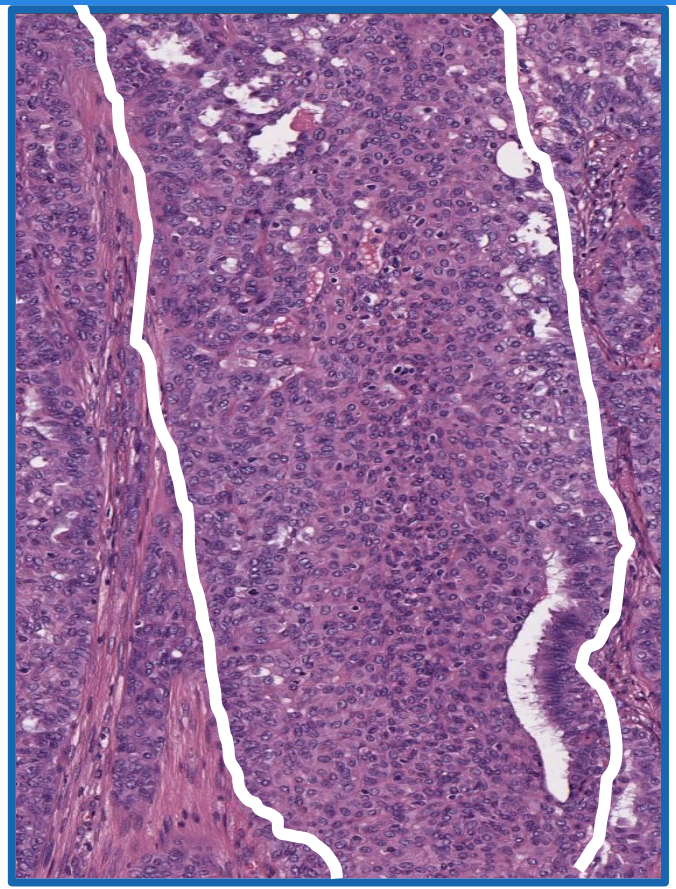
Myoepithelial cells and papillary neoplasms



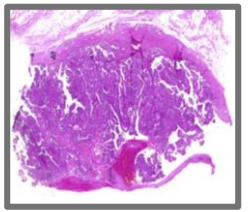
Evaluate the epithelial proliferation between adjacent fibrovascular cores as if it were in a duct

Papilloma with UDH

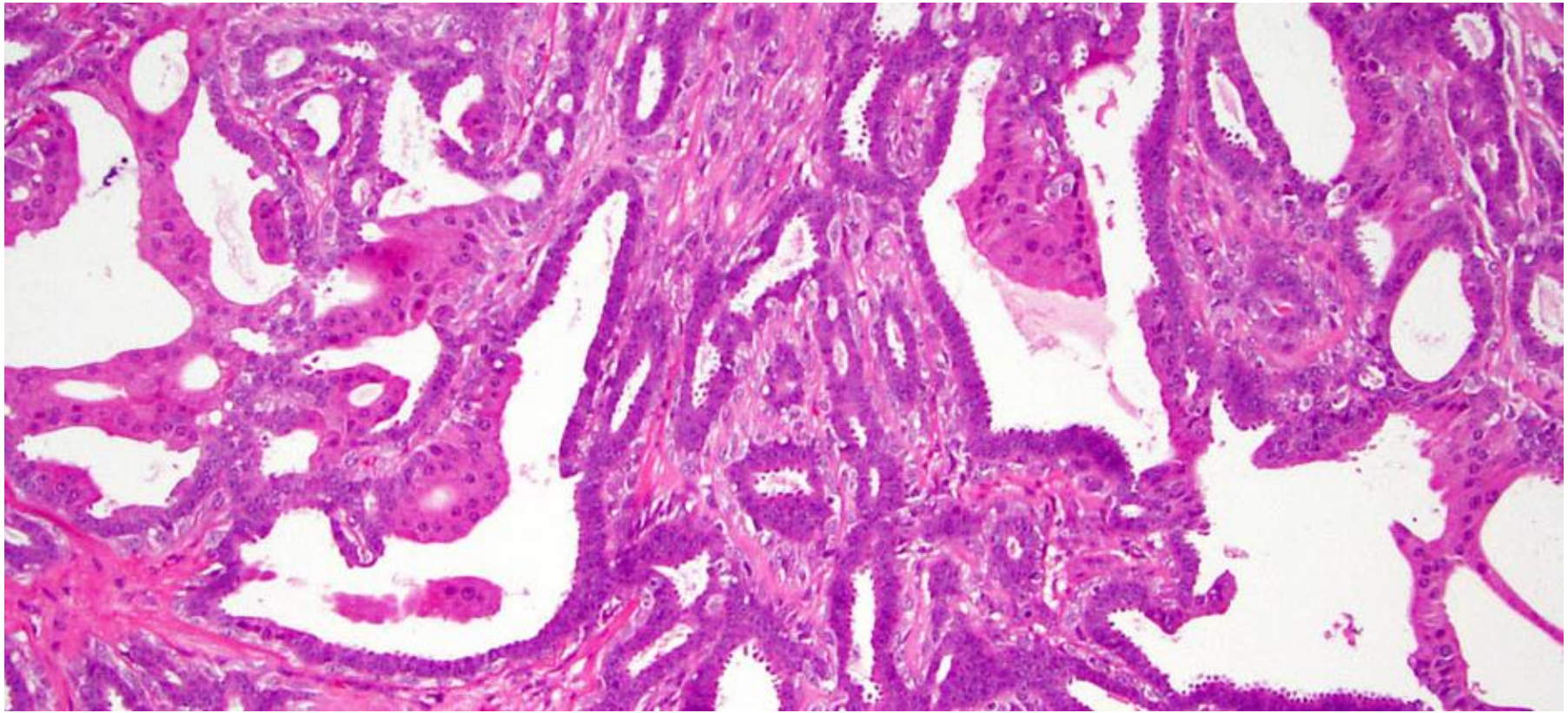




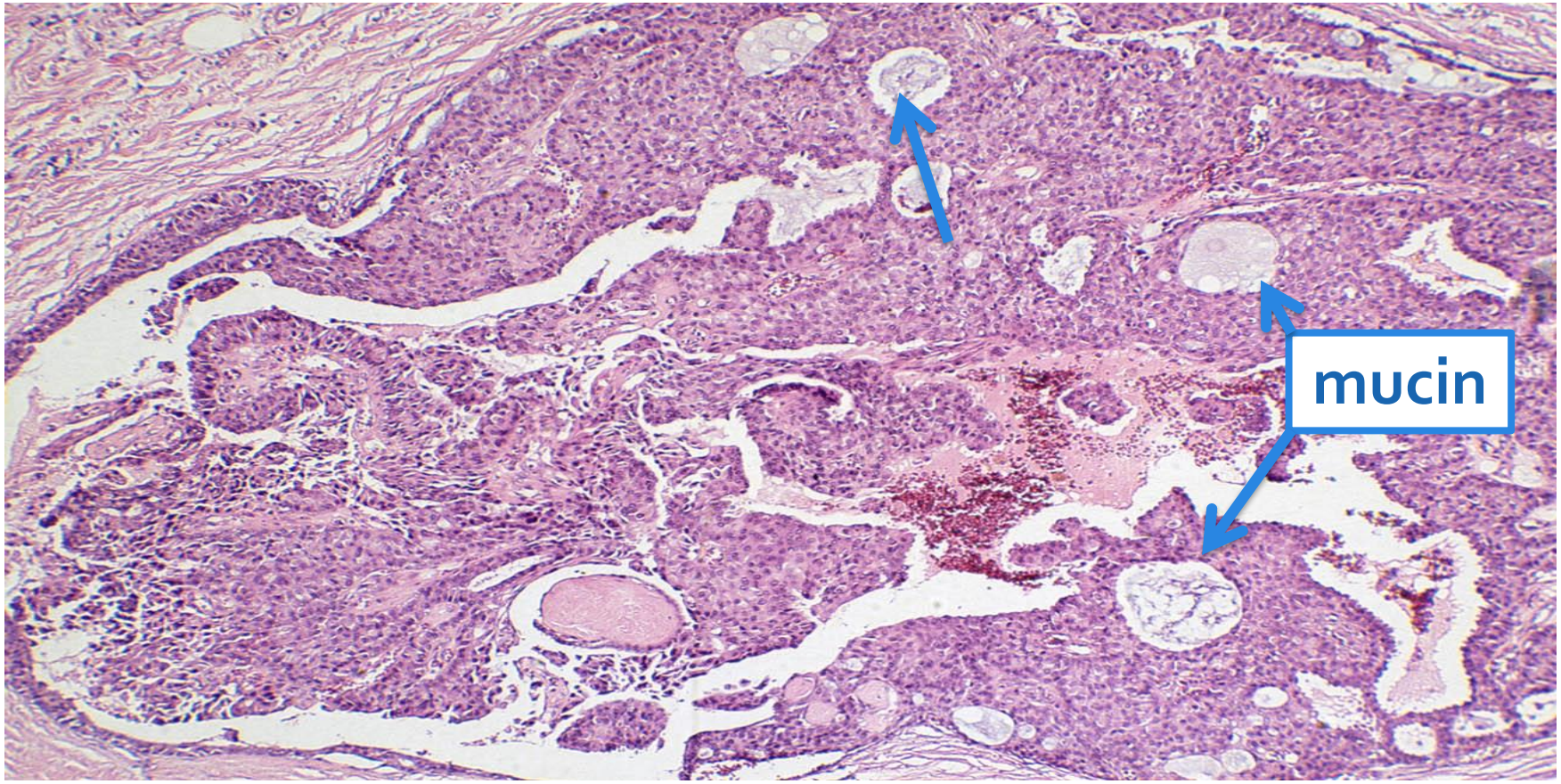
Papillary carcinoma



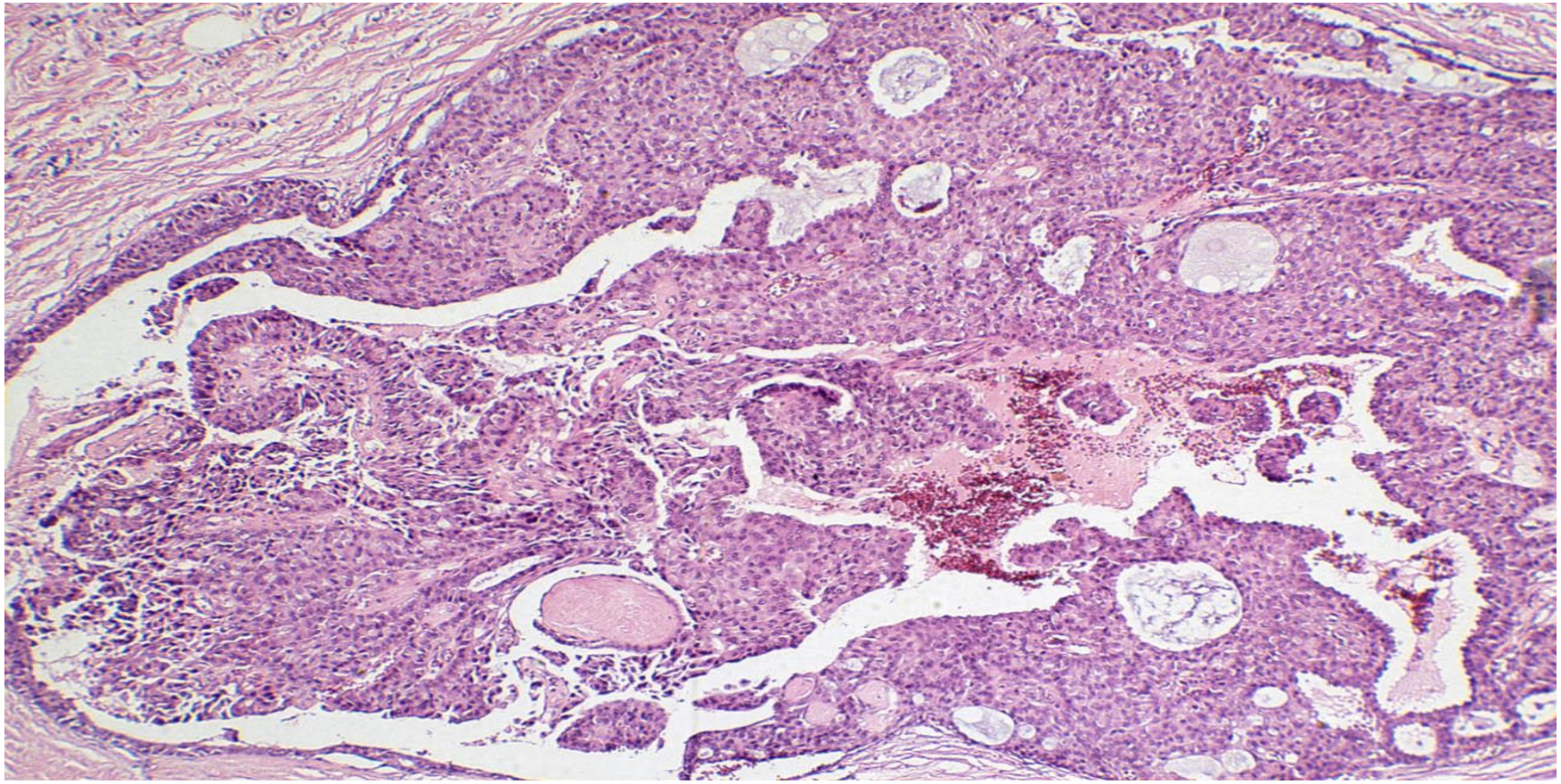
Apocrine metaplasia merging with duct epithelium→ favor benign epithelial proliferation



Extracellular mucin in a papillary neoplasm → rule/out solid and papillary carcinoma



Patient age: Papillary neoplasms in postmenopausal women frequently are malignant



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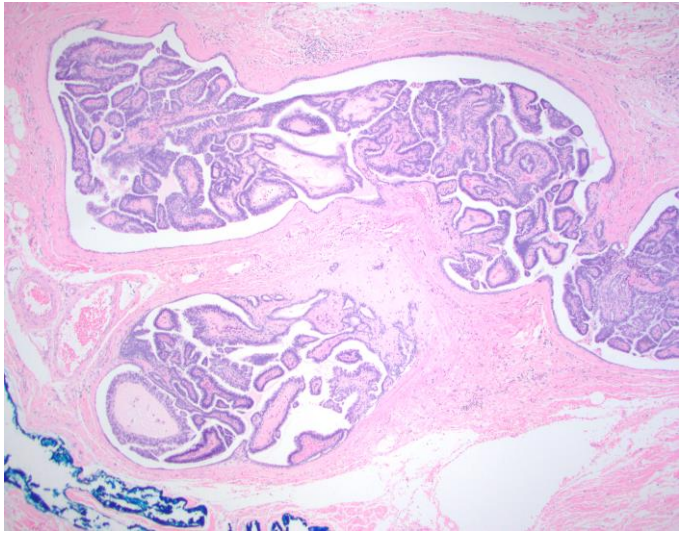
Intraductal Papilloma

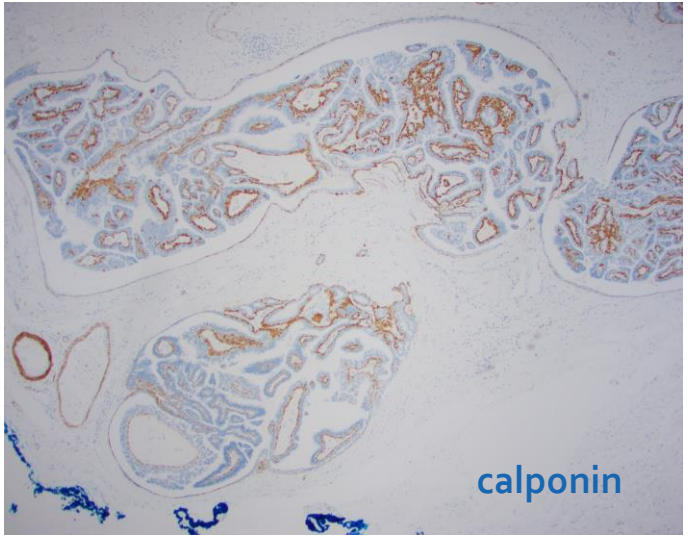
Intraductal Papilloma (IDP)

Benign lesion located within a duct in a central (solitary) or peripheral (multiple) location, composed of papillary projections with fibrovascular cores, covered by an epithelial and myoepithelial layer.

WHO Breast Tumours 5th ed. 2019

IDP is the only papillary neoplasm of the breast with a continuous layer of myoepithelial cells along the papillae and around the duct that contains it





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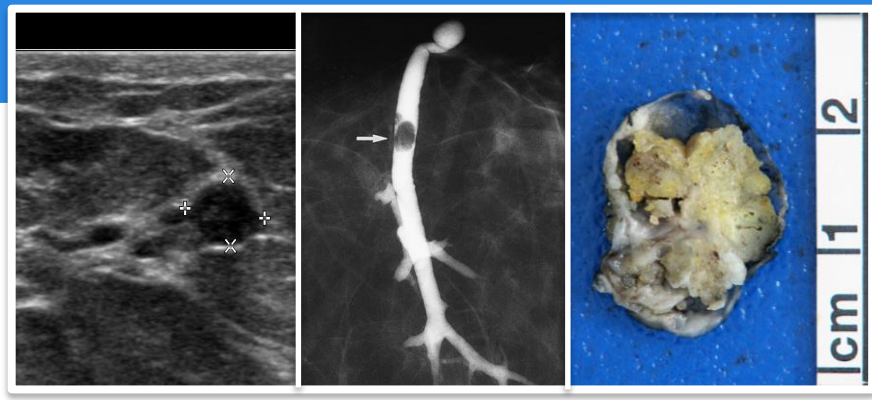
Intraductal Papilloma (IDP)



U/S galactogram gross exam*

IDP +/- atypia in 5.3% of >9000 benign breast excisions

Lewis JT et al.*Am J Surg Pathol* 2006;30:665-672

Central and solitary: most common

Clinical Presentation

- Unilateral clear (rarely bloody) nipple discharge
- Rarely detected as a palpable mass
- May occur at any age, more frequent in 30-50 y women

Imaging studies

- Mammography: benign-appearing, circumscribed retroareolar mass; +/- Ca^{2+}; may be occult
- Ultrasound (U/S): Well-defined, smooth–walled cystic lesion with solid component; +/- adjacent dilated ducts
- Galactography: Intraductal filling defect

Gross appearance

- Well-circumscribed mass composed of papillary fronds attached by one or more pedicles to the wall of the dilated duct
- Size: ranges from few mm to >5 cm

Peripheral papillomas: uncommon, usually incidental

*courtesy T. D'Alfonso MSKCC

Intraductal papilloma (IDP)

IDP without atypia

Atypical IDP
ADH in IDP
IDP with ADH

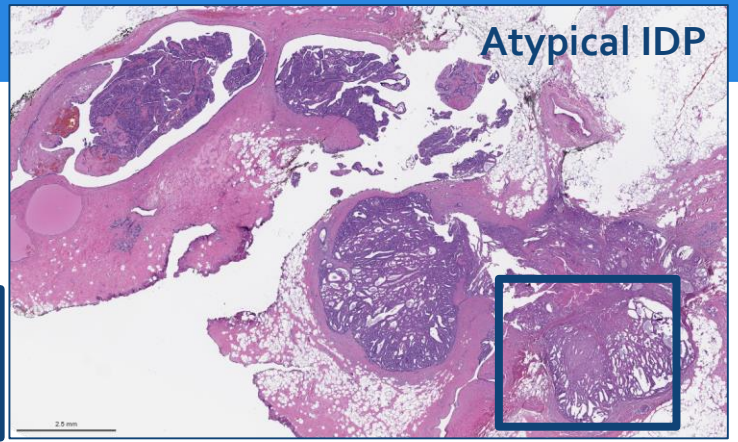
- **ADH <3mm**
- **ADH *in* the IDP (not *near* it)**

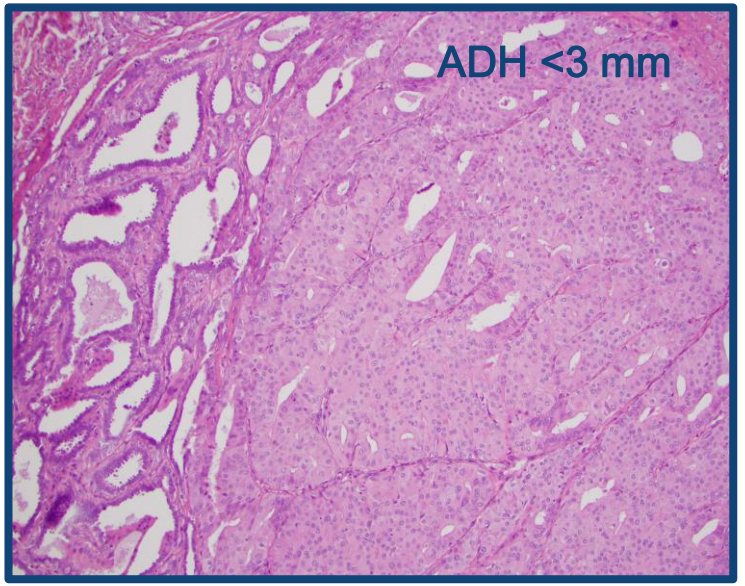
IDP with ALH not included

DCIS in IDP

low nuclear grade and size ≥3 mm

Intermediate or high nuclear grade, any size

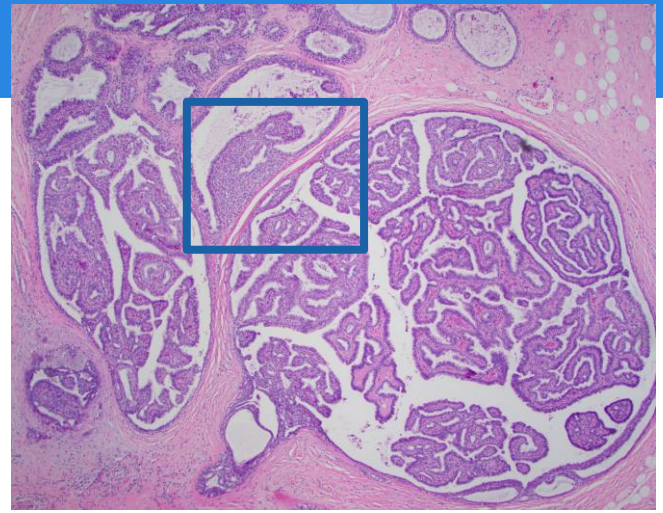


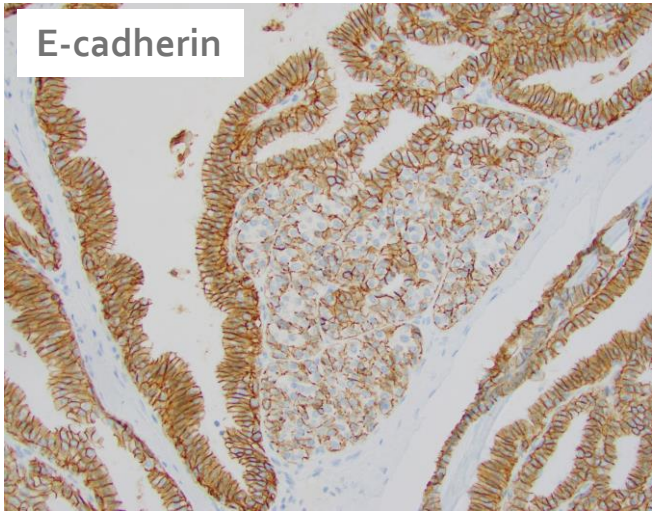


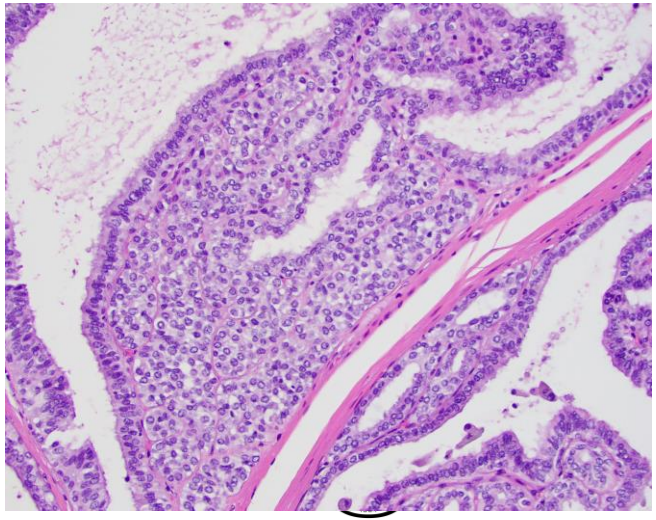
Page et al. *Cancer* 1996;78: 258-266
WHO 4th ed. (2012) and WHO 5th ed. (2019)

Lobular neoplasia in a papilloma

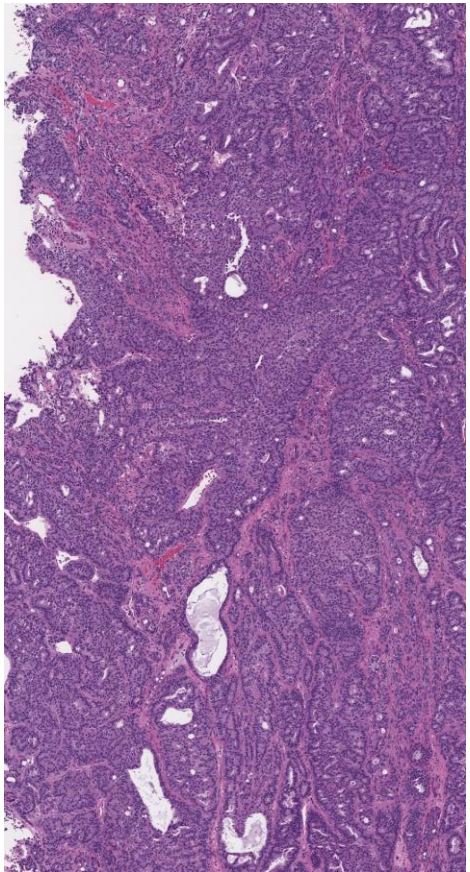
- ALH/ Classic LCIS
- Florid or Pleomorphic LCIS: very rare
- report and manage as per guildelines



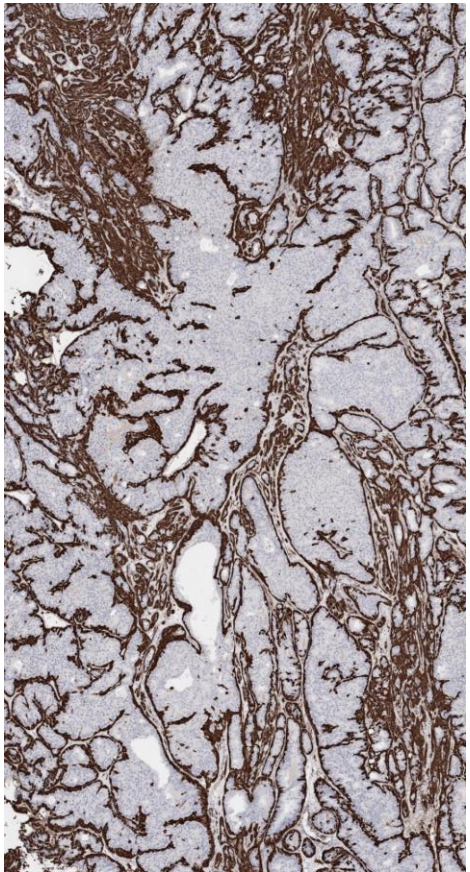




IDP with ADH



calponin



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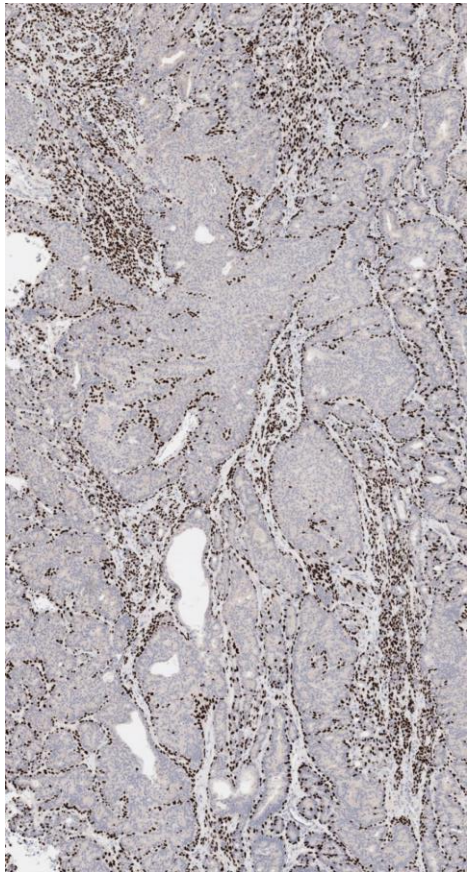

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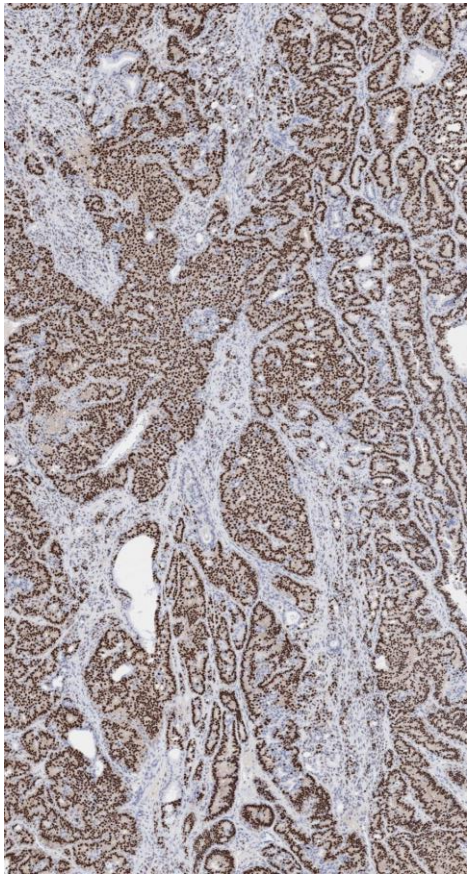

Nashville cohort - nested study
IDP +/- atypia
Study group: 31 pts with cancer @F/U
Control group: 91 pts w/o cancer (F/U 17y)

IDP with atypia: 5-7.5x Relative Risk (RR) of subsequent carcinoma

IDP w/o atypia: RR comparable to proliferative change w/o atypia

Mayo Benign Breast Disease Cohort
480 excisions with IDP
- 352 single IDP w/o atypia
- 54 single IDP + ADH or ALH
- 41 multiple (>5) IDPs w/o atypia
- 13 multiple (>5) IDPs with ADH or ALH

Age-Adjusted Relative Risk of IBC in Women with Intraductal Papillomas

Numerator of relative risk	No.[a]	Denominator of relative risk	No.[a]	Relative risk	95% Confidence interval	*P* value
AH-PAP	6/8	nonAH-PAP	25/114	9.6	1.62–56.91	0.013
AH-PAP no AH	2/3	nonAH-PAP no AH	22/105	7.5	1.14–48.71	0.036
AH-PAP + AH	4/5	nonAH-PAP no AH	22/105	15.8	0.44–57.13	0.131
EH-PAP no AH	7/35	nonEH-PAP no AH	17/73	0.78	0.32–1.90	0.576

IBC: invasive breast cancer; AH-PAP: papilloma with atypical hyperplasia within papilloma; nonAH-PAP: papilloma without atypical hyperplasia within papilloma; AH-PAP + AH: papilloma with atypia within and in breast parenchyma outside papilloma; no AH: no atypical hyperplasia in surrounding parenchyma; EH-PAP: papilloma with moderate or florid degrees of nonatypical hyperplasia (noAH-PAP); nonEH-PAP: no epithelial hyperplasia within the papilloma.

[a] These fractions indicate the number of women developing invasive carcinoma divided by the total number of women in the group: (women with later cancer/all women in group).

Page et al. *Cancer* 1996;78:258-266

	Relative Risk (95% CI) of subsequent carcinoma			
	No IDP		Single IDP	Multiple (>5) IDPs
w/o atypia	non-proliferative	1.28 (1.16-1.42)	NS	NS
w/o atypia	proliferative	1.90 (1.66-2.16)	2.04 (1.43-2.81)	3.01 (1.10-6.55)
with atypia (ADH/ALH)		4.17 (3.10-5.50)	5.11 (2.64-8.92)	7.01 (1.91-17.97)

Lewis J et al. *AJSP* 2006;78:258-266

Management of Papillary Neoplasms diagnosed at Radiology-Pathology Concordant Core Needle Biopsy

Papilloma without atypia	Does it require excision?
ADH in papilloma	Follow-up excision is warranted
DCIS in Papilloma	
Papillary DCIS	
Encapsulated Papillary Carcinoma (EPC)	
Solid Papillary Carcinoma (SPC) In situ an/or invasive	
Invasive Papillary carcinoma	

Management of Papillary Neoplasms diagnosed at Radiology-Pathology Concordant Core Needle Biopsy

Papilloma without atypia	Does it require excision?

Regional differences

Northern America, Australasia

European countries

USA perspective: Papilloma w/o atypia in radiology-pathology concordant CNBs
Upgrade rates @F/U Excision (EXC)

author year	#	# carcinoma at EXC			Predictors of upgrade	Routine EXC
		Total (%)	Invasive (%)	DCIS (%)		
Bennet 2010	45	0	0	0	not investigated	No
Chang 2010	100	4 (4%)	1 (1%)	3 (3%)	2 of 4 CNBs with upgrade deemed rad-path discordant on re-review	size>15 mm
Chang 2011	64	2 (3.1%)	0	2 (3.1%)	none	Yes
Swapp 2013	77	0	0	0	not investigated	No
Nakhlis 2015	45	3 (6.6%)	1 (2.2%)	2 (4.4%)	palpable mass	No
Pareja 2016	171	4 (2.3%)	2 (1.1%)	2 (1.1%)	synchronous carcinoma	No
Hong 2016	234	14 (6%)	5 (2%)	9 (4%)	age >54 y; size >10 mm	No
Kim 2016	141	6 (2.6%)	2 (0.8%)	4 (1.8%)	none	No
Han 2018	383	3 (0.8%)	0	3 (0.8%)	Significant in multivariate analysis: - clinical symptoms/ bloody discharge; - synchronous contralateral carcinoma; - multifocality - peripheral lesion - palpable mass or size>15 mm	No
Ahn 2018	250	17 (6.8%)	6 (2.4%)	15 (6%)		No
Grimm 2018	136	0	0	0	not investigated	No
Chen 2019	206	8 (3.9%)	0	8 (3.9%)	All 8 cases “concordant”	Yes
Genco 2020	126	2 (1.6%)	0	2 (1.6%)	Size >10 mm	No

USA perspective: Papilloma w/o atypia in radiology-pathology concordant CNBs
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Prospective Excision of IDP w/o atypia @CNB with Rad-Path Concordance
multi-institutional study (TBCRC 034)

Inclusion criteria

- Imaging–detected abnormality **BI-RADS score ≤4**
  No palpable mass and/or nipple discharge
- **CNB DX: IDP w/o atypia**
  No ADH and/ or **non-classic LCIS** in the same CNB
- **No personal Hx of breast carcinoma**

Study Cohort

116 patients (10 centers)

- median age 56 y (24-82)
- 59% postmenopausal

Imaging target

108 (93%) BI-RADS score 4

- **77 (66%) Mammographic mass/ distortion**
- 25 (22%) Mammographic Ca^{2+}
- 10 (9%) MRI-detected mass
- 4(3%) MRI non-mass enhancement

Nakhlis et al. *Ann Surg Oncol* 2021

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Prospective Excision of IDP w/o atypia @CNB with Rad-Path Concordance
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LOCAL pathology

- 116 IDPs w/o atypia

CNB

- **Carcinoma in 2/116 (1.7%) cases**
  - 3 mm low grade DCIS
  - ADH approaching low grade DCIS
- **Atypia in 4/116 (4%) cases**
  - 1 ADH
  - 3 ALH+ LCIS

EXC

Nakhlis et al. *Ann Surg Oncol* 2021

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Prospective Excision of IDP w/o atypia @CNB with Rad-Path Concordance
multi-institutional study (TBCRC 034)

	LOCAL pathology	CENTRAL pathology
CNB	• 116 IDPs w/o atypia	• **85/116 (73%) IDPs w/o atypia confirmed** including 2 cases with upgrade • *31/116 (27%) IDP w/o atypia NOT confirmed*
EXC	• **Carcinoma in 2/116 (1.7%) cases** - 3 mm low grade DCIS - ADH approaching low grade DCIS • **Atypia in 4/116 (4%) cases** - 1 ADH - 3 ALH+ LCIS	• **DCIS dx NOT confirmed → NO upgrades (0%)** • **Atypia in 11/85 (13%) cases** - 8 (9%) ADH - 3 (4%) ALH + LCIS

Nakhlis et al. *Ann Surg Oncol* 2021

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Radiology-Pathology concordant CNB Dx of IDP w/o atypia
American Society of Breast Surgeons Statement

"The decision to excise a papillary lesion without atypia needs to be individualized based on risk, including such criteria as size; symptomatology, including palpability and presence of nipple discharge; and breast cancer risk factors.

Those not excised should be followed closely with imaging."

https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/Concordance_and_High%20RiskLesions.pdf

CBX diagnosis of papilloma w/o atypia

- Diagnostic accuracy is critical
- Possible misdiagnosis
  - Underdiagnosis of atypia
  - Overdiagnosis of papilloma

Prospective Excision of IDP w/o atypia @CNB with Rad-Path Concordance
multi-institutional study (TBCRC 034)

LOCAL pathology

- 116 IDPs w/o atypia

CNB

CENTRAL pathology

- **85/116 (73%) IDPs w/o atypia confirmed**
  including 2 cases with upgrade

- ***31 (27%) IDP w/o atypia reclassified***
  - ***8/31 (26%) ADH near IDP***
  - ***2/31 (6%) atypical IDPs***
  - 21/31 (68%) benign mimics of IDP
    - papillary apocrine metaplasia
    - plicated subareolar ducts
    - usual ductal hyperplasia (UDH)
    - fibroadenomatous change

Nakhlis et al. *Ann Surg Oncol* 2021

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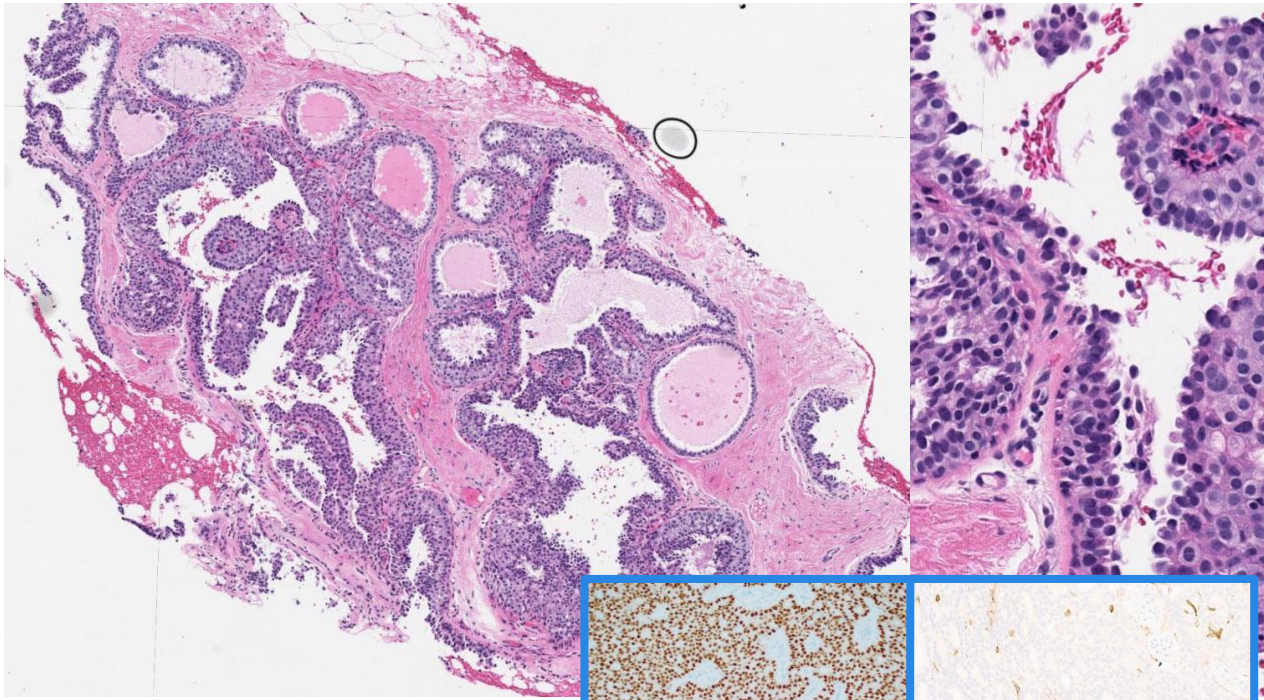
ADH may mimic papilloma w/o atypia

Original DX: IDP w/o atypia

Revised DX: ADH (papillary)



ER-high and CK5/6-low = atypia

Case NOT part of the TBCRC study

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multi-institutional study (TBCRC 034)

LOCAL pathology

- 116 IDPs w/o atypia

CNB

CENTRAL pathology

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Nakhlis et al. *Ann Surg Oncol* 2021

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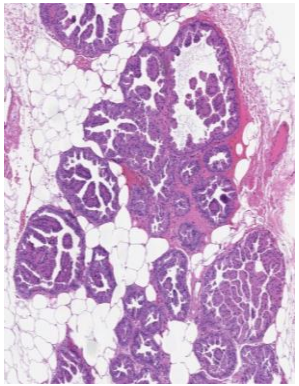
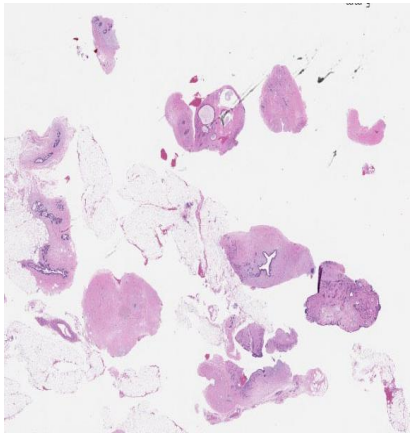
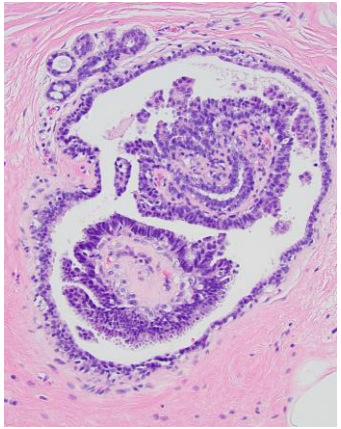
Benign mimics of IDP without atypia

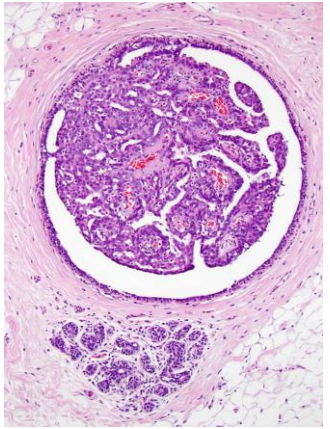


papillary apocrine metaplasia

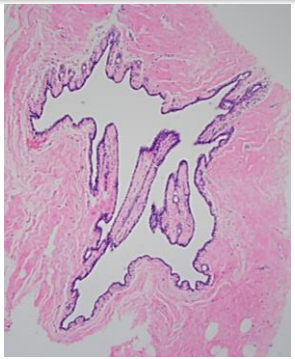


fibroadenomatous change

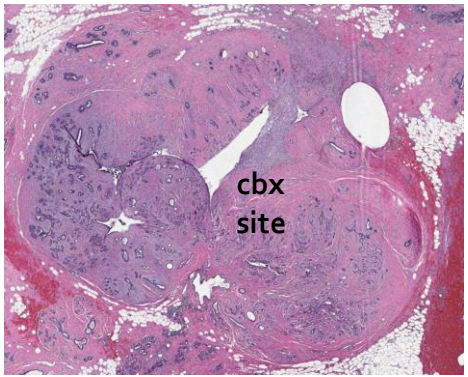




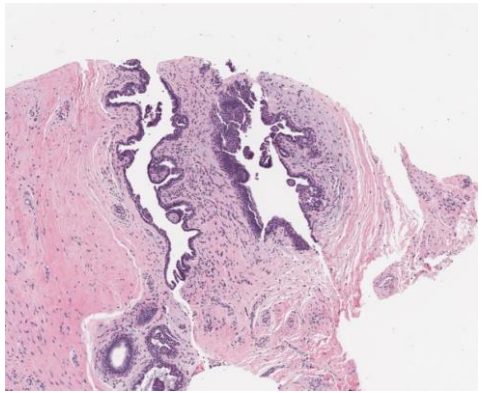
papillary usual ductal hyperplasia (small papillomas?)



plicated subareolar ducts



excision: fibroadenoma



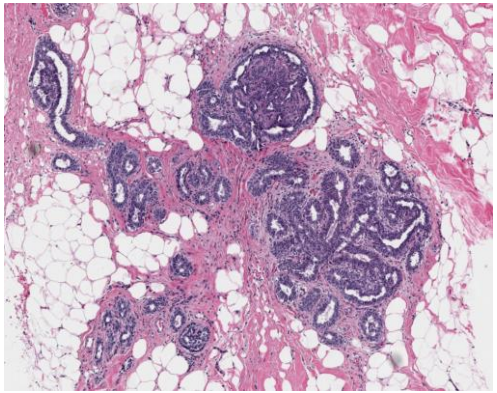


Table 6 Summary of the recent literature on PL since 2015

Author and year	Number of patients analyzed or type of publication if no patients have been analyzed (e.g., review or comment)	Findings	Conclusions
Ahn et al. 2018 [58]	$n=520$ PL in CNB 250 with OE Upgrade	Upgrade in 17 of 250 cases (6.8%)	Factors in upgrade -Bloody nipple charge -Size on imaging ≥ 15 mm -BI-RADS≥ 4b -Peripheral location -Palpability
Armes et al. 2017 [59]	$n=103$ PL on CNB Upgrade	Upgrade Overall in 30% With atypia in 72% Without atypia in 7%	Conservative management for those without atypia, including those without atypia in which the papillary lesion was found incidental to microcalcification in an adjacent benign lesion
Bianchi et al. 2015 [60]	Upgrade in PL lesions 46 Cases with atypia 68 Cases without atypia	Upgrade in 47.8% (22/46) cases with atypia 13.2% (9/68) without atypia	Underestimation rate in PL without atypia is lower
Khan et al. 2017 [61]	$n=259$ PL on CNB Upgrade in OE ($n=147$)	Upgrade 7% without atypia (8/107) 33% with atypia (13/40)	Higher upgrade in PL with atypia
Kim et al. 2016 [62]	$n=230$ PL in CNB Upgrade In VAB ($n=86$) In OE ($n=144$)	Upgrade in 2.6% (6/230)	Upgrade in BI-RADS 3-4a :1.4% resp. 1.8% BI-RADS 4b-5: 13% resp. 50% No association with age and size lesion
Ko et al. 2017 [63]	$n=346$ PL in CNB Upgrade In VAB ($n=211$) In OE ($n=135$)	Upgrade Overall in 2.3% If size < 1cm: 0.9%	Size of PL correlates with upgrade Close follow-up with ultrasound instead of excision
Moon et al. 2016 [64]	$n=65$ PL in CNB Upgrade In VAB ($n=12$) In OE ($n=53$)	Upgrade In OE in 9% (5/53) In VAB 8% (1/12)	No recommendation
Niinikoski et al. 2018 [65]	$n=80$ PL in CNB		Small PL in selected patients-OE can be avoided
Pareja et al.. 2016 [66]	Upgrade in OE ($n=171$) after PL Without atypia In CNB	Upgrade In OE 2.3% (4/171)	Regardless of size, observation is appropriate at radiologic–pathologic concordant CNB
Seely et al. 2017 [67]	$n=107$ PL in OE Upgrade after VAB ($n=60$) CNB ($n=47$)	Upgrade in OE After VAB in 1.6% (1/60) After CNB in 8.5% (4/47)	Higher upgrade in OE if PL is diagnosed on CNB
Tatarian et al. 2016 [68]	$n=16$ PL in CNB Upgrade in OE	Upgrade in OE In 2/16 cases (12.5%)	Surgical excision should be considered in patients with benign papillomas
Tran et al. 2017 [69]	$n=43$ PL in CNB Upgrade in OE	Upgrade in OE In 1/43 cases (2%)	Low-upgrade rate in OE
Wyss et al. 2014 [70]	$n=156$ PL in CNB Upgrade In VAB ($n=135$) and Follow-up ($n=21$) (Median 3.5 years)	Upgrade after follow-up 1.2% (2/156)	VAB is recommended as the method of choice for removal of PL
Yamaguchi et al. 2015 [71]	$n=142$ PL Follow-up imaging After VAB ($n=125$) After CNB ($n=17$)	Upgrade in OE ($n=17$) 4/17	Discordant lesions should undergo OE
Yang et al. 2018 [72]	$n=116$ PL (On CNB or VAB) 10 mm or smaller OE $n=74$ Surveillance $n=42$	Overall upgrade 11% (13/116) Upgrade after VAB (0%) Upgrade after CNB (16.5%)	Higher upgrade in OE -After CNB -Older age -PI with atypia

European perspective on the management of papillary lesions favors VAB

Papilloma without atypia

Broad range of upgrade rates at EXC:
2.3% - 7% - 13.2%
(radiology-pathology concordance?)

EXC after VAB has significantly lower upgrade rate (1.6%) than EXC after CNB (8.5%)

Rageth C et al *Breast Cancer Research and Treatment* (2019) 174:279–296

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Papillary lesion without atypia - classified as B3 lesion

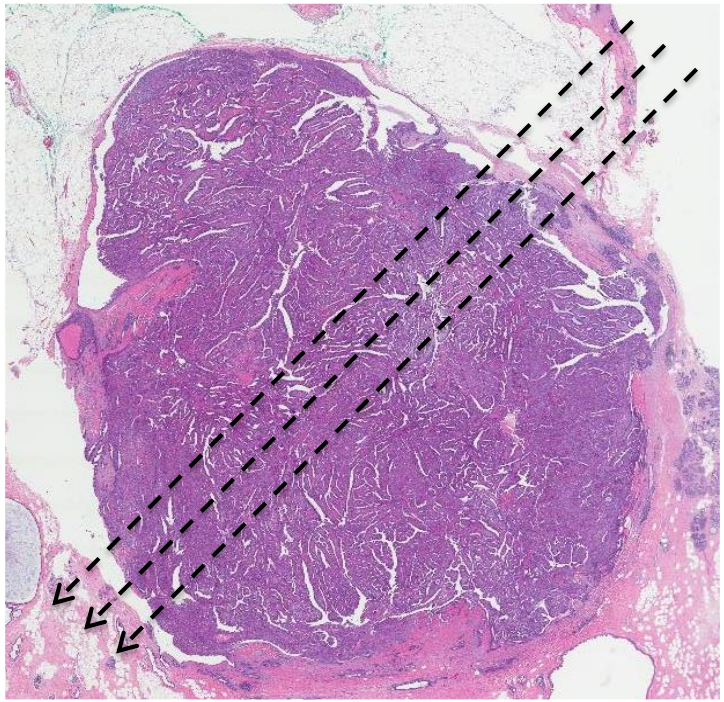
Consensus recommendation for management of papillary lesion (w/o atypia) by a European multidisciplinary expert panel

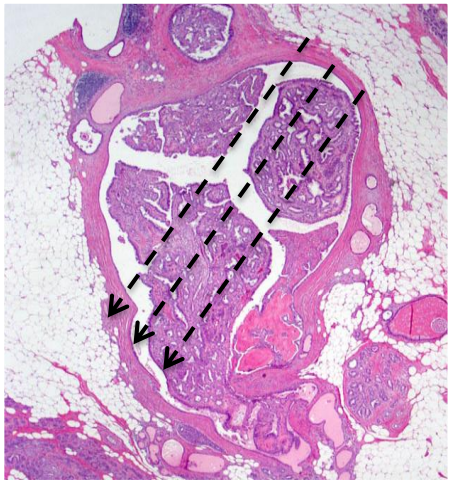
A papillary lesion which is visible on imaging should undergo excision with Vacuum Assisted Biopsy (VAB).
Larger lesions which cannot be completely removed by VAB need open excision.
Thereafter surveillance is justified.

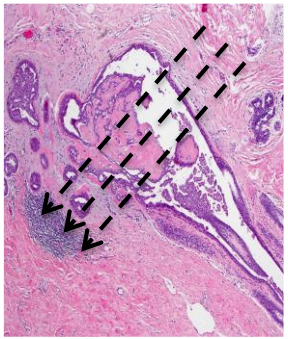
Rageth C et al *Breast Cancer Research and Treatment* (2019) 174:279–296

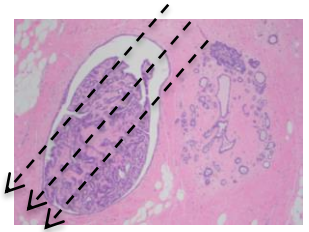
VAB: usually the lesion should not exceed 2.5 cm in diameter.

Intraductal papillomas: wide range in size









"micropapilloma"
size <2 mm
CNB may remove it entirely
No upgrades at excision
No excision required

"B2 lesion if completely surrounded by a duct structure"
Rageth et al 2019

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Intraductal Papilloma +/- Atypia – Differential Dx

Benign mimics of IDP

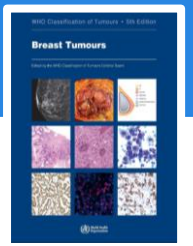
Papillary neoplasms

- Papillary DCIS
- Encapsulated papillary carcinoma (EPC)
- Solid papillary carcinoma (SPC) in situ

Tumors that may look papillary

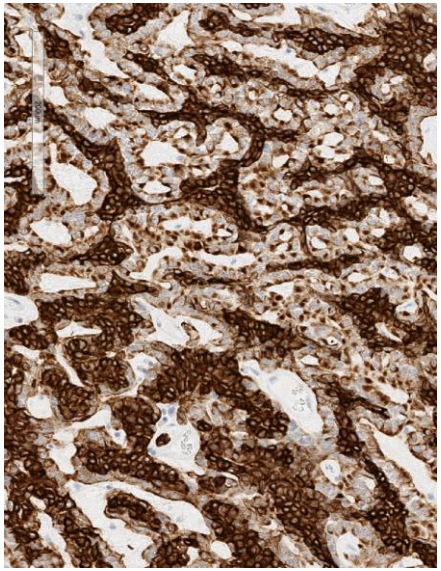
- **Adenomyoepithelioma (AME)**
- **Tall cell carcinoma with reversed polarity (TCCRP)**
- Fibroepithelial tumors with polypoid stromal architecture
- Nipple duct adenoma
- Hidradenoma (skin)/ mucoepidermoid carcinoma (breast)
- Etc…

Adenomyoepithelioma (AME)

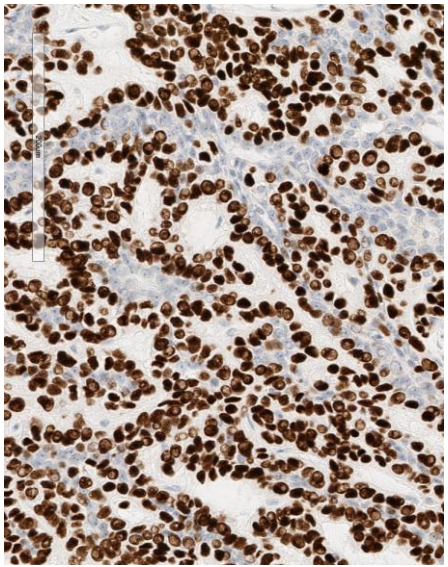


- Rare tumor, incidence unknown
- Can occur at any age, but predominantly affects elderly women
- Biphasic neoplasm composed of
  - small epithelium-lined spaces with inner luminal ductal cells
  - variably enlarged and clearly noticeable abluminal myoepithelial cells

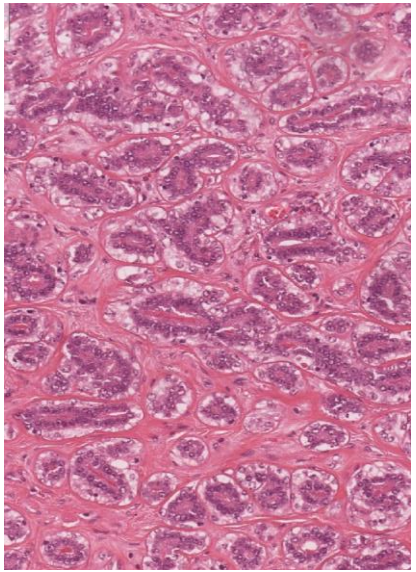
WHO classification
Breast Tumours 5th (2019)

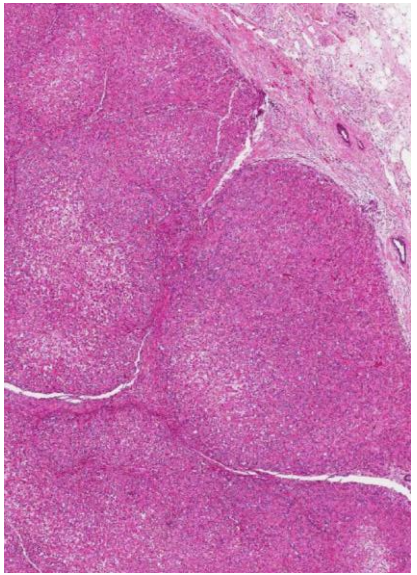


CK7



p63





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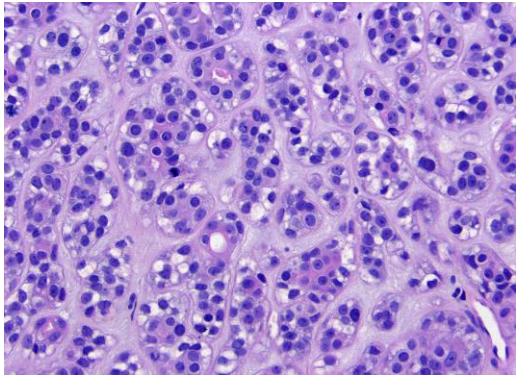
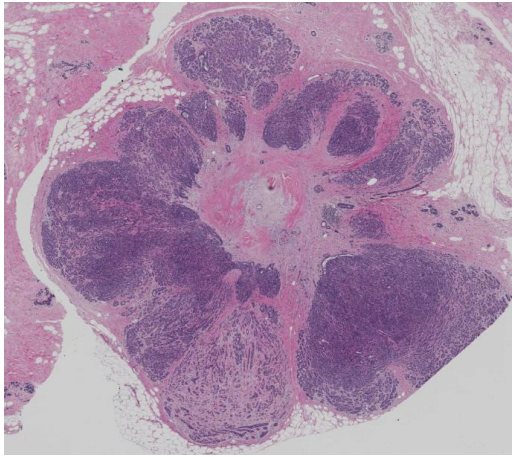
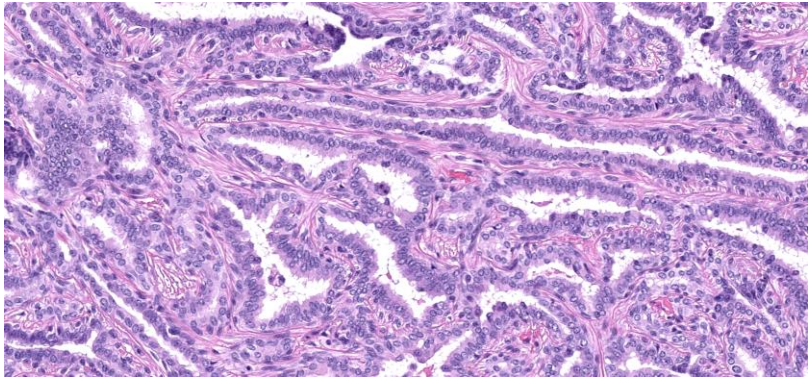
AME - Differential diagnosis

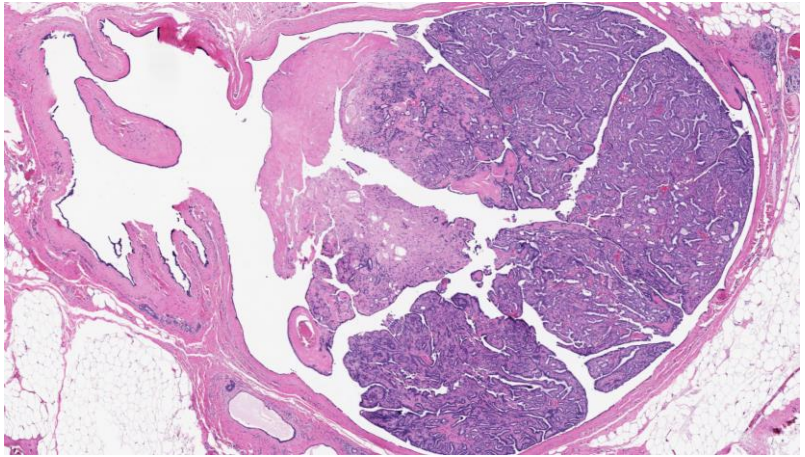
AME





Intraductal Papilloma (IDP)





IDP is contained within a duct/ cystic space

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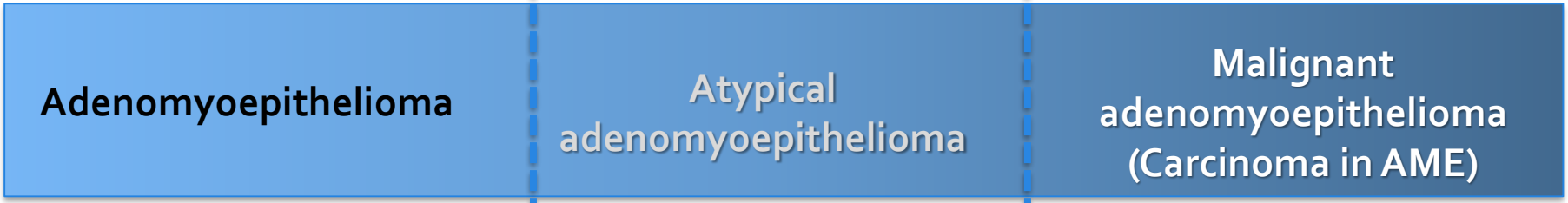
Diagnostic criteria not well defined



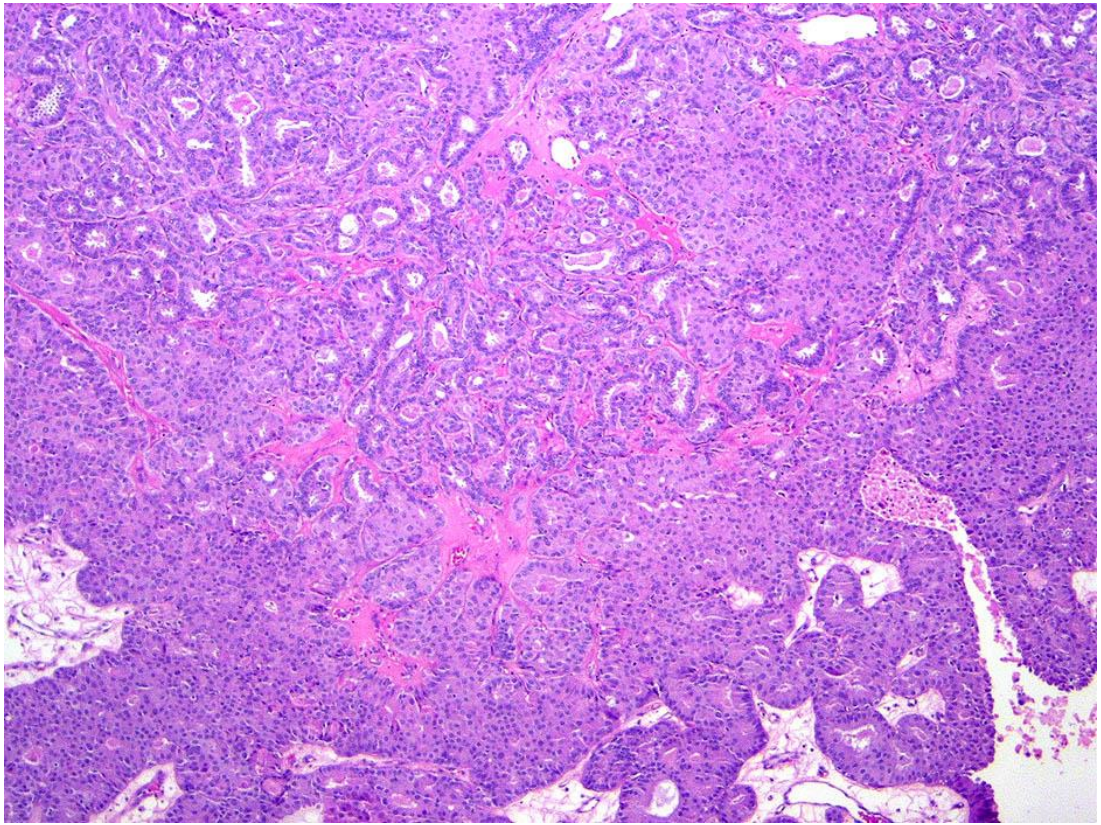
Carcinoma may develop from the epithelial or myoepithelial component, or from both (epithelial-myoepithelial carcinoma)

Malignant AME - carcinoma arising in AME

<u>Carcinoma can arise from the epithelium</u>

(usually AME with ADH/ DCIS/ LCIS)

- **Invasive no special type**
- Invasive lobular carcinoma



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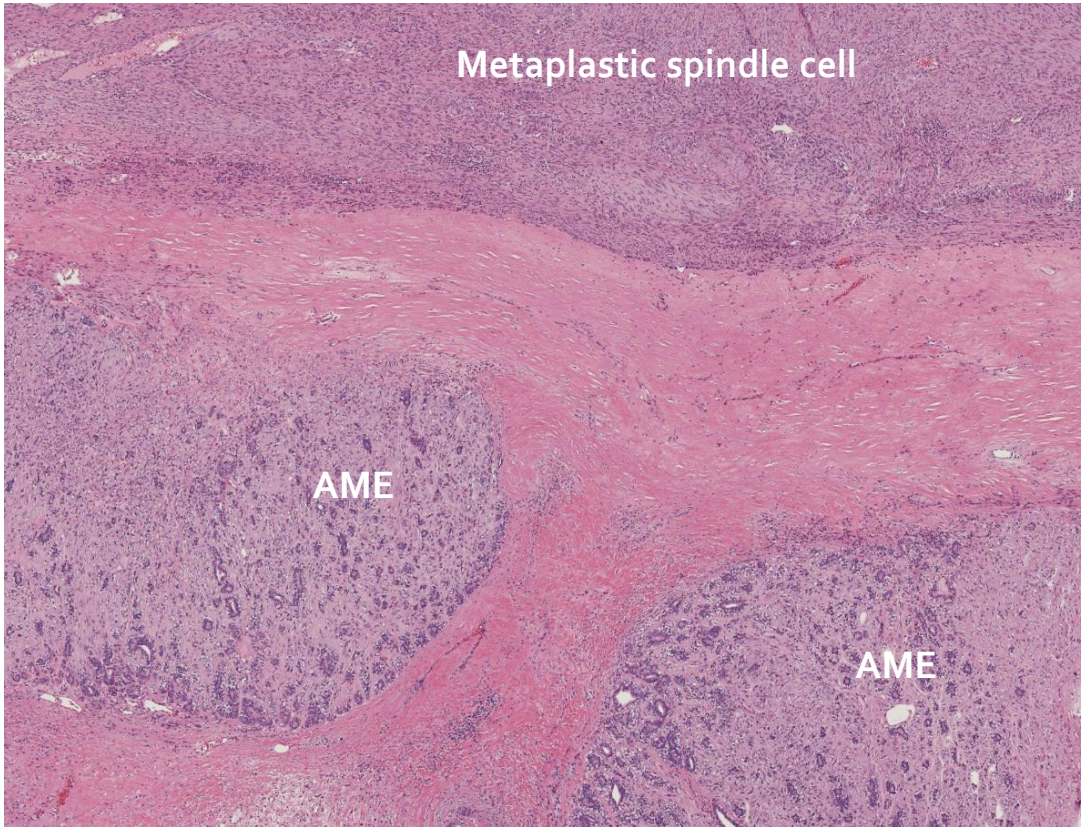
Malignant AME - carcinoma arising in AME

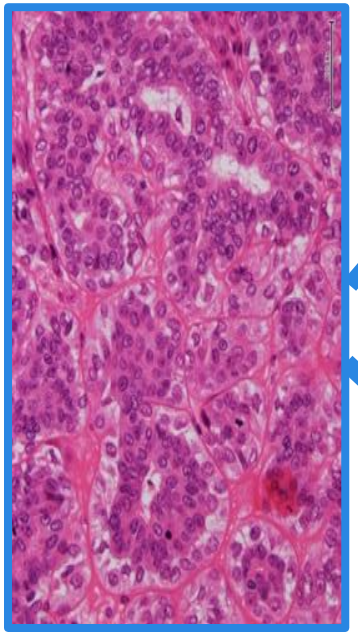
<u>Carcinoma can arise from the myoepithelium</u>

Metaplastic carcinoma

- Squamous cell
- Low grade adenosquamous
- **Spindle cell**
- Matrix-producing



Genetic subtypes of AMEs vary by ER status
Most malignant AMEs develop from ER(-) AMEs



AME

ER(+)

PIK3CA* +/- *AKT1

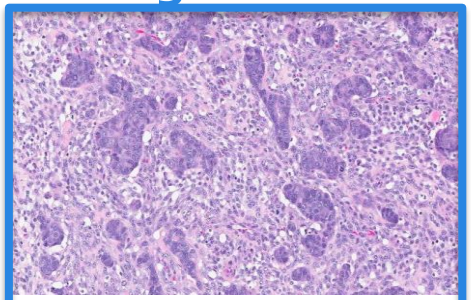
Same hotspot mutations found in IDPs
Troxell M. *Mod Pathol.* 2010

ER(-)

HRAS* Q61^{R} and *PIK3CA

***+/-CDKN2A* homozygous deletions**

Malignant AME



Usually triple neg

HRAS* Q61^{R} and *PIK3CA

***+/-CDKN2A* homozygous deletions**

No *AKT1* mutations
No *TP53* mutations
HER2 not amplified

Geyer F. et al
Na*ture Comm* 2018

HRAS Q61K, G13R, G12S and *G12D* found in atypical and malignant AMEs

Bièche I. *J Hematol Oncol* 2021
Lubin D et al. Am J Surg Pathol 2019
Ginter P. *Mod Pathol* 2020

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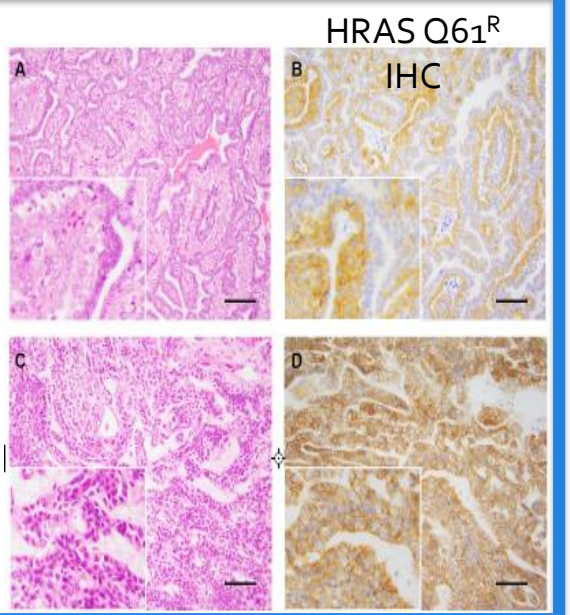
HRAS Q61^{R} IHC(+) (SP174 atb) in ER(-) AME and AME-M with *HRAS* Q61R mutation; 100% specificity, 70% sensitivity; potential diagnostic utility

5/7 *HRAS Q61^{R}* AMEs were IHC(+) *(mostly in the MECs)*

17/17 AMEs with no *HRAS Q61^{R} were IHC(-)*



Pareja F. *et al. Histopathology* 2020

HRAS Q61^{R} IHC
possible diagnostic application

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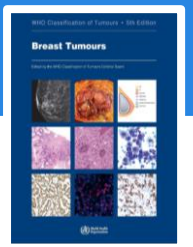
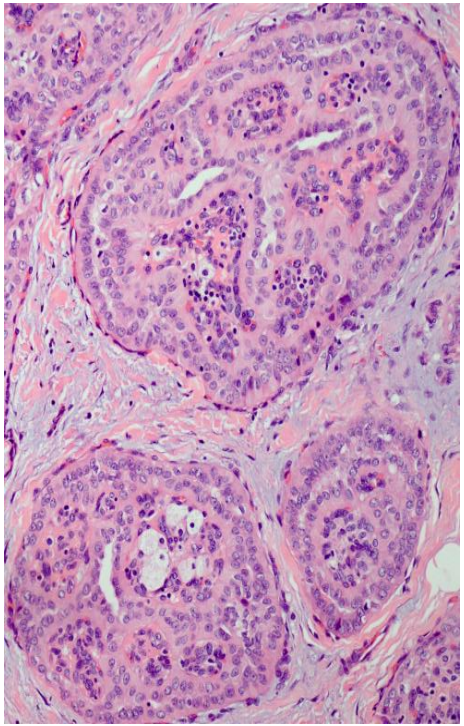
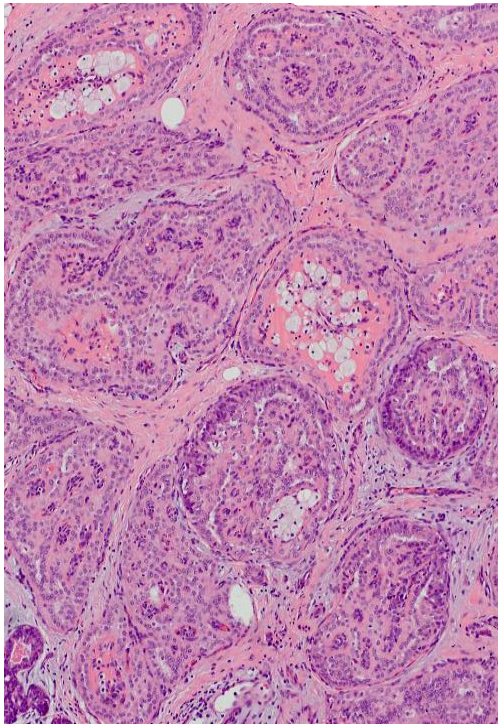
Tall Cell Carcinoma with Reversed Polarity (TCCRP)



- Rare subtype of invasive carcinoma
- Median age 64 years (45-80)
- Triple negative or ER/PR/AR low
- CK5/6(+), CK7(+), calretinin(+)
- *IDH2* p.Arg172 *and* PIK3CA mutations
- Indolent behavior





Eusebi V et al *Am J Surg Pathol*. 2003
Chiang S et al. *Cancer Res*. 2016
Foschini MP et al. *Am J Surg Pathol* 2017
Lozada JR et al. *Histopathology*. 2018
Alsadoun N et al. *Mod Pathol* 2018

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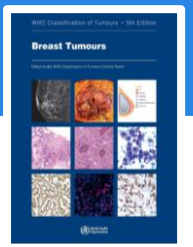
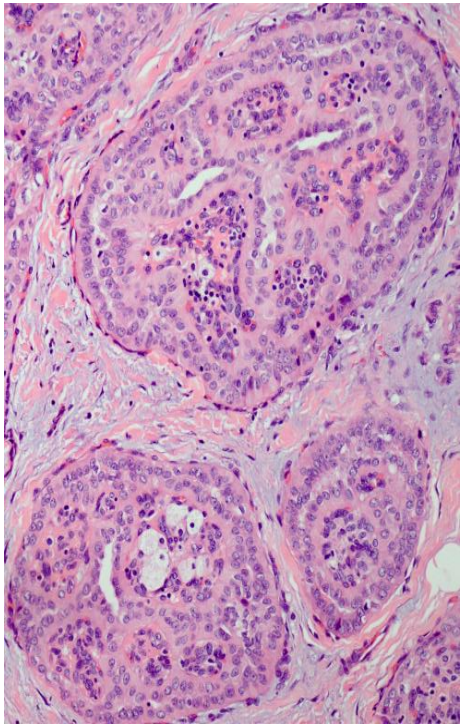
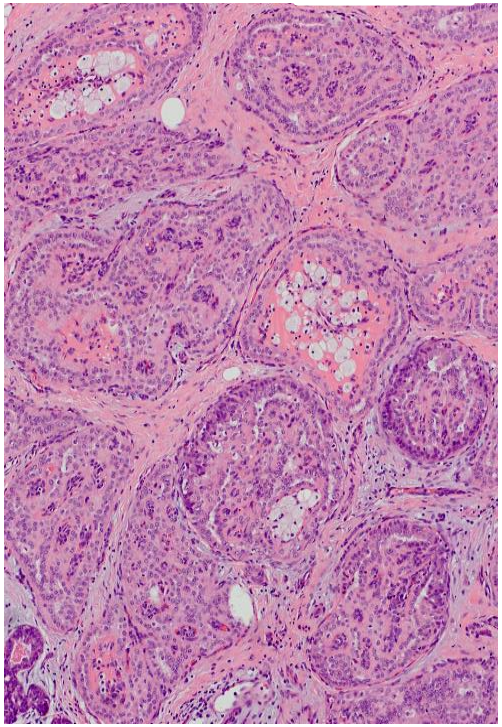
Tall Cell Carcinoma with Reversed Polarity (TCCRP)



- Solid and papillary patterns
- Solid nests with central fibrovascular cores and foamy histiocytes
- Composed of tall columnar cells with abundant eosinophilic cytoplasm
- Reversed nuclear polarity





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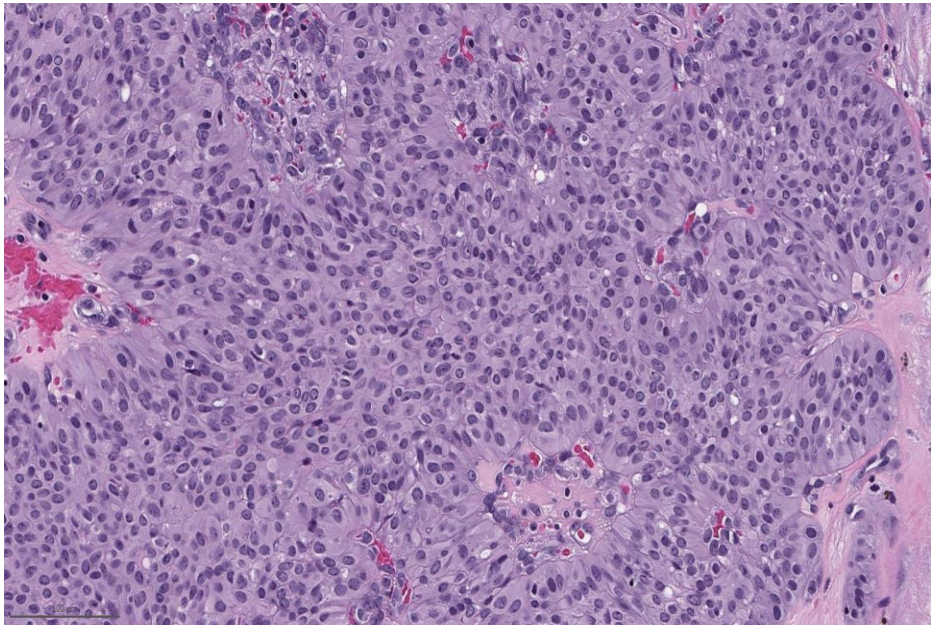
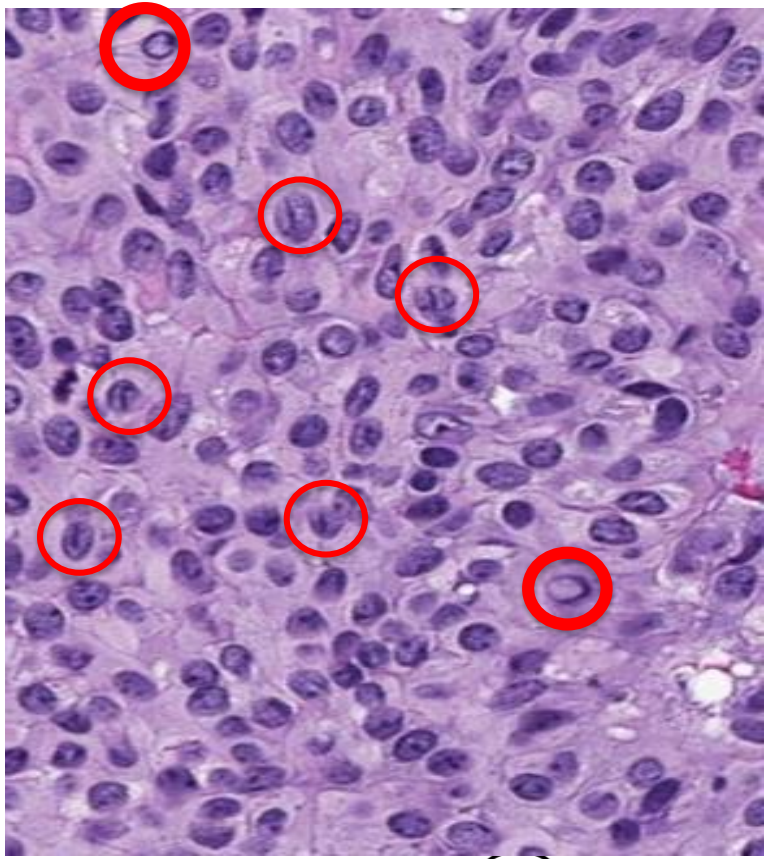
Tall Cell Carcinoma with Reversed Polarity (TCCRP)

- Columnar cells with nuclei at the apical poles
- Bland, round to ovoid nuclei, with grooves and intranuclear cytoplasmic inclusions

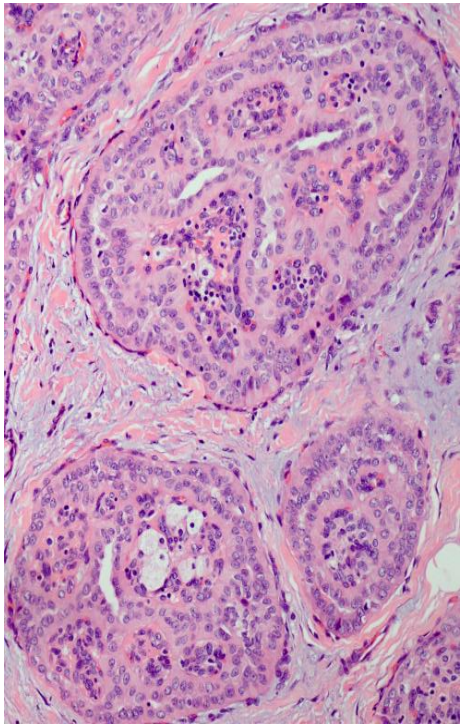


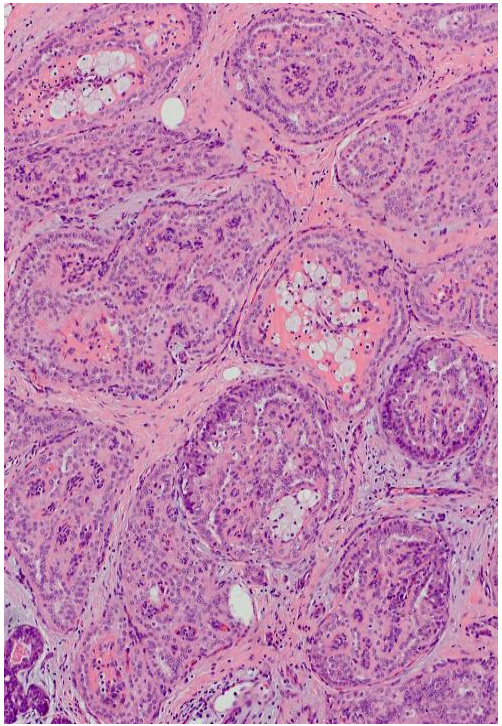


TCCRP Differential diagnosis

- **Intraductal papilloma +/- atypia**

- DCIS
- Solid papillary carcinoma
- Secretory carcinoma
- Metastatic papillary thyroid carcinoma





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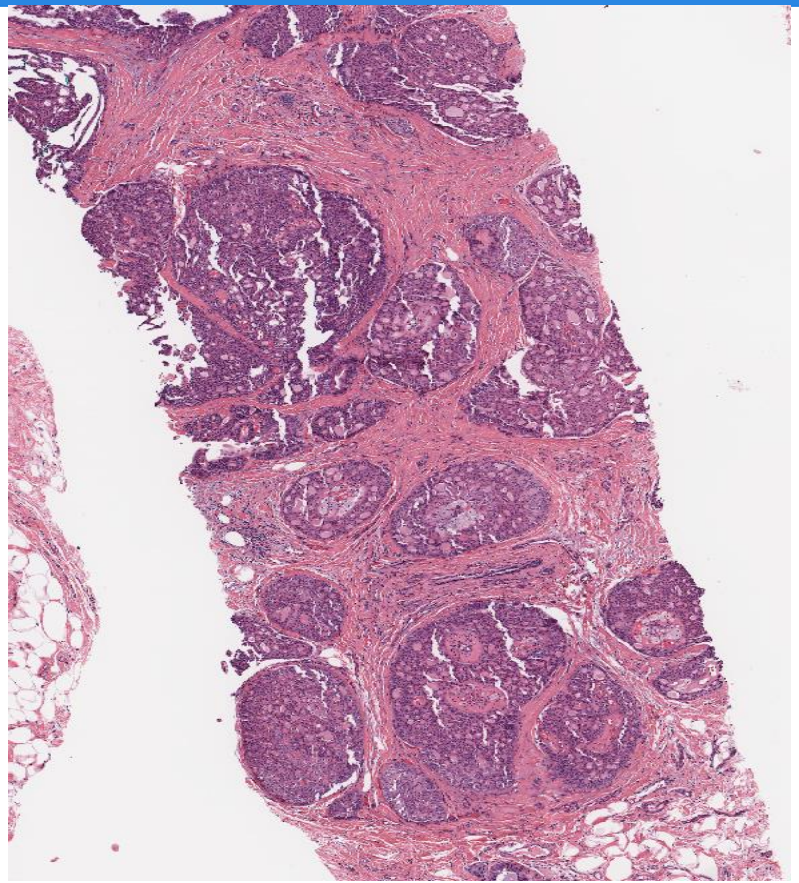
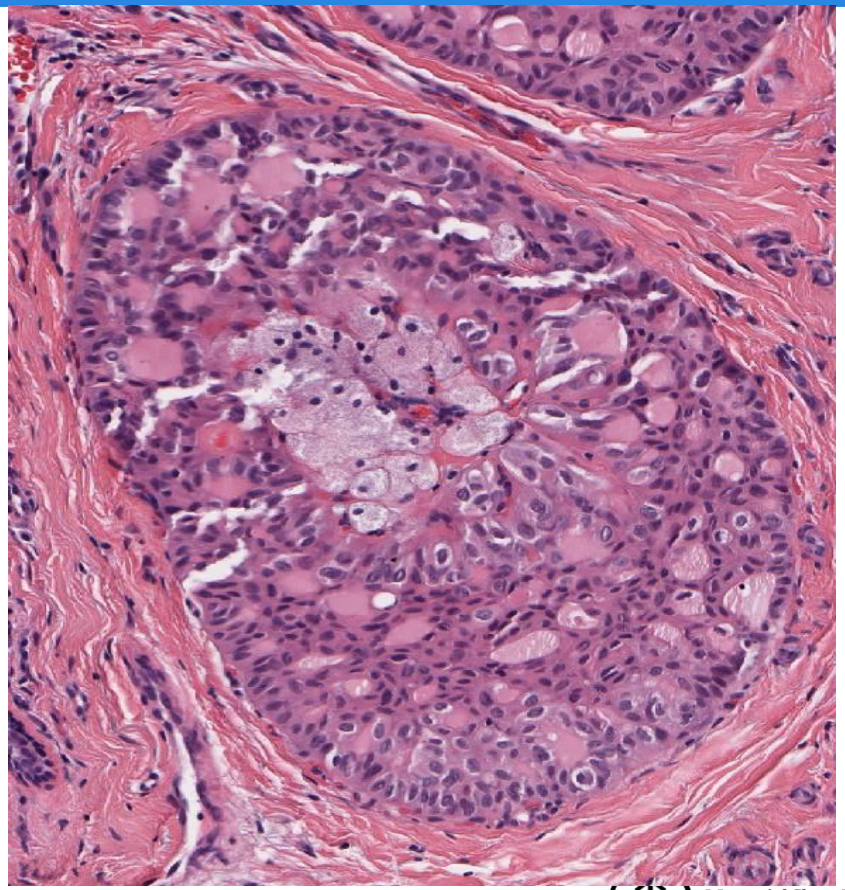
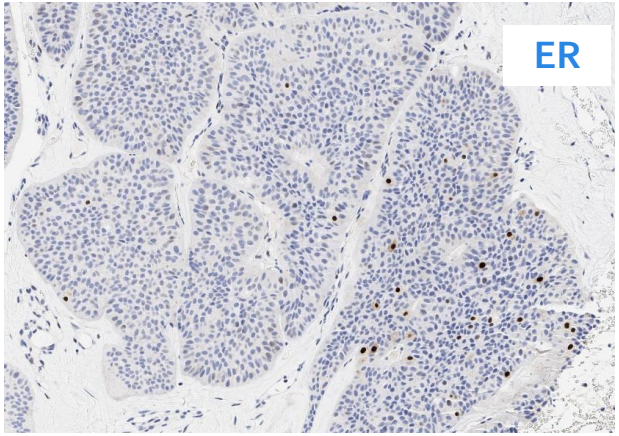
CNB of Tall Cell Carcinoma with Reversed Polarity (TCCRP)

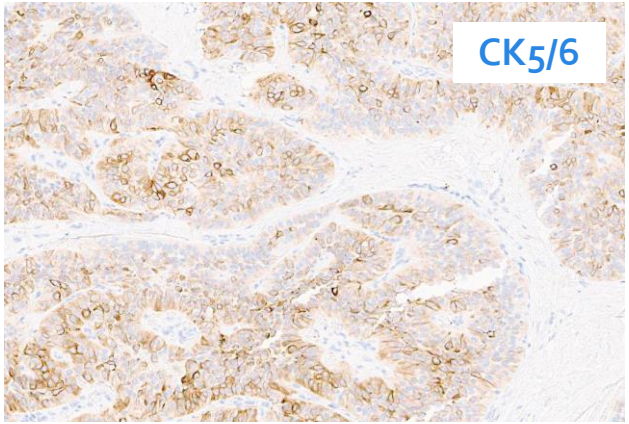




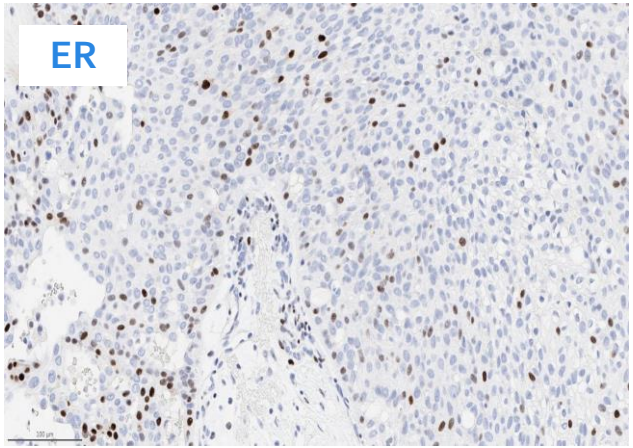
TCCRP IHC: ER low, CK5/6 scattered to diffuse positivity

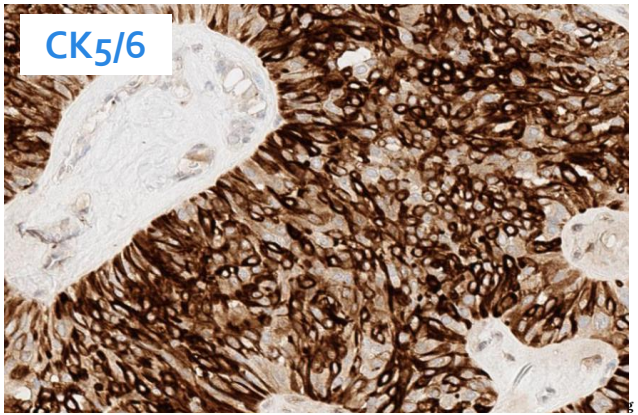
The immunoprofile of TCCRP overlaps with that of UDH, often present in IDP





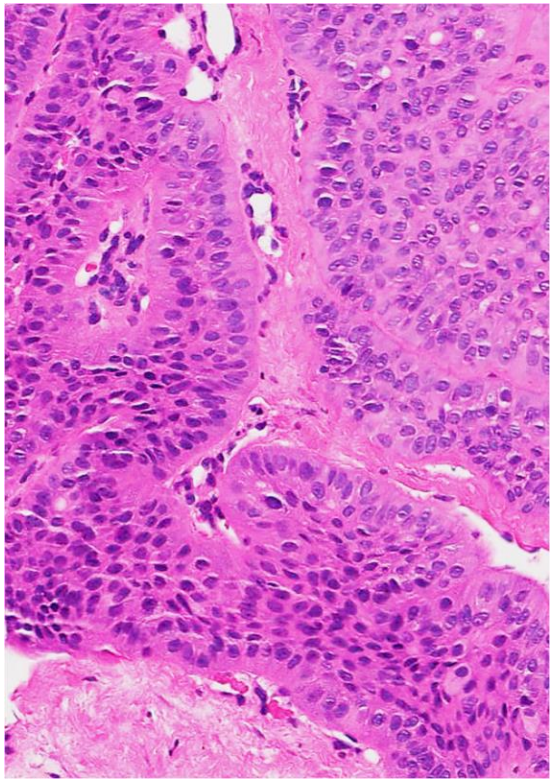
TCCRP case 1 cbx

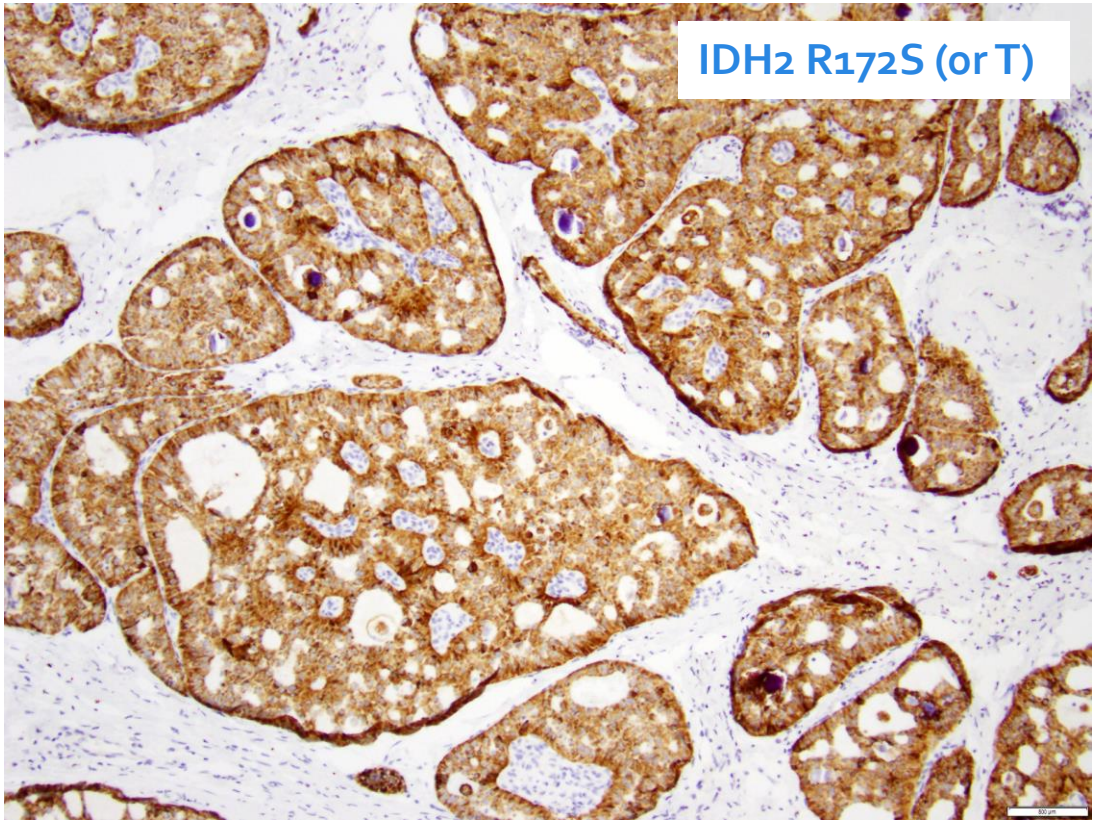




TCCRP case 2 cbx

IHC for IDH2 R172S and R172T protein
100% specificity, 70% sensitivity





Alsadoun et al *Mod Path* 2018;31:1367–1380; Pareja et al. *Mod Pathol* 2020;33:1056-64

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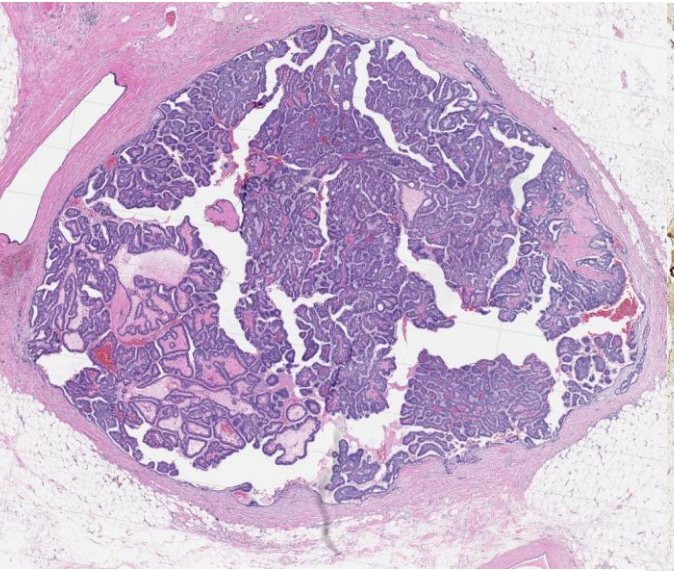
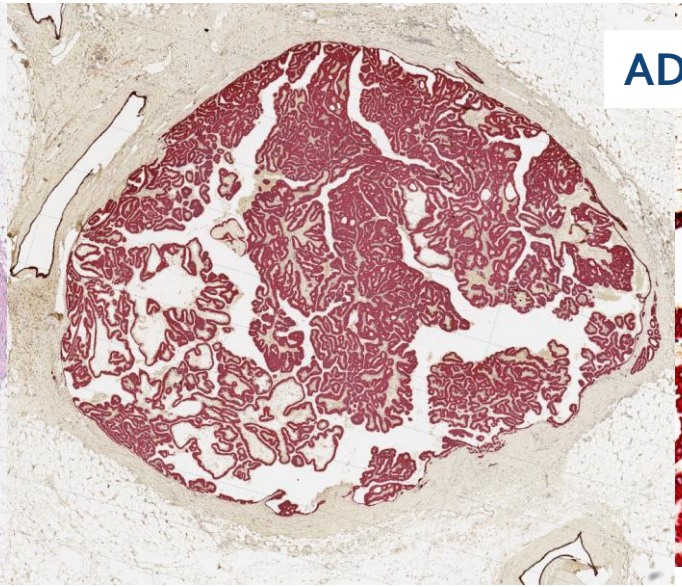
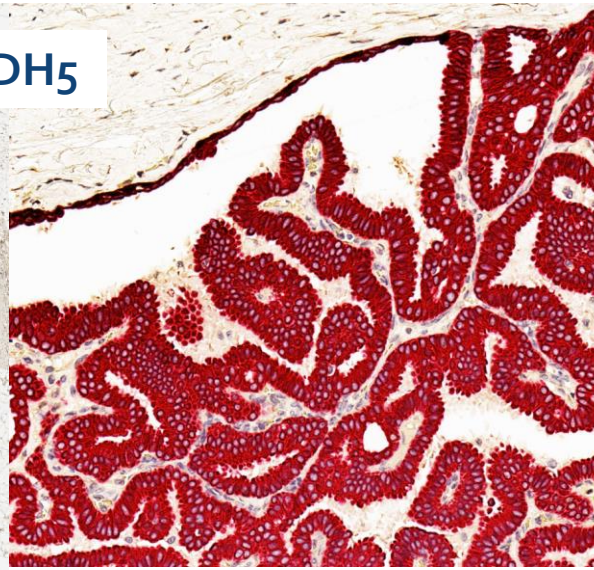
Papillary DCIS

- Fibrovascular cores with carcinoma devoid of MECs, but contained within a duct with MECs
- May occur in isolation, but usually is one of several architectural patterns in a case of DCIS
- Nuclear atypia determines grade





ADH5



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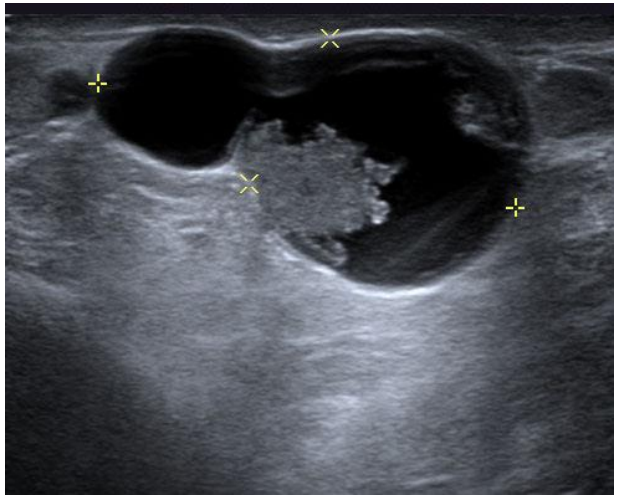
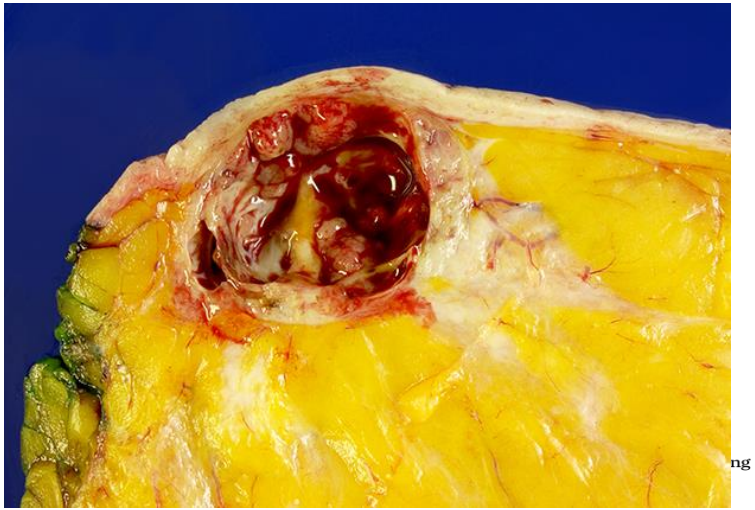
Encapsulated Papillary Carcinoma (EPC)

Tends to occur in postmenopausal women (7th decade)
can occur in men

<u>Clinical presentation</u>

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

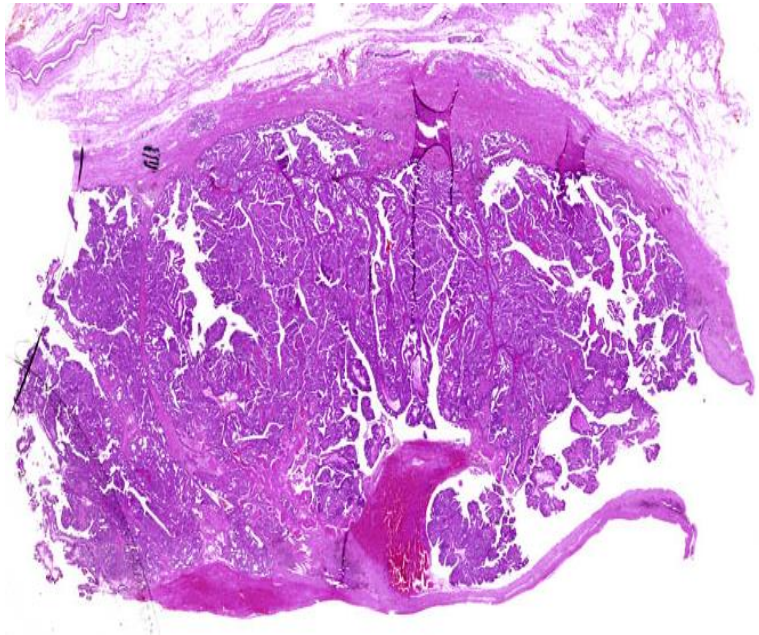




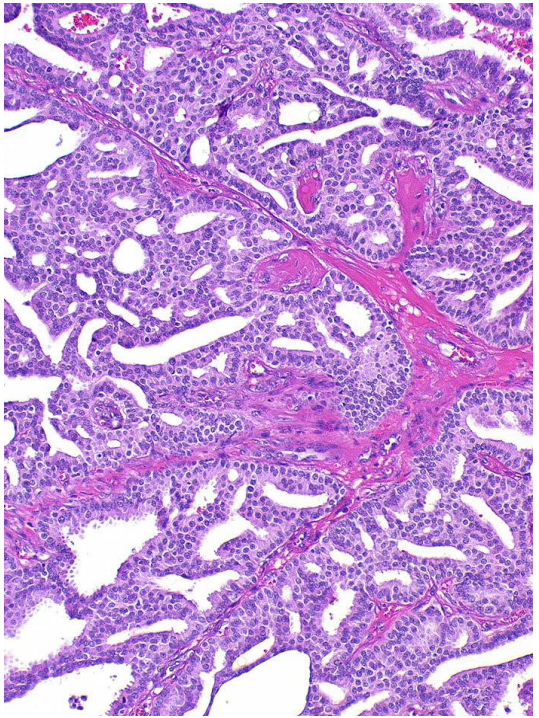
Encapsulated Papillary Carcinoma (EPC)

WHO 5th NEW

- Cystic mass, with rounded, pushing border
- +/- thick fibrous capsule
- Thin fibrovascular cores
- Cribriform pattern most common, *focal* solid areas



EPC only if nuclear grade is LOW OR INTERMEDIATE



WHO Breast Tumours 5th ed. (2019)

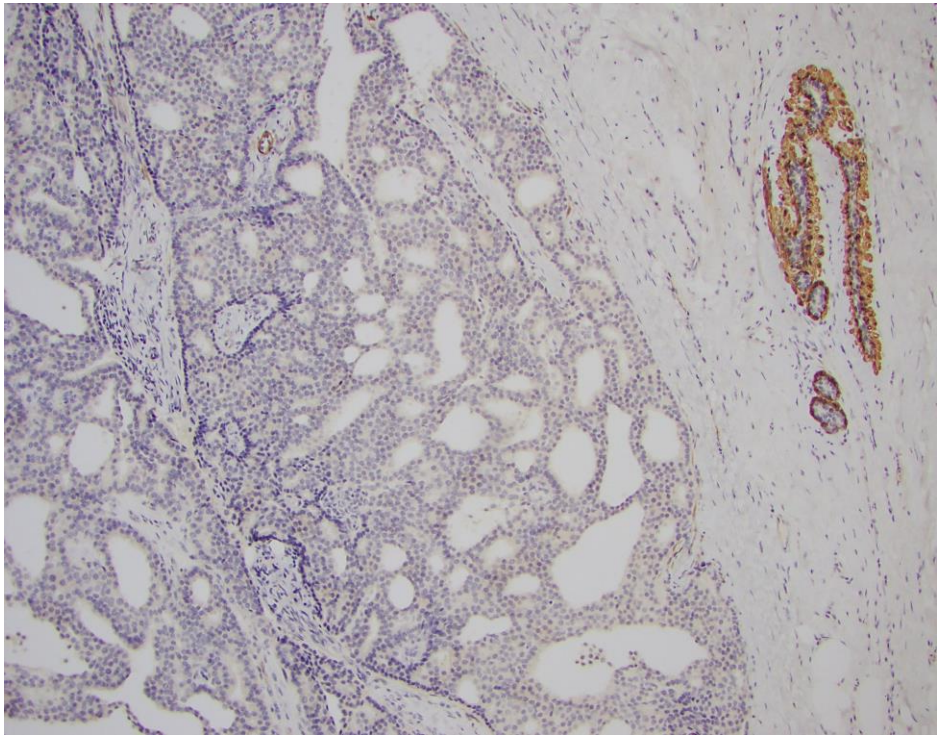
EPC: no myoepithelial cells

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



calponin

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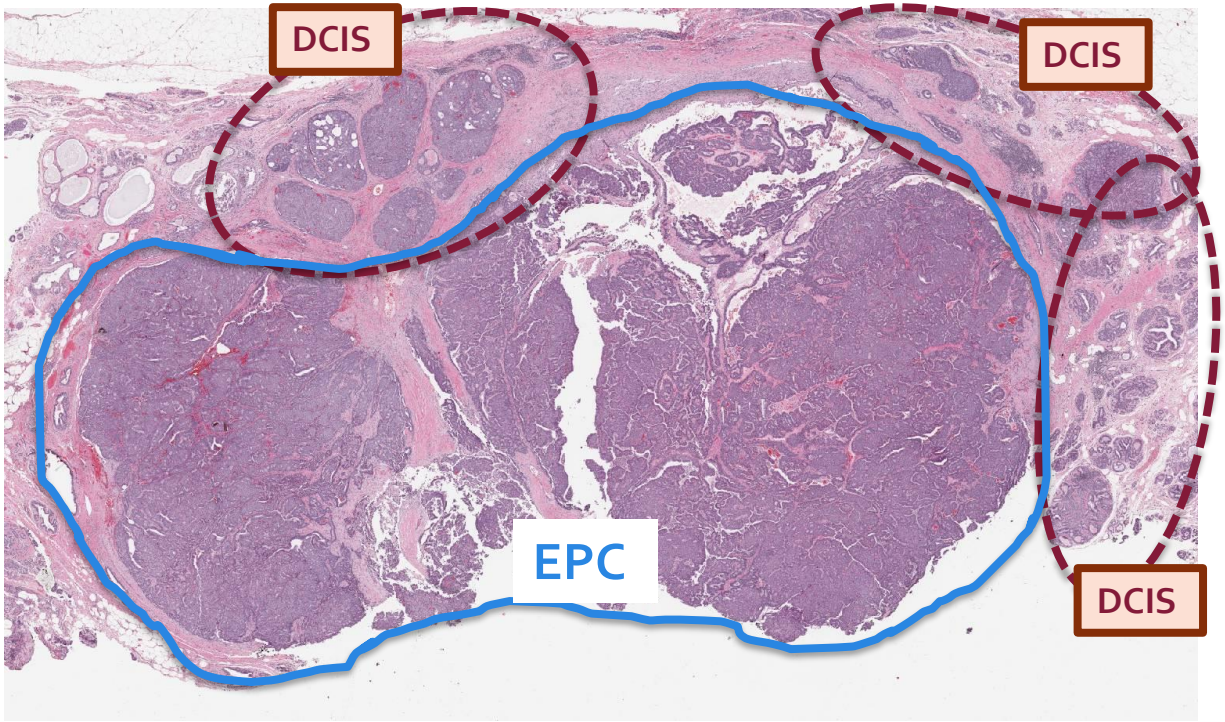
EPC *versus* papillary DCIS

Ducts with Papillary DCIS have substantially smaller diameter than EPC foci



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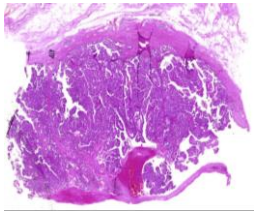
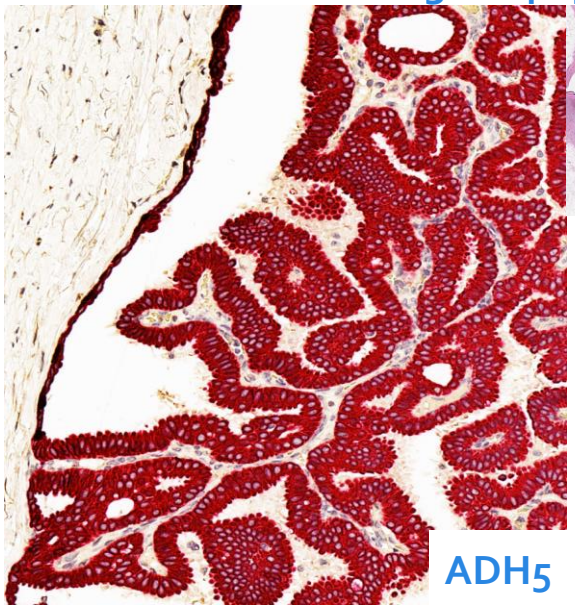
EPC *versus* papillary DCIS

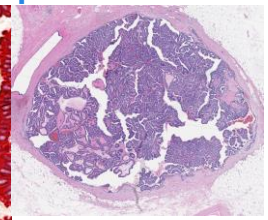
No MECs along the papillae
and around the tumor



calponin

MECs around the tumor,
but *NOT* along the papillae

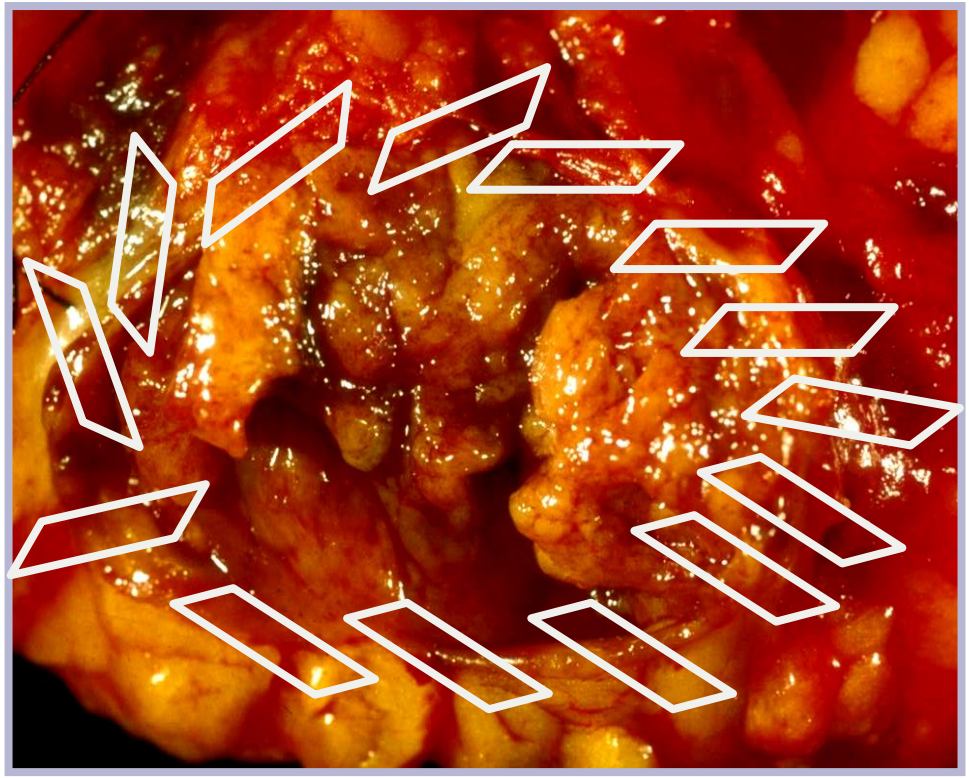




ADH5

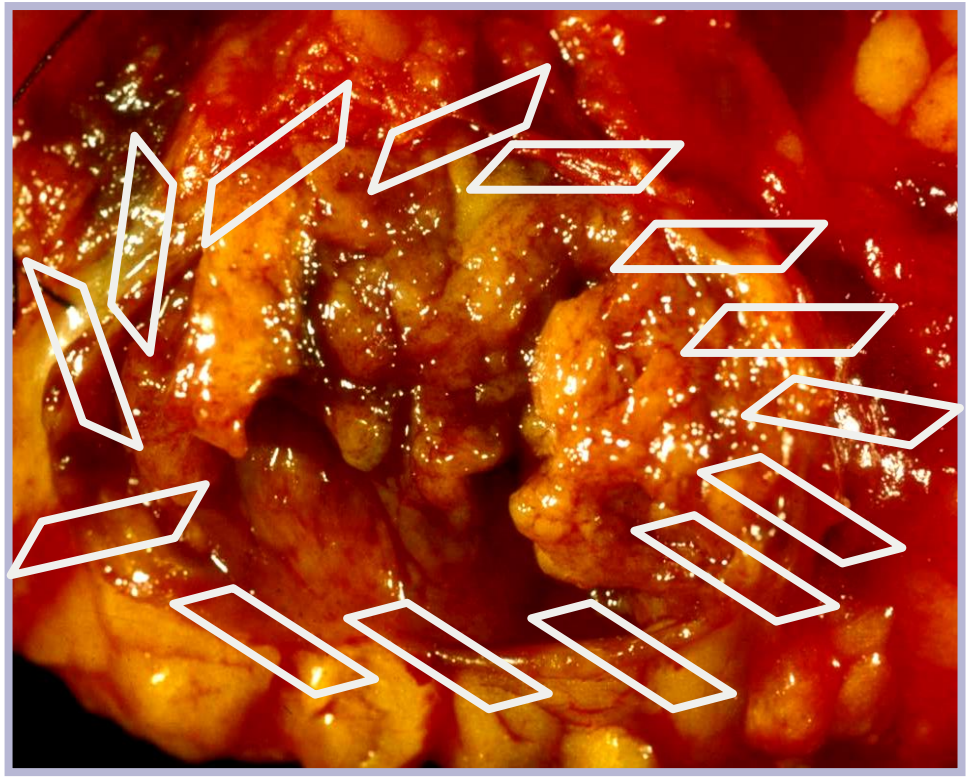
EPC without associated conventional invasion is staged as pTis because behavior is similar to DCIS

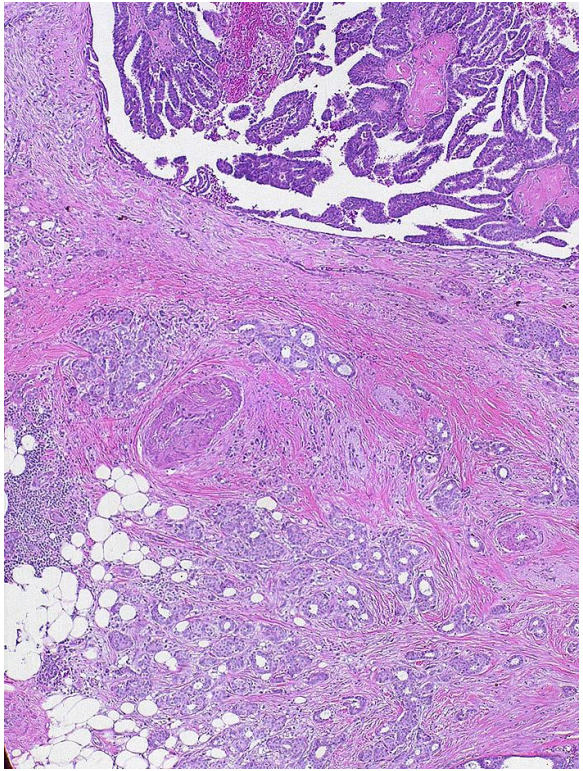
Thorough sampling of EPC capsule + adjacent tissue to rule out frank invasion



Frank invasion = carcinoma with unequivocal invasive pattern ***beyond*** the fibrous capsule

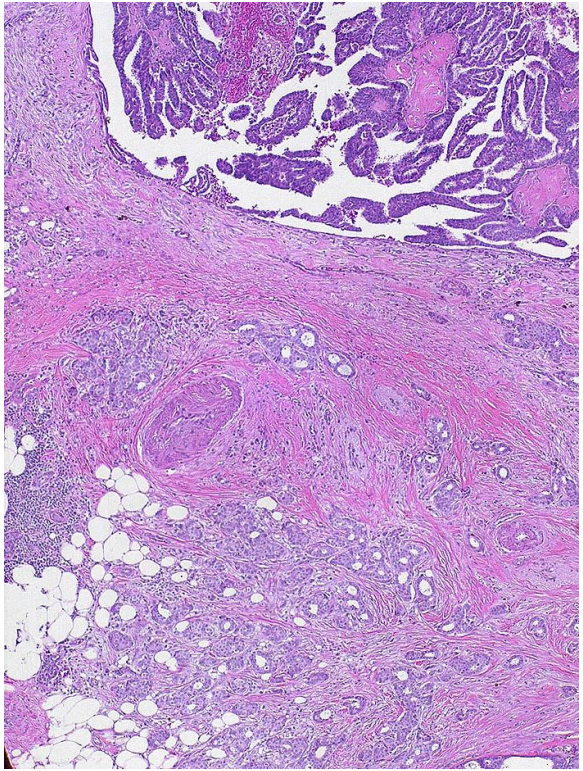
Thorough sampling of EPC capsule + adjacent tissue to rule out frank invasion





Invasive carcinoma associated with EPC

- Identified in 20-60% of cases
  - 27 EPCs: 6 (22%) with invasion
    Esposito NN et al Am. J. Clin. Pathol. 2009;131:228-242
  - 42 EPCs; 19 (45%) with invasion
    Wynveen CA et al. *Am J Surg Pathol.* 2011;35:1-14
  - 25 EPCs; 15 (60%) with invasion
    Jackson CR et al. *Breast J* 2021;27(3):209-215
- Presence of invasive carcinoma unrelated to EPC size
- 70% well diff IDC-NST
  (also mucinous, tubular, inv cribriform)
- all pT1 (0.2- 1.25 cm)
- majority ER-positive, HER2-negative
  Wynveen CA et al. *Am J Surg Pathol.* 2011;35:1-14
  Jackson CR et al. *Breast J* 2021;27(3):209-215



EPC: staging and management

Frank invasion + EPC +/- DCIS

Stage based on frankly invasive component

- Report:
  - Size
  - Nottingham grade
  - ER, PR and HER2 status
- Management as invasive carcinoma of similar stage and receptor status

EPC +/- DCIS

Stage: pTis (DCIS)

- Report nuclear grade, ER status

(in a note, may report size EPC and DCIS, separately and together)

- Management as DCIS
  +/- Sentinel LN bx

Prognosis: favorable

Rakha E. et al.. AJSP 2011
Mogal H et al. *Breast* 2016

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Rare reports of EPC with LN or distant mets

LN metastases

- 5.9 cm EPC → 1/3 LNs
- 4.0 cm EPC → 2/11 LNs
- All micrometastases

Mulligan and O'Malley *Breast Cancer, 2005*

Distant Metastases

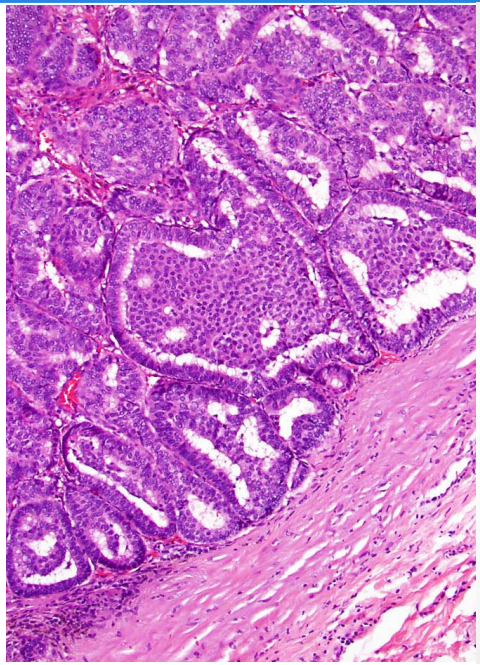
- 2.6 cm EPC + 0.5 mm invasive carcinoma
- Synchronous liver metastases

Okita, et al. *Int J Surg Pathol, 2007*

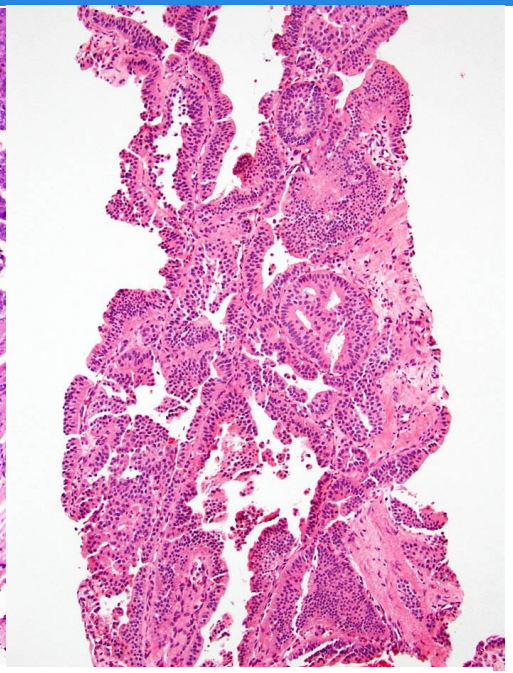
- EPC + DCIS → lung metastasis

Fayanju, et al. *Am J Surg 2007*

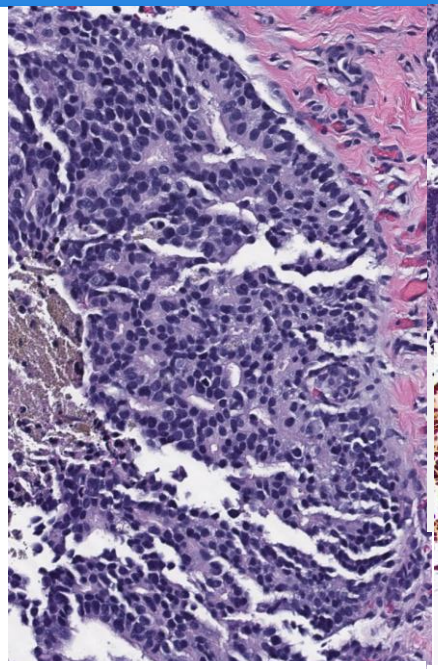
EPC with distant metastases (personal observations)



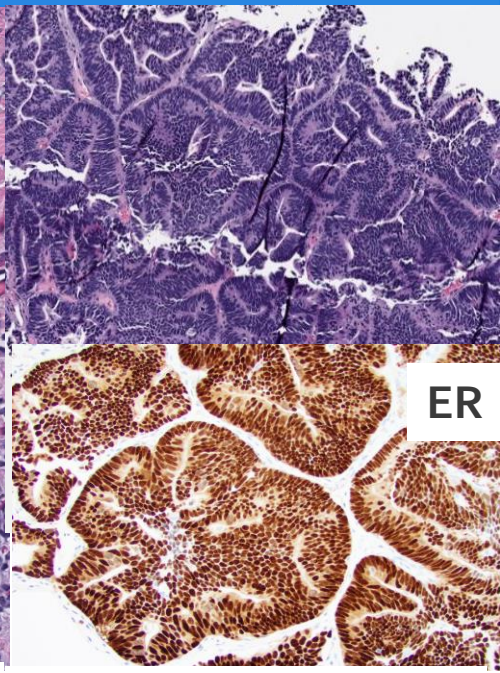
EPC in a
44 yo woman



bone met
17 y later



EPC in a
74 yo man



Lung met
4 y later

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EPC - Differential Diagnosis

Papillary DCIS

- MECs = continuous layer at the periphery of the duct; absent along papillae
- May be near EPC; ducts with papillary DCIS usually much smaller than EPC

Solid Papillary Carcinoma in situ (SPC in situ)

- Solid papillary growth with inconspicuous or hyalinized fibrovascular cores, not cribriforming
- intra- and/or extra-cellular mucin common
- +/- NE features/ differentiation

Invasive Papillary Carcinoma

- High NG, usually high mitotic rate, +/- necrosis, +/- capsule, usually triple neg or HER2+
- If no DCIS is identified, rule out extramammary origin

DCIS or ADH in a Papilloma

- Underlying papilloma identifiable at least focally
- MECs around the periphery of the duct and along (some) papillae

Papilloma with UDH

- ER low and CK5/6 mosaic pattern
- MECs around tumor periphery and along papillae

Solid Papillary Carcinoma (SPC)

Postmenopausal women (>6o y), may occur in men

Palpable breast mass, mammographic mass/ abnormality, and/or bloody nipple discharge

<u>Imaging features</u>

Mammography: rounded, circumscribed mass, +/- irregular borders/ architectural distortion if invasive

Ultrasound: solid, well-defined, hypoechoic or heterogeneous mass; +/- irregular edges if invasive

Gross appearance: soft, well-circumscribed, tan-pink mass

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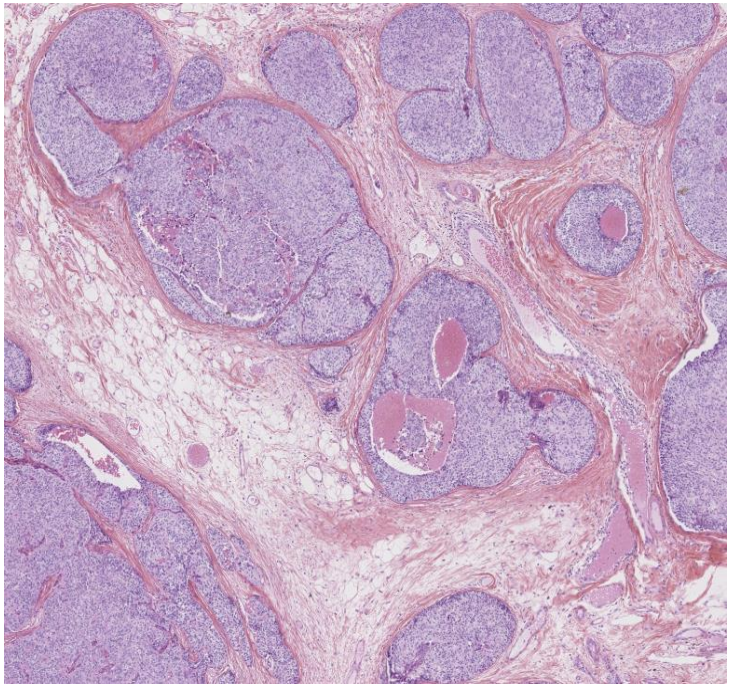
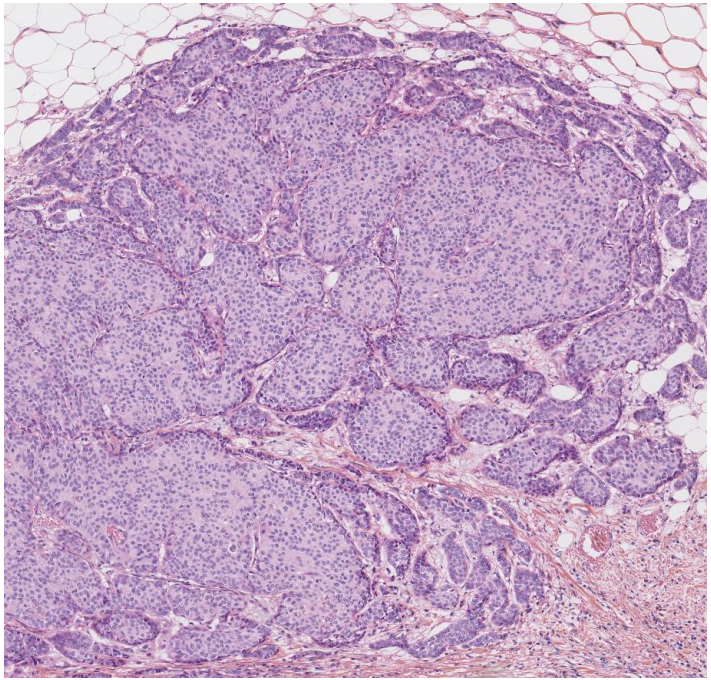
Solid Papillary Carcinoma (SPC)

WHO 5th NEW

In situ



Invasive



WHO Breast Tumours 5th ed. (2019)

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SPC in situ

- Expansive, round-oval, solid nodules
- ***A distribution pattern consistent with an in situ process, regardless of the presence of MECs around the nodules***

  WHO Breast Tumours 5th ed. 2019

- **Monotonous, round to spindled epithelial cells with (usually) mild to moderate nuclear atypia**
- **Inconspicuous fibrovascular cores**

Maluf and Koerner 1995; Tsang WY, Chan JK. 1996; Nicolas, Wu et al. 2007; Otsuki, Yamada et al. 2007; Nassar, Qureshi et al. 2006

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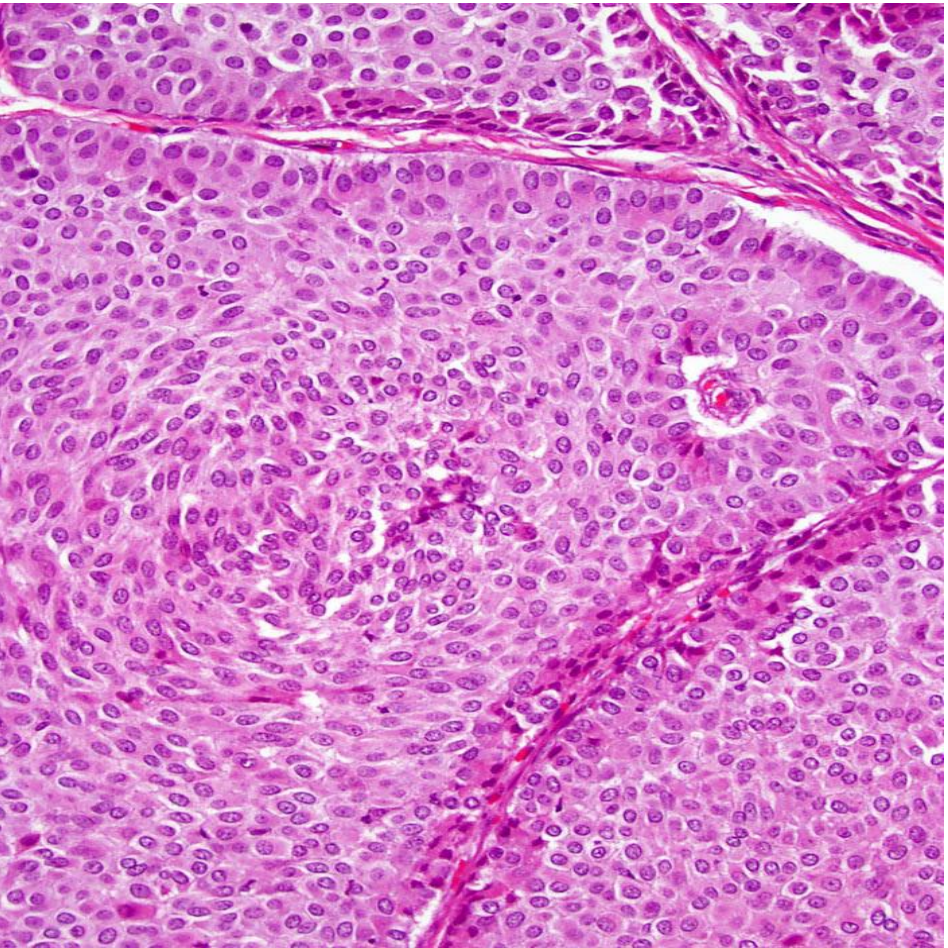
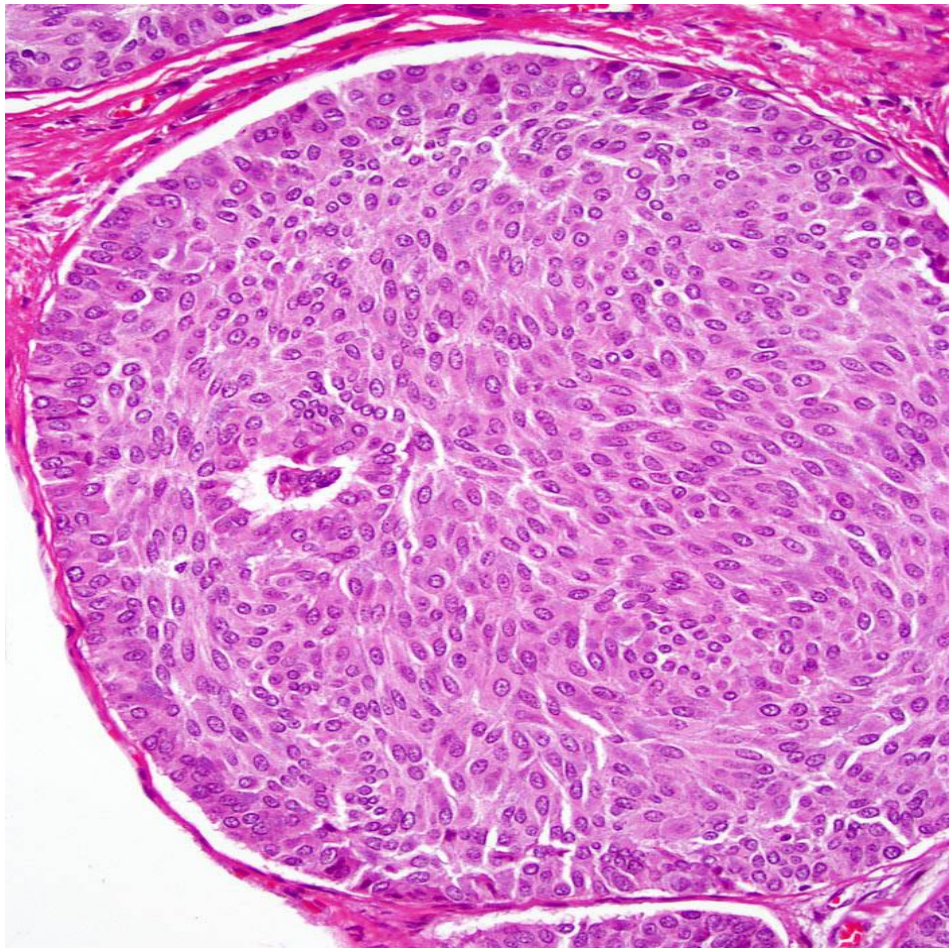
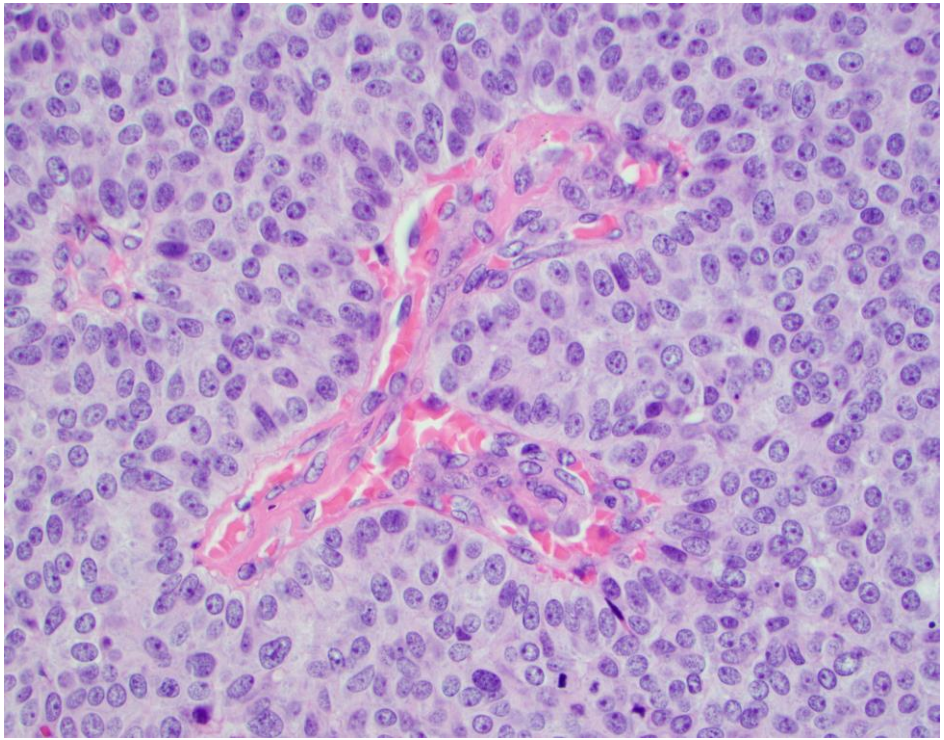
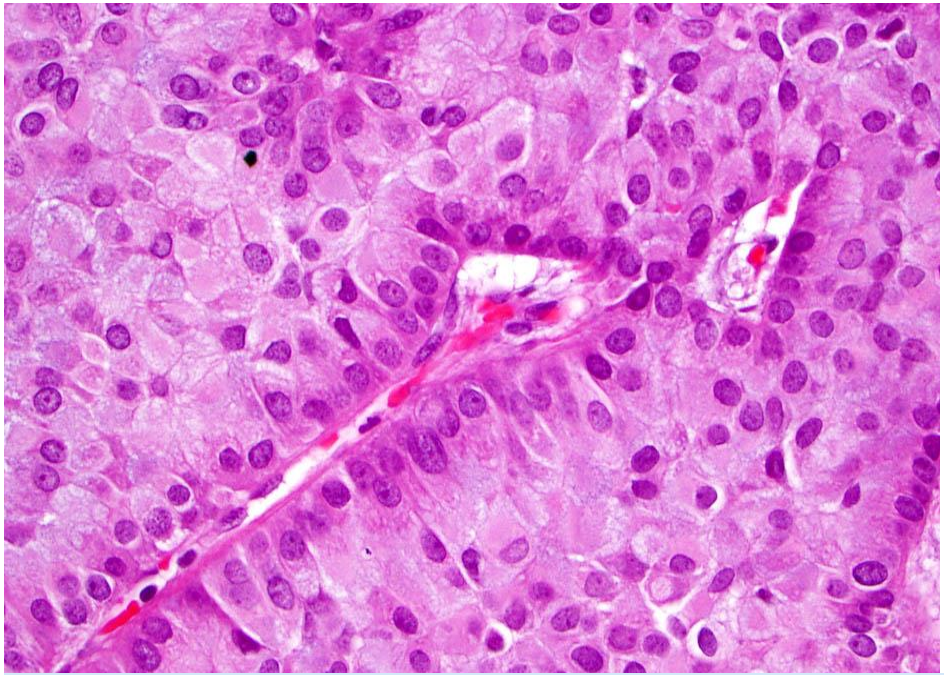
spindle cell morphology (no “maturation” across the duct)





Palisading nuclei along fibrovascular cores

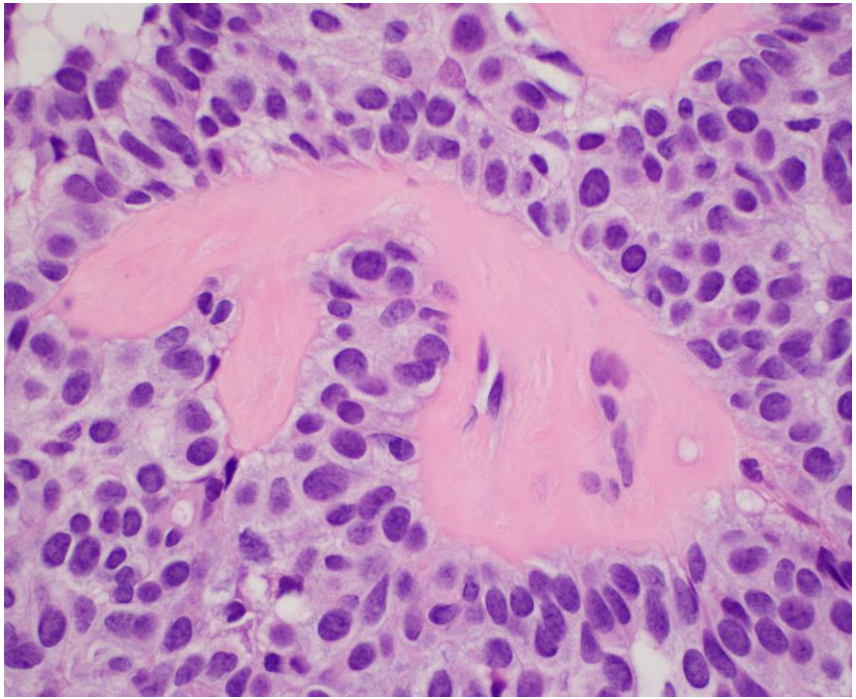


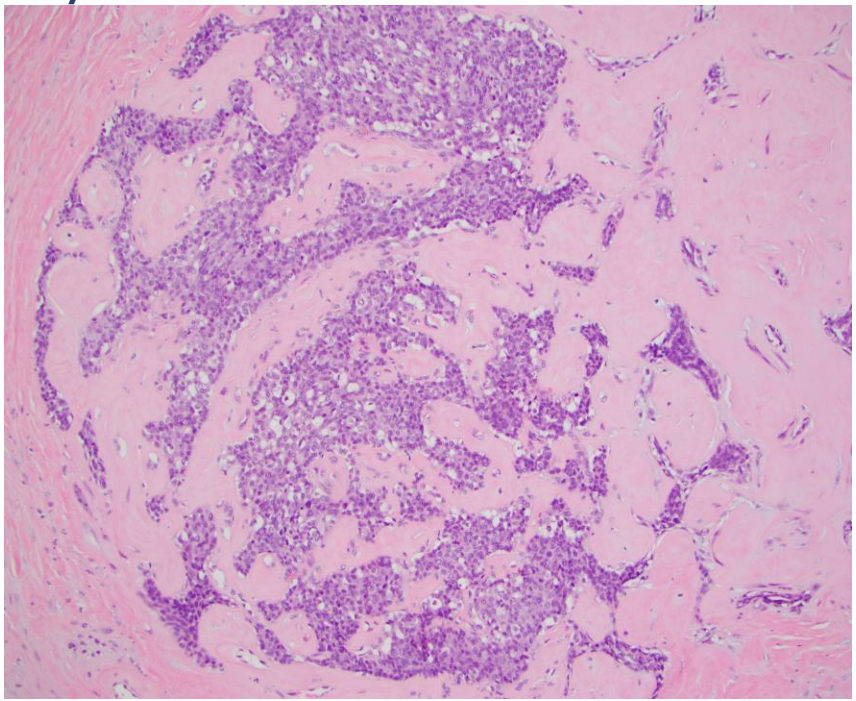


Intracytoplasmic mucin

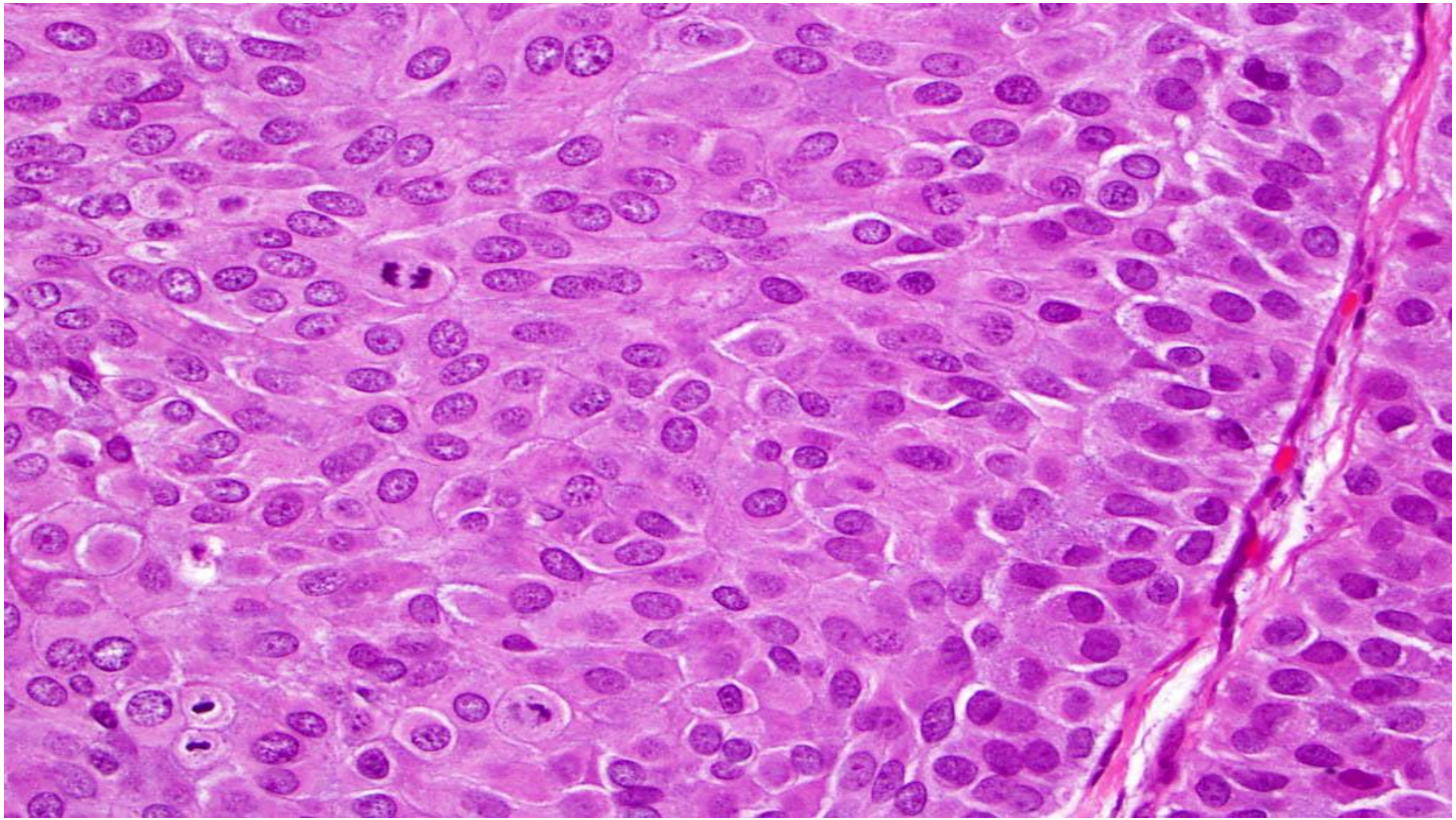
hyalinized and sclerotic fibrovascular cores

may mimic stromal invasion



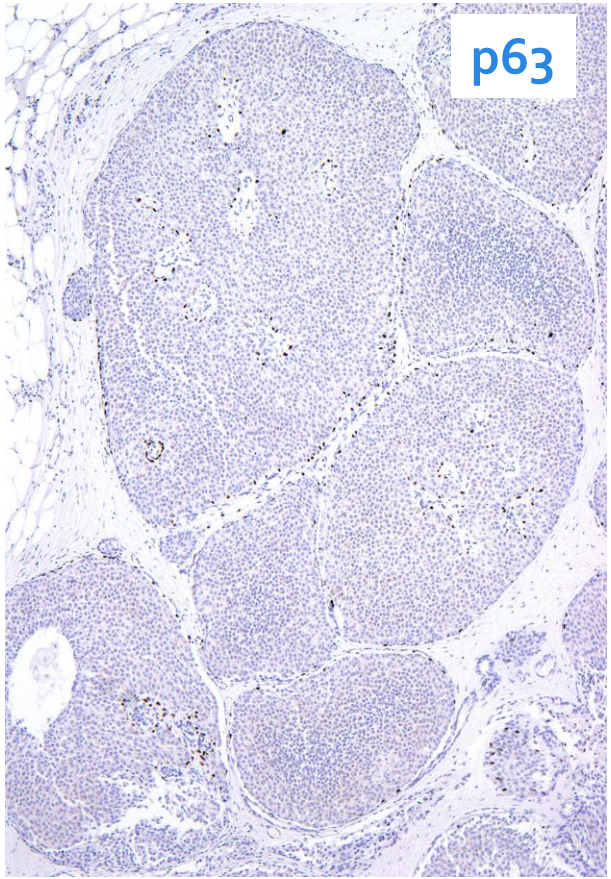


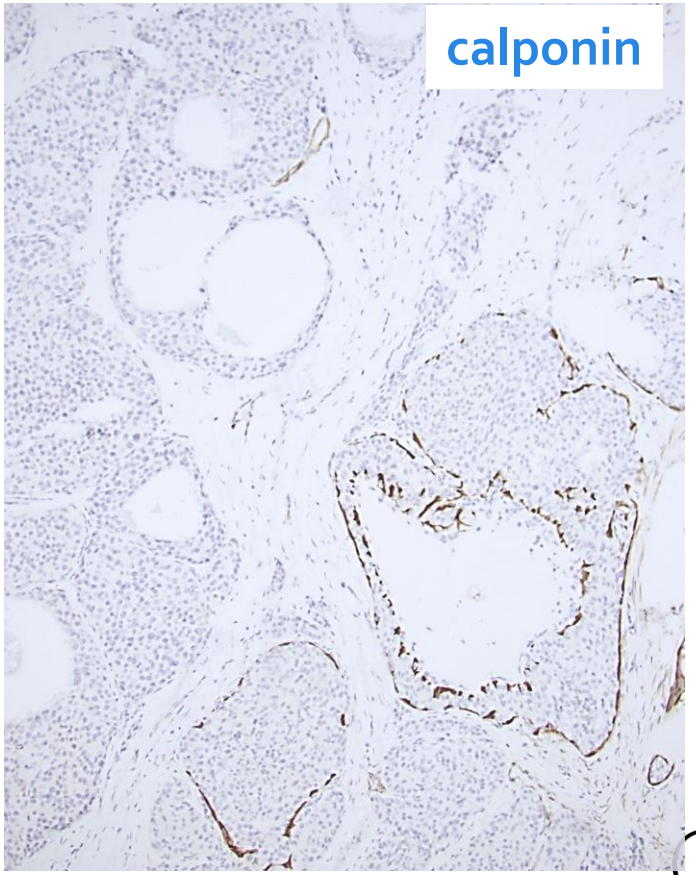
scattered mitoses



SPC in situ: round-oval nests, regardless of MECs

WHO 5th NEW





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SPC with invasion (invasive SPC)

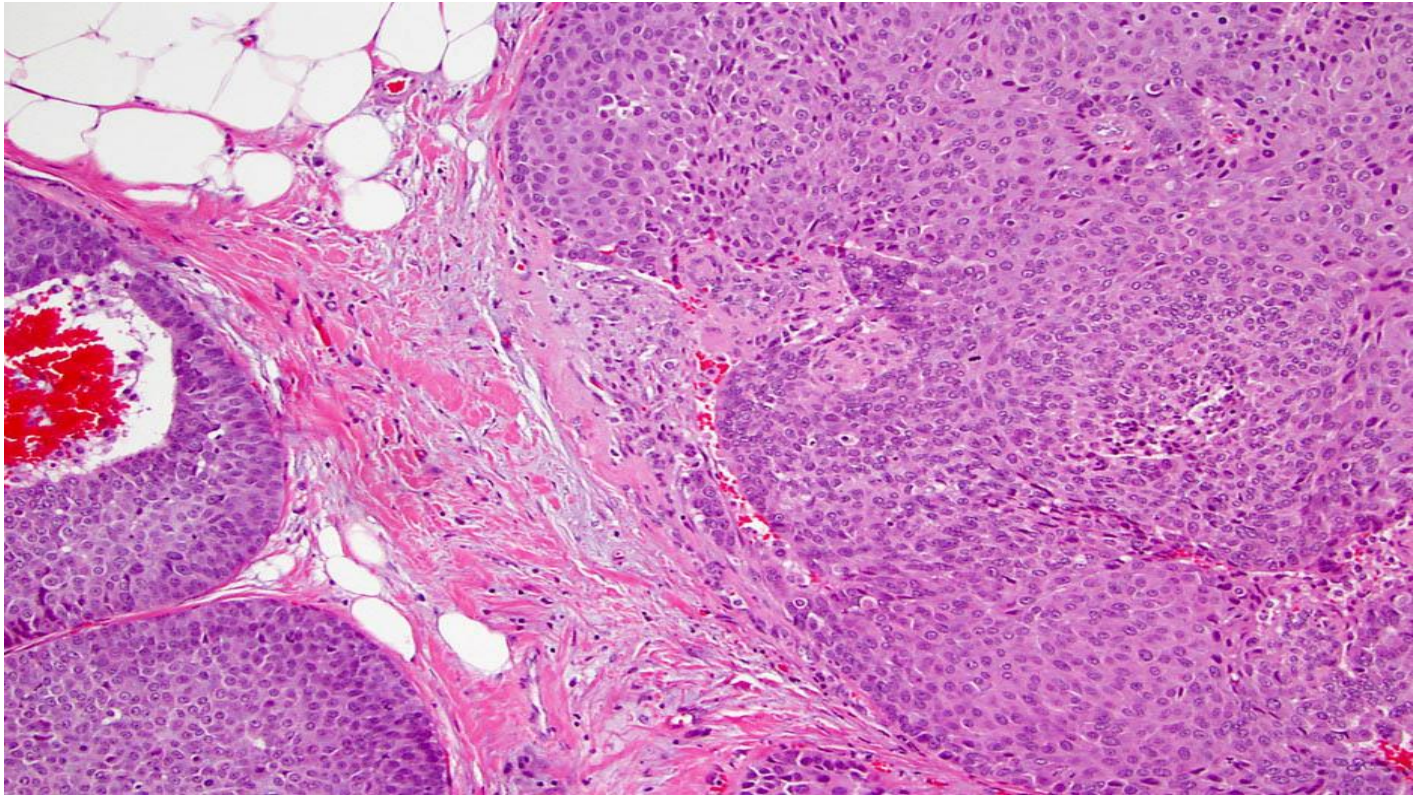
- The invasive component may be solid papillary and/or mucinous carcinoma (+/- NE antigens)
  - rarely invasive carcinoma of no special type (NST), lobular, cribriform, tubular carcinoma
- Large nests with irregular outline, pattern not consistent with involvement of pre-existing acini, ducts, or benign alterations thereof
- Carcinoma in extracellular mucin pools infiltrating at the periphery of the lesion), corresponding to mucinous carcinoma
- Usually ER(+) and PR(+), HER2-negative/not amplified

WHO Classification Breast Tumors 5th Ed

Solid Papillary Carcinoma

In situ

Invasive



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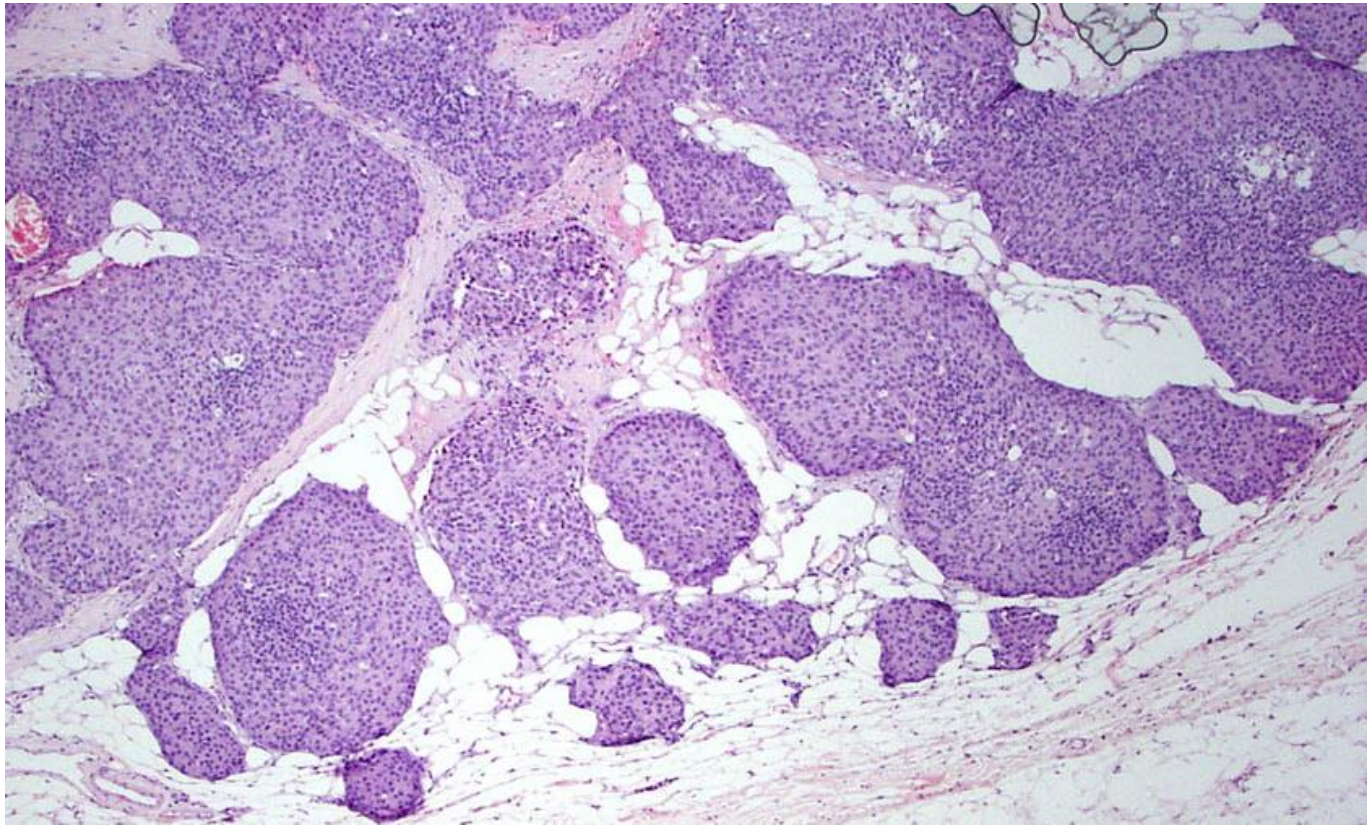
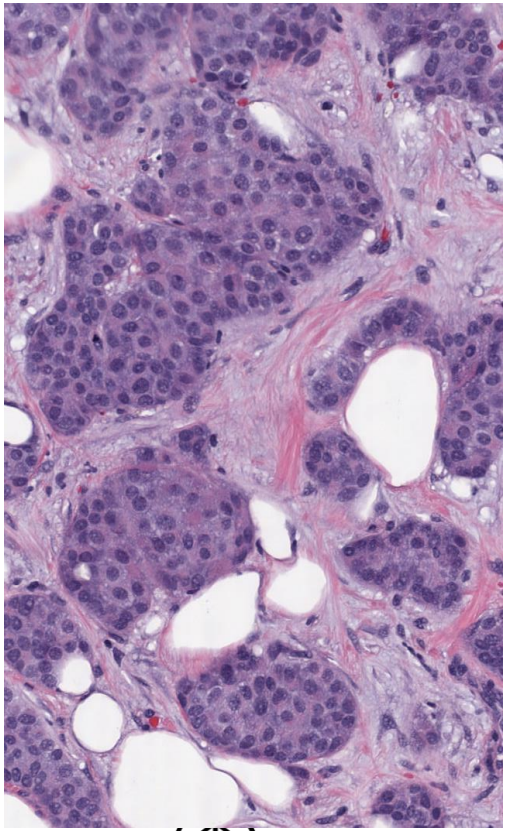
SPC Invasive – nests with irregular outline +/- haphazard distribution





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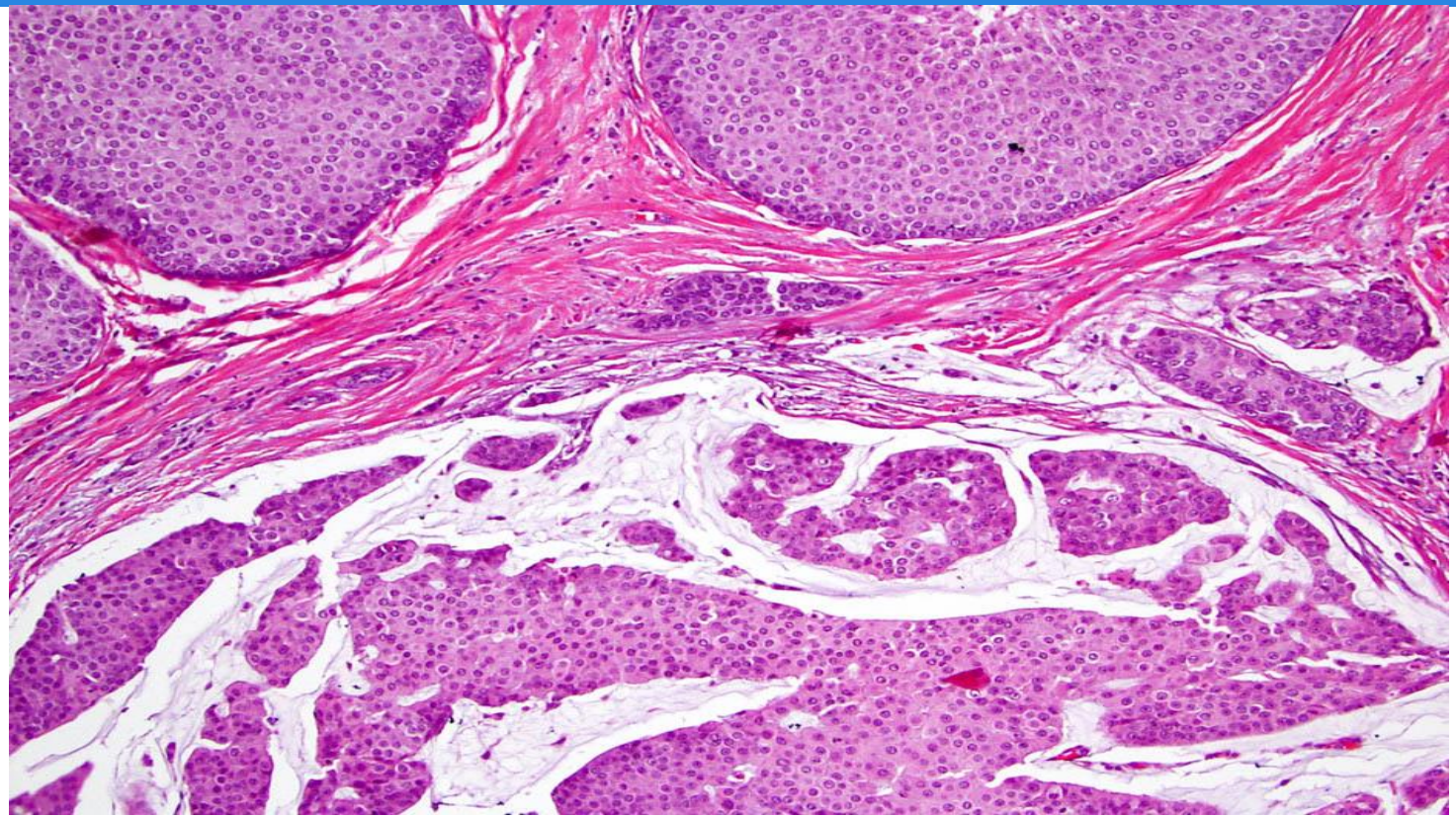
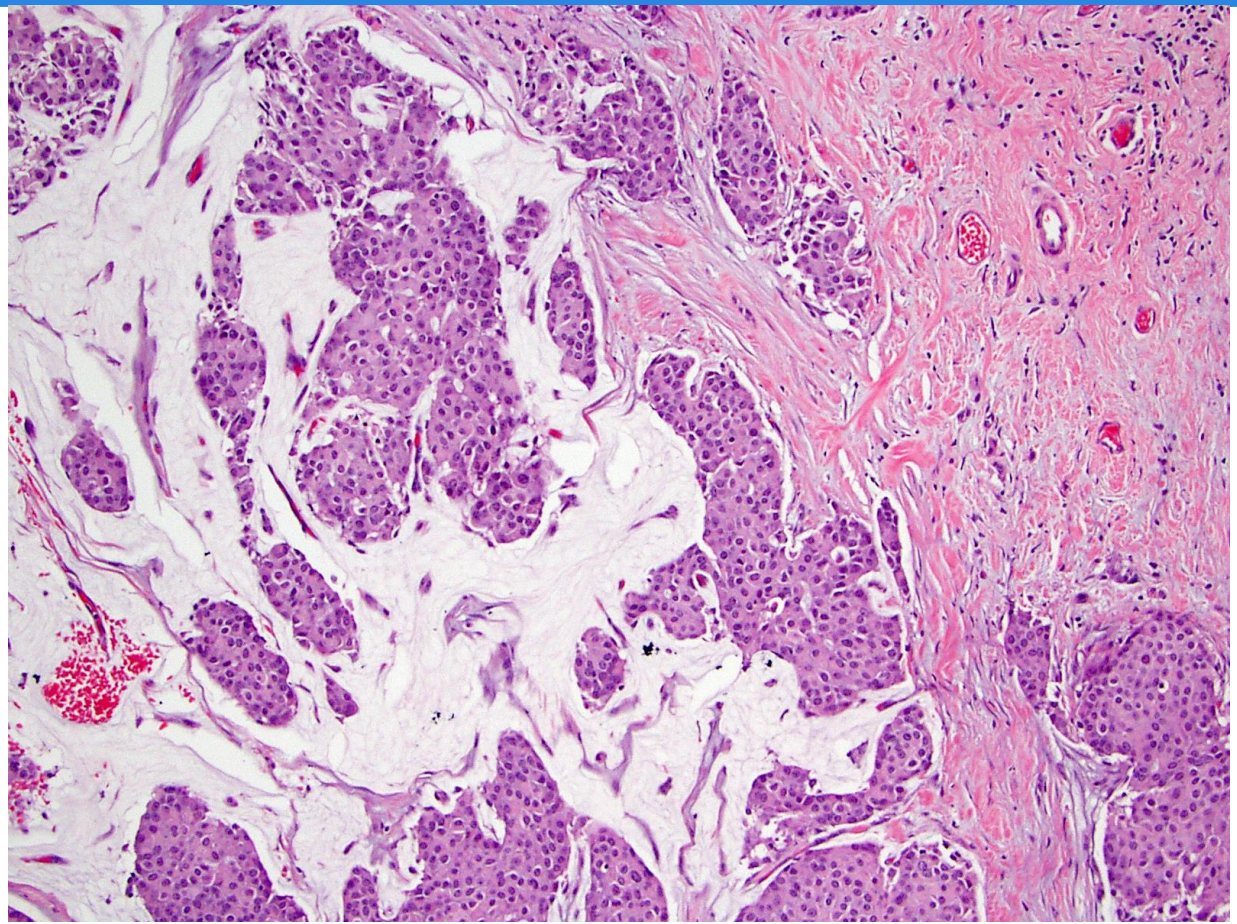
Mucinous carcinoma near SPC, predominantly in situ



SPC with invasion and mucinous carcinoma



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Solid Papillary Carcinoma (SPC): Staging

SPC in situ: pTis (DCIS)

- Round to oval nests with smooth border
- Regardless of MECs
- Report size (as for DCIS)
- Assess ER

SPC with invasion

Diagnose only if frank invasion is present

- Nests with irregular border
- Haphazard arrangement
- +/- mucinous carcinoma

Report:

- Size
- Nottingham grade
- ER, PR and HER2 status of invasive component ONLY

Excellent prognosis

Duprez, Wilkerson et al. 2012
Piscuoglio, Ng et al. 2014
Guo, Wang et al. 2016

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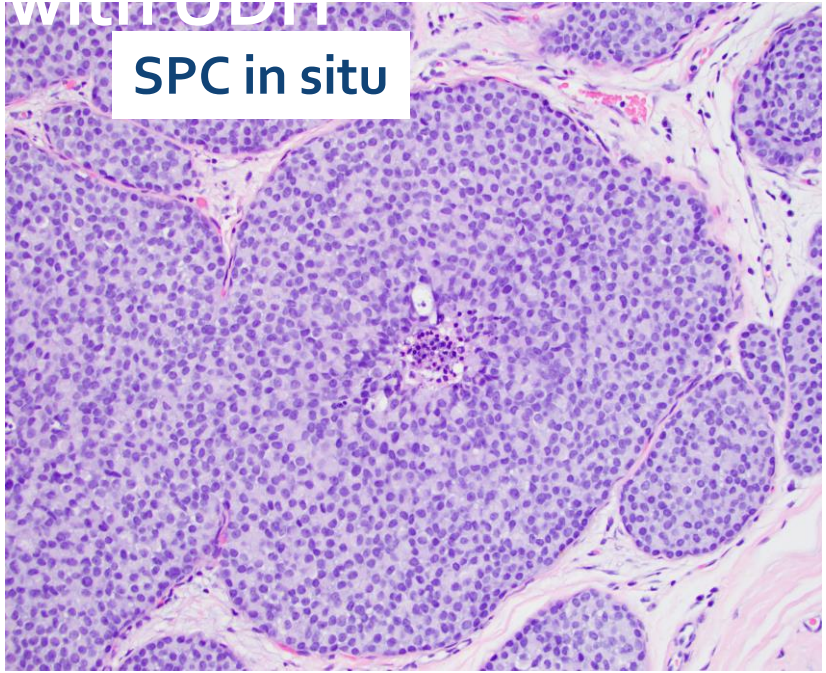
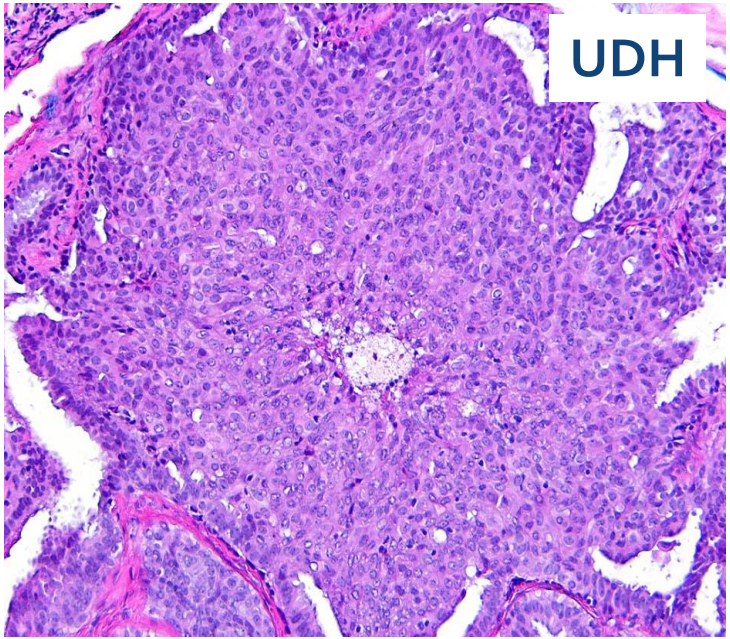
DDX: SPC in situ may mimic UDH in a papilloma with UDH



ER(+)
CK5/6(-)



ER sparsely(+)
CK5/6(+) strong and heterogeneous

Rabban JT et al. *Hum Pathol.* 2006;37:787-93

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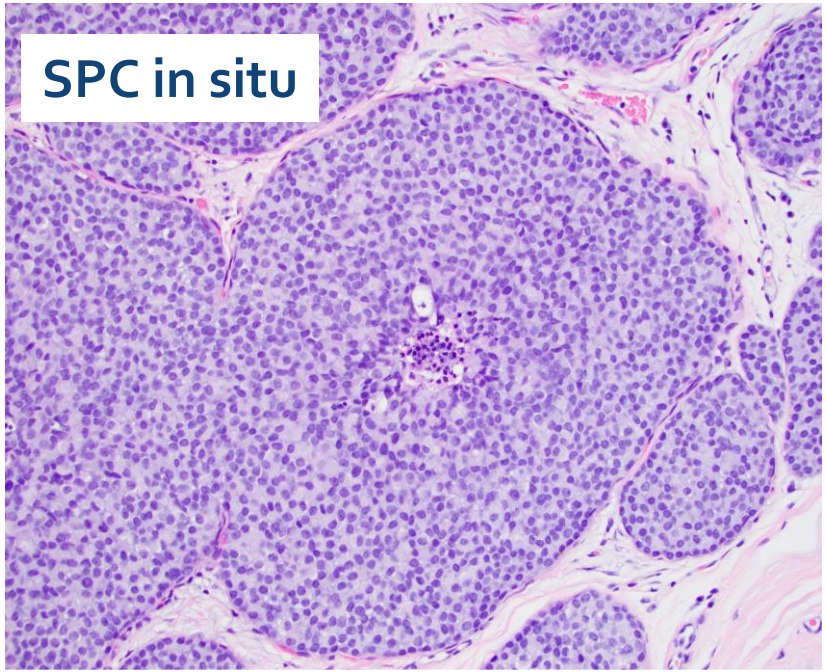
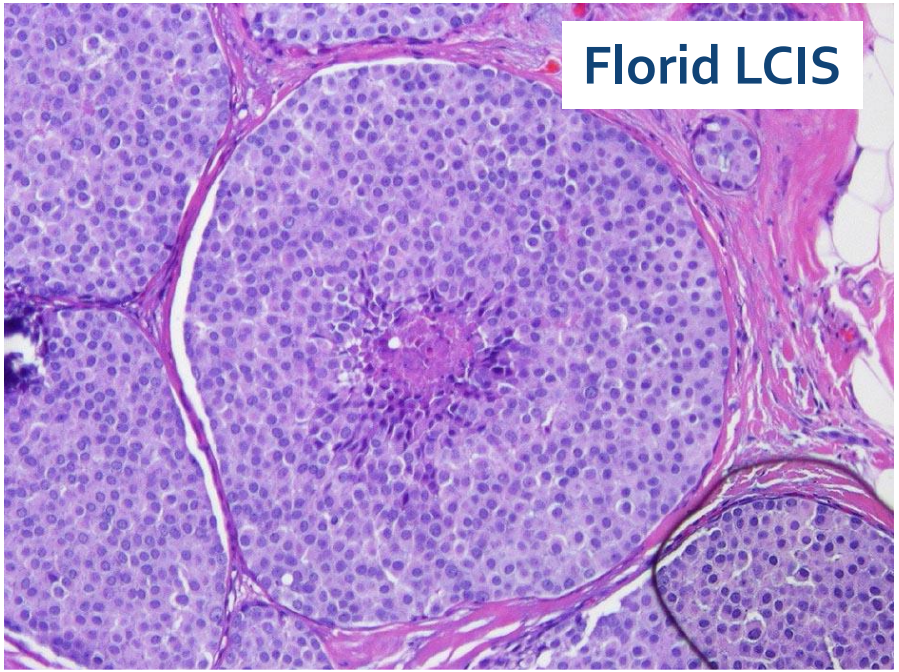
DDX: SPC in situ may mimic Florid LCIS





Cell membrane	**E-cadherin**	Loss of expression
Cell membrane	**p120**	Cytoplasmic stain

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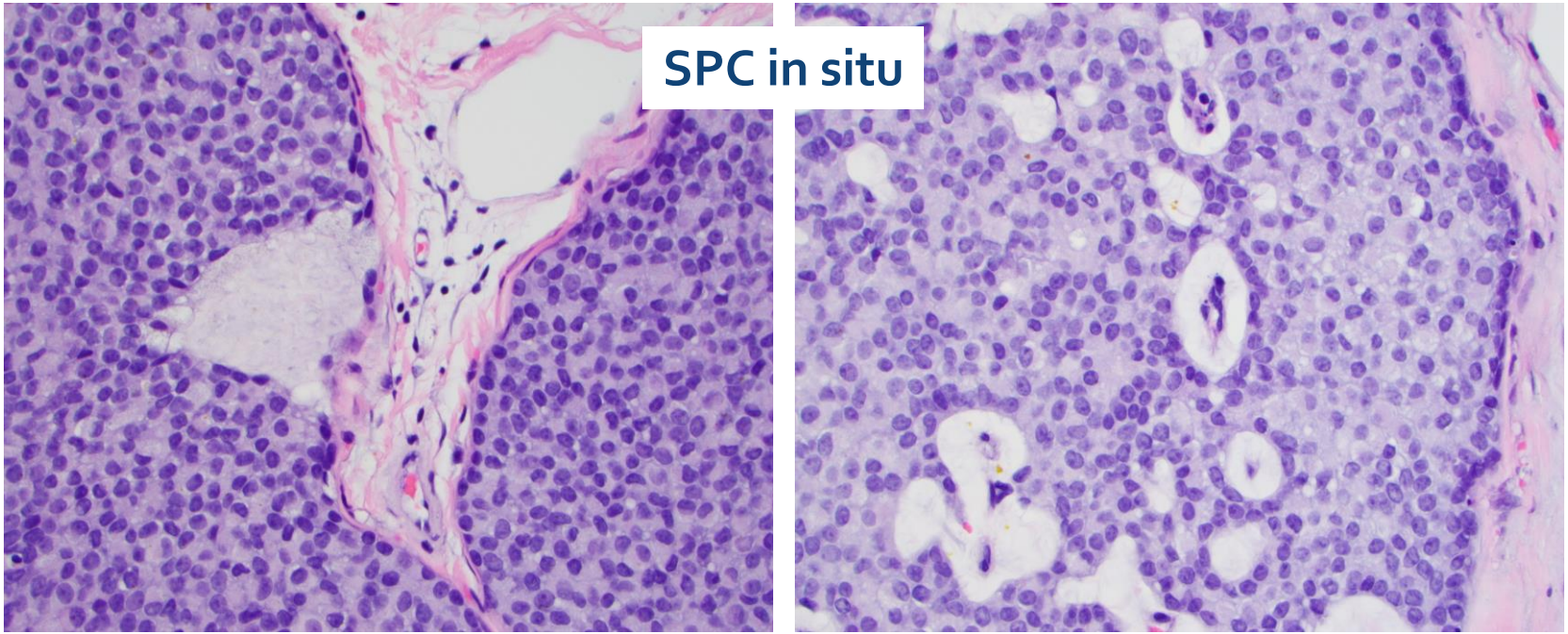
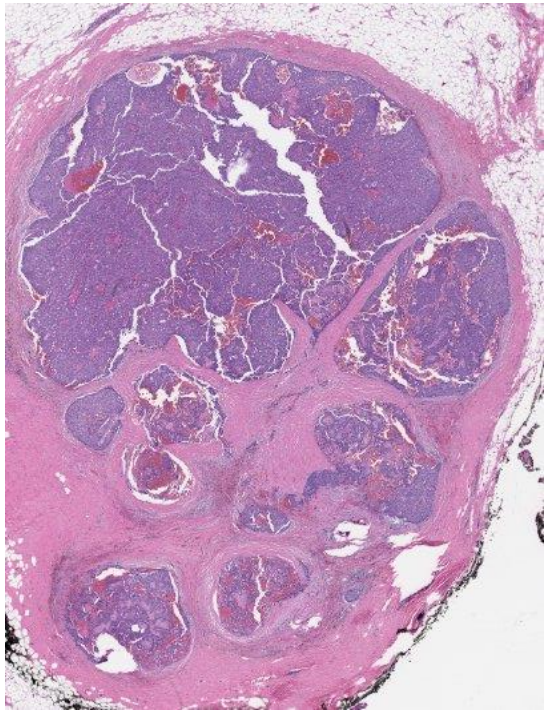
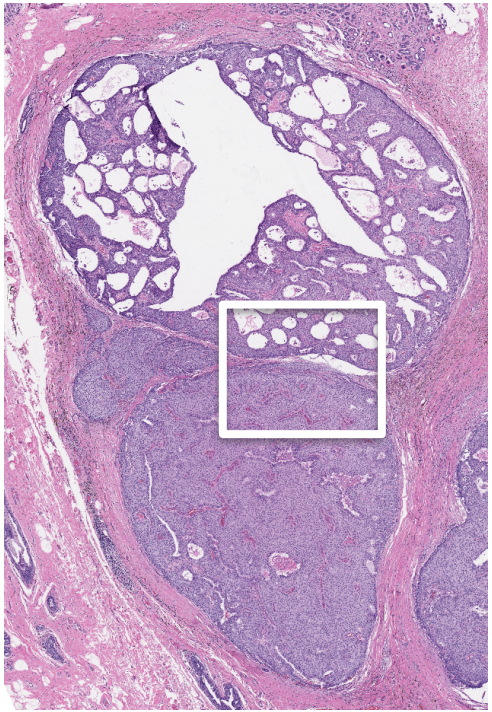
DDx: SPC in situ may mimic florid LCIS

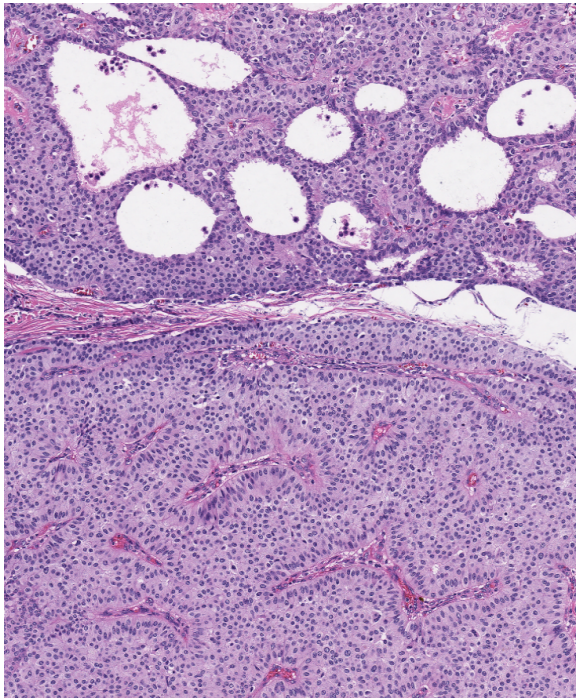


SPC in situ has fibrovascular cores, +/- extracellular mucin

DDx: SPC may mimic EPC

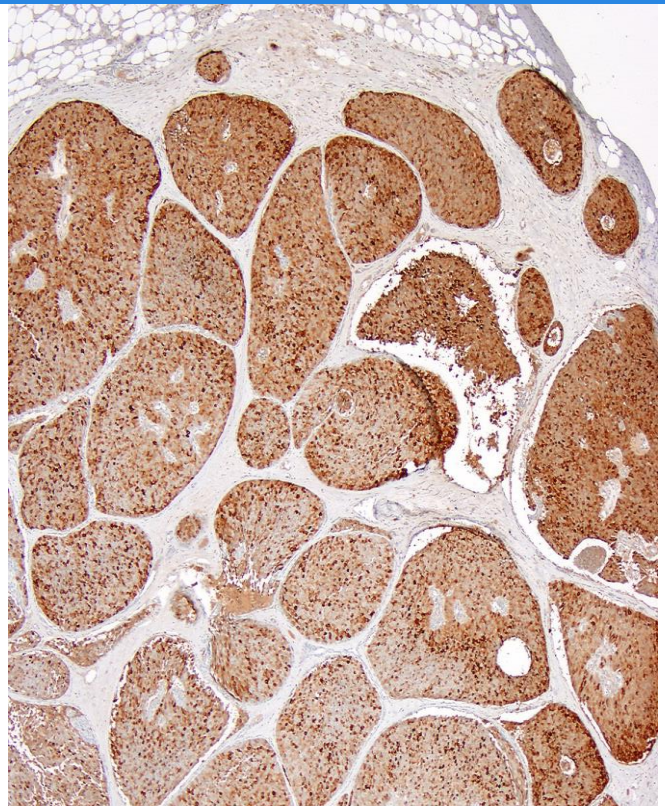




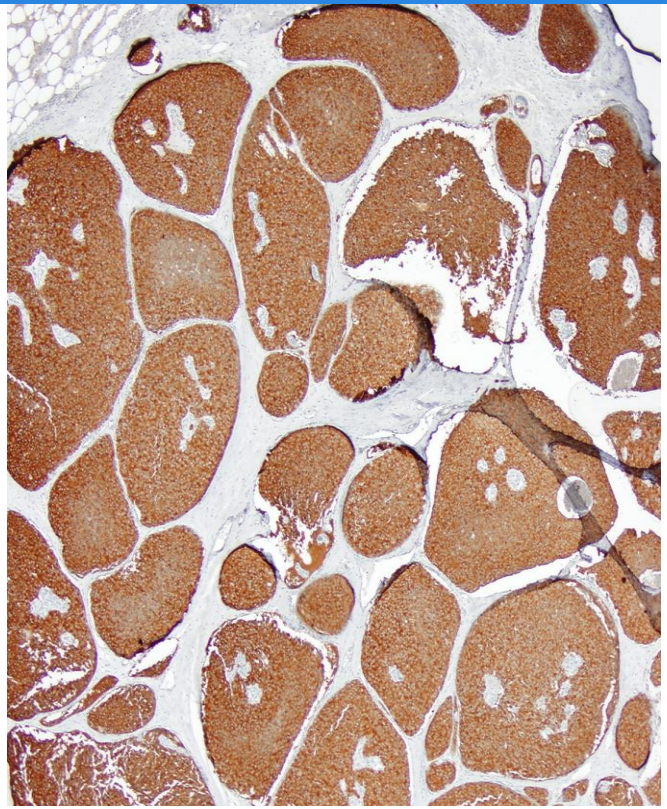


Solid growth predominates in SPC, but is only focal in EPC

Neuroendocrine (NE) markers often (+) in SPC (in situ/ invasive)
(NE markers positivity NOT required for diagnosis of SPC)



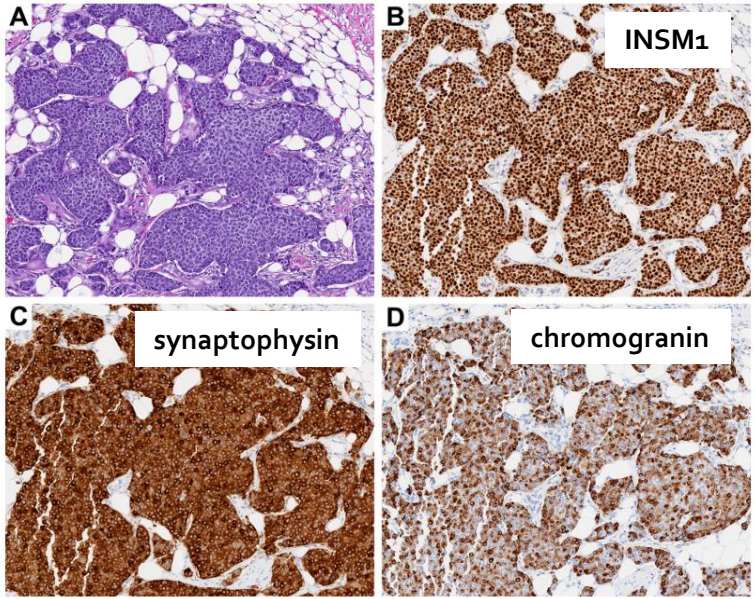
chromogranin



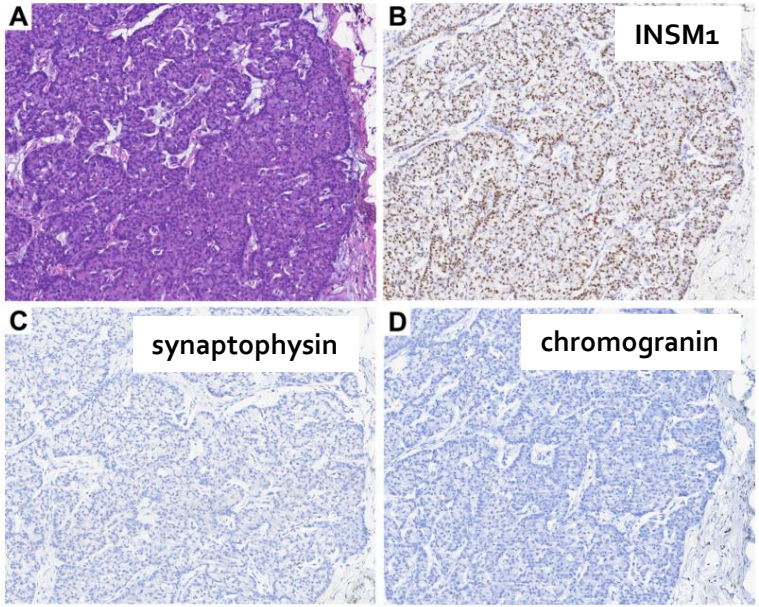
synaptophysin

INSM-1: NE marker expressed in most breast SPCs

Invasive SPC(+) for multiple NE markers



Invasive SPC(+) **only** for INSM1



Zhong E et al. *Hum Pathol* 2022 (e-pub)

Yanay H et al. *Oncol Lett* 2022
Metovic J et al. *Endocr Pathol* 2021
Kudo N et al. *Pathol Int* 2021

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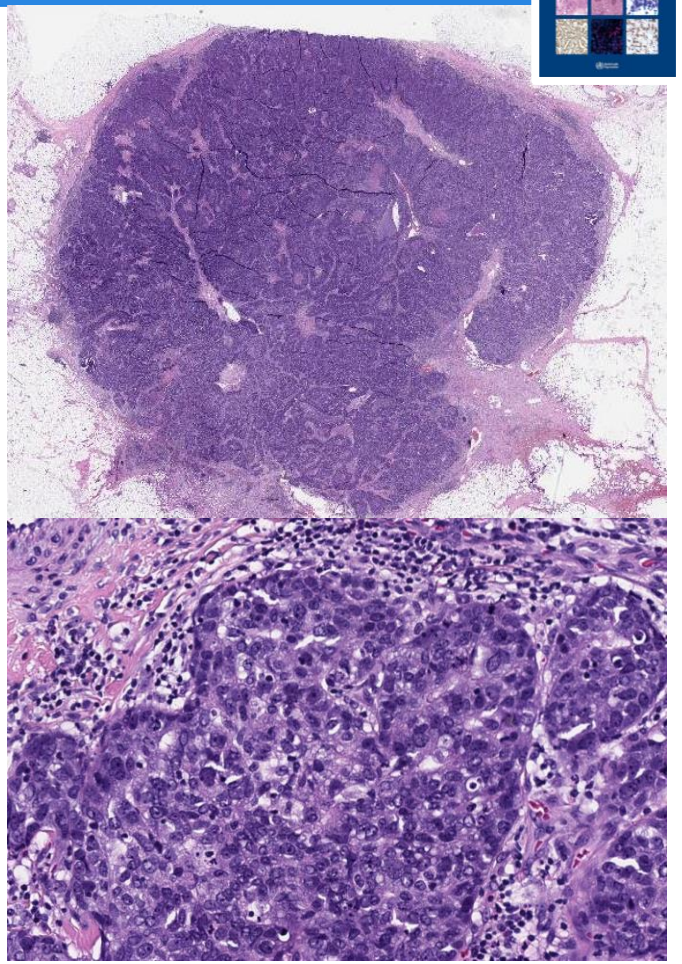
Invasive Papillary Carcinoma (IPC)

- Extremely rare
- **Entirely** papillary
- Frankly invasive growth pattern
- No MECs present around and within the carcinoma
- Grade IPC according to the Nottingham grading system
- Limited to no F/U info (but regarded as having poor prognosis)

WHO Breast Tumours 5th ed. (2019)

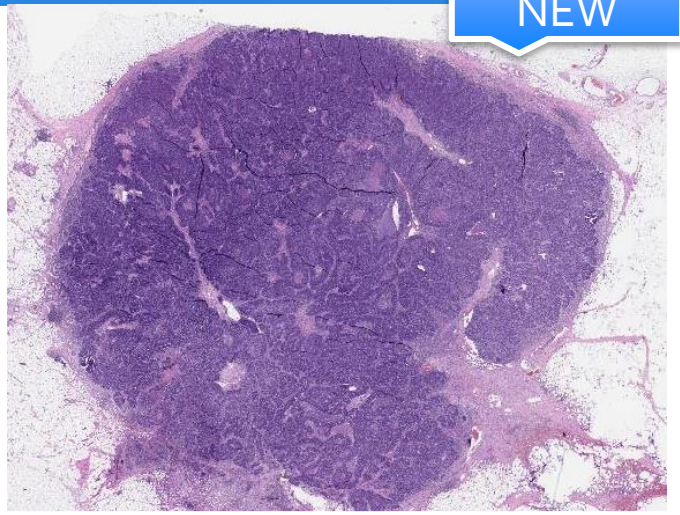


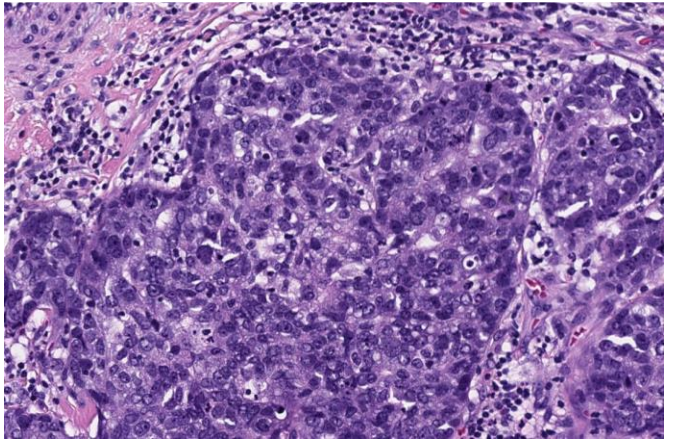
IPC includes "EPC-like" carcinoma with high nuclear grade

WHO 5th NEW

A papillary carcinoma
of high nuclear grade
entirely devoid of MECs
and triple negative or HER2+
=
INVASIVE PAPILLARY CARCINOMA

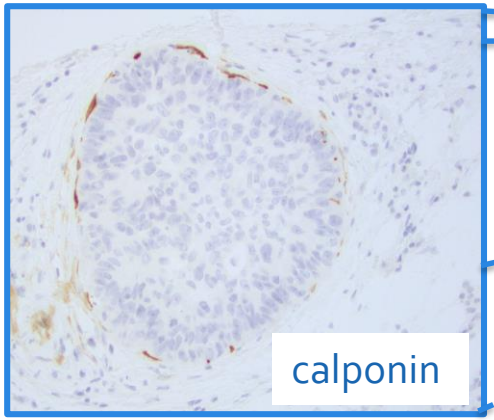
do NOT use the term EPC





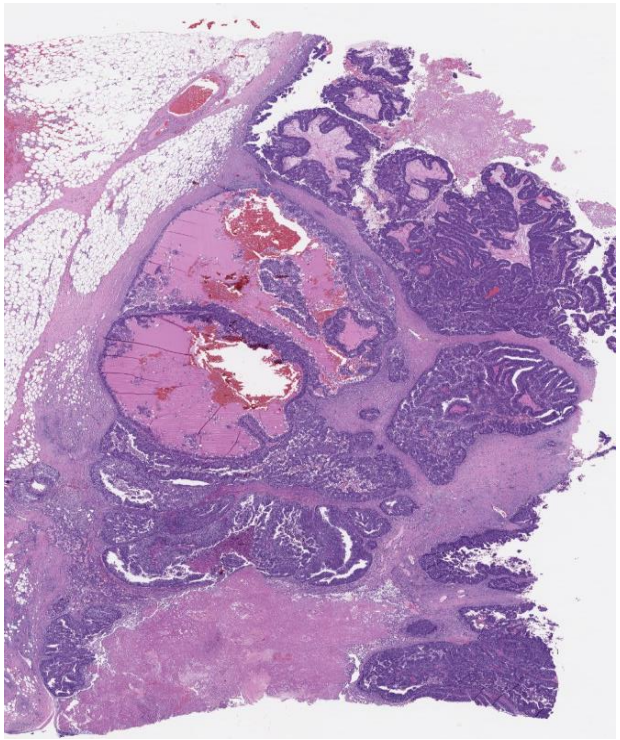
WHO Breast Tumours 5th ed. IARC, Lyon, France 2019

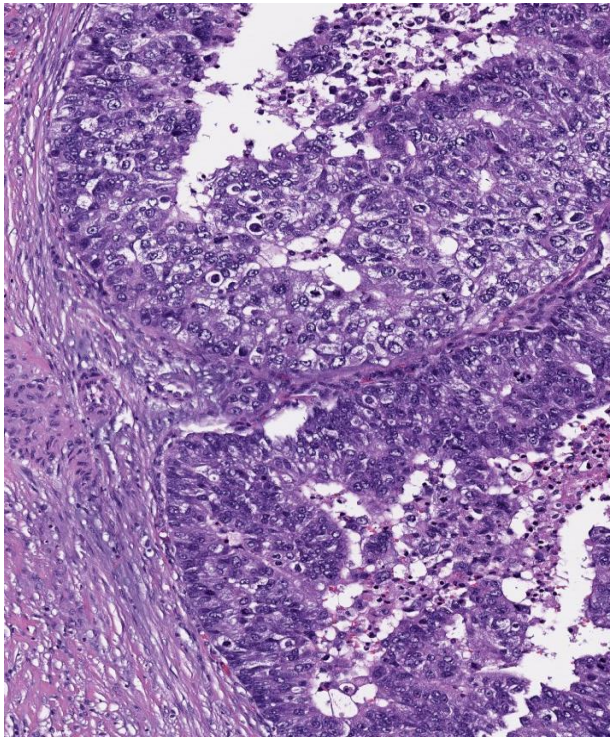
Invasive papillary carcinoma

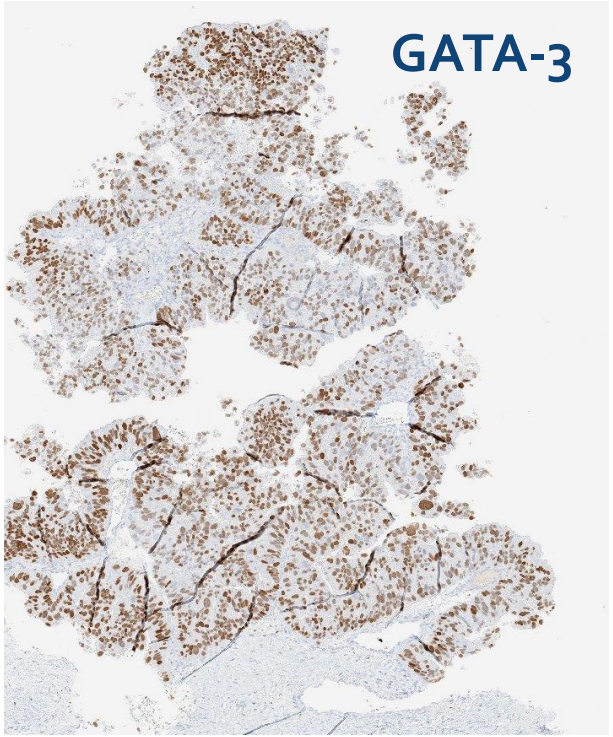


DCIS may be present (usually focal)

No DCIS is present ? → IHC to rule out metastasis







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

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Papillary Neoplasms – take home messages

Many different morphologies and different clinical behavior

Immunohistochemistry may contribute to classify some tumors

myoepithelial markers, ER and CK5/6, GATA3, SOX10 and TRPS1

Papilloma w/o atypia @radiology-pathology concordant CNB: low upgrade rates

- *USA/ Canada/ Australasia: individualized EXC based on clinical symptoms, imaging size and patient's hx of breast carcinoma*
- *European countries approach: B3 lesion → vacuum assisted biopsy, then observation*

NEW in the WHO 5th ed.

- Encapsulated papillary carcinoma (EPC): low or intermediate nuclear grade only
- Invasive papillary carcinoma (IPC): entirely papillary, no MECs
  - includes "EPC-like" carcinoma of high nuclear grade, triple negative or HER2+
  - No DCIS → rule out metastatic carcinoma
- Criteria for the diagnosis of SPC in situ [distribution pattern consistent with an *in situ* process, *regardless of the presence of MECs around the nodules]* vs SPC invasive

Thank you