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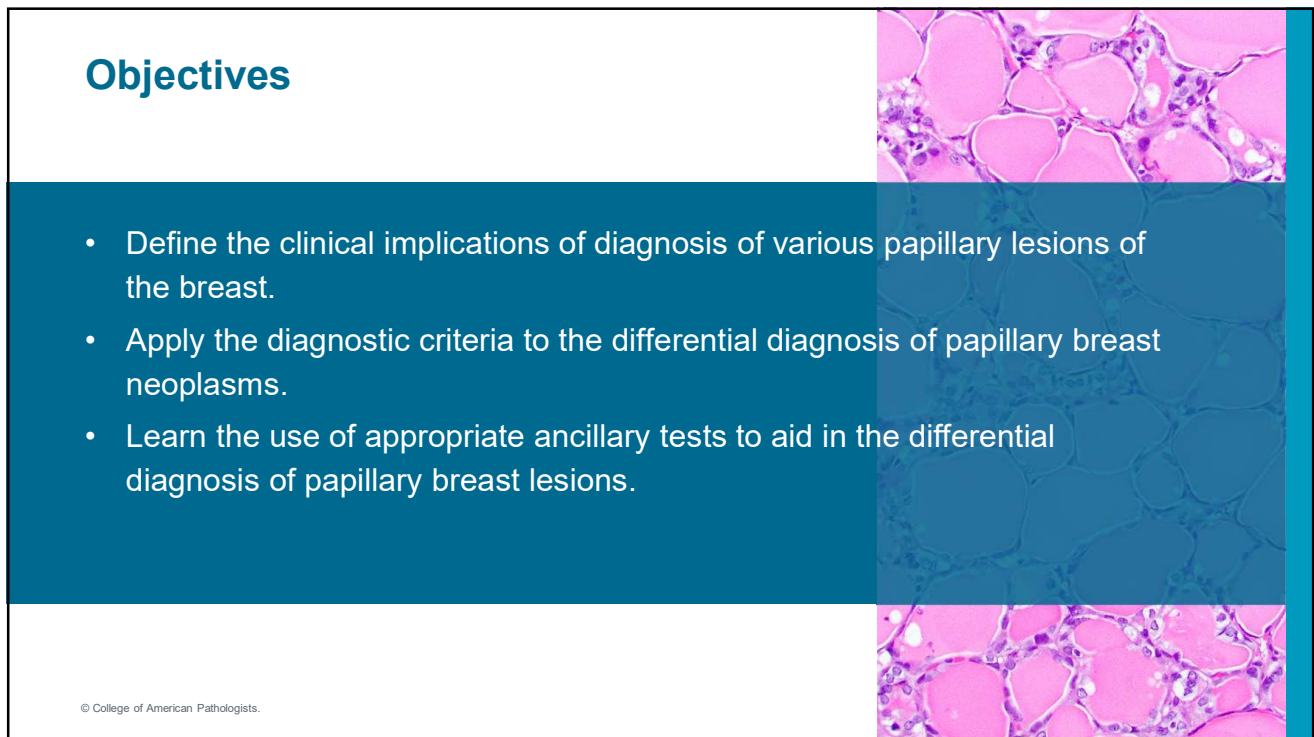
Papillary Lesions of the Breast, Simplified

Pathology on the Coast

Dr. Olga Ioffe, MD

Monday, June 9, 2025

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Objectives

- Define the clinical implications of diagnosis of various papillary lesions of the breast.
- Apply the diagnostic criteria to the differential diagnosis of papillary breast neoplasms.
- Learn the use of appropriate ancillary tests to aid in the differential diagnosis of papillary breast lesions.

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Outline

Benign lesions with papillary/sclerosing component

Intraductal papilloma and its variants

Complex sclerosing lesion/radial scar

Adenomyoepithelioma

Intraductal papilloma with ADH

Intraductal papilloma with DCIS

Papillary DCIS

Encapsulated papillary carcinoma (with or without definite invasion)

Solid papillary carcinoma (with or without definite invasion)

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Intraductal papilloma and its variants

- **Intraductal papilloma**
 - Subareolar
 - Peripheral
- **Sclerosing papilloma**
- **Papilloma with usual epithelial hyperplasia**

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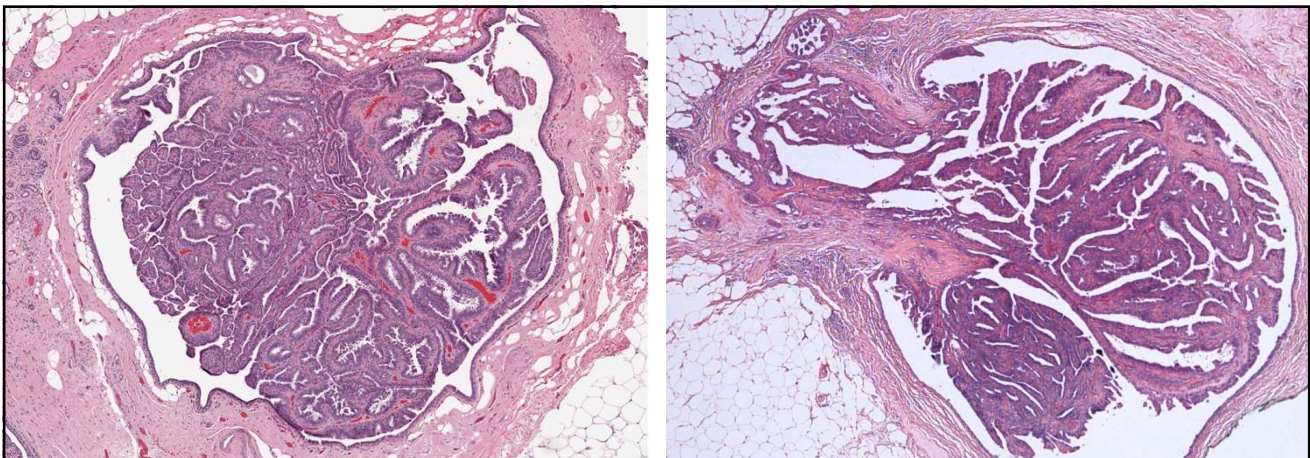
Intraductal papilloma

- Large duct papilloma
 - Subareolar, solitary
 - Nipple discharge
 - Sixth decade
 - Cancer risk x 2; with ADH x 5-7.5
- Peripheral papillomas
 - Younger patients
 - Usually multiple (sometimes called papillomatosis)
 - Cancer risk x 3 ; with ADH x 5-7.5

» *Am J Surg Pathol* 2006; 78:258 (Mayo Benign Breast Disease Cohort)

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Intraductal Papilloma

Definition: *Benign lesion located within a distended duct ... with a fibrous wall ..., composed of papillary projections with fibrovascular cores ... a papillary aggregate/nodule*

WHO Breast Tumours 5th ed. 2019

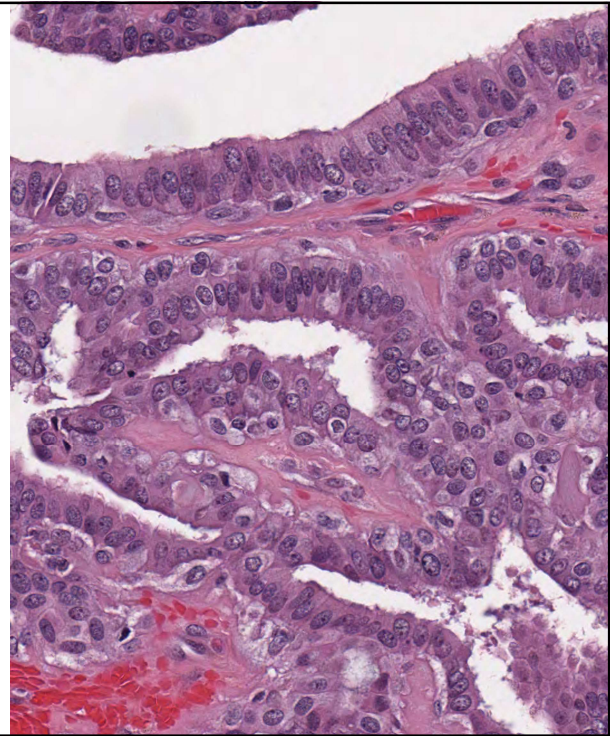
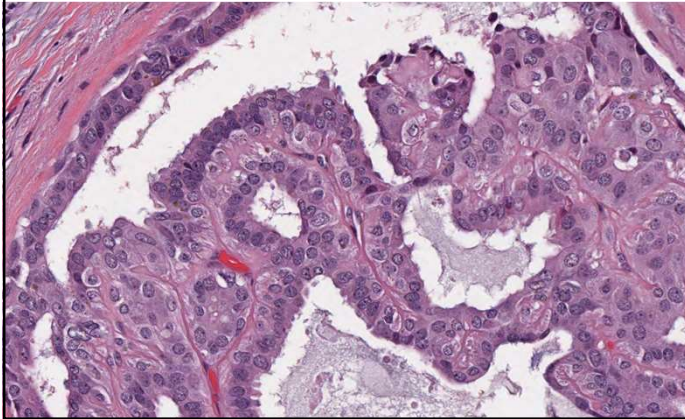
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Intraductal Papilloma

- Definition: **Benign lesion located within a duct..., composed of papillary projections with fibrovascular cores, covered by an epithelial and myoepithelial layer**

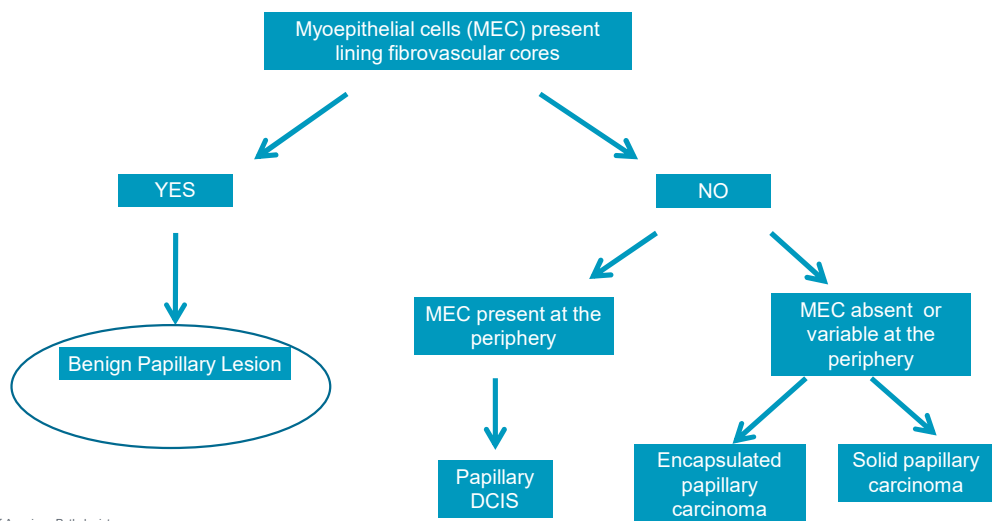
- WHO Breast Tumours 5th ed. 2019



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Diagnosis of Papillary Breast Lesions

Modified from Collins & Schnitt, 2015



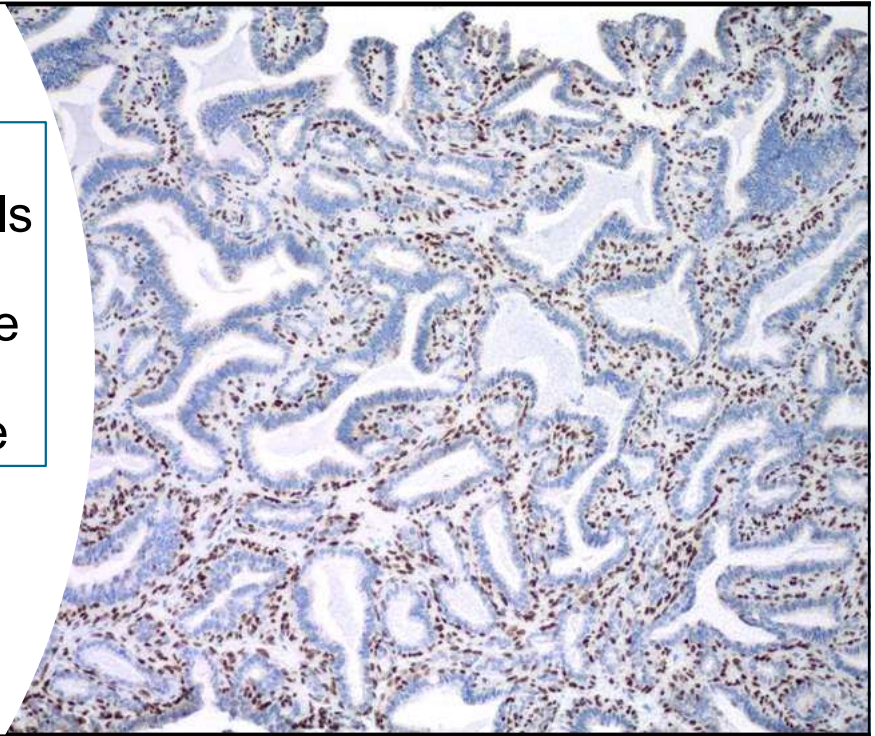
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Myoepithelial cells
are continuous
along the papillae
and around the
duct/cystic space

p63

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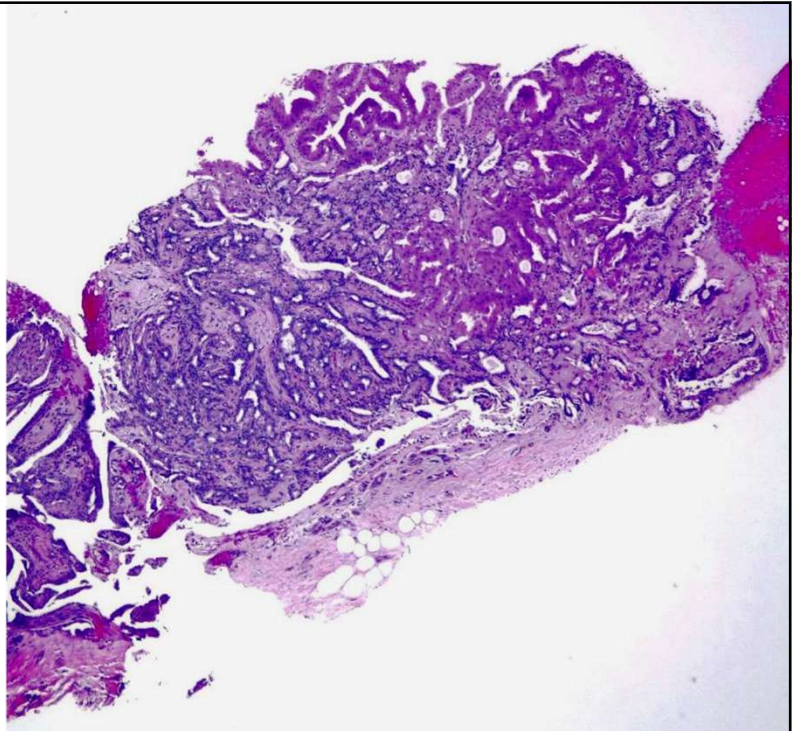


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Intraductal Papilloma

Focal apocrine metaplasia

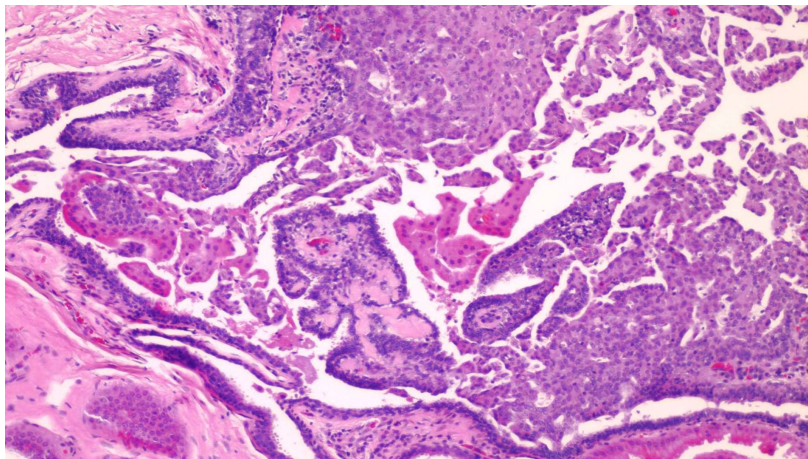
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Intraductal Papilloma

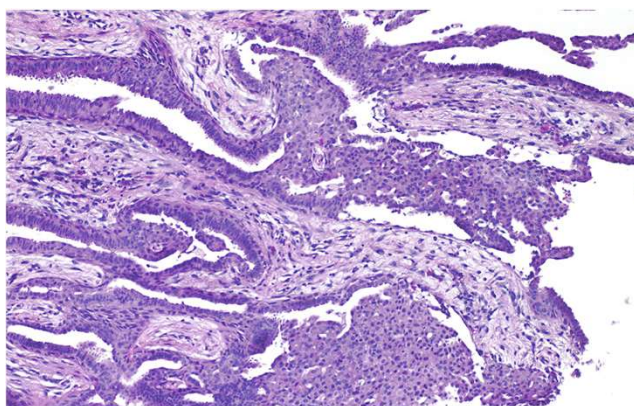
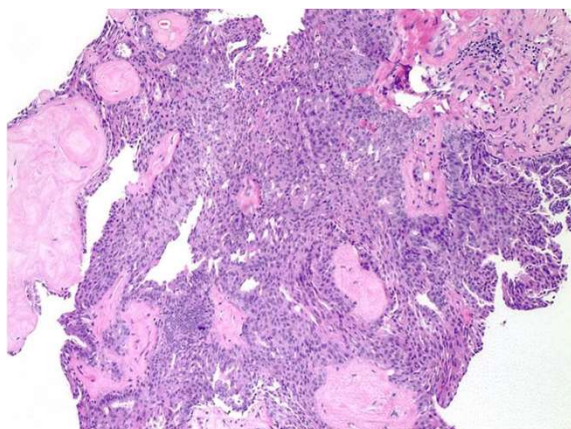
Focal apocrine metaplasia



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Florid usual ductal hyperplasia in intraductal papilloma



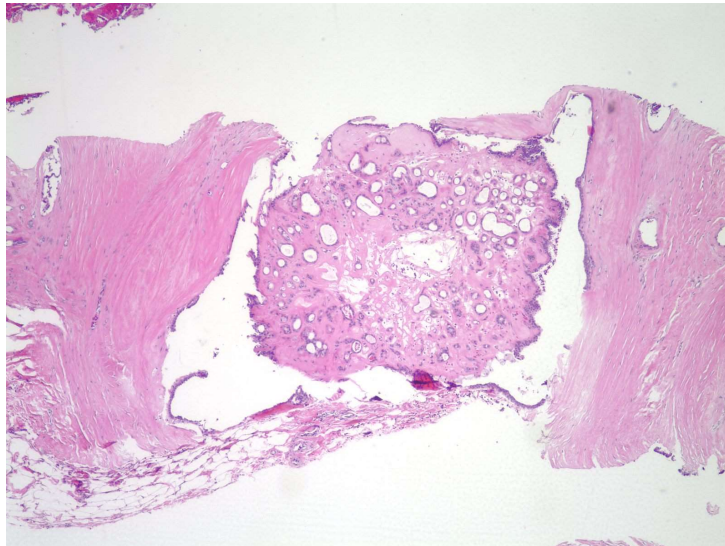
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Sclerosing papilloma



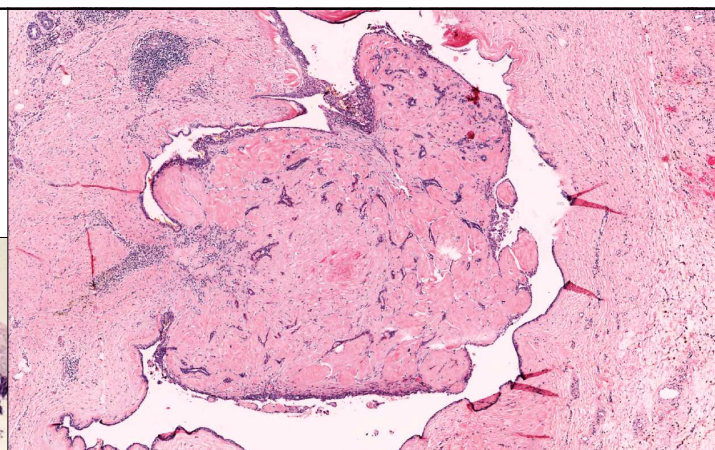
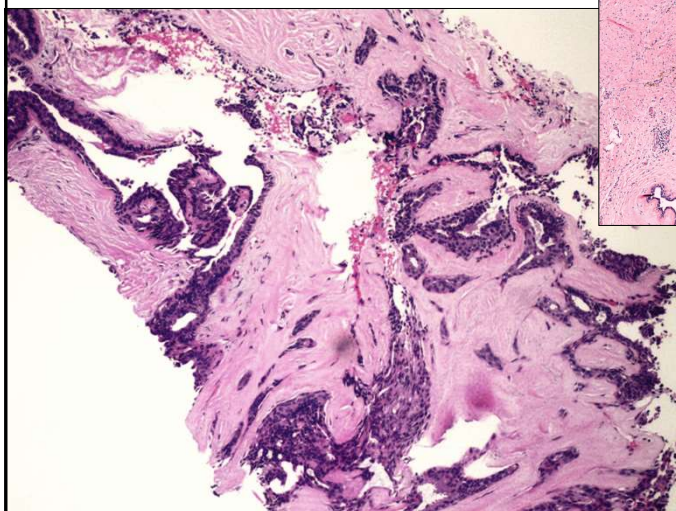
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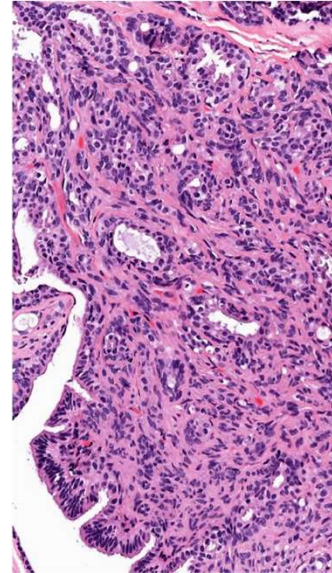
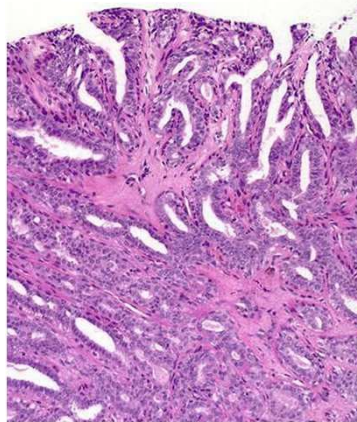
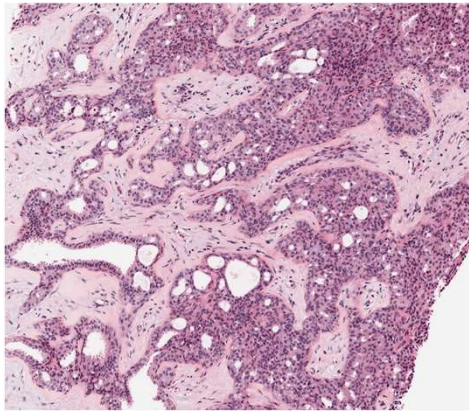
SCLEROSING PAPILLOMA



Proliferation of residual myoepithelial cells

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Myoepithelial cell hyperplasia in intraductal papilloma



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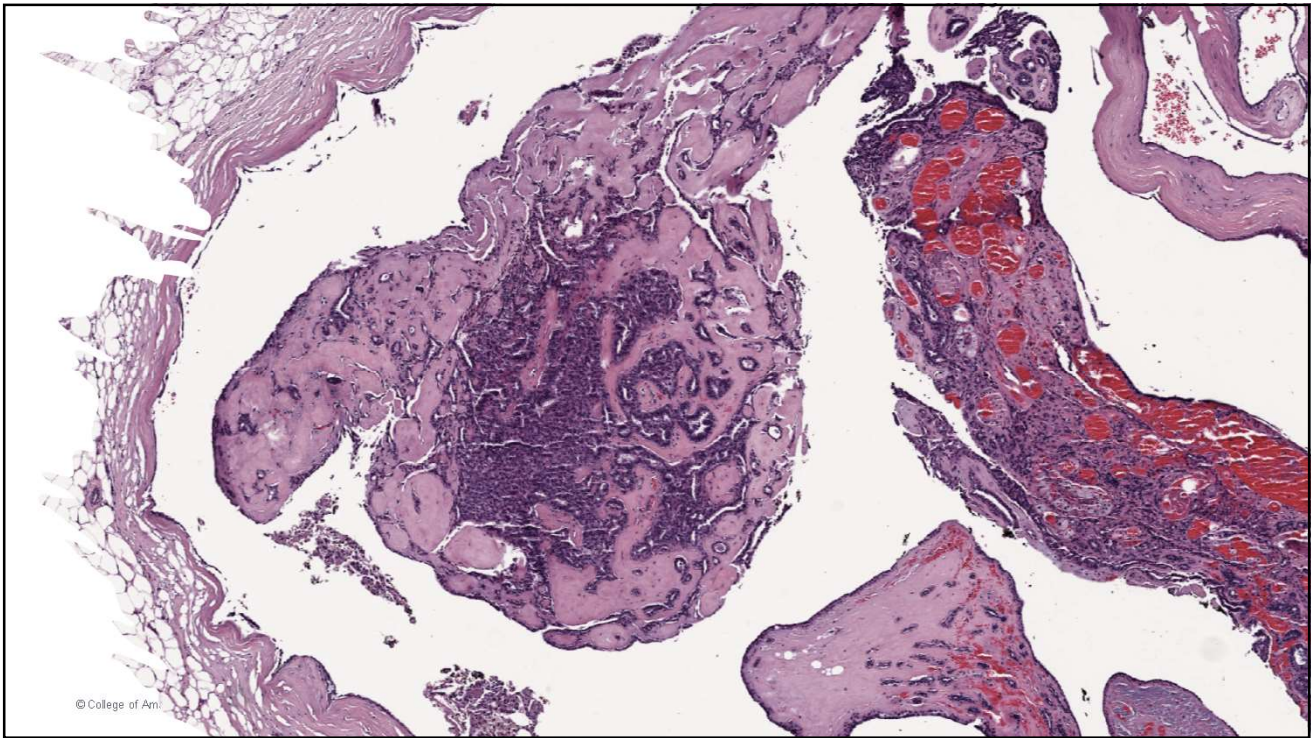
If needed, multiple IHC markers for myoepithelial cells (cytoplasmic and nuclear) and ER should be used since there may be variable staining with each in any given case

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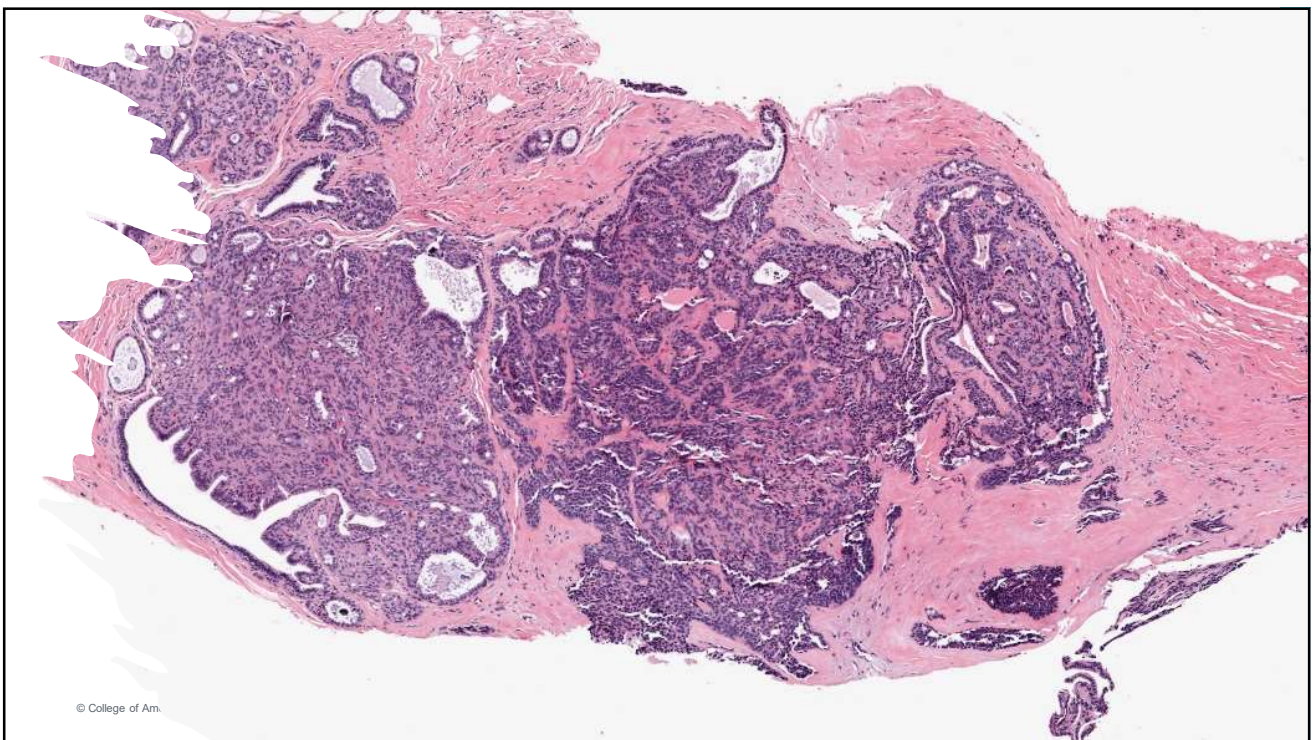
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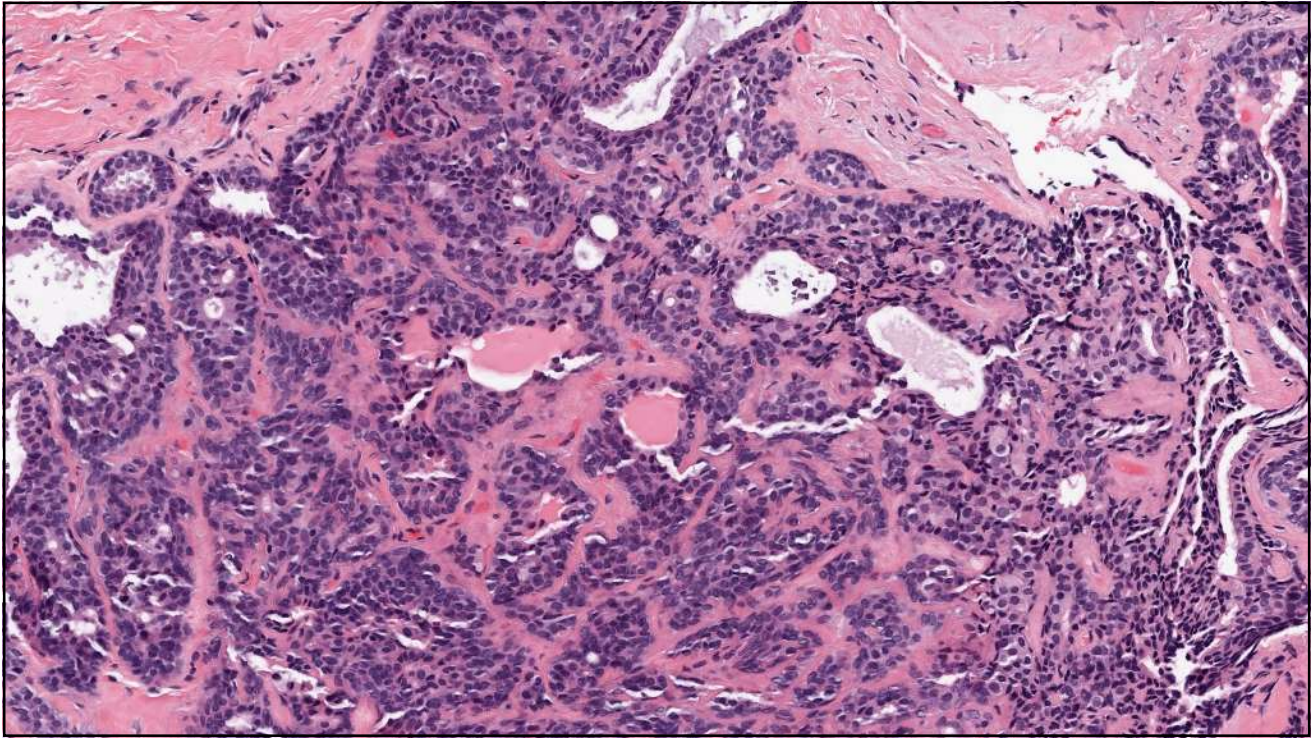
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Papilloma on core biopsy

- Intralesional heterogeneity – may be focally involved by carcinoma in situ
- May fragment or fall out in core biopsies
- Difficult to classify, especially in a limited sample
 - Sometimes even confused with FA on core bx!
- Malignancy on excision – 0-21%
- Predictors of malignancy on excision:
 - » Mass lesion
 - » Residual mass after core biopsy
 - » Multiple papillomas
 - » Large size
 - » Calcifications
 - » Older patient

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SAMPLING!

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Upgrade of papillomas diagnosed on core bx

- **Prospective multicenter study institutional study (TBCRC 034)**
 - 116 patients
 - 10 centers
 - 2 cases of LG DCIS (1.7%) on excision
 - Central review:
 - 85/116 (73%) IDPs w/o atypia confirmed
 - 31/116 (27%) IDP w/o atypia NOT confirmed (!)
 - None of the upgrades confirmed (DCIS → ADH)

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Nakhlis et al. Ann Surg Oncol. 2021;28:2573

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Papillomas rejected by central review???

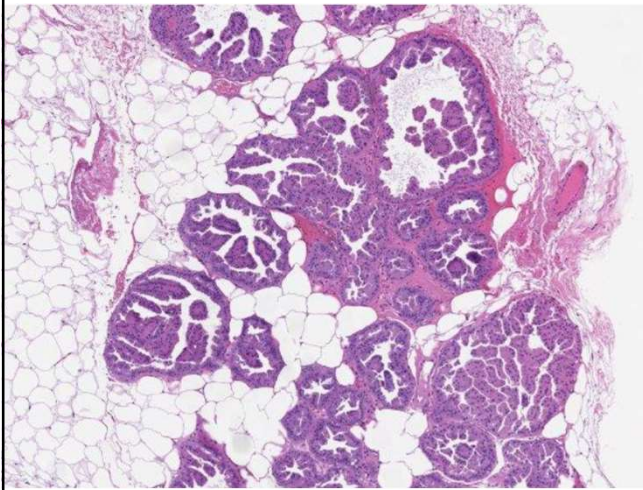
- **21/31 (68%) benign mimics of intraductal papilloma:**
 - Papillary apocrine metaplasia
 - Plicated subareolar ducts
 - Usual ductal hyperplasia (UDH)
 - Fibroadenomatous change
- **This is the differential diagnosis of papillomas on core bx!**

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Nakhlis et al. Ann Surg Oncol. 2021;28:2573

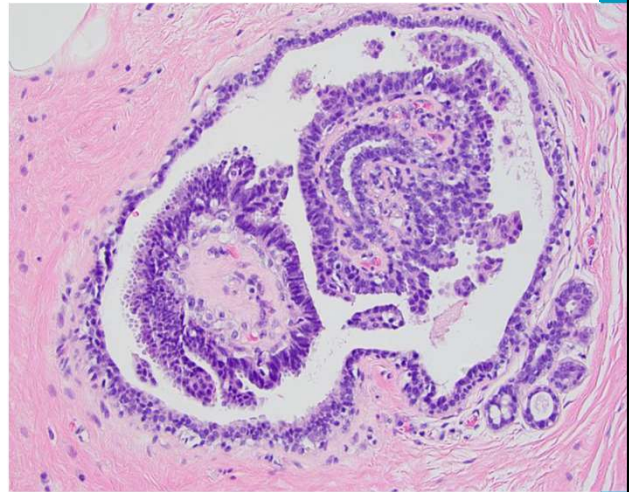
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Papillary apocrine metaplasia



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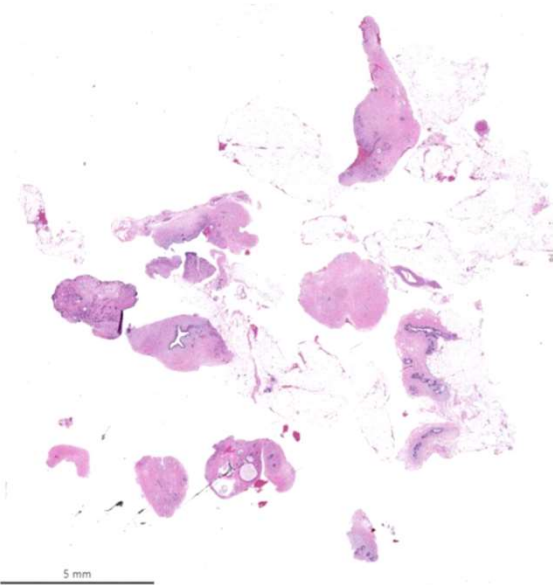
UDH, papillary



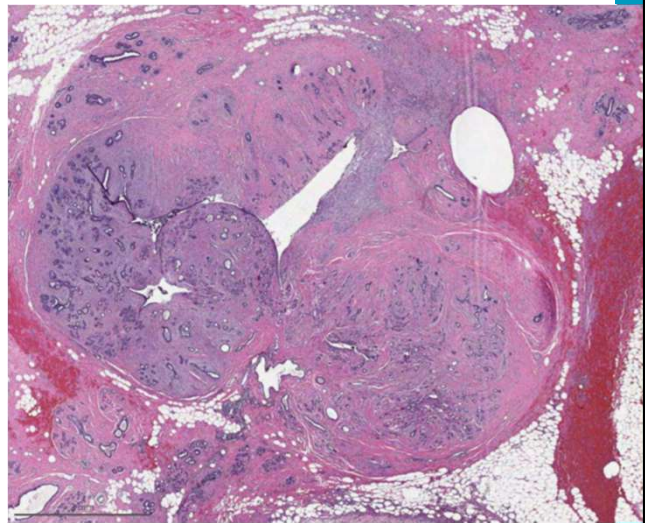
E. Brogi, 2021

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Fibroadenomatoid nodule



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E. Brogi, 2021

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Management of papillomas diagnosed on CNB

- Subareolar/single papilloma concordant with imaging – never upgraded - may be followed
- Very small incidental papillomas (confined within a core) – never upgraded - may be followed
- Lesion completely removed by CNB - may be followed

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Management of papillomas diagnosed on CNB

- ***“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”***

(American Society of Breast Surgeons Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions)

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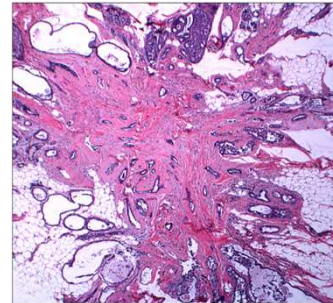
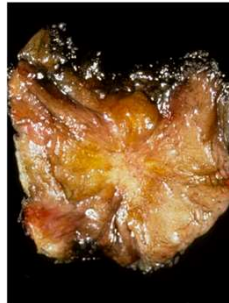
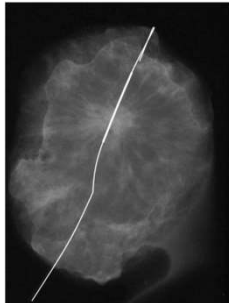
Solid papillary carcinoma (with or without definite invasion)

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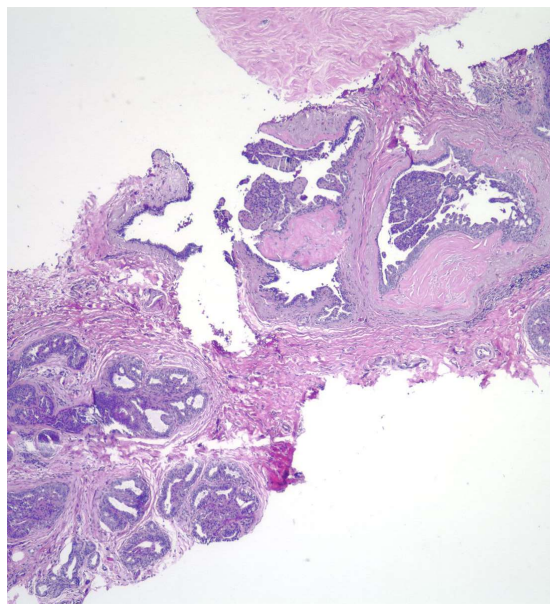
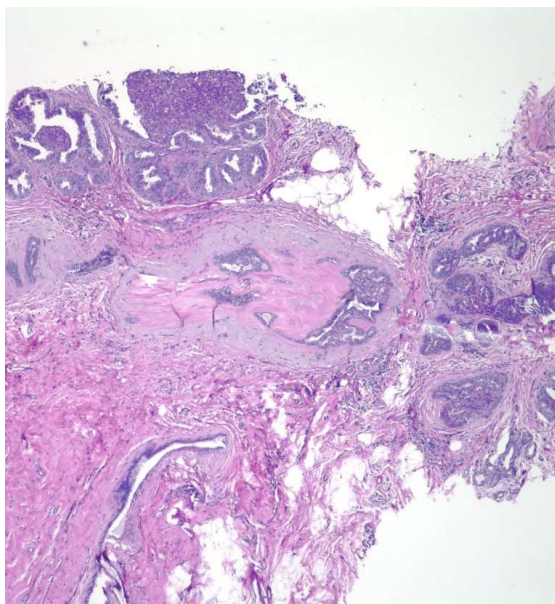


Radial Scar/ Complex Sclerosing Lesion

- **Radial scar:**
 - Central hyalinized zone and an irregular border
 - Mimics a scar
- **Complex sclerosing lesion:**
 - More general term that also includes lesions with papilloma(s) and sclerosing adenosis
- **Radial sclerosing lesion:**
 - Another term for radial scar that avoids confusion with true scars

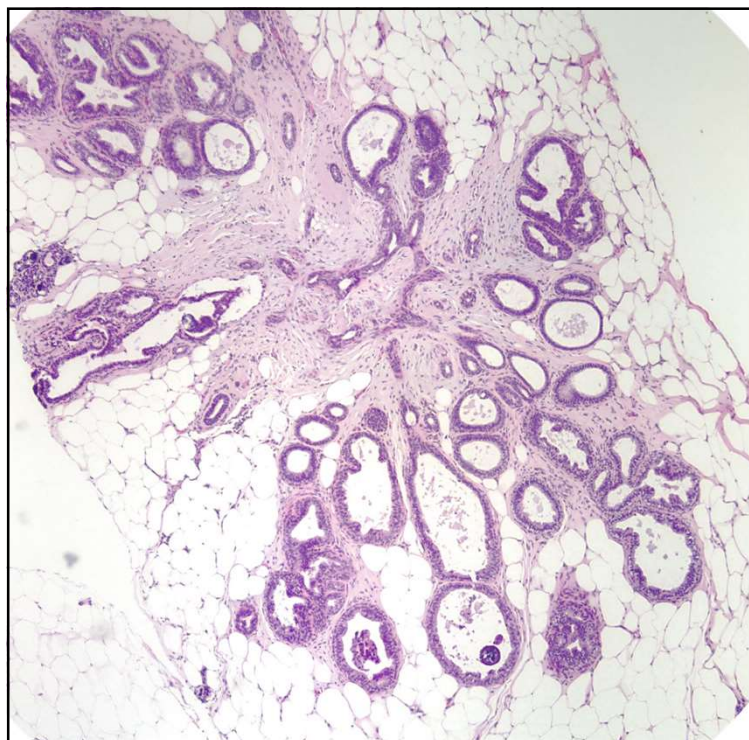
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Why excise radial scars?

- May show intra-lesional heterogeneity and harbor focal atypia, DCIS & invasive tubular carcinoma
- Co-existing malignancy may be focal and not present in cores
- Excision is diagnostic

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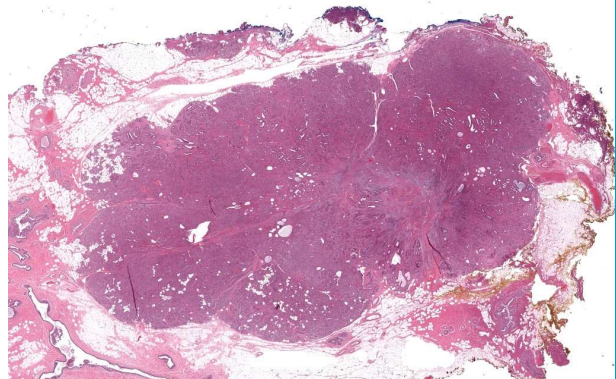
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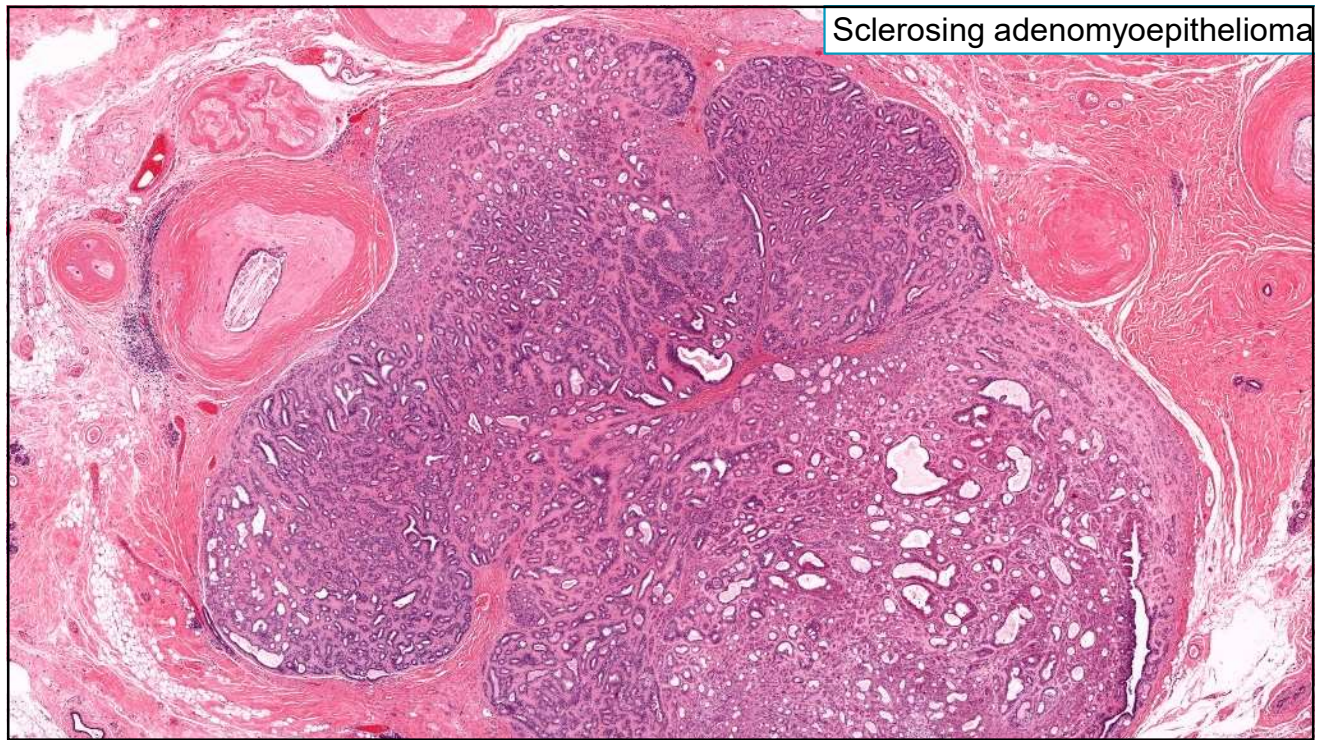
Adenomyoepithelioma

- *“Rare biphasic neoplasm characterized by small epithelium-lined spaces with inner luminal ductal cells and a proliferation of variably enlarged and clearly noticeable myoepithelial cells” WHO 2019*
- Lobulated, tubular and papillary architectural patterns
- AME with predominantly papillary pattern may mimic IDP with myoepithelial hyperplasia

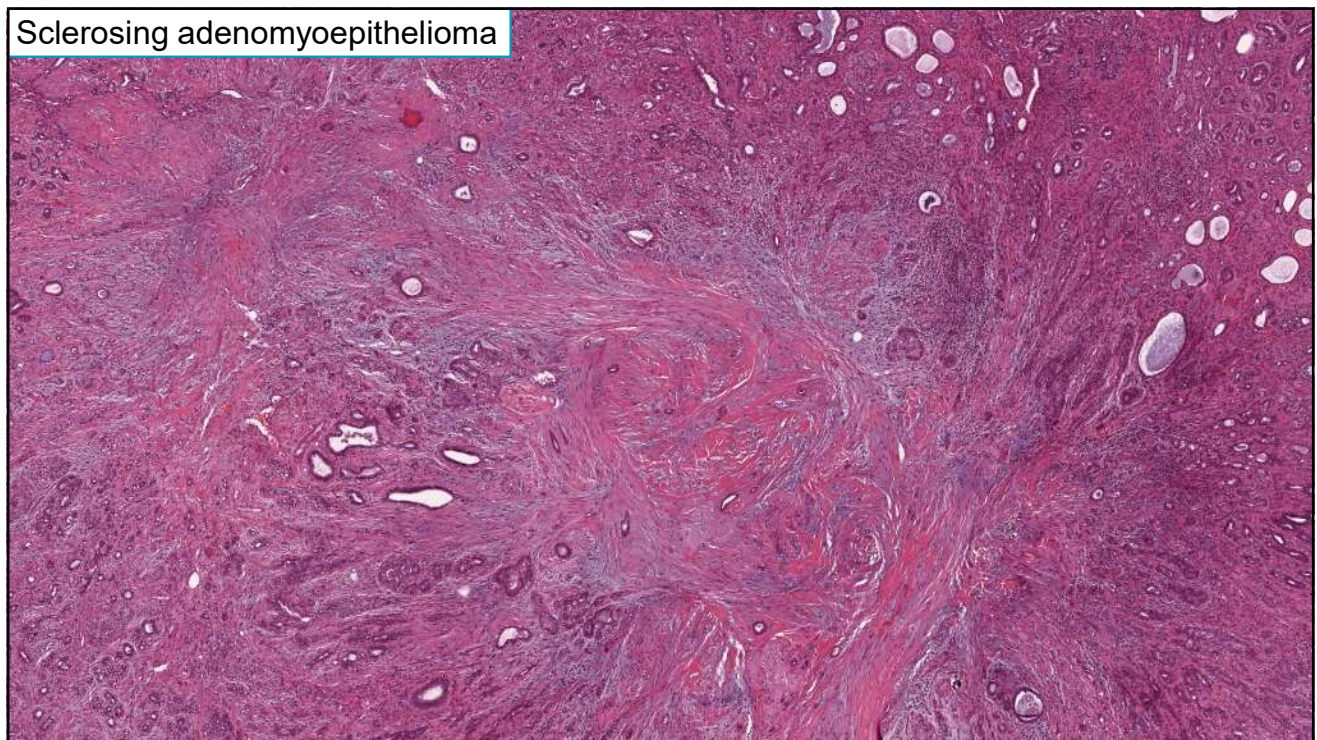


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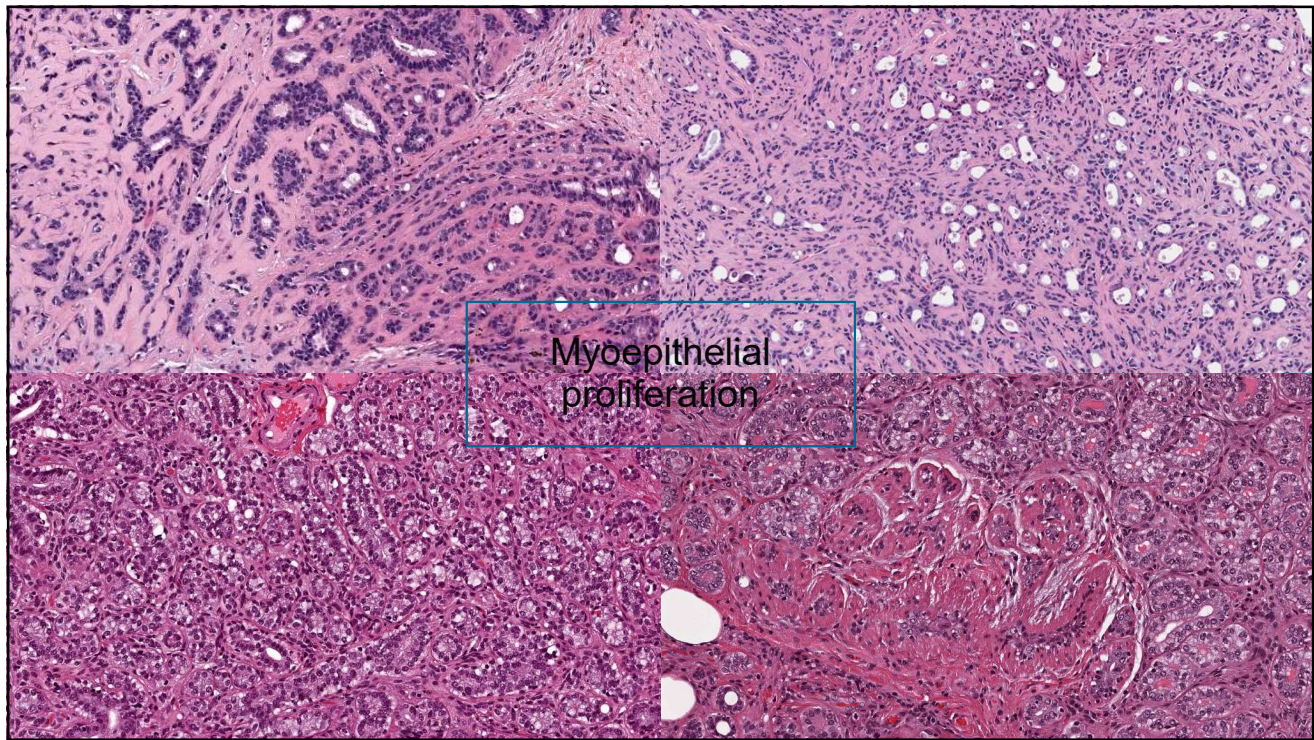
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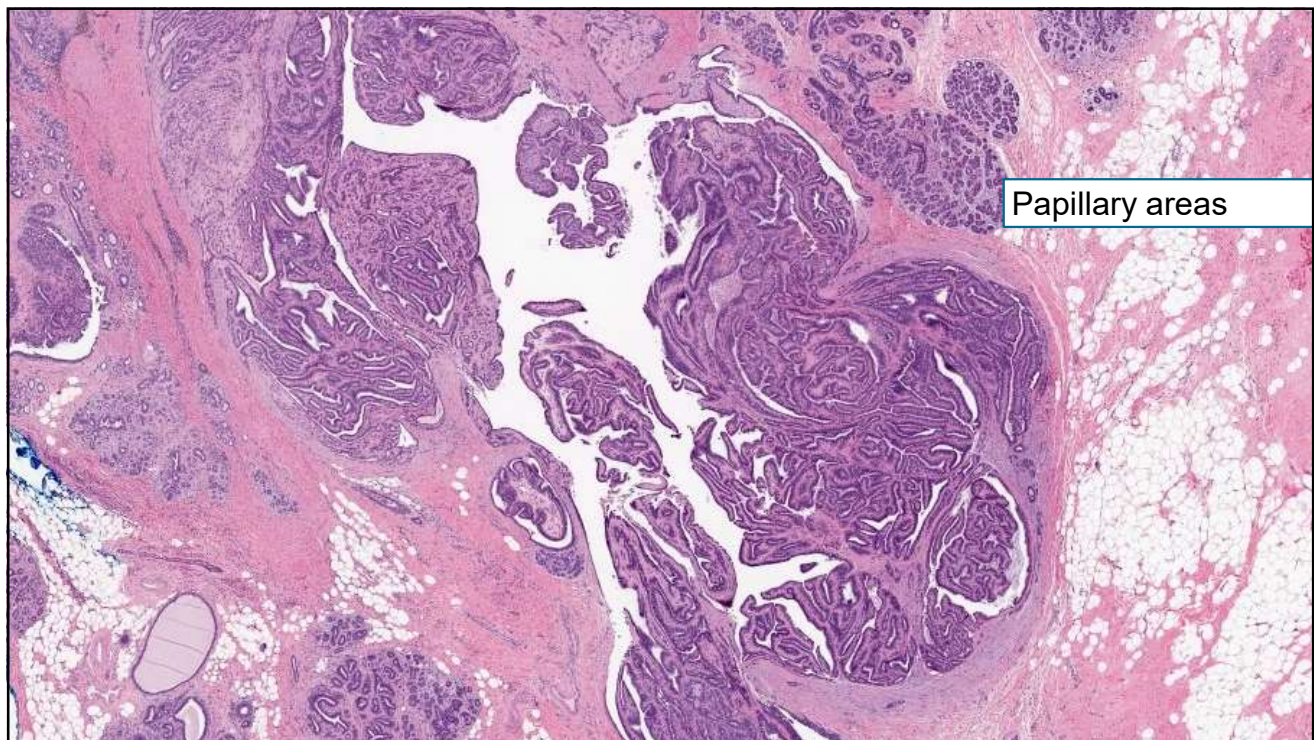
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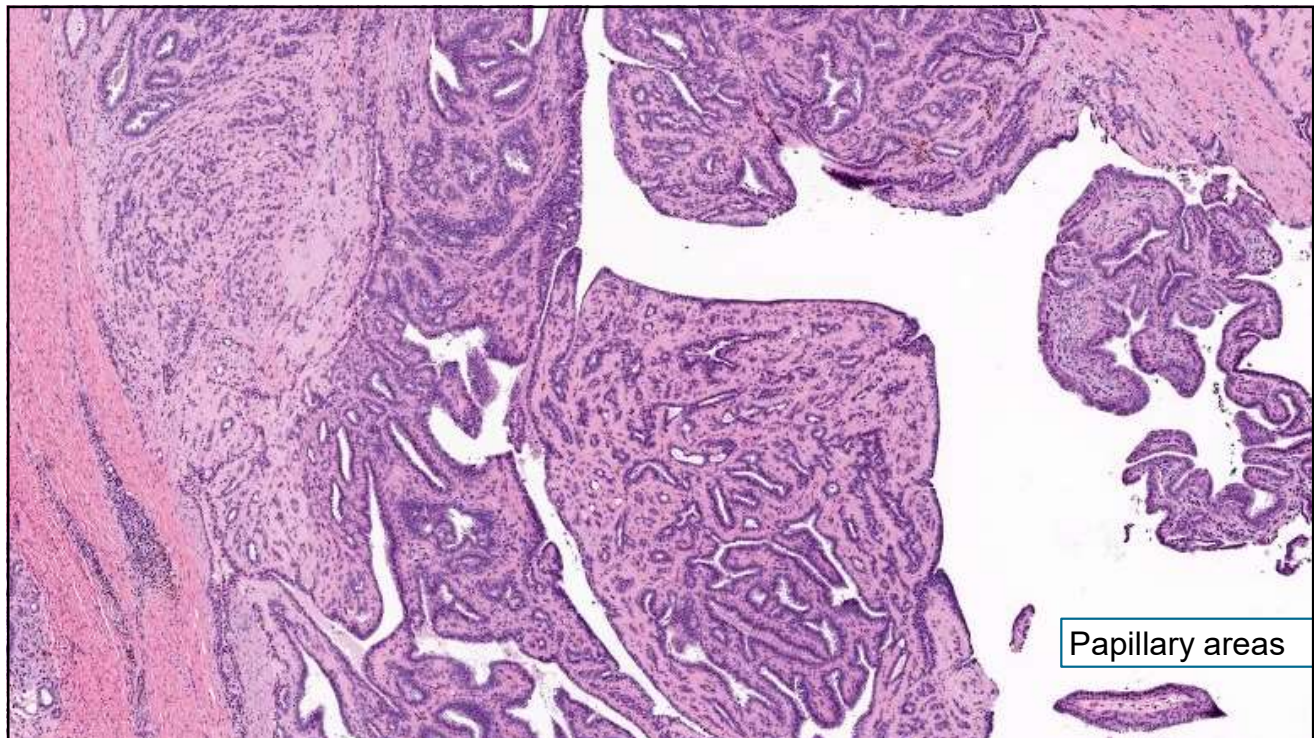
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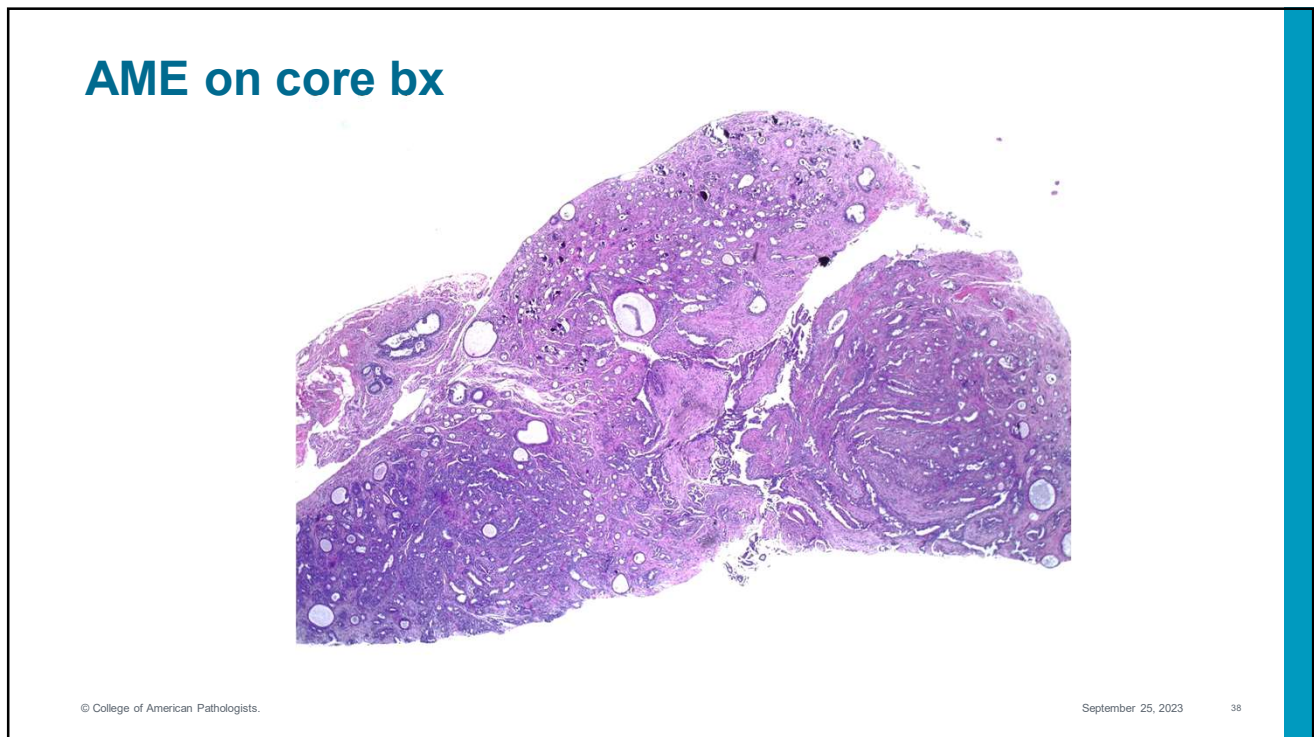
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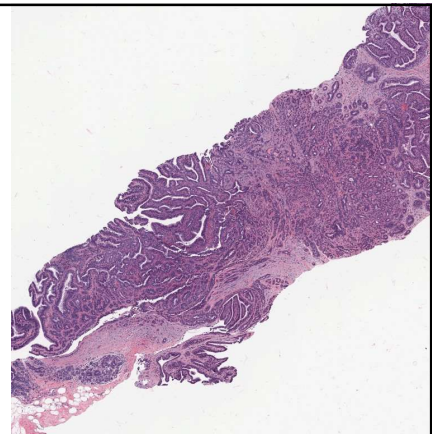
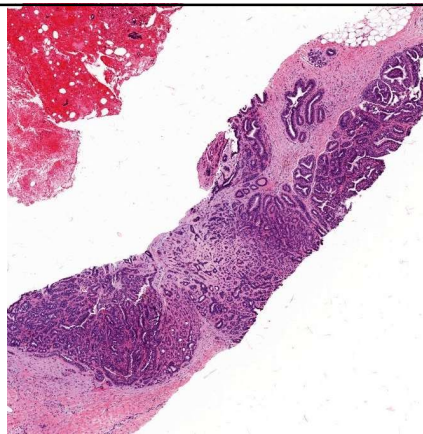
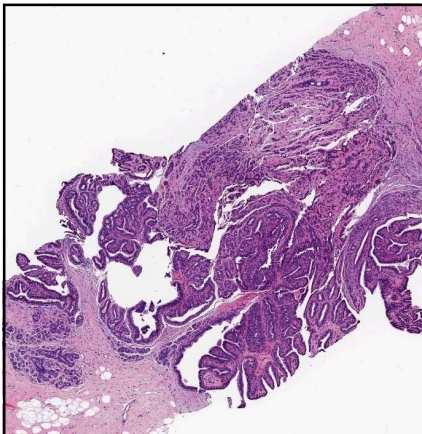
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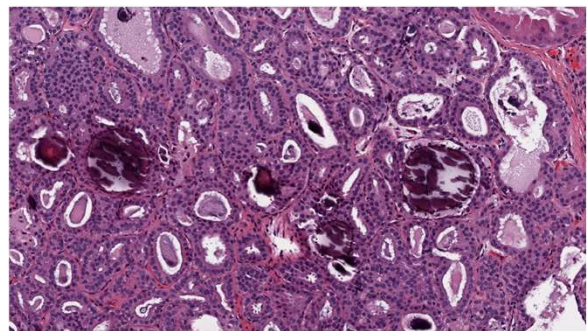
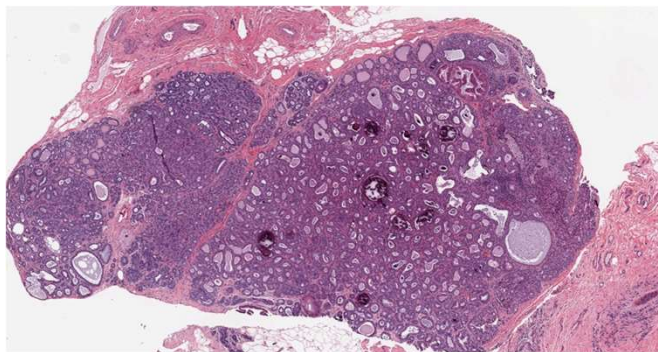
AME or IDP on core bx???

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- “When papillary architecture predominates, AME may be difficult to distinguish from IDP with myoepithelial hyperplasia.” (WHO 2019)
- AME is a variant of intraductal papilloma (Collins LC, Schnitt SJ, “Bx book” 2017)
- If in doubt, call it a complex sclerosing lesion
- Recommend excision to examine the whole thing

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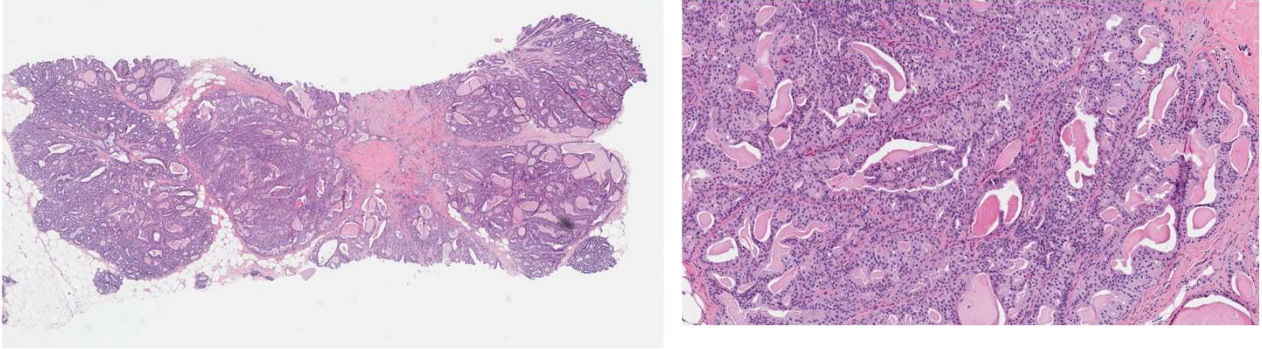
AME with atypia (ADH)



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AME with DCIS



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Adenomyoepithelioma

- ER usually negative but can be focally positive
- Management
 - No data on upgrade rates of AME w/o atypia
 - All need to be excised

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Solid papillary carcinoma (with or without definite invasion)

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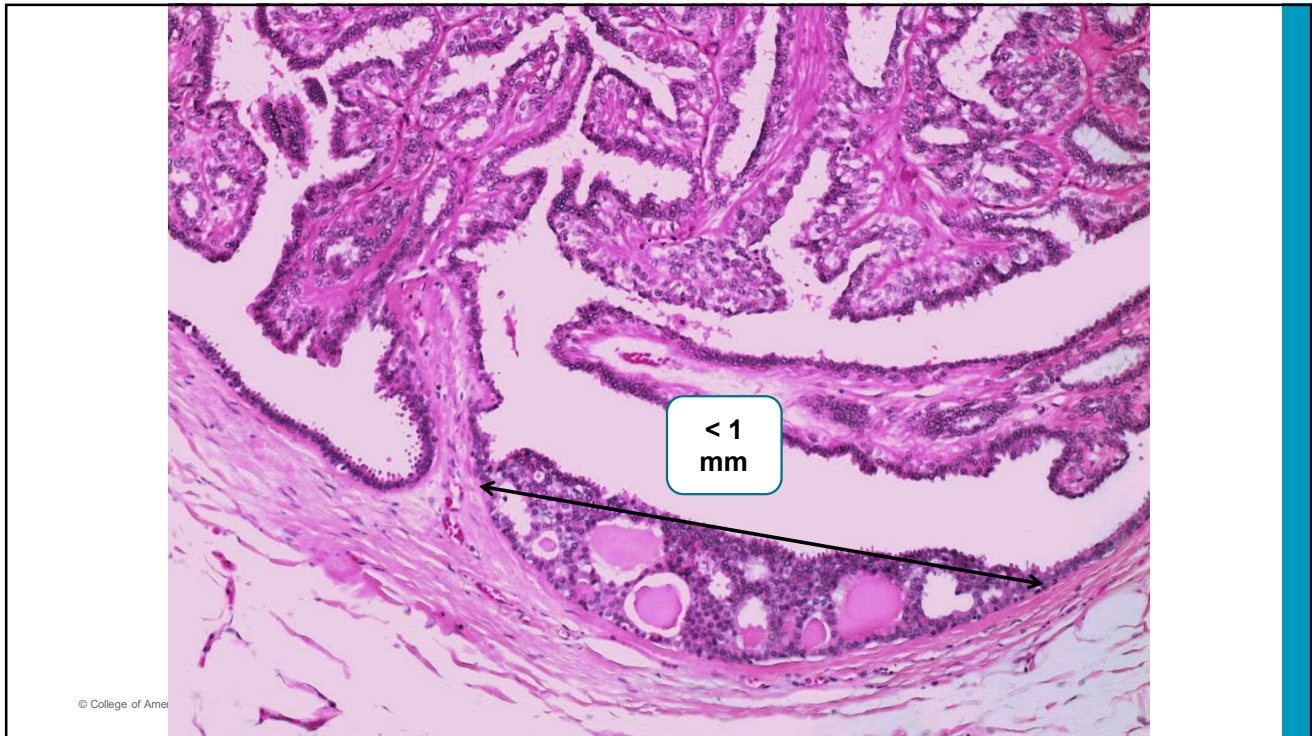
Intraductal papilloma with ADH

- A low nuclear grade atypical epithelial proliferation **measuring <3 mm within an underlying identifiable benign papilloma (not outside!)**
- **OR space between adjacent fibrovascular cores is equivalent to a duct space (also in WHO 2019) – SO less than 2 full spaces**
- **IF HIGH GRADE – DCIS REGARDLESS THE AMOUNT!**
- Indication for excision
- Malignancy on excision – up to 77%
- Negative margins recommended (good luck with that!)

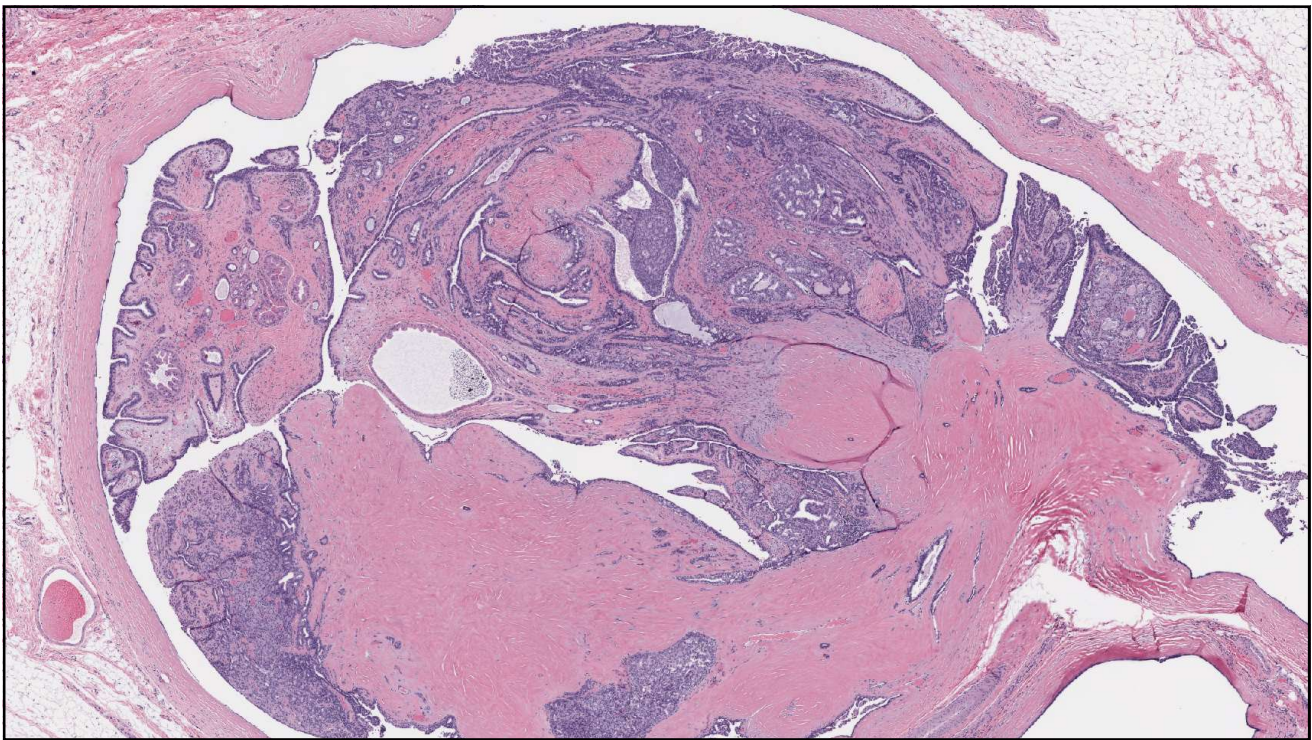
(“atypical papilloma” is not a recommended term)

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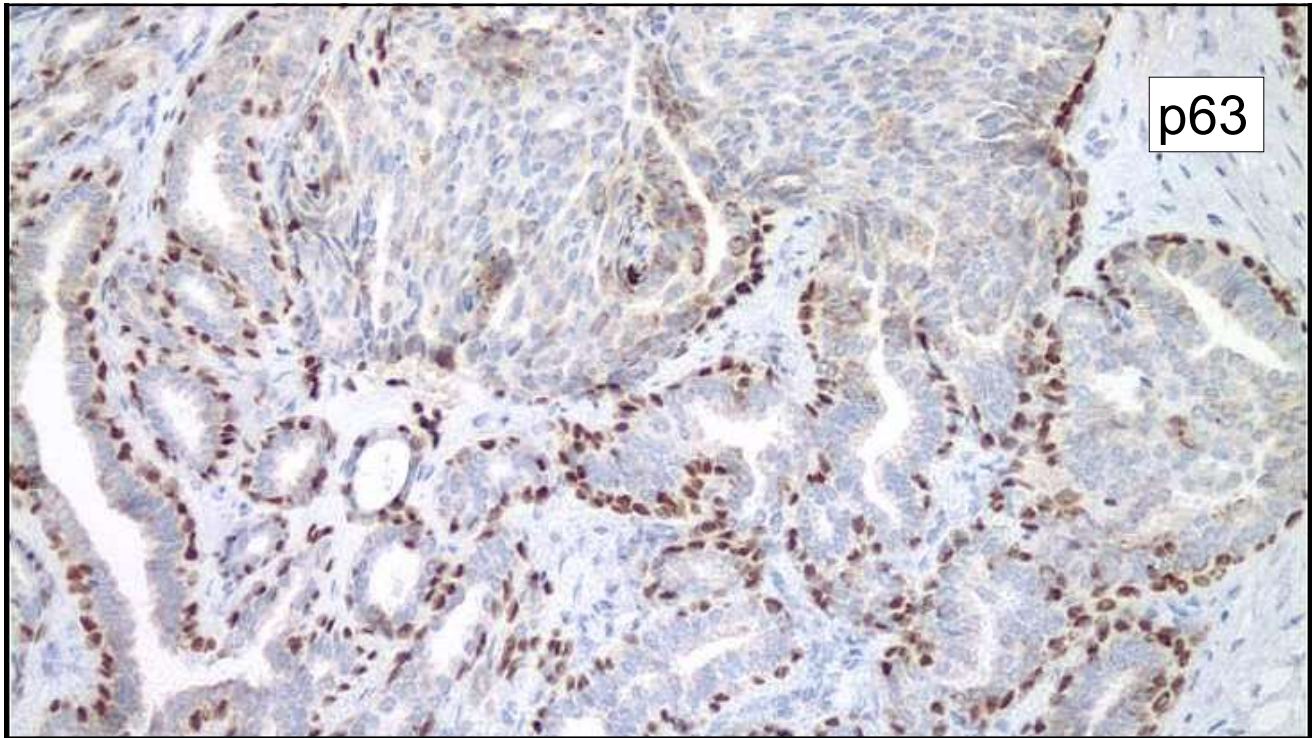
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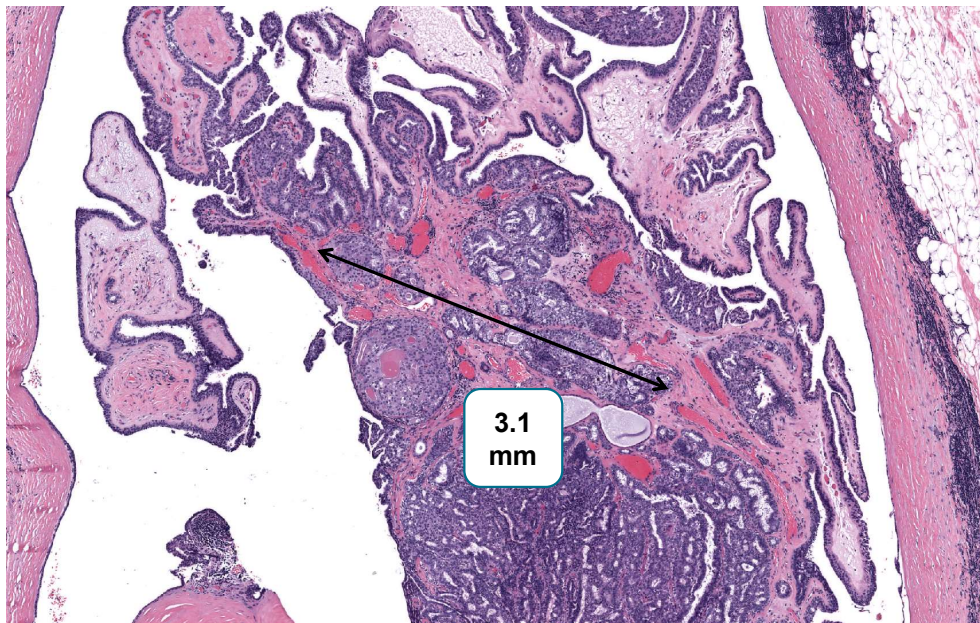
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Papilloma with DCIS

- *“Focal population of monotonous cells with cytological and architectural features of low-grade ductal neoplasia”*
- **>3 mm within an intraductal papilloma**
(WHO 2019)

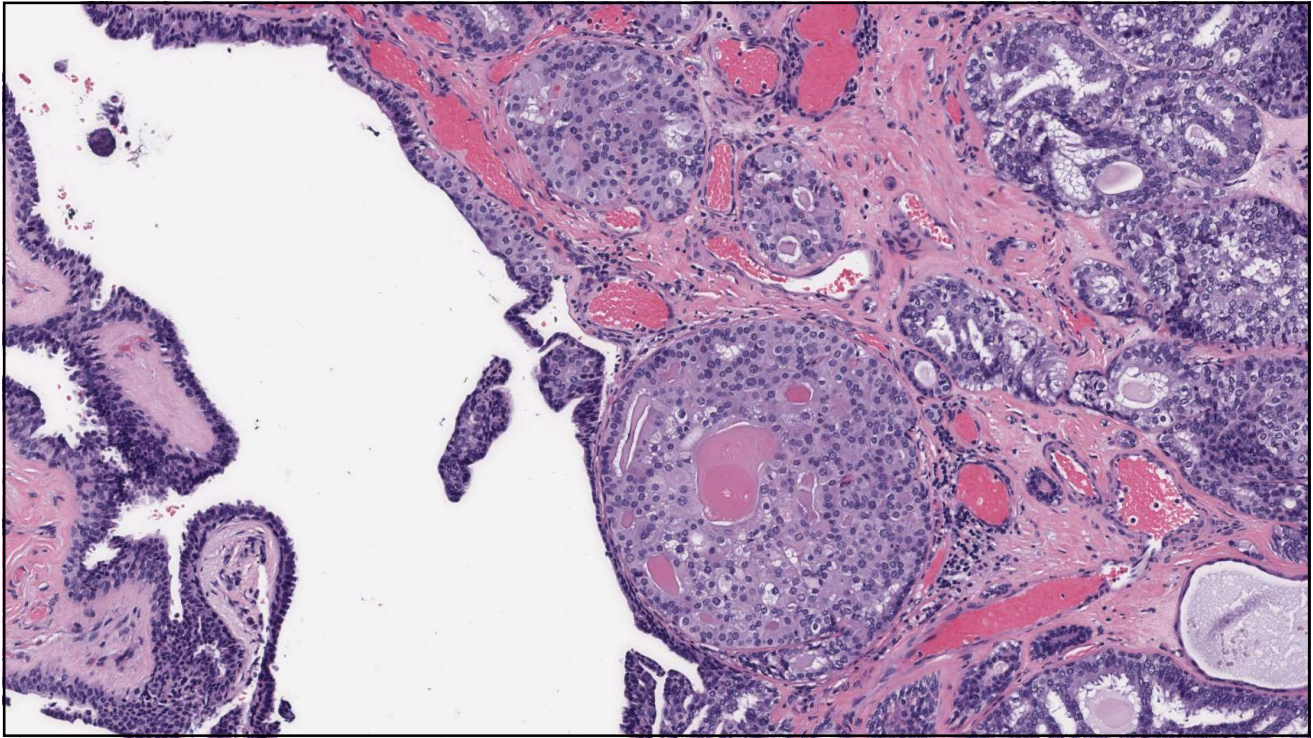
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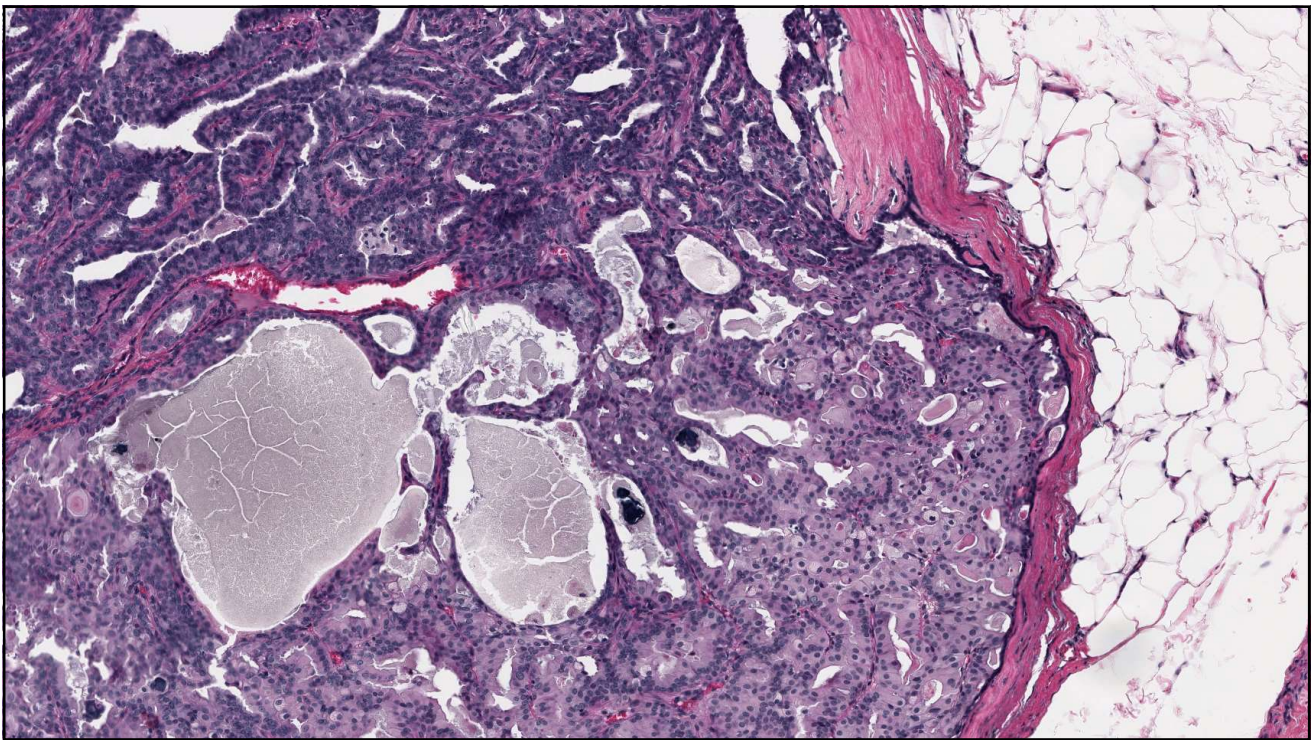


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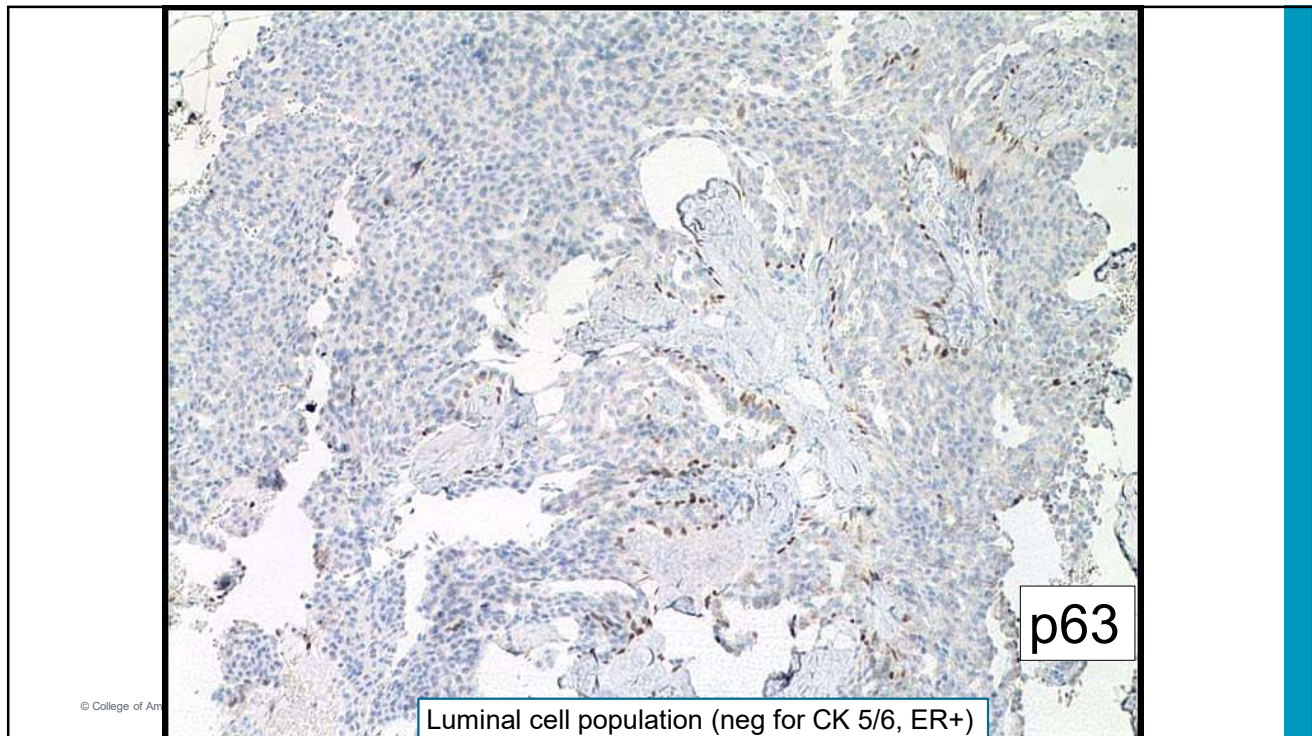
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Papilloma with DCIS

- “Focal population of monotonous cells with cytological and architectural features of low-grade ductal neoplasia”
- >3 mm within an intraductal papilloma

(WHO 2019)

- DCIS (may be other architectural patterns) may be present outside papilloma
 - Example DX: “DCIS, low grade, patterns, focally involving a (sclerosing) intraductal papilloma”

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Papilloma with DCIS

- “Focal population of monotonous cells with cytological and architectural features of low-grade ductal neoplasia”
- >3 mm within an intraductal papilloma
(WHO 2019)
- **Intermediate or high nuclear grade proliferations = DCIS regardless of size**

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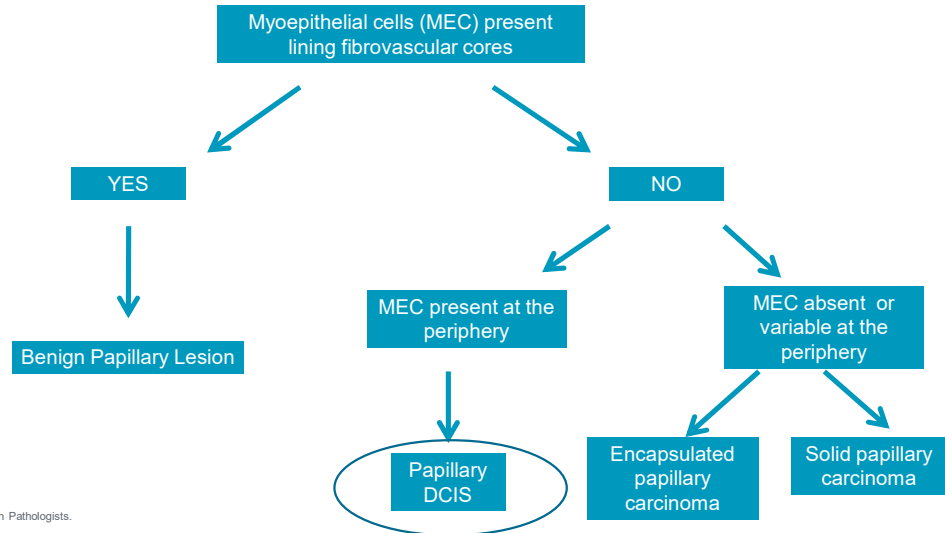
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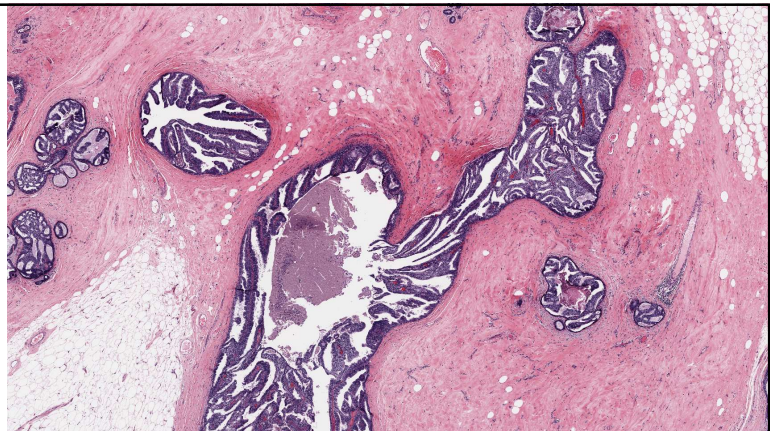
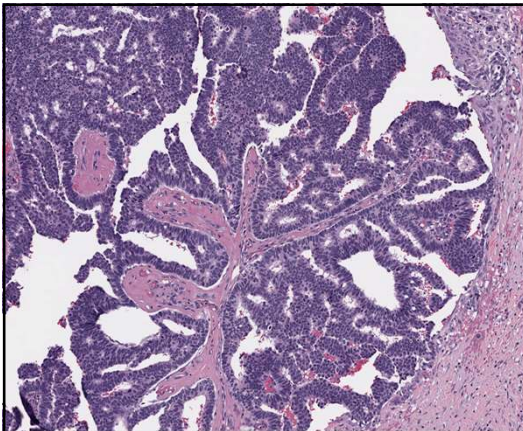
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Diagnosis of Papillary Breast Lesions

Modified from Collins & Schnitt, 2015



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Papillary DCIS

- Architectural pattern of DCIS with fibrovascular cores; other patterns usually present
- No residual benign papilloma
- Cores are more thin and delicate

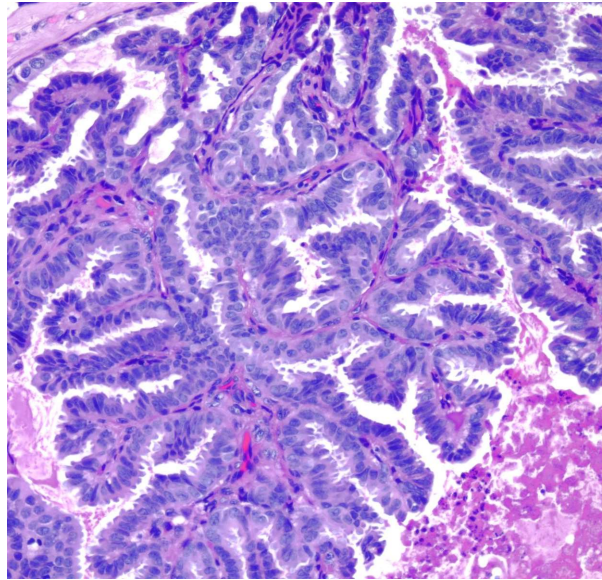
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- **No myoepithelium along the cores but retained myoepithelium at the periphery**

Presence of myoepithelial cells does not exclude papillary DCIS as long as morphology = DCIS

A panel of myoepithelial stains – p63, CK5/6, ER may be used

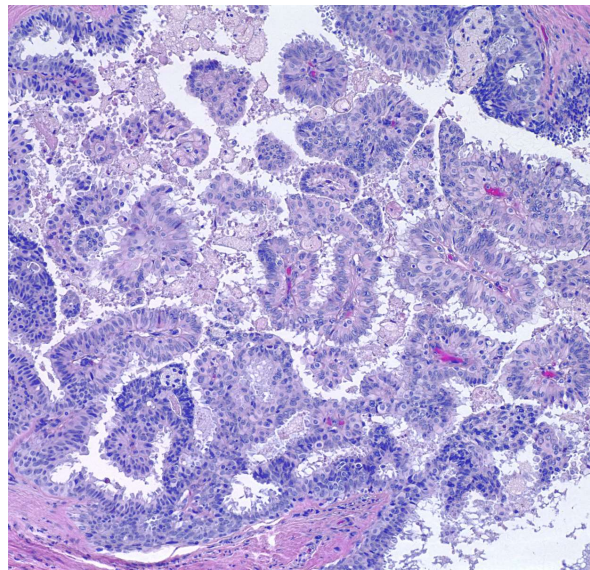


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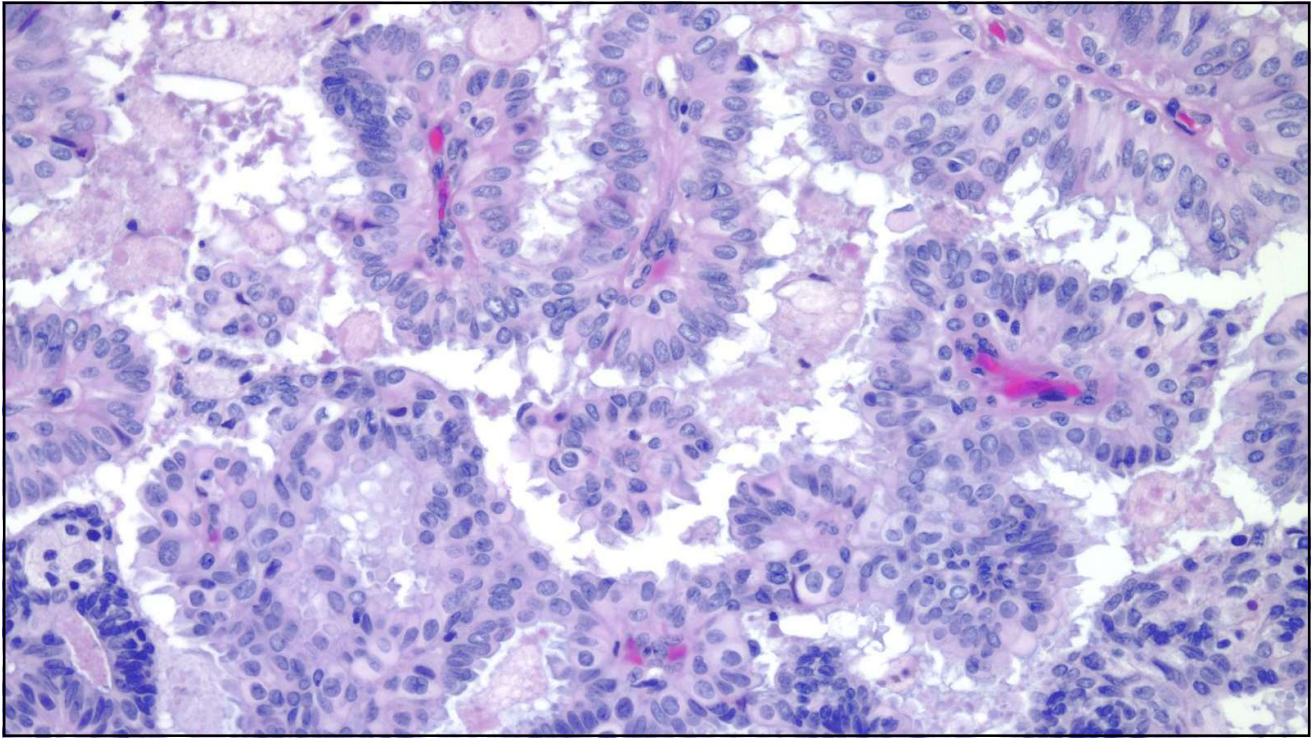
Dimorphic cell population ("globoid cells" mimic myoepithelial cells)

- **Single (rarely, dimorphic) cell population, often stratified**
- **May be admixed with other architectural types of DCIS**



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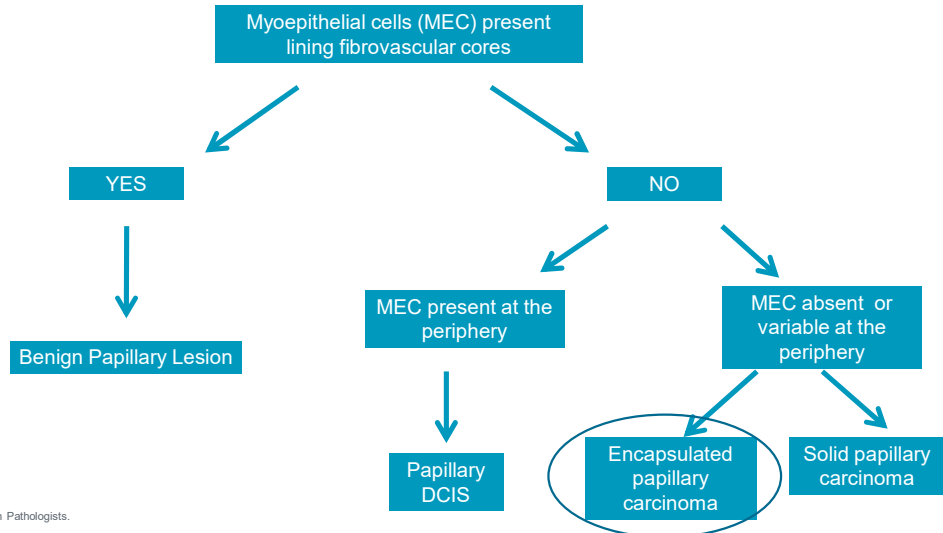
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Solid papillary carcinoma (with or without definite invasion)

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Diagnosis of Papillary Breast Lesions

Modified from Collins & Schnitt, 2015



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Encapsulated papillary carcinoma

- Previously known as “intracystic” or “encysted” (not recommended for use)
- Post-menopausal women, most in seventh decade of life
- Solitary, often central/retroareolar palpable mass
- With or without bloody nipple discharge

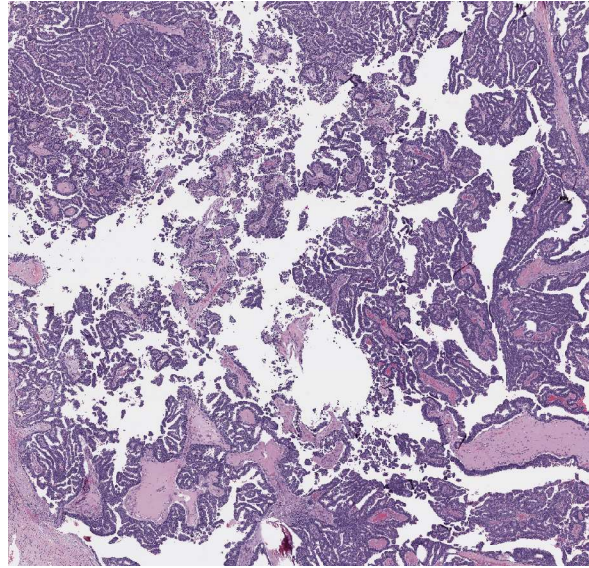


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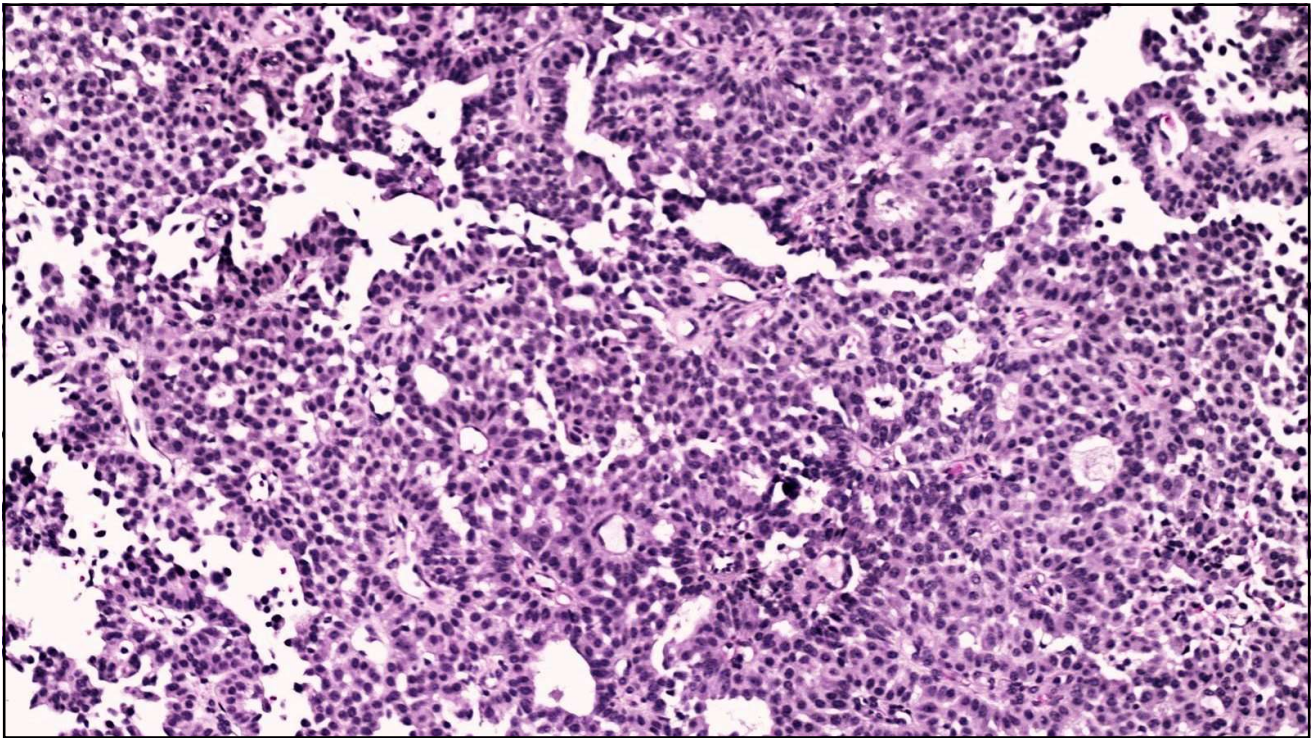
Encapsulated papillary carcinoma

- Cystic structure surrounded by fibrous wall
- Complex arborizing papillary structures
- Cores mostly thin and delicate
- Patterns of papillary DCIS
- Malignant monotonous epithelium
 - Low- or intermediate nuclear grade
 - High-grade lesions exceedingly rare
- More than 95% neoplastic (not on core bx)

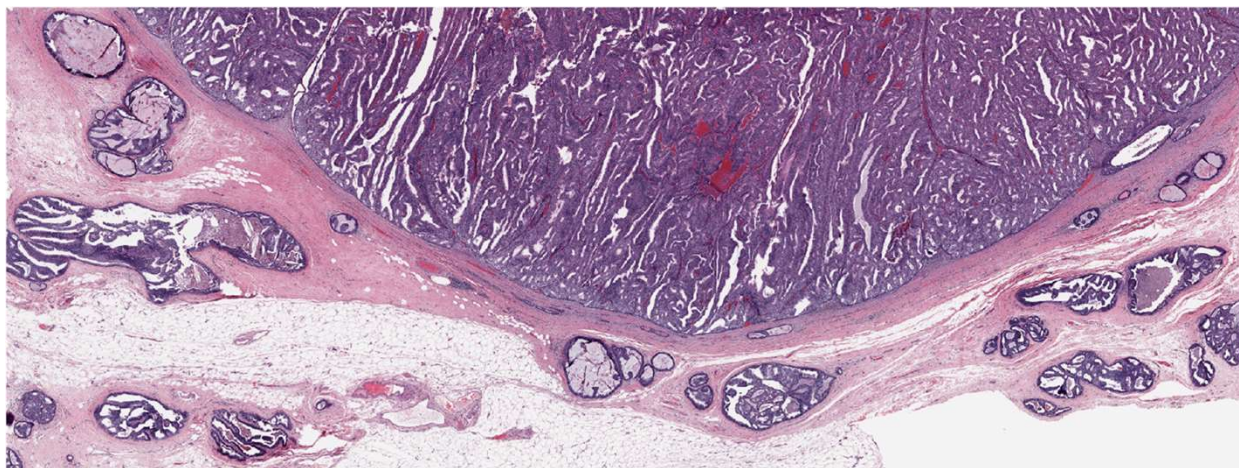


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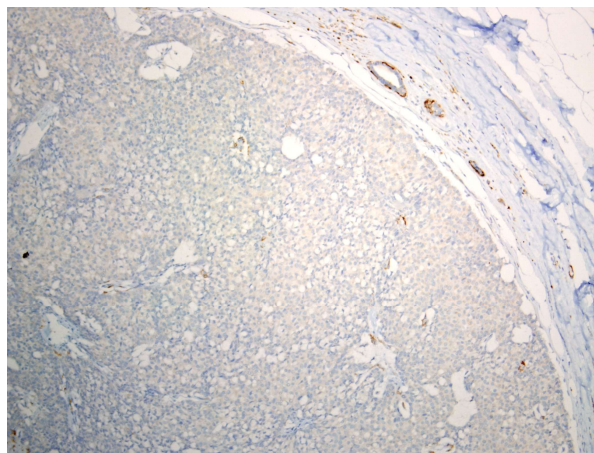
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Myoepithelial cells are absent within papillae as well as around the periphery of the tumor



Myosin heavy chain

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Encapsulated Papillary Carcinoma Questions

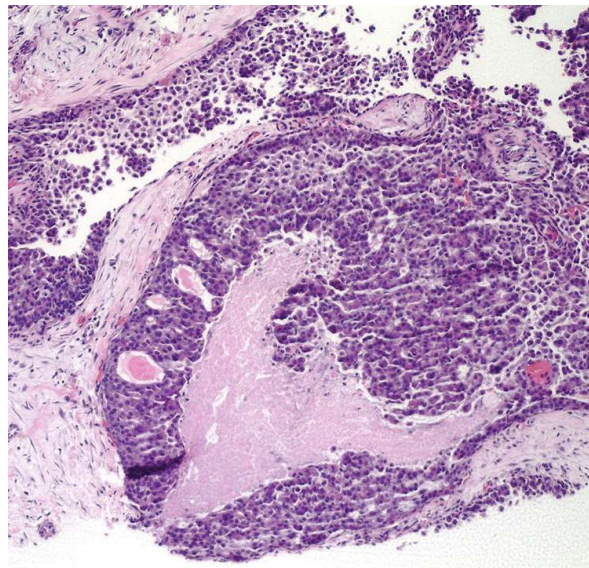
- Traditionally considered an in situ process
 - Circumscribed growth
 - Indolent clinical behavior
- Possible invasive features?
 - Lack of myoepithelial cells at the periphery (Collins et al, 2007)
 - Discontinuity of type IV collagen
 - Axillary lymph node metastases (Mulligan & O'Malley, 2007)
- Tumor with pushing rounded invasion, or a minimally invasive form of low-grade carcinoma?
- Tumor in transition from *in-situ* to invasive?
- Gene expression: invasion-associated markers intermediate between DCIS and invasive cancer (Rakha et al, J Clin Pathol 2012)

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Encapsulated papillary carcinoma

- High-grade lesions exceedingly rare
- Behave more aggressively



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Current recommendations

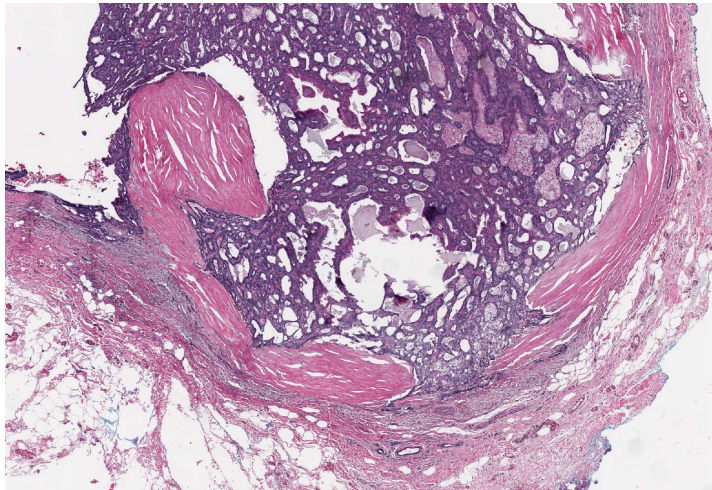
- ⦿ EPCs are considered – and staged – as in situ lesions OF LOW TO INTERMEDIATE NUCLEAR GRADE
 - Adequate local excision with hormonal therapy
 - Local recurrence not uncommon
 - Not enough evidence for sentinel lymph node biopsy
- ⦿ High grade EPCs should be graded, staged and managed as invasive breast carcinoma
 - ⦿ with nuclear pleomorphism and increased mitotic activity
 - ⦿ and/or a triple-negative or HER2-positive
- ⦿ Unequivocal conventional invasive carcinoma outside the capsule measured and staged not including EPC
- ⦿ Prior biopsy changes and entrapment need to be excluded

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Post core biopsy changes: Pseudoinvasion

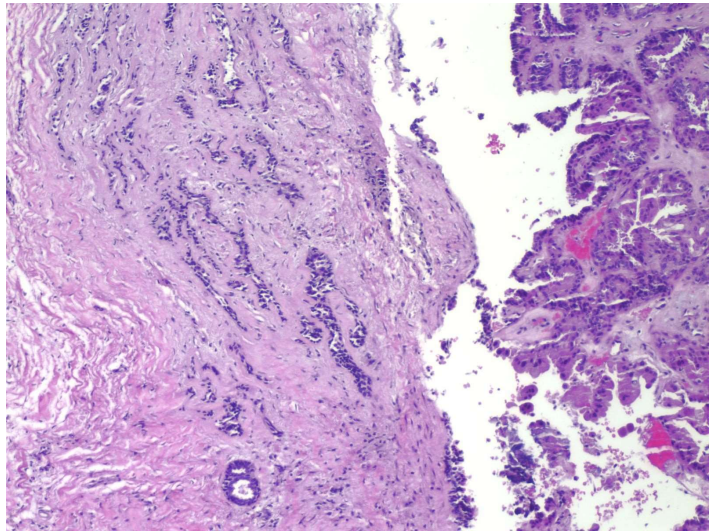
- Entrapment is very common
- Invasion = invasive component is completely beyond the capsule and into the surrounding tissue



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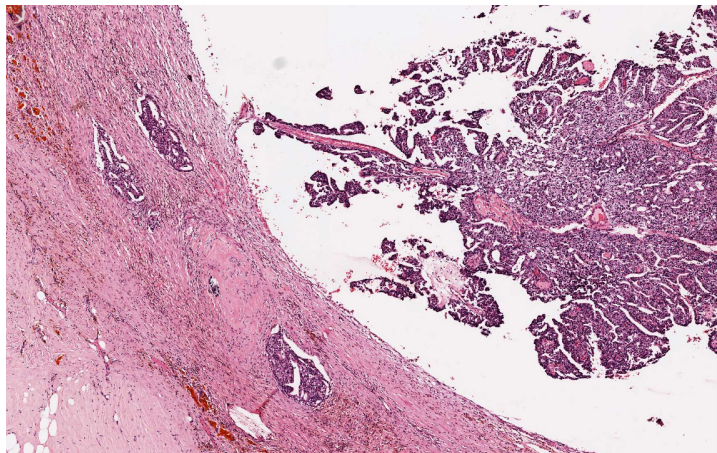
Entrapment



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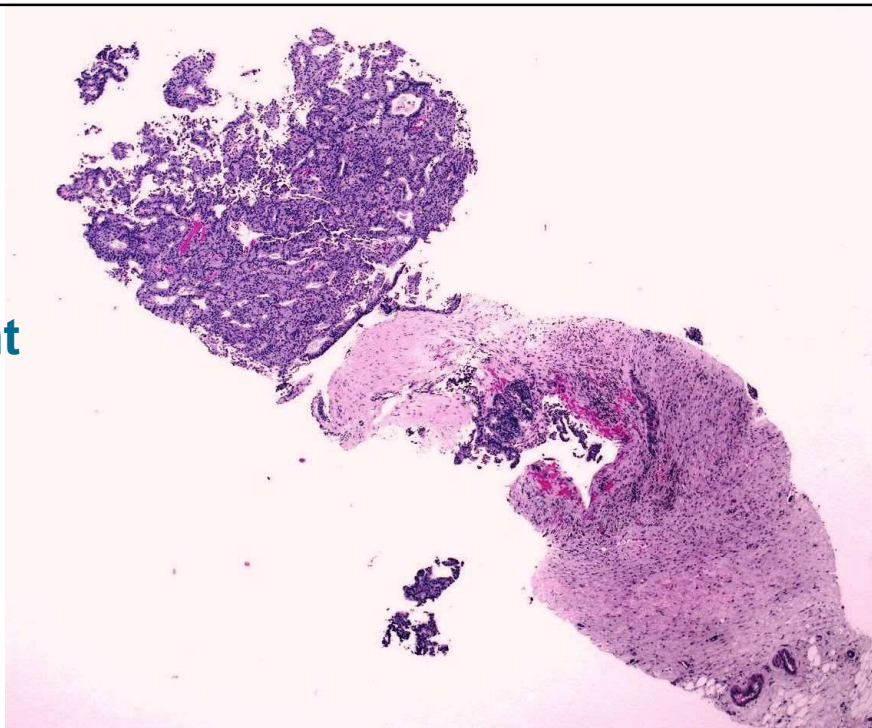
Entrapment



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Entrapment

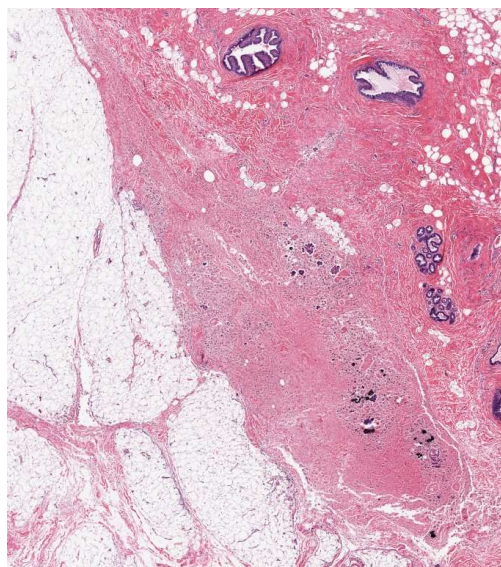


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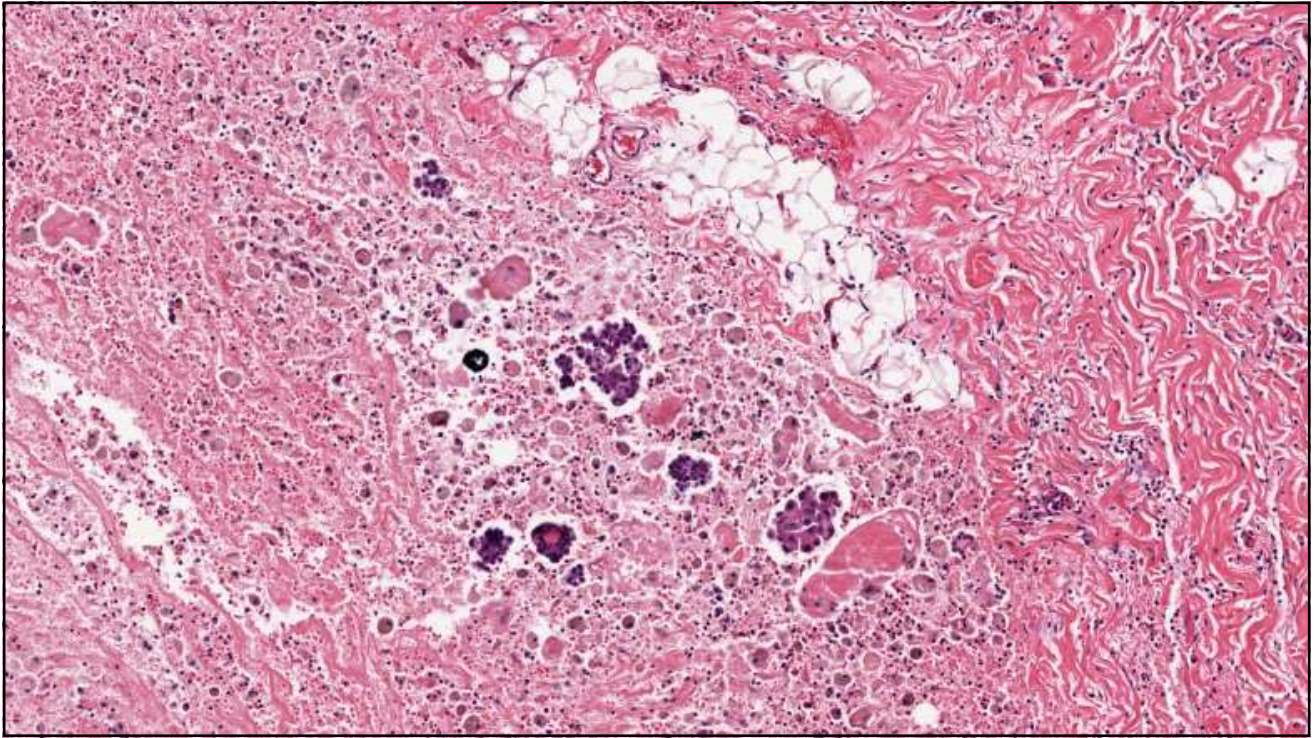
Post core biopsy changes

- Epithelial displacement
 - Linear track
 - Associated with old hemorrhage, fat necrosis

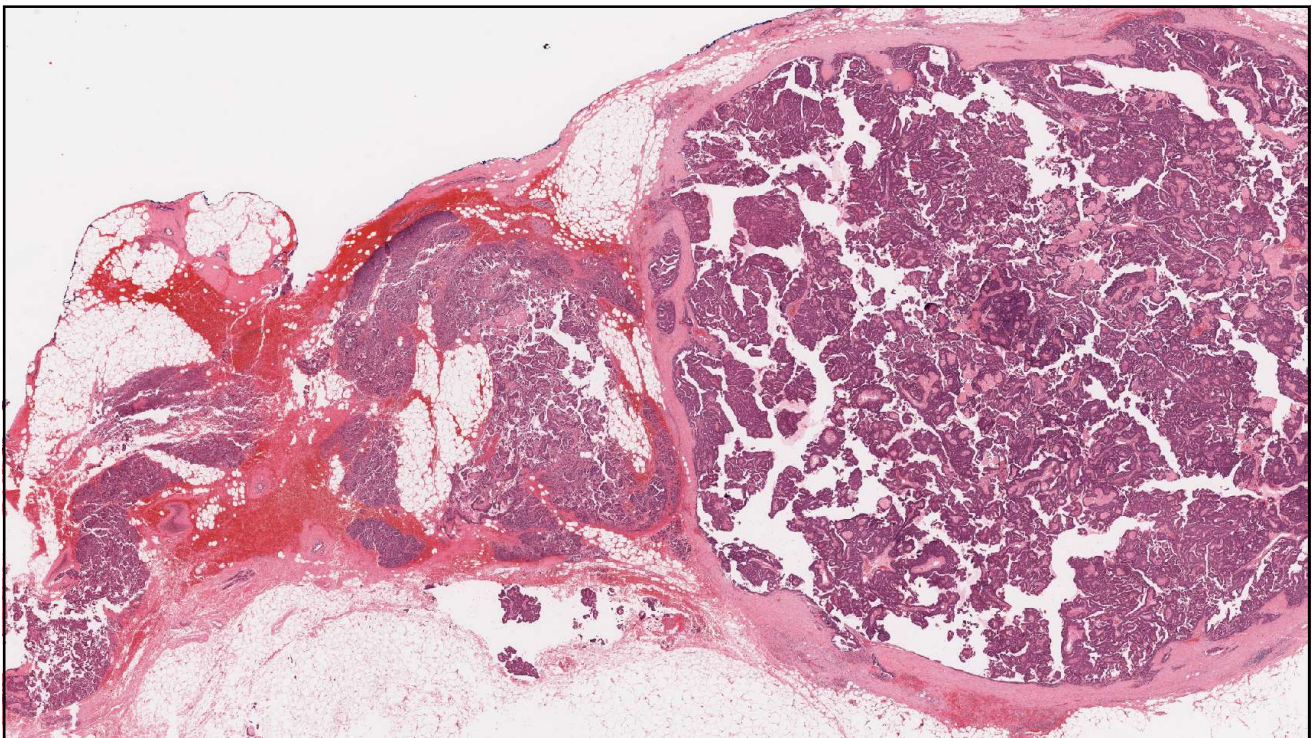


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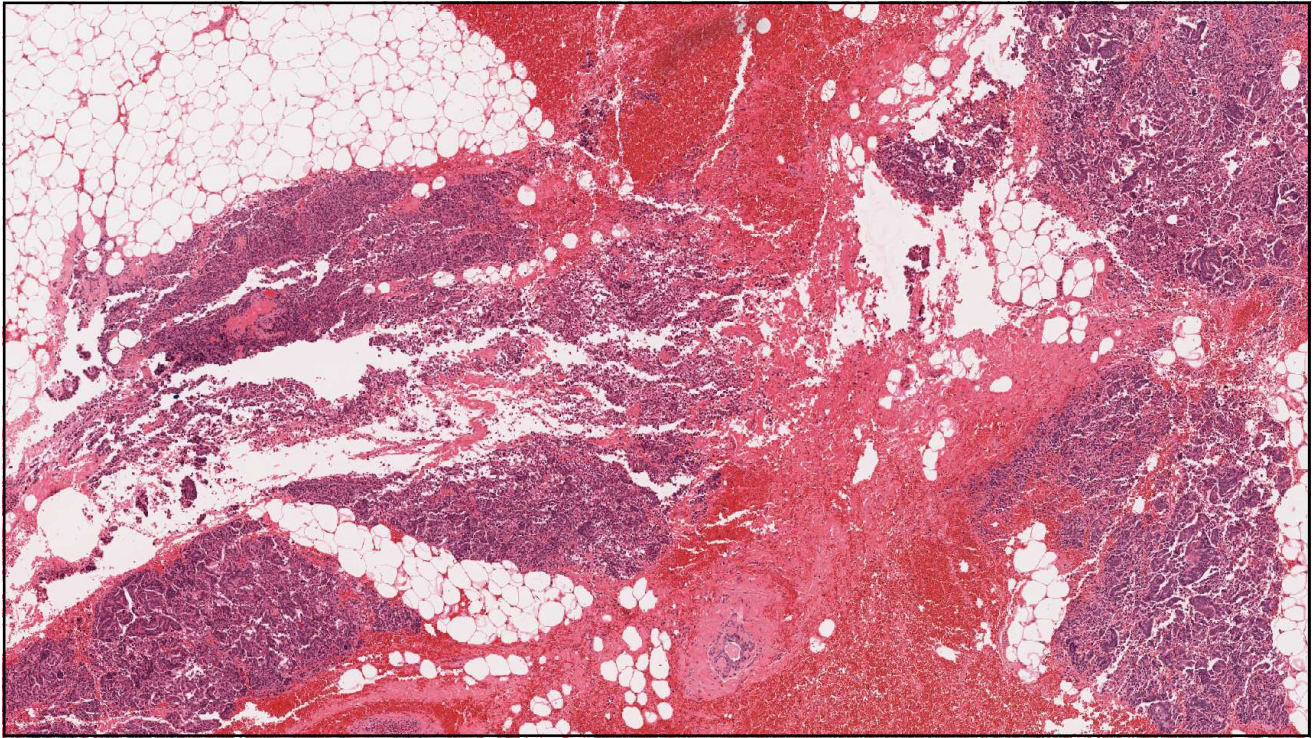
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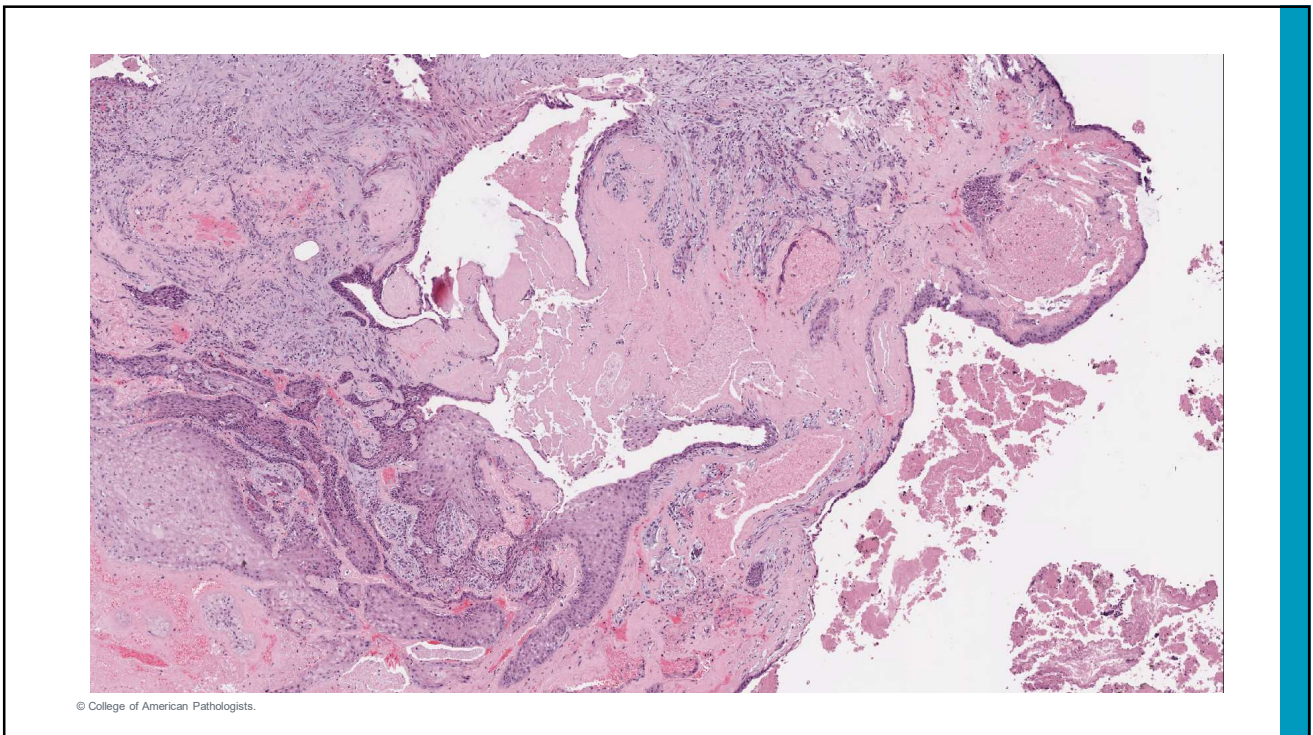
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Outline

Benign lesions with papillary/sclerosing component

Intraductal papilloma and its variants

Complex sclerosing lesion/radial scar

Adenomyoepithelioma

Intraductal papilloma with ADH

Intraductal papilloma with DCIS

Papillary DCIS

Encapsulated papillary carcinoma (with or without definite invasion)

Solid papillary carcinoma (with or without definite invasion)

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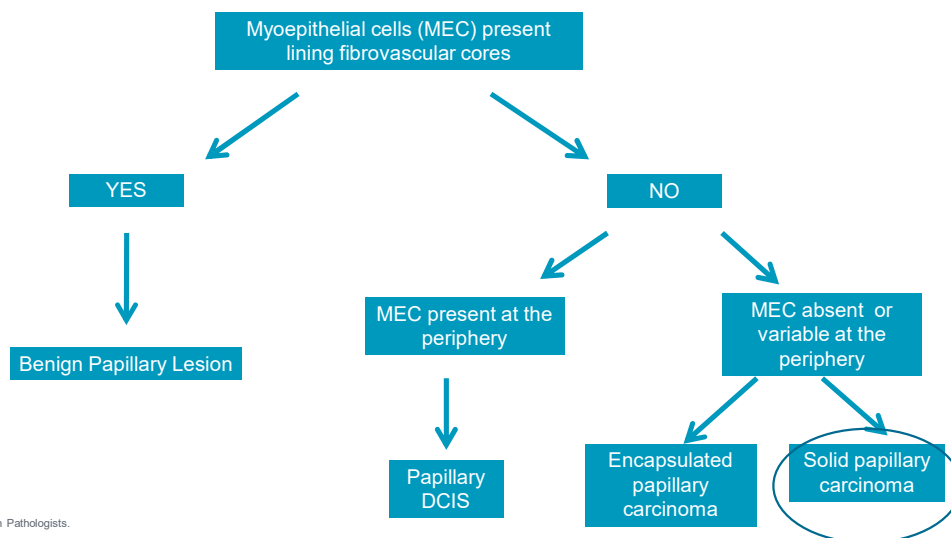
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Diagnosis of Papillary Breast Lesions

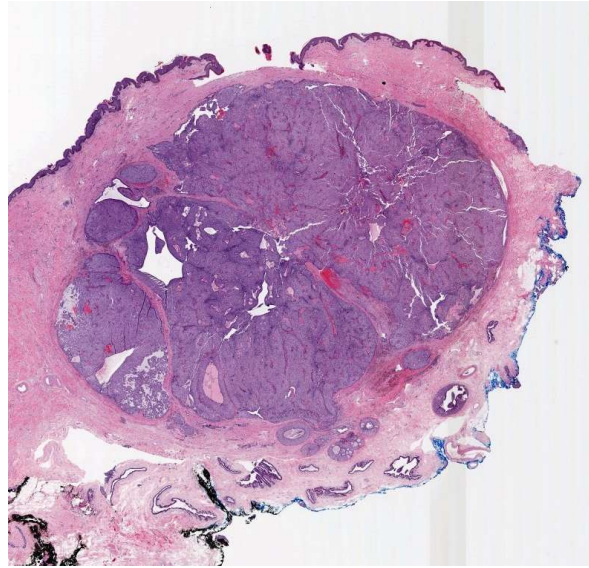
Modified from Collins & Schnitt, 2015



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Solid Papillary Carcinoma

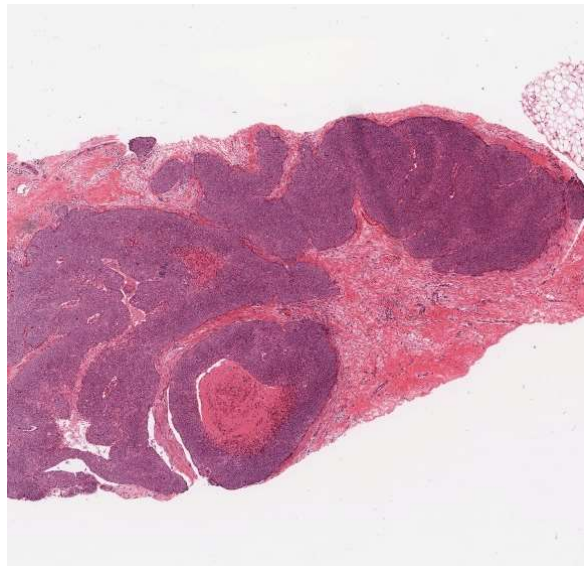
- Older patients
- Solitary, often central, mass
- One or several closely apposed expansile nodules surrounded by fibrous wall
- May be referred to as
 - Endocrine ductal carcinoma in situ
 - Neuroendocrine ductal carcinoma in situ
 - Spindle cell ductal carcinoma in situ



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Solid expansile nests fit together like jigsaw puzzle

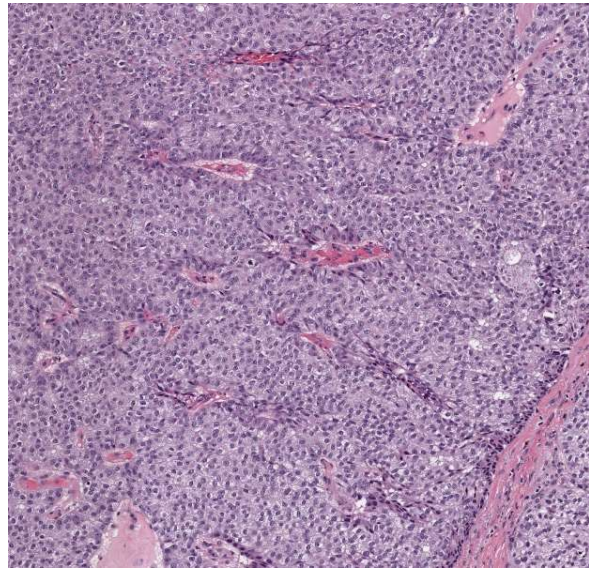


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Solid Papillary Carcinoma

- **Solid rounded densely packed nests of cells which attenuate the underlying papillary architecture**
- **Delicate branching fibrovascular cores/ septa**

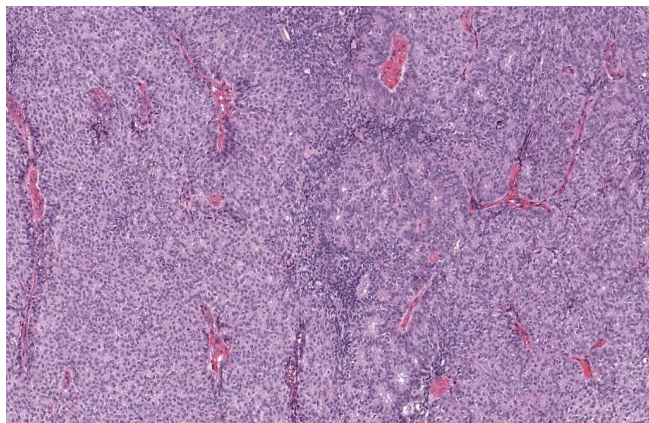


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Solid Papillary Carcinoma

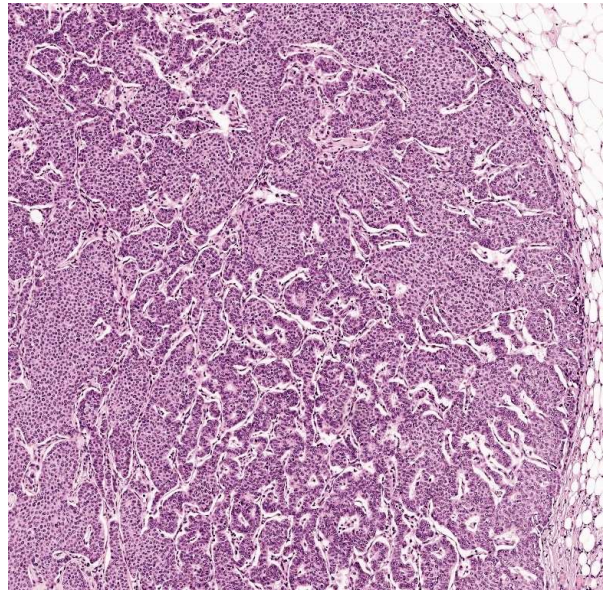
Solid, spindle patterns and rosettes



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Cells polarized around fibrous septa/organoid pattern

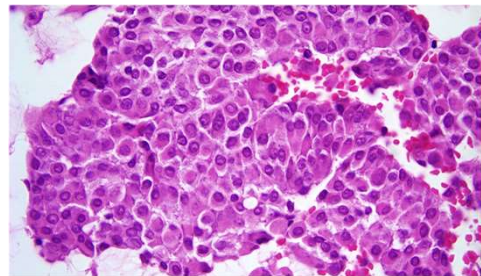
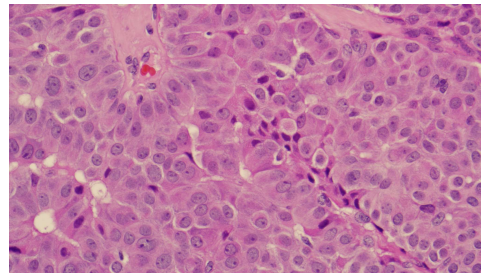


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Solid Papillary Carcinoma

- **Plasmacytoid to spindled cells**
- **Low or intermediate nuclear grade**
- **Neuroendocrine features common (eosinophilic granular cytoplasm, fine chromatin, synaptophysin /chromogranin, INSM1 +)**

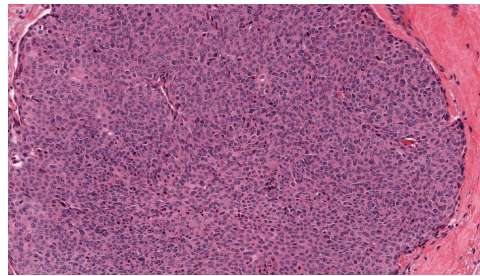
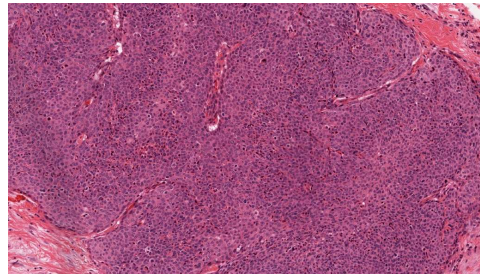


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Solid Papillary Carcinoma

- Spindle cell morphology
- Ddx - florid usual ductal hyperplasia (UDH)
 - Cellular monotony (no myoepithelial cells)
 - CK 5/6 neg
 - ER strong, diffuse

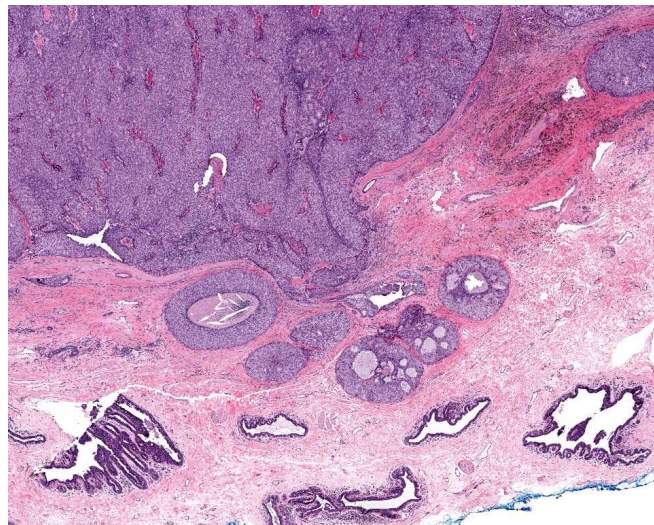


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Solid Papillary Carcinoma

Adjacent DCIS – same morphology



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Encapsulated or Solid???

	EPC	SPC
Nodule(s)	One	Usually multiple
Architecture	With cystic component	Solid
Capsule	Well defined (well, usually 😊)	Ill-defined, thin or none
Internal fibrovascular cores	Obvious (but thin)	Inconspicuous
Epithelial cells	Columnar	Polygonal
Neuroendocrine differentiation	Absent	Present
Extracellular mucin	Absent	Present
Unequivocal invasion	Uncommon	Less uncommon

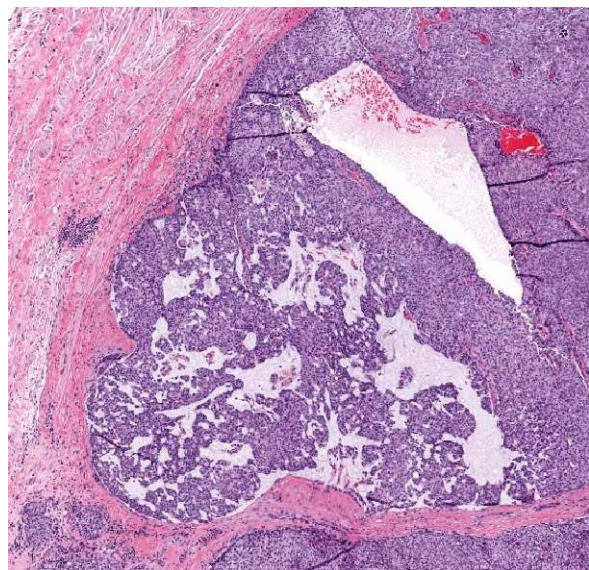
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A. Patel, Int J Surg Pathol 2021

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Solid Papillary Carcinoma

Intra- and extracellular mucin common



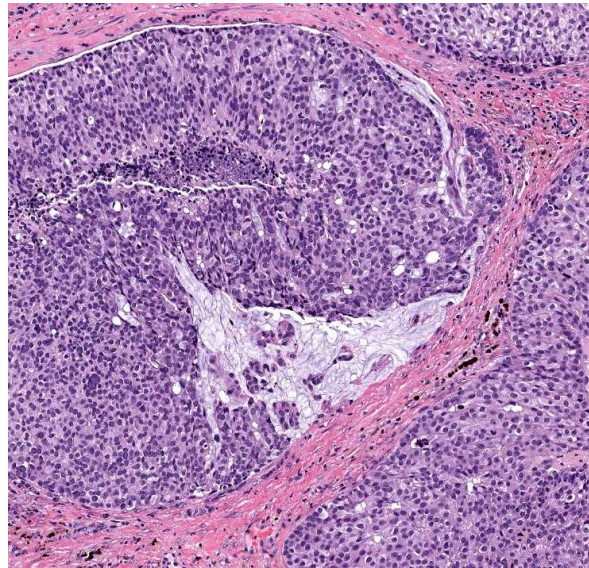
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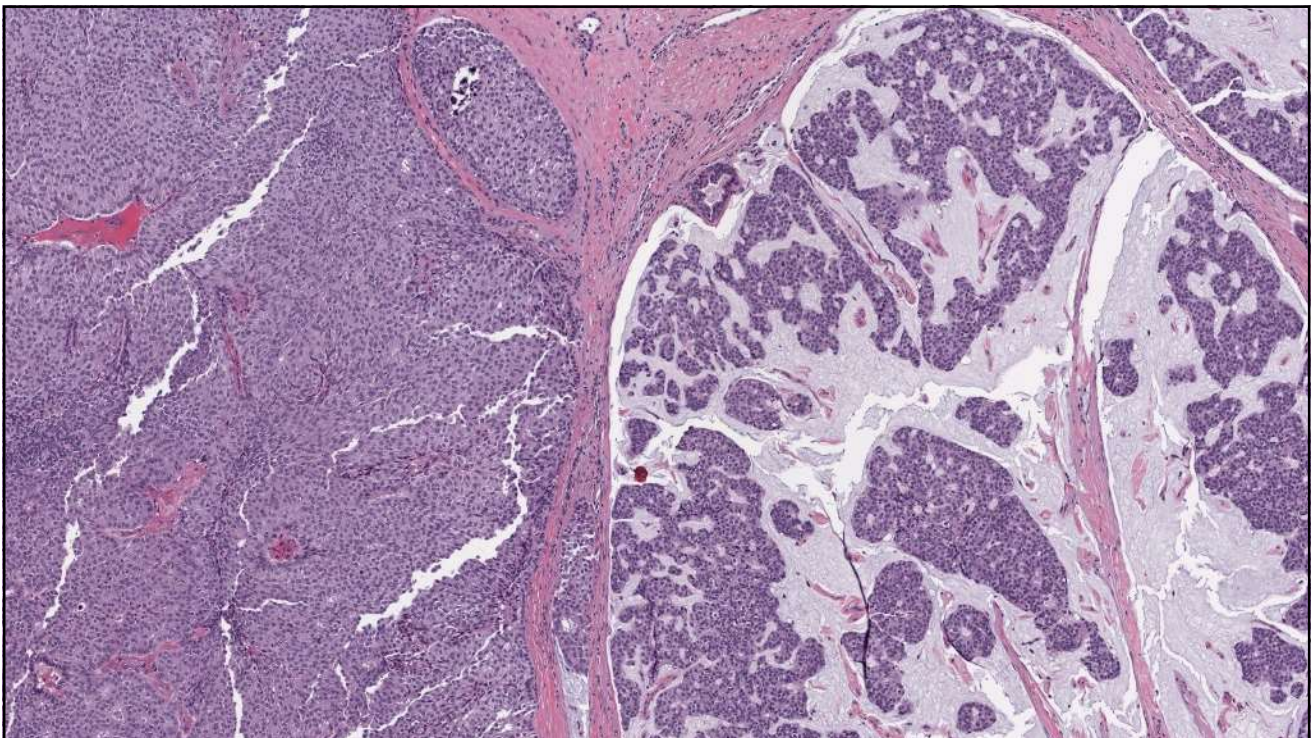
Invasion in solid papillary carcinoma

Cases with extracellular mucin reminiscent of mucinous carcinoma even if confined within encapsulated architecture: considered as having coexisting invasive carcinoma

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Solid Papillary Carcinoma: in situ or invasive?

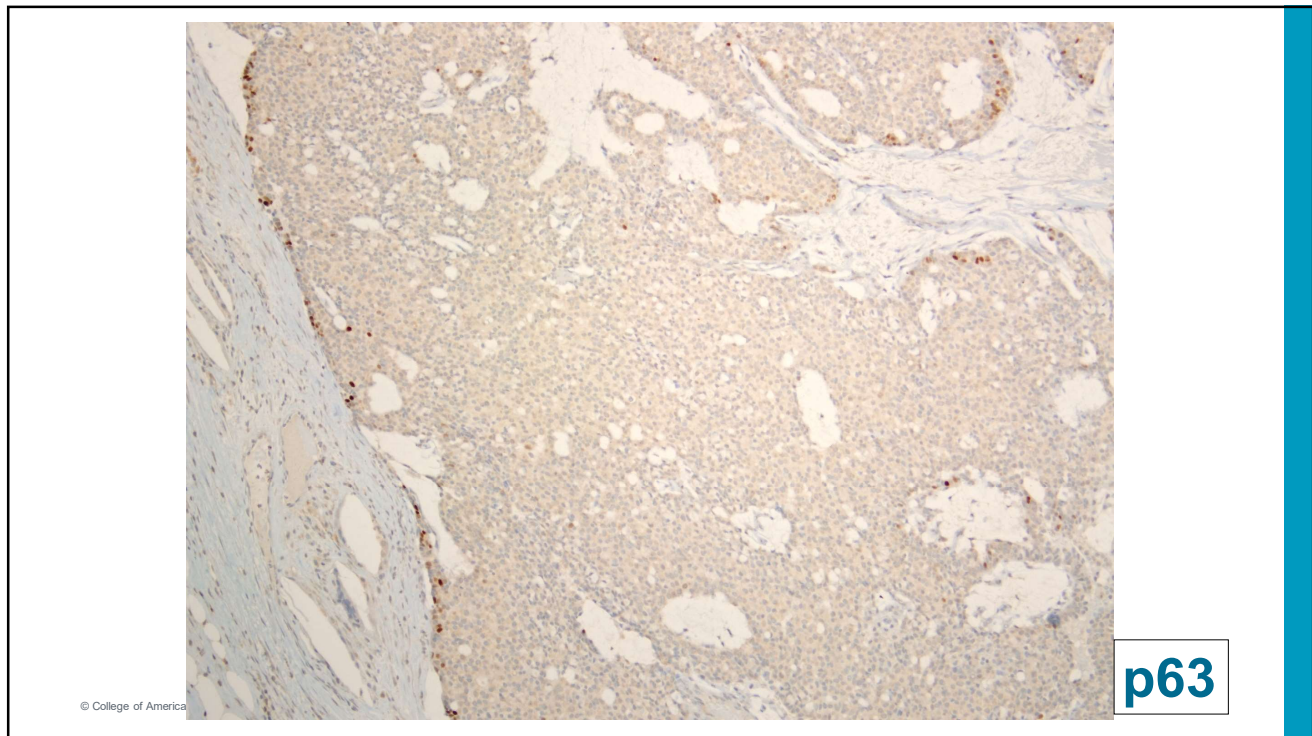
- **Myoepithelial cells at periphery (not within)**
 - Absent (Koerner, 1995 nad 1997; Carlo, 2006)
 - Variable (Moritani, 2007)
 - Present in 25% (Nicolas, 2007)
 - Present in all cases (Tsang 1996)
- **Reports of LN and distant metastases (Nassar, 2006, Nicolas 2007)**
- **Invasive carcinoma found in 75.4% cases, associated with higher nuclear grade of SPC**
 - 1 patient developed distant metastases and DOD (Tariq et al, 2019)

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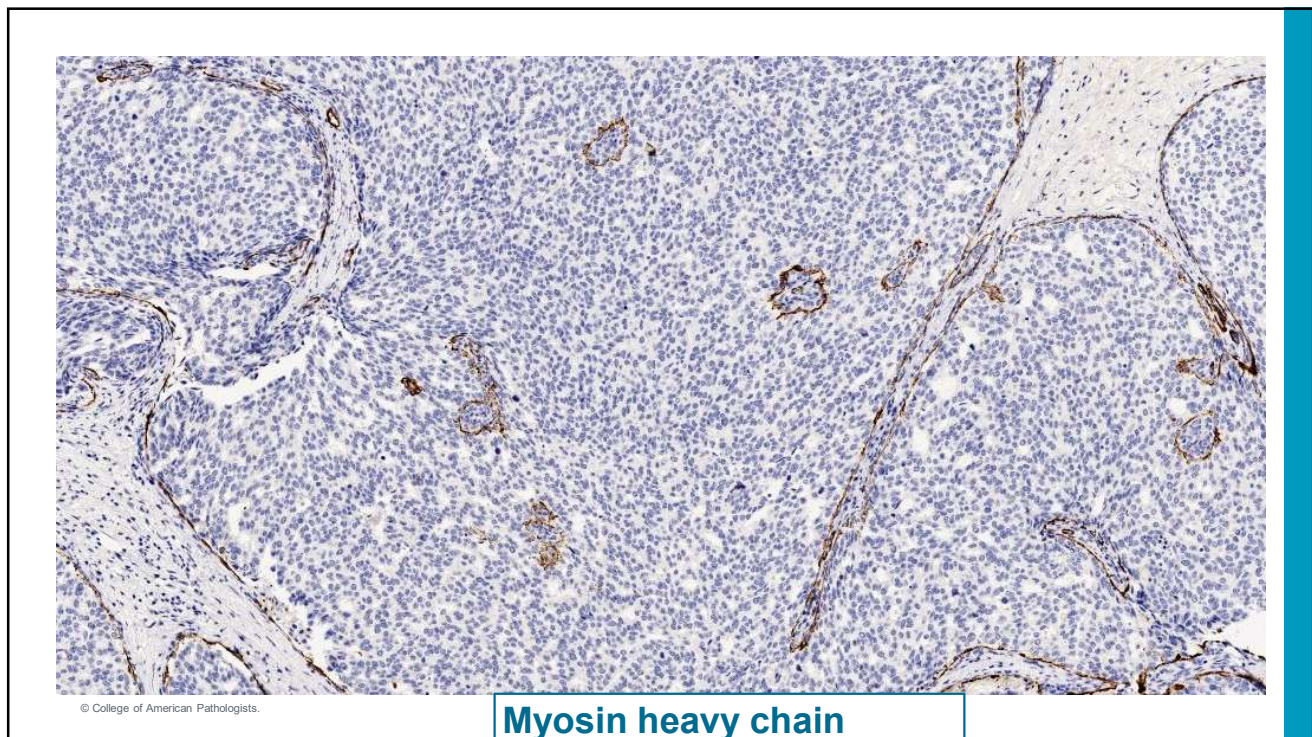
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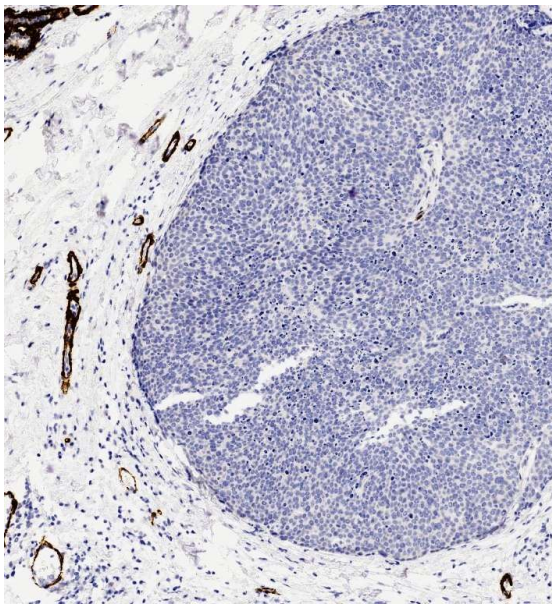
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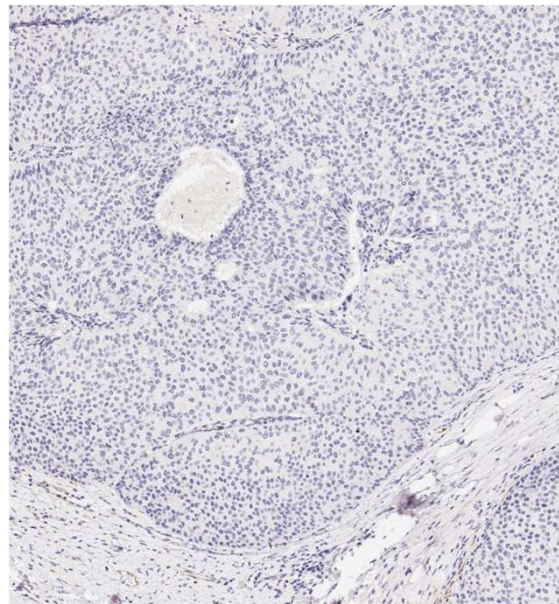


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Myosin heavy chain



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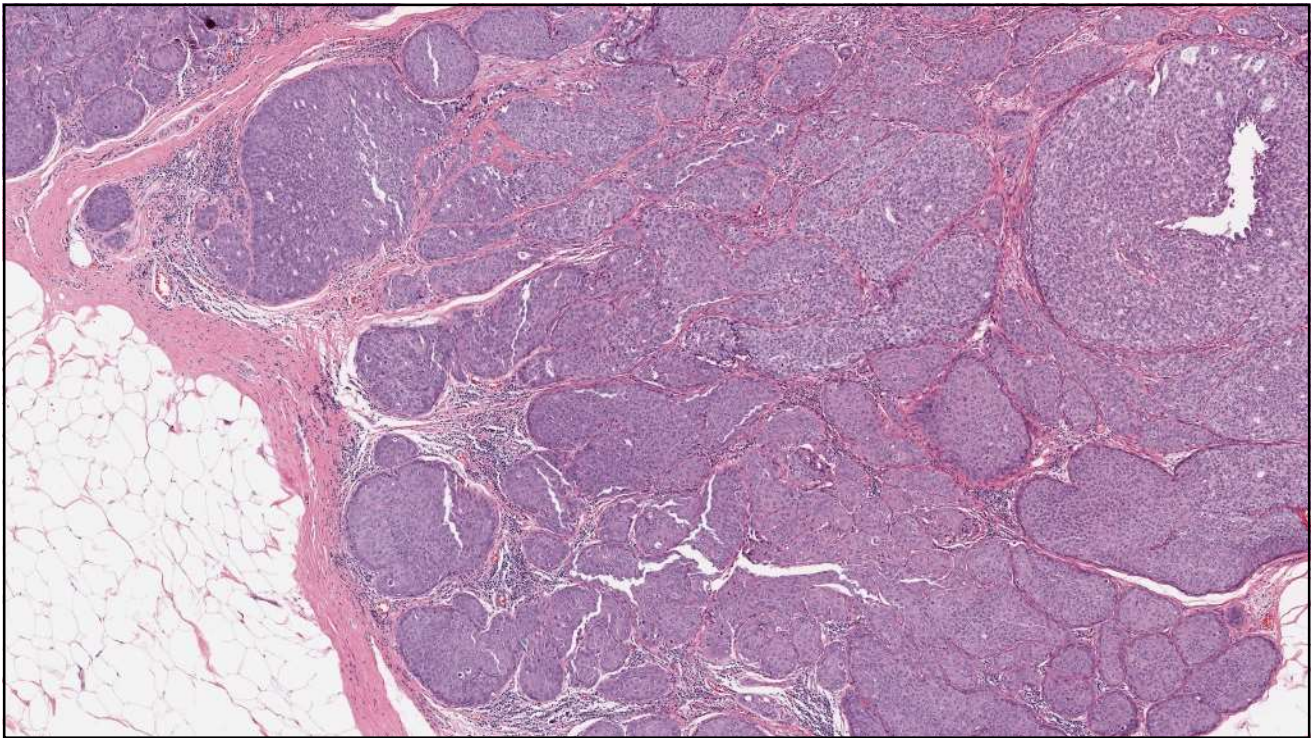
Solid Papillary Carcinoma: in situ or invasive?

- **Need myoepithelial stains**

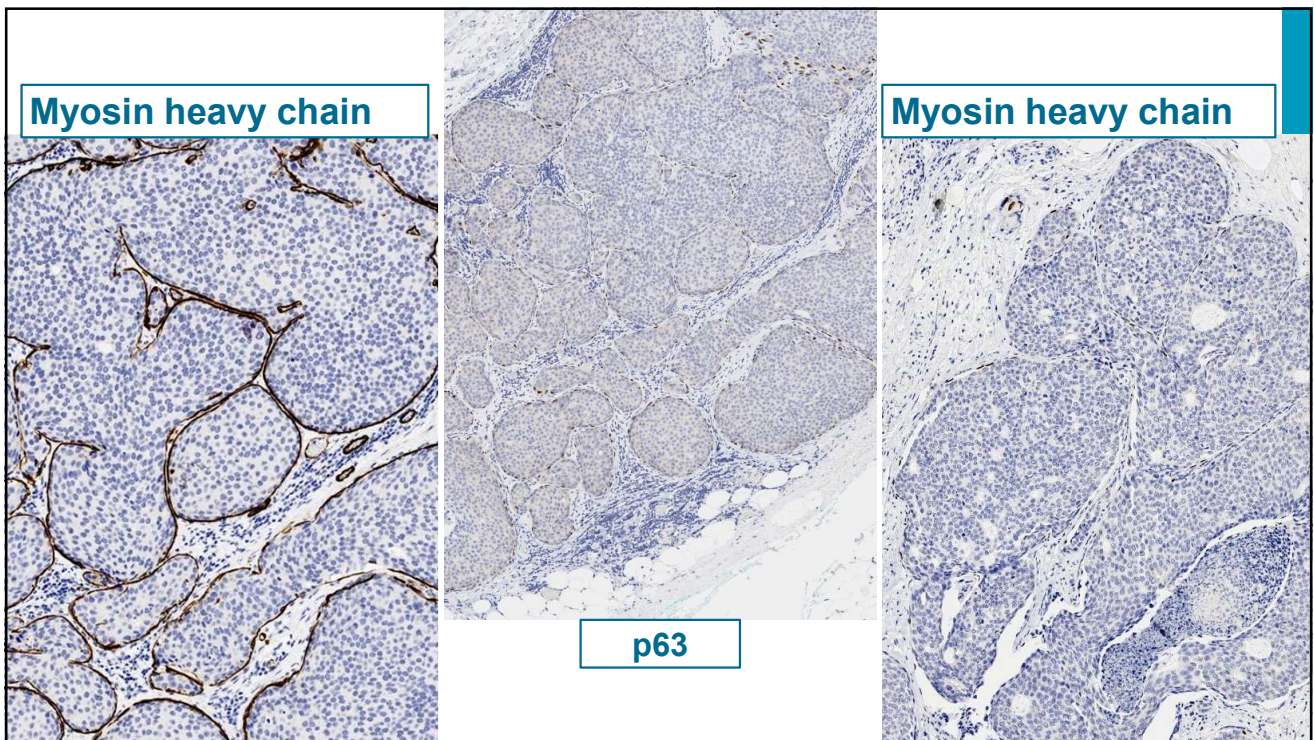
- **Rounded nodules:**
 - Myoepithelial cells present (usually patchy): DCIS, solid papillary type
 - Myoepithelial cells absent: probably indolent invasive carcinoma with pushing type of invasion **BUT report as *in-situ* disease for staging purposes** (indolent behavior and extremely favorable prognosis)
- Irregular, geographic, jagged or jigsaw-like nodules within desmoplastic stroma - invasive carcinoma
- **Most such tumors show conventional IDC features – IDC, NOS arising in the background of SPC**

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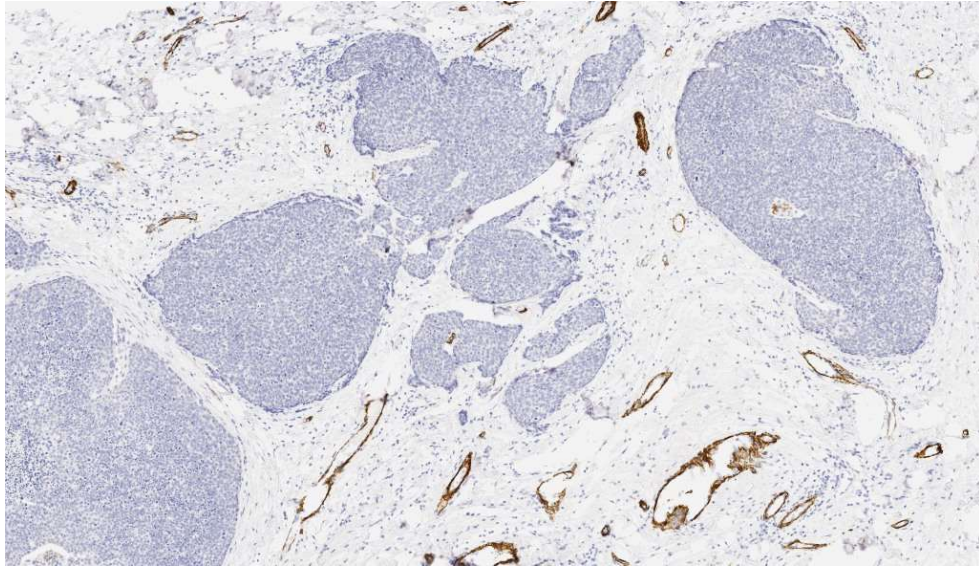
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Myosin heavy chain

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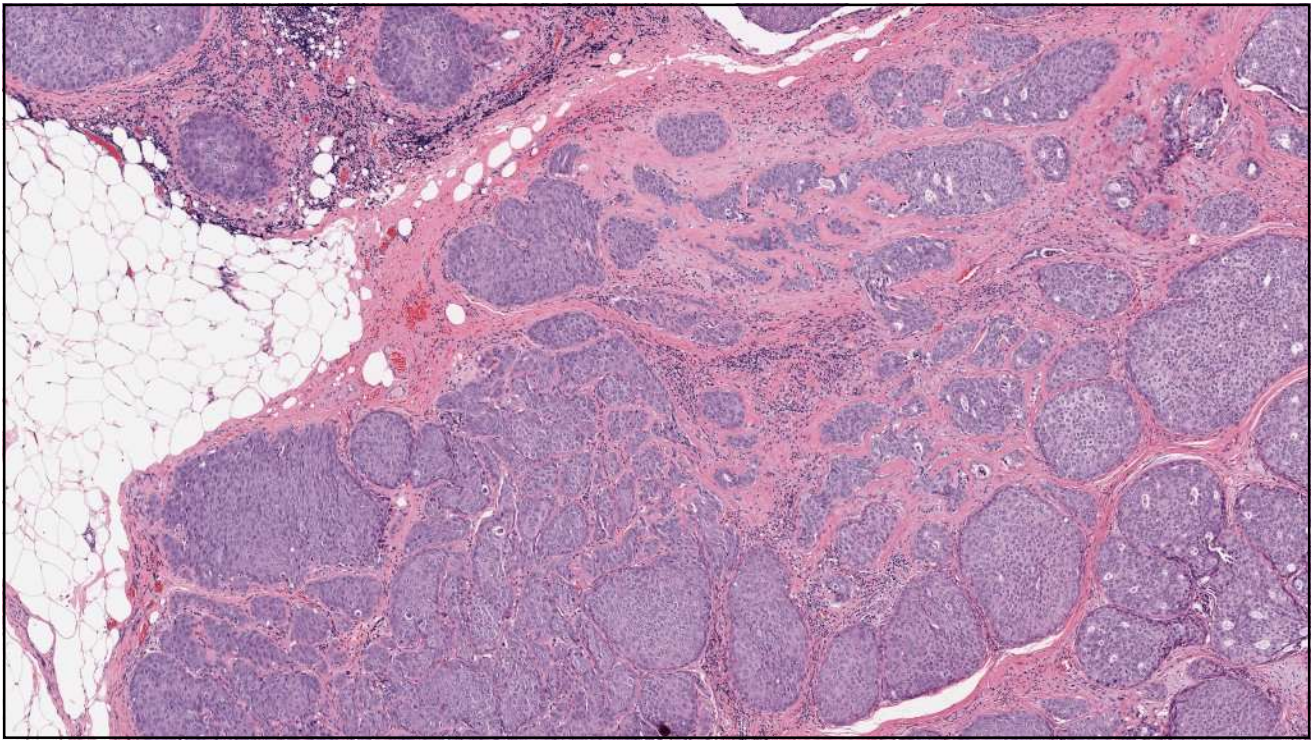
103

Problems with invasion in SPC

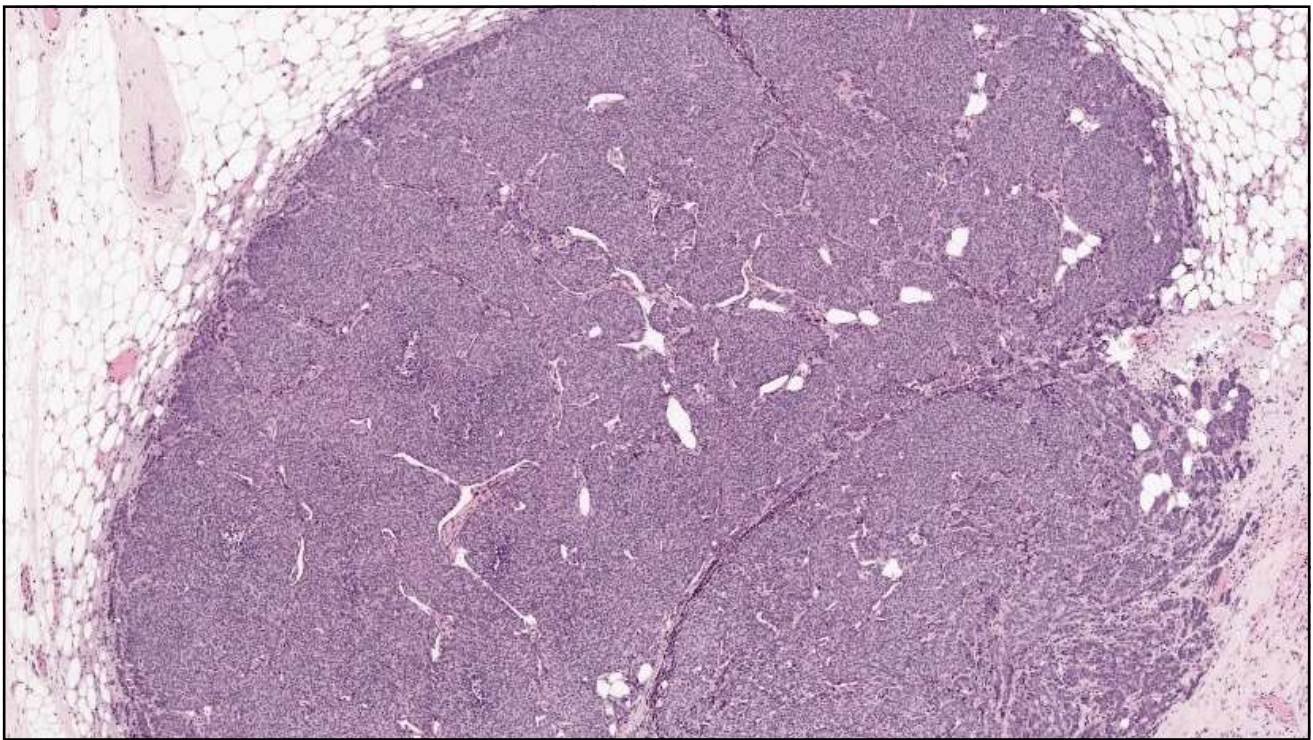
- **How do you measure/stage?**
 - Similar to measuring in EIC situations:
 - Largest contiguous focus of obvious invasion, and report the number of foci
 - Unless two foci are less than 5 mm apart – then measure together (if similar morphology)
 - If mucinous, then entire mucinous lesion, and not just with cells
 - **H&E overrides IHC!**

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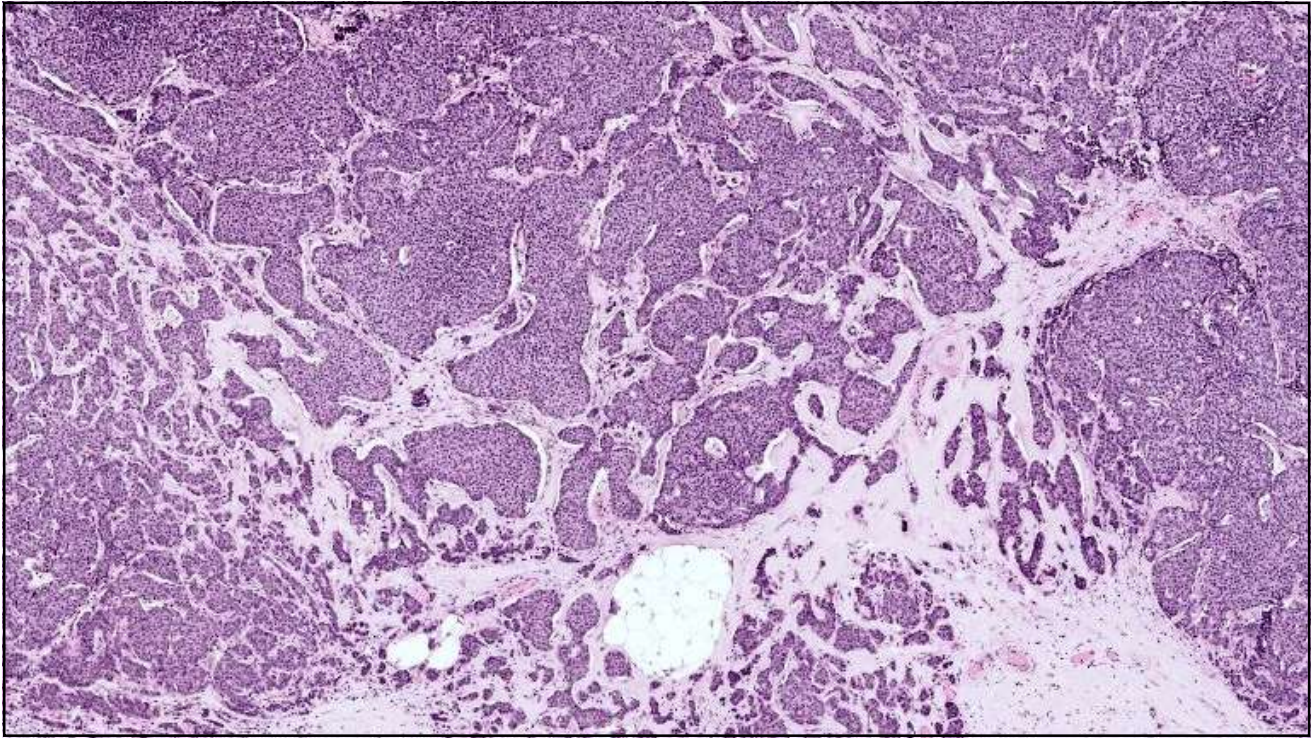
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Solid Papillary Carcinoma: in situ or invasive?

- “a significant difficulty was found in differentiating *in-situ* from invasive foci, even with the use of myoepithelial-associated markers”
 - Rakha et al. *Histopathology* 2015 Apr;66(5):740-6

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ENCAPSULATED AND SOLID PAPILLARY CARCINOMA: SAME IMPLICATIONS AND MANAGEMENT

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Encapsulated and Solid Papillary Carcinoma: in situ or invasive?

- Probably indolent invasive carcinoma with pushing type of invasion
- **BUT report as in-situ disease for staging purposes** (indolent behavior and extremely favorable prognosis)

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Management of EPC and SPC

- Need to examine the entire tumor
- Core biopsy: “Papillary carcinoma”, recommend excision + suggest sentinel LN biopsy
- Low-grade and intermediate-grade and no invasive component staged as *in-situ* disease (pTis)
 - Adequate local excision with hormonal therapy
 - Local recurrence not uncommon
- Conventional invasive carcinoma (mucinous carcinoma or invasive ductal carcinoma) that arises in association with solid papillary carcinoma and should be classified and staged accordingly (**only invasive component measured!**)

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Management of EPC and SPC

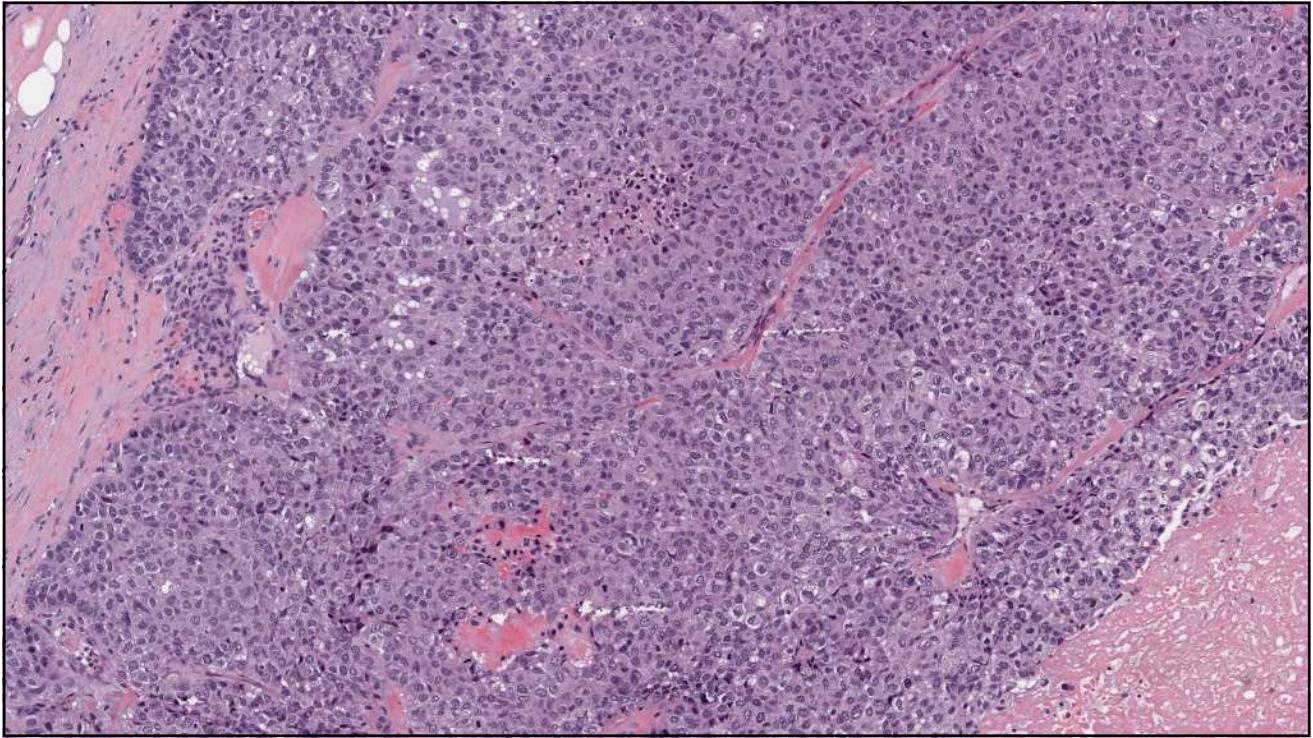
- A diagnosis of ‘solid papillary carcinoma’ without further qualification is not recommended
 - Recommended to explicitly state whether a particular solid papillary carcinoma is *in-situ* or has an invasive component: **SPC in situ** or **SPC with invasion**

Exception: high-grade lesions

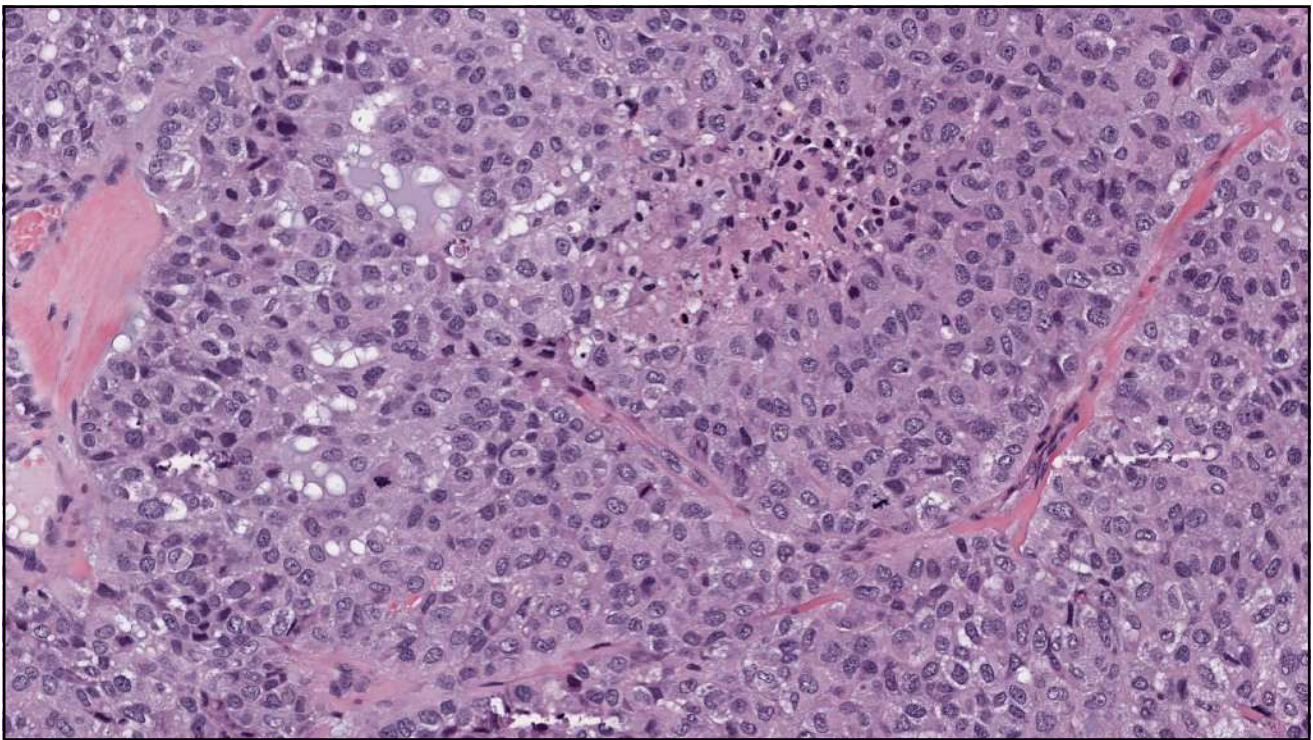
Form of invasive high-grade carcinoma with SPC-like features

Entire lesion staged as invasive carcinoma!

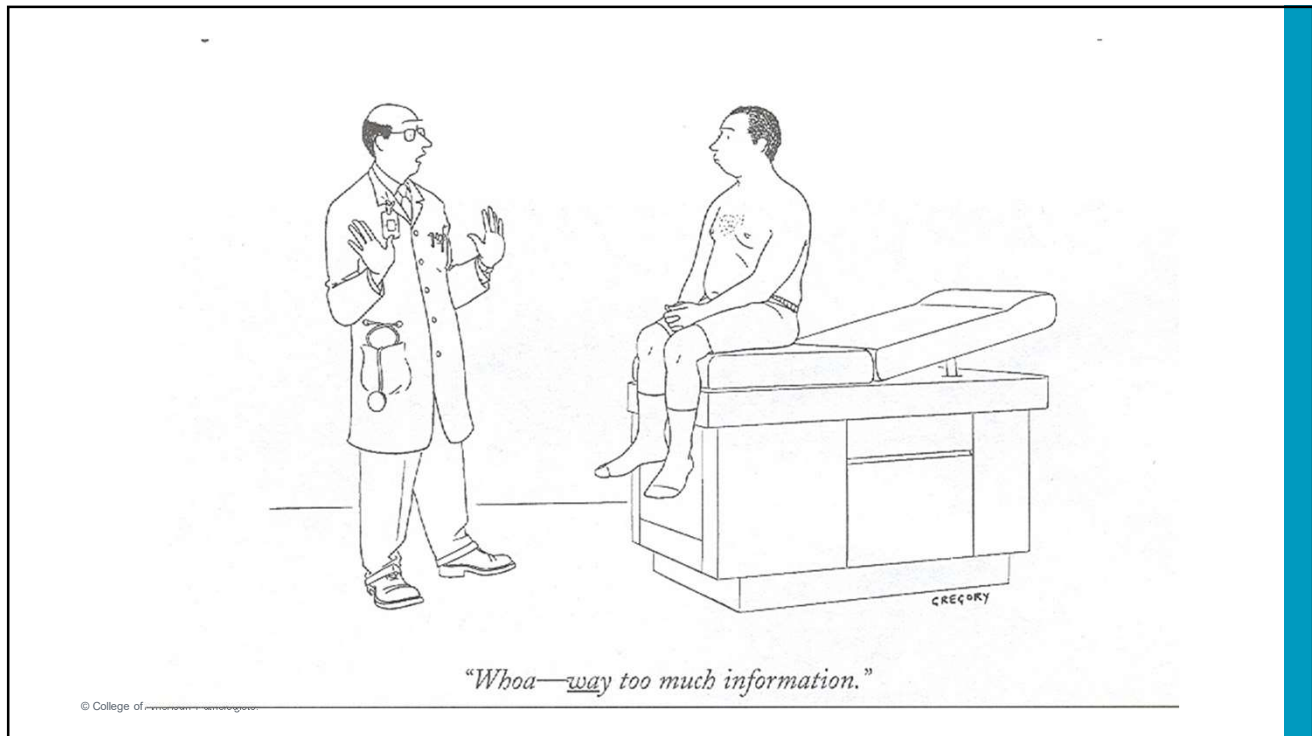
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Closing Comments & Summary

- **Small/incidental/single papillomas don't need excision post core biopsy; other papillomas – it depends**
- **Atypical papillomas (with ADH) have to be excised after CNB, with negative margins; associated with increased risk of breast cancer**
- **Radial scars, CSL and adenomyoepitheliomas need excision after CNB**

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Closing Comments & Summary

- There is overlap between malignant papillary lesions (“*man-made divisions*”, Azzopardi)
- Papillary DCIS: absent myoepithelial cells in cores, present at periphery
- Encapsulated papillary carcinoma and solid papillary carcinoma:
 - No/variable myoepithelial cells; H&E overrides IHC
 - Low/intermediate grade staged as pTis unless overt invasion outside the capsule/into surrounding breast
 - High-grade tumors are rare, aggressive, staged entirely as invasive carcinomas

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Questions?

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