Contemporary Management of High Risk Lesions Diagnosed on Breast Core Needle Biopsy

Laura C. Collins, M.D.
Vice Chair of Anatomic Pathology
Professor of Pathology
Beth Israel Deaconess Medical Center
and Harvard Medical School
Boston, MA

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Outline

Correlation and Concordance

- Discuss how breast core needle biopsy diagnosis guides next management steps in radiology, surgery and oncology
- Discuss some commonly encountered diagnostic challenges on breast core needle biopsy

Other considerations

- Consequences of core needle biopsy
- Other “high risk” scenarios

Definition-High Risk Lesions

- A breast lesion that carries an increased risk for the future development of breast cancer
- A breast lesion that carries suspicion of a more sinister pathology (i.e. DCIS or invasive carcinoma) around or in association with a non-malignant lesion
- Excision of lesions in the second category has historically been recommended when diagnosed on core needle biopsy

High Risk Lesions

Conferring an increase in subsequent breast cancer risk

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

- Atypical ductal hyperplasia (3-5x RR)
- Lobular carcinoma in situ/Atypical lobular hyperplasia (4-5x RR)

- Proliferative disease without atypia (1.5-2x RR)
  - UDH, sclerosing adenosis, intraductal papilloma
  - Columnar cell lesions and FEA

High Risk Lesions

Associated with frequent upgrade on excision (historically)

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

- ADH
- LCIS/ALH
- Intraductal papilloma
- Radial scar/CSL
- Flat epithelial atypia
- Mucocele-like lesion

Excision Upgrade rates ranged from 0-~30%

Factors Influencing Contemporary Management

- Higher resolution imaging has led to detection of smaller lesions
- Use of larger gauge needles and vacuum assistance provides greater sampling and/or results in complete removal of the lesion
- Better radiologic pathologic correlation
- Trend toward de-escalation of therapy
- Combined with newer, better data, management has become more conservative

Clinical Correlation

Correlation and Concordance

Determining radiologic pathologic correlation

- Masses
- Microcalcifications
- Non-mass enhancing lesions

Lesions easily overlooked

Common diagnostic dilemmas and their management impact

Radiologic-Pathologic Correlation

The pathologic diagnosis on a core biopsy must be concordant with the impression from imaging studies

Knowing clinical history, imaging findings, and differential diagnostic considerations is key to thorough evaluation

Discordant diagnoses must be reconciled; may require repeat core biopsies or surgical excision

Radiology-pathology correlation conferences

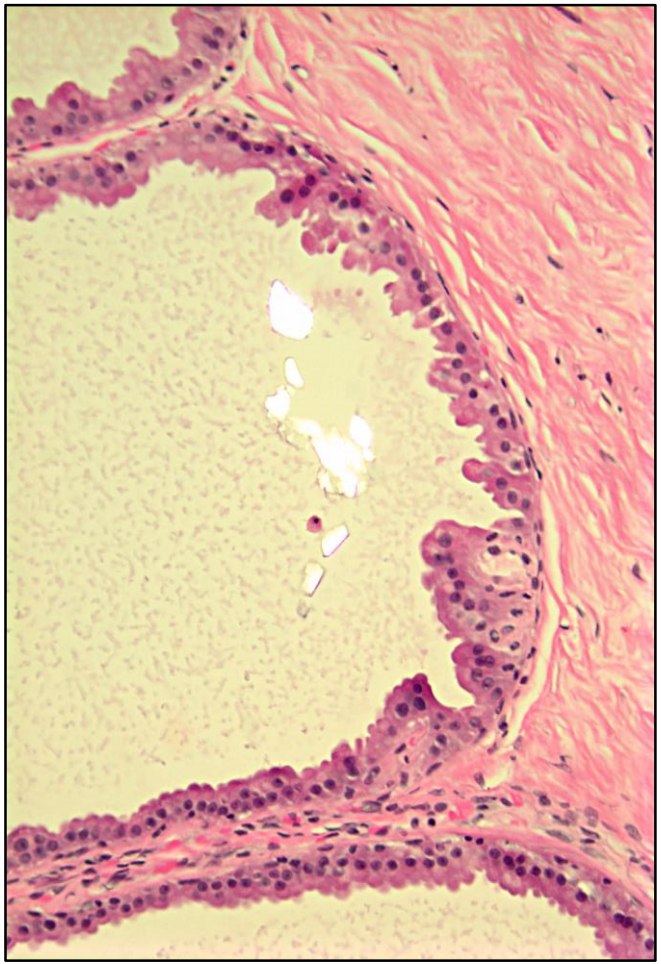
Radiologic-Pathologic Correlation

CNB for calcifications

- Specimen should be x-rayed
- Cores with and without calcifications should be submitted separately
- Very helpful to have access to specimen radiograph
- Calcifications seen on slide must correlate with those seen on radiograph
- Document location of calcifications in report

CNB for mass/NME/AD

- Must identify the pathologic correlate
- Beware of overemphasizing PASH
- Additional levels
- Note, if no mass identified



Missing Calcifications

- Calcium oxalate
- Additional levels (if one or two blocks)
- Radiograph blocks (if many blocks)
- Look for holes/tears in tissue

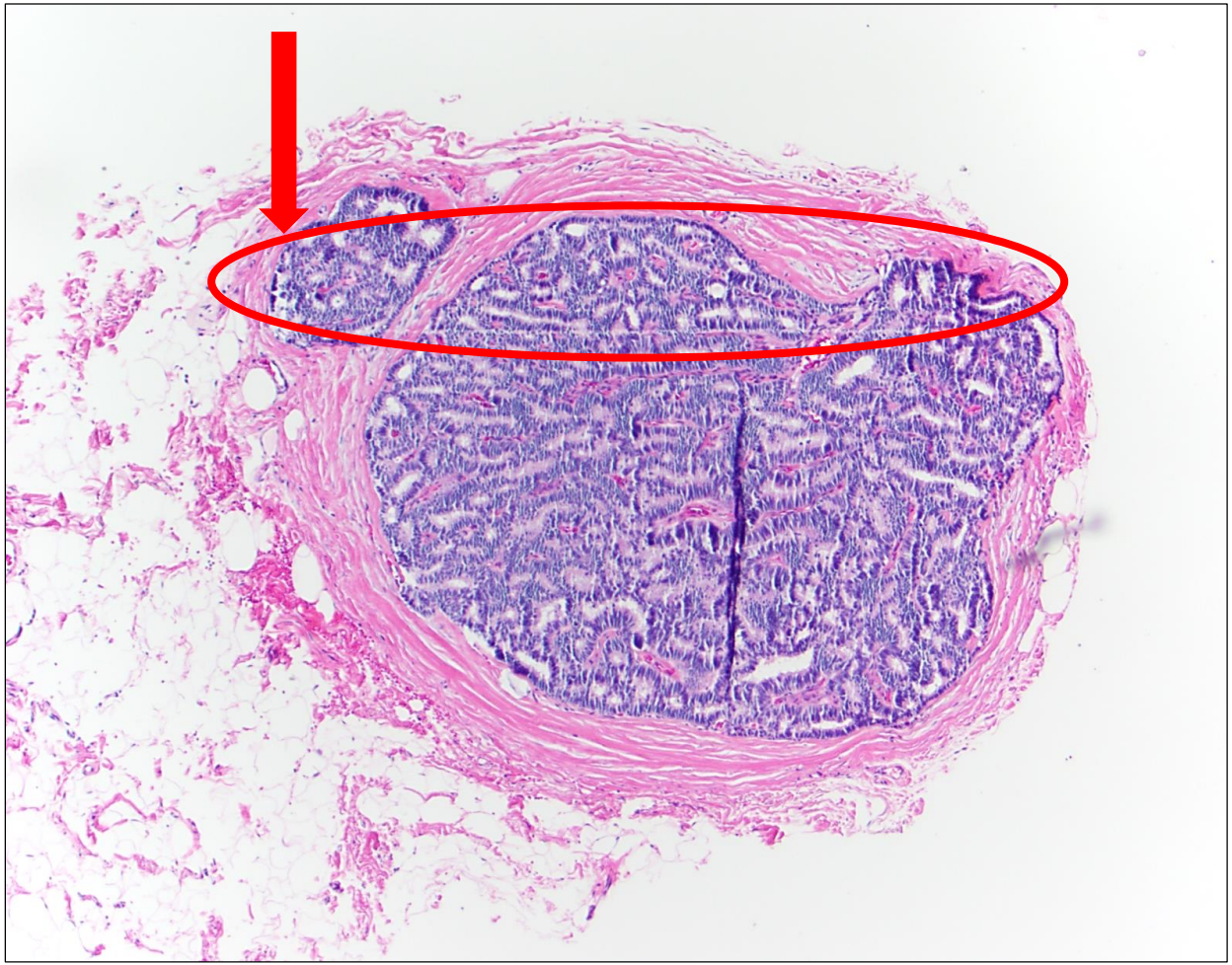


Table 2 Pathologic diagnosis category of NME lesions.

Category	No.
Malignant (20.5%)	**91**
Ductal carcinoma in situ	63
Invasive ductal carcinoma	14
Invasive lobular carcinoma	11
Invasive mixed carcinoma	3
Atypical (11.5%)	**51**
Atypical ductal hyperplasia	23
Flat epithelial atypia	4
Lobular carcinoma in situ	20
Atypical lobular hyperplasia	4
Benign breast diagnoses (68.0%)	**301**
Fibrocystic changes	214
Fibroadenoma	9
PASH	13
Inflammation	2
Fat necrosis	1
Blood clot	1
Normal breast tissue	61

Abbreviations: PASH, pseudoangiomatous stromal hyperplasia; NME, nonmass enhancement.

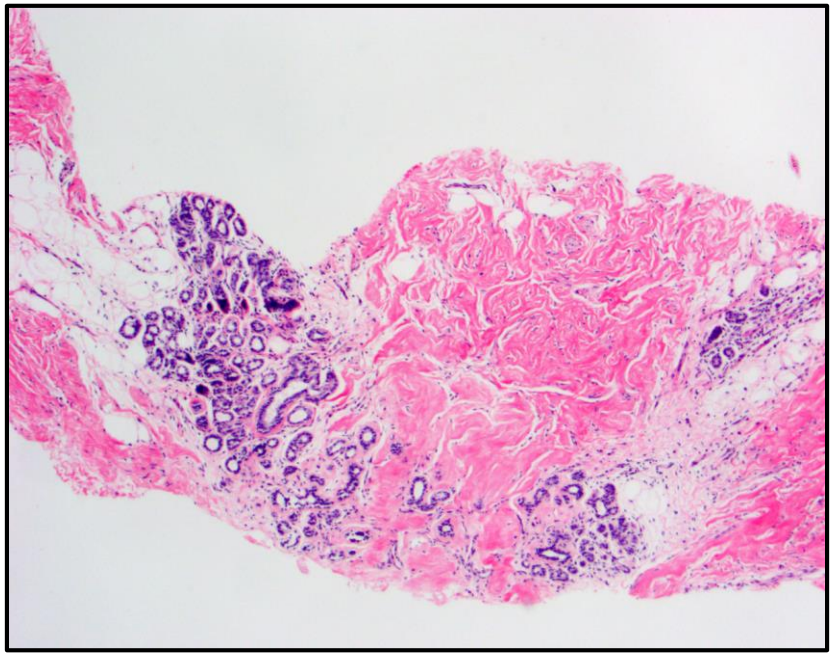
Bartels, Hum Pathol, 2021

Among MRI-directed biopsies:

- Majority are benign (60-70%)
- 10-15% atypia
- ~20% malignancy
- Benign and malignant lesions detected by MRI share similar morphologic and kinetic characteristics necessitating biopsy for histologic confirmation

Jabbar, Arch Pathol and Lab Med, 2017
Lilly, Ann Diag Pathol, 2020
Torous, Arch Pathol Lab Med, 2021

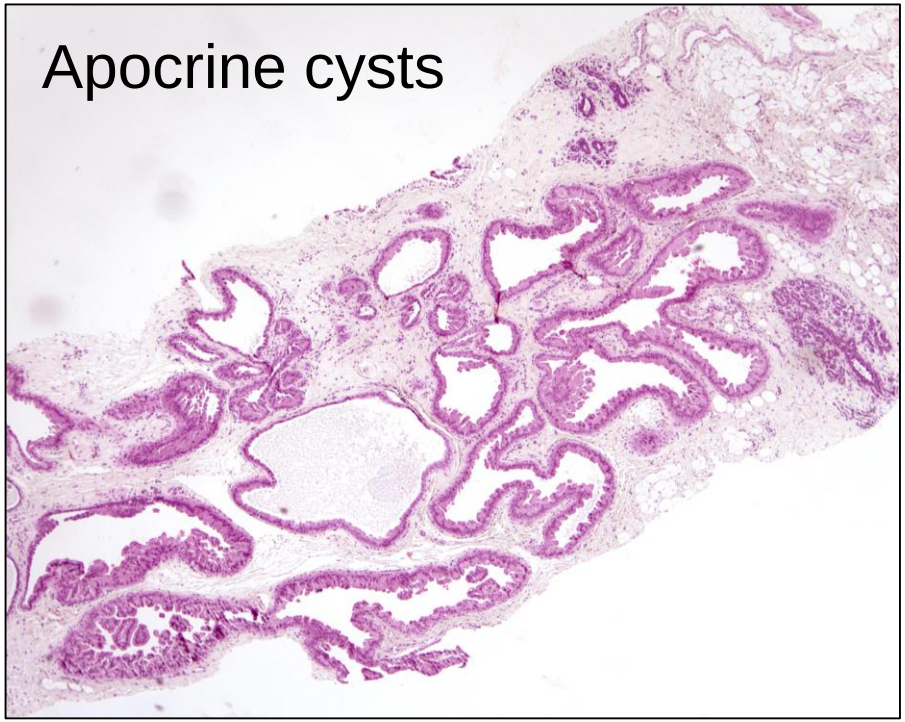
Radiologic Pathologic Correlation



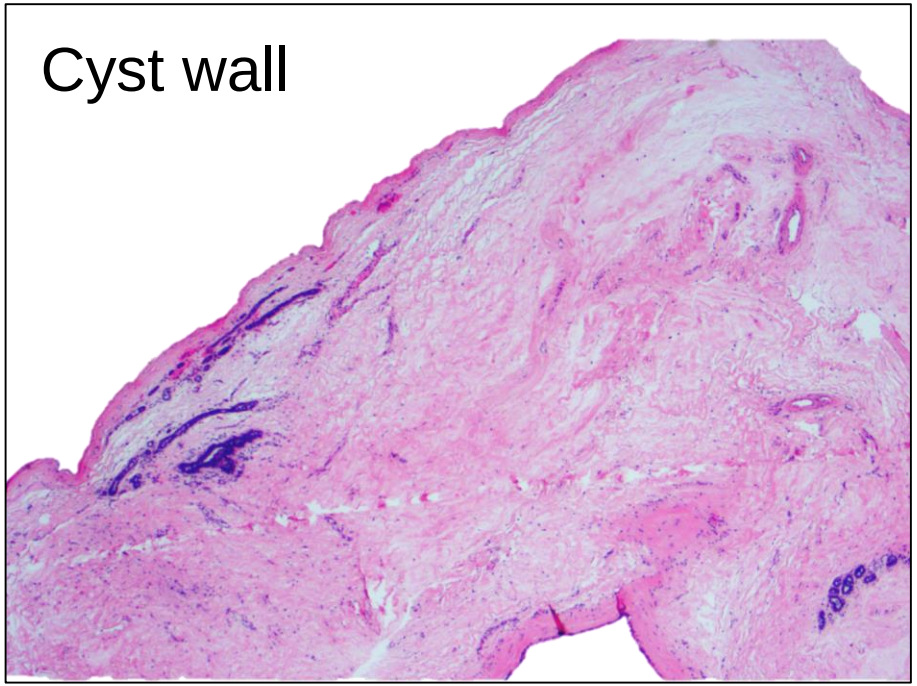
- Vague mass/developing density on imaging
  - Variably fibrotic breast tissue on CNB with no discrete mass-forming lesion
  - PASH on CNB
    - Found in ~25% of all benign breast biopsies

CORRELATES EASILY OVERLOOKED

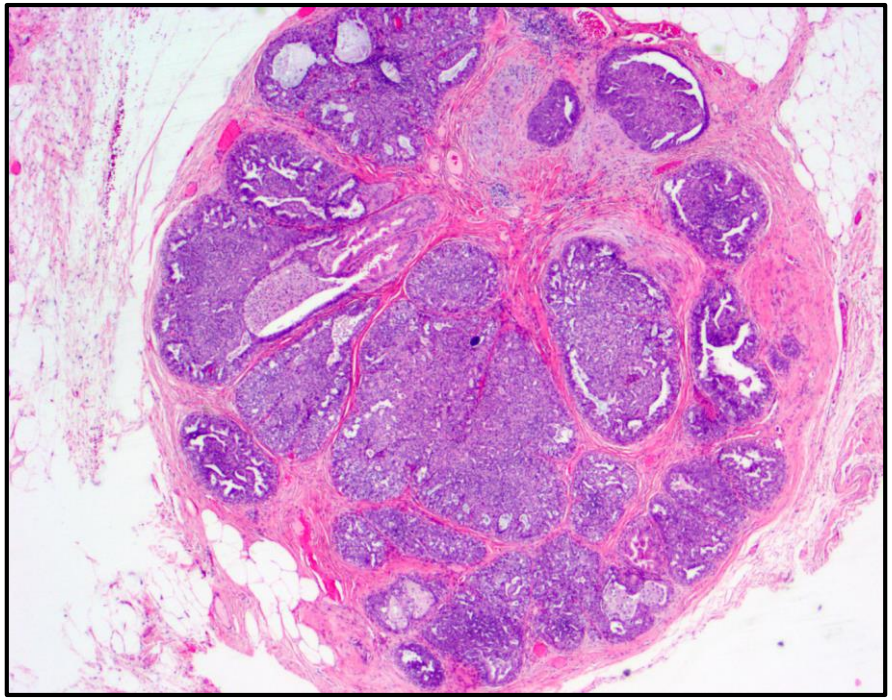
Apocrine cysts



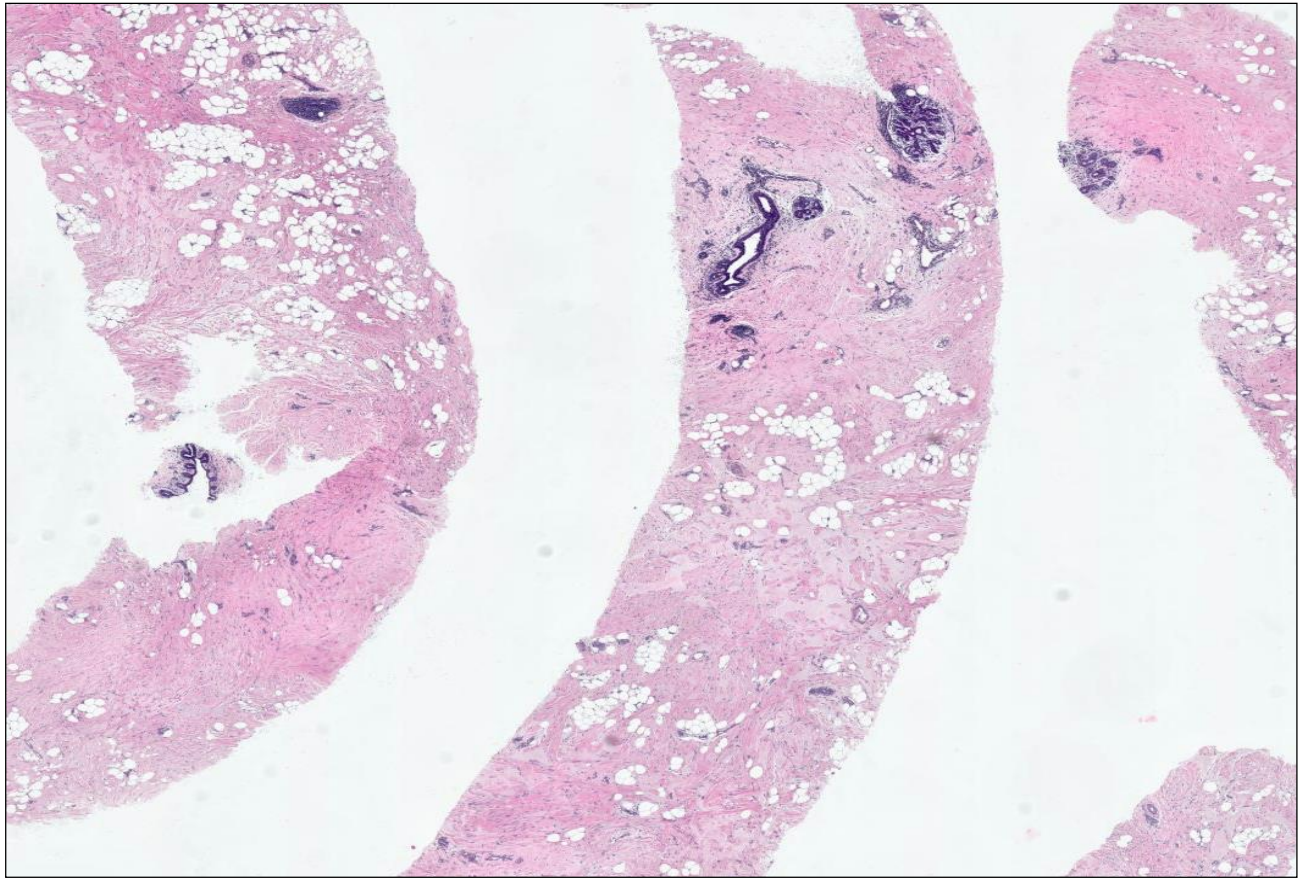
Cyst wall

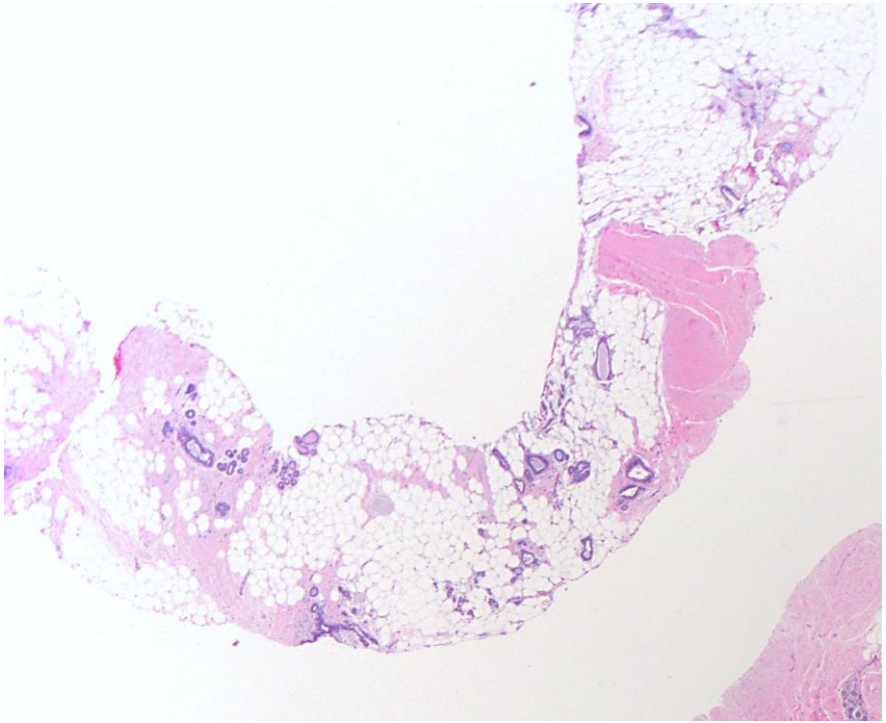


UDH as target NME lesion

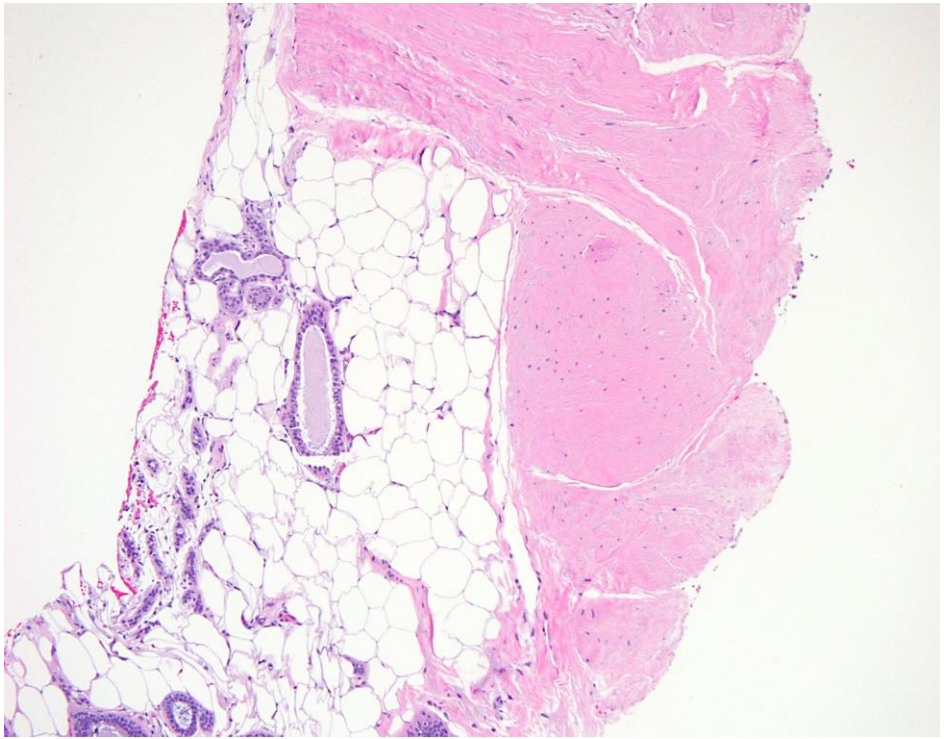


Lymphocytic mastopathy





?Desmoid-type Fibromatosis
?Scar
?Bland spindle cell proliferation

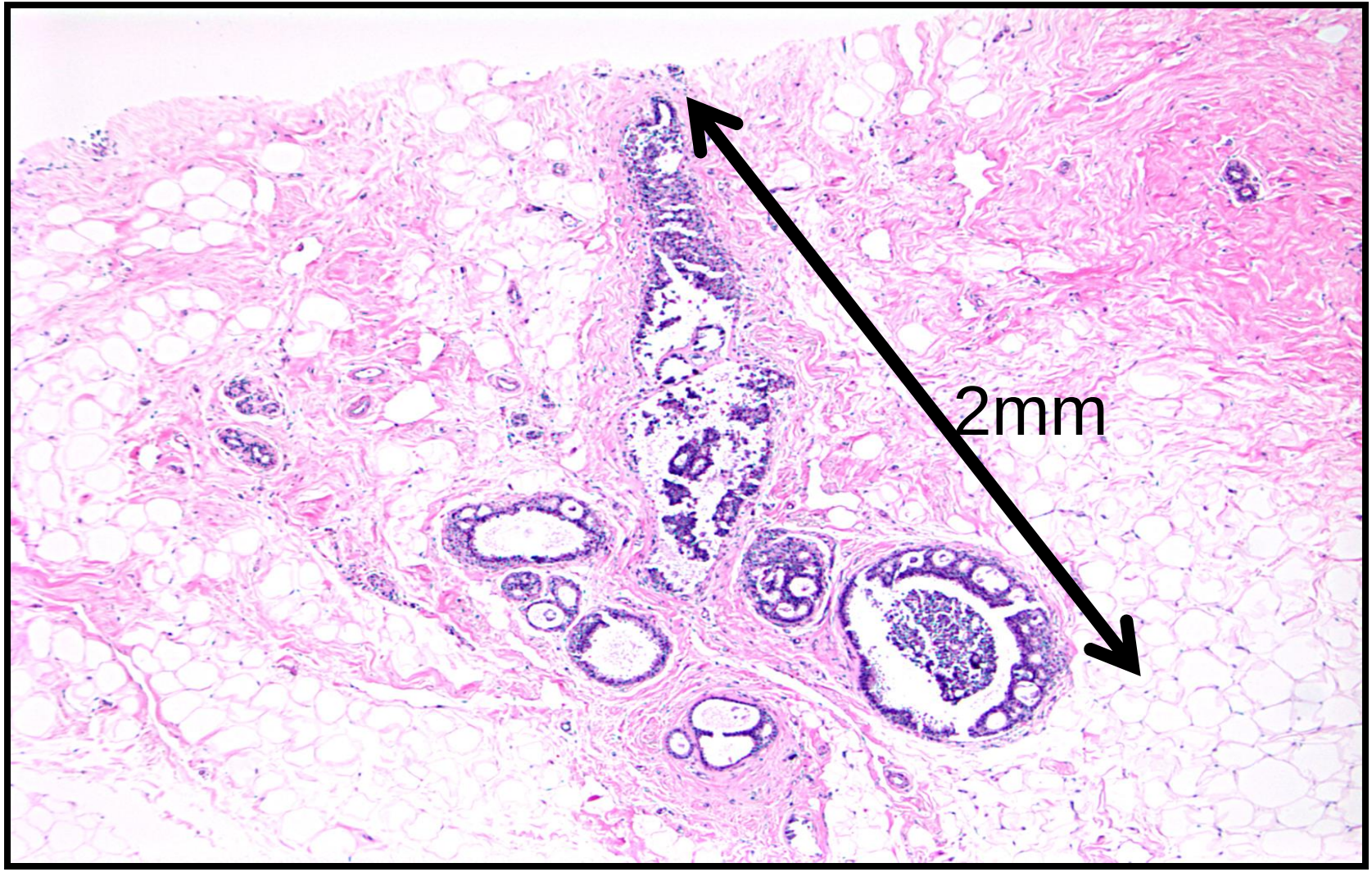


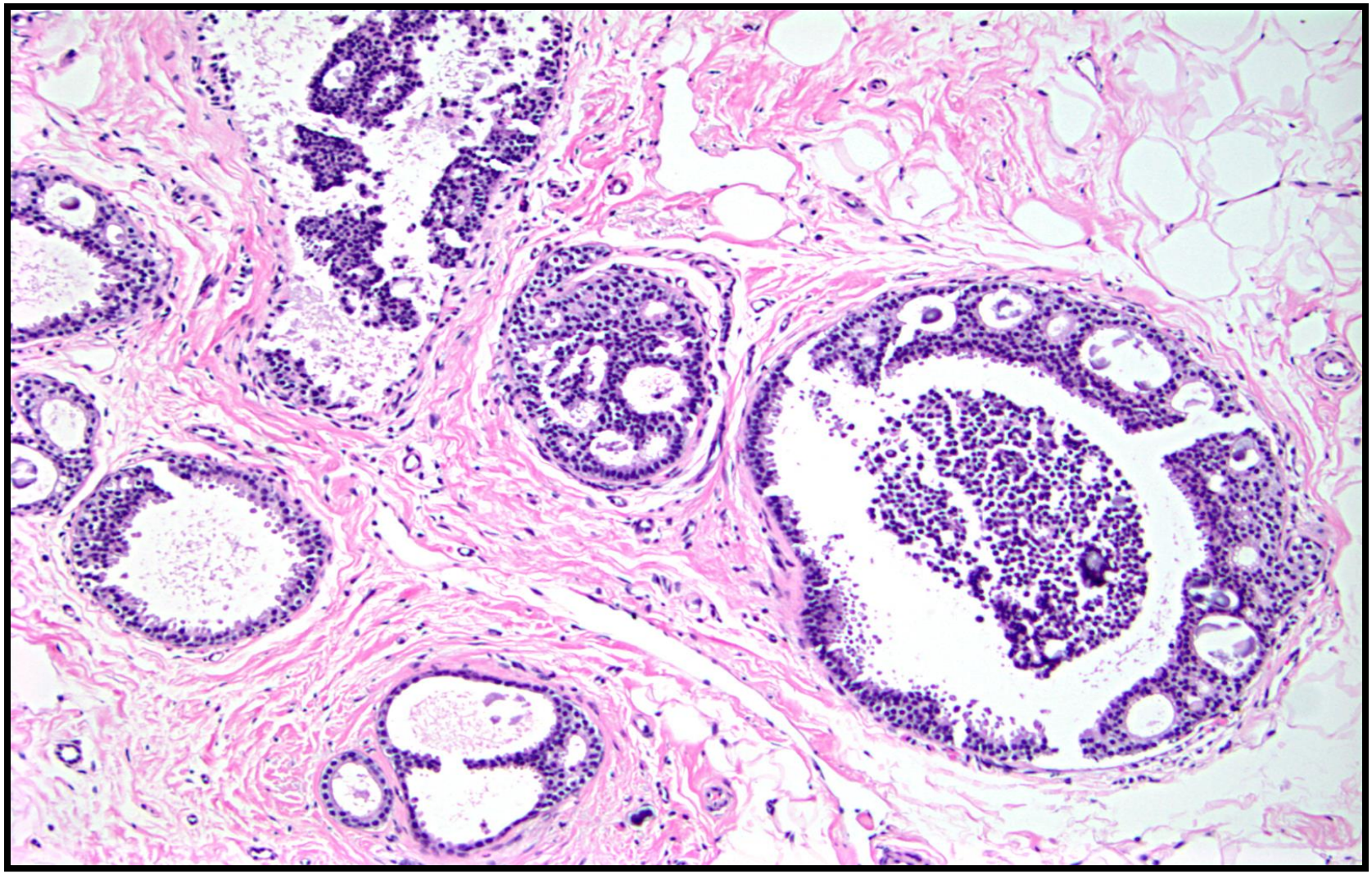
Practical Advice

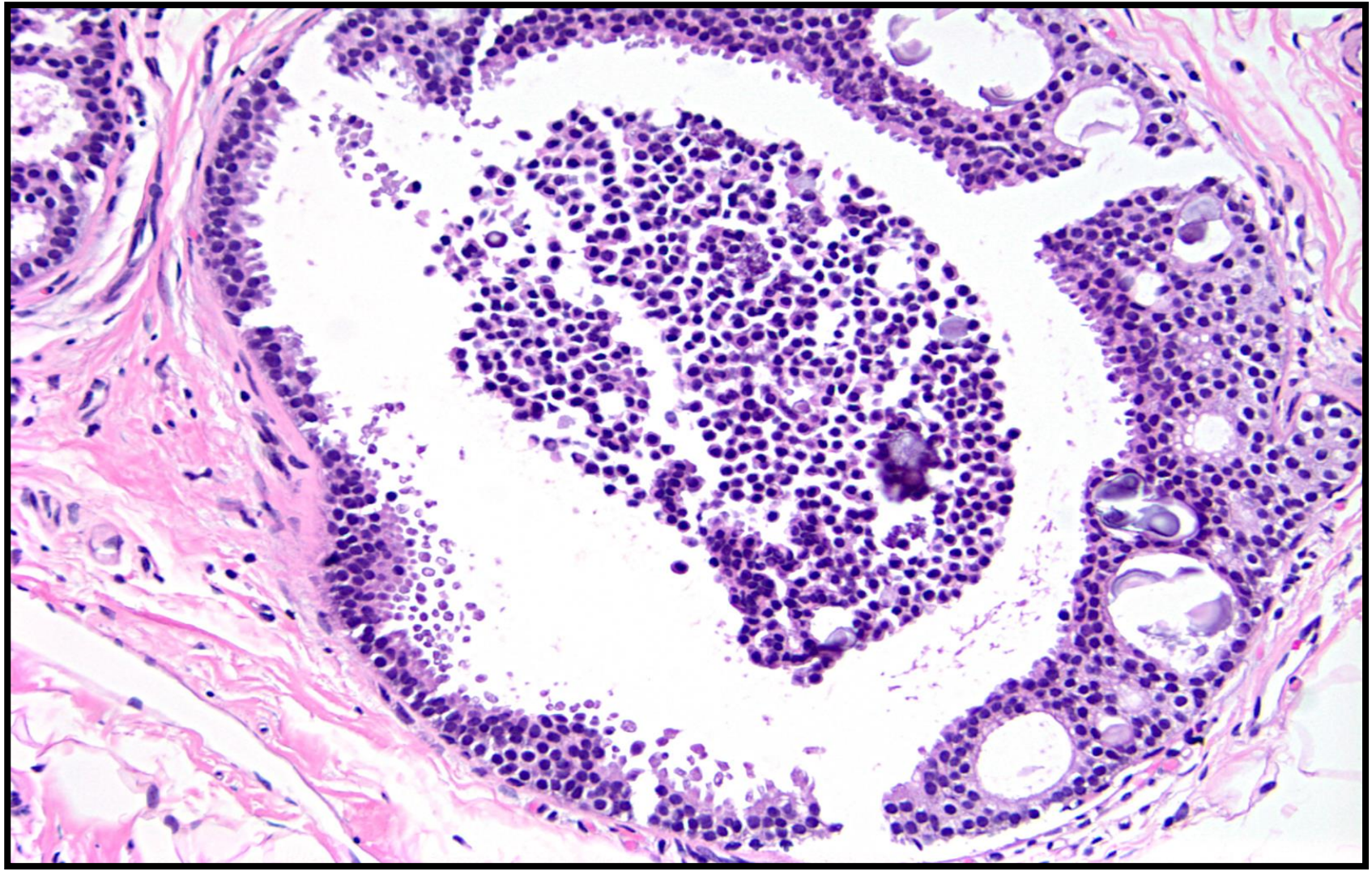
- Be aware of the clinical and imaging findings as well as differential diagnostic considerations
- Obtain levels often
- Use immunostains judiciously
- Be conservative; don’t overcommit when findings are equivocal
- Establish concordance for all cancers at the time of receptor signout, in particular triple negative cancers
- Check patient history

Atypical Ductal Hyperplasia

Excision remains standard of care
Exceptions occur in the setting of multidisciplinary “HRL tumor boards”


2mm





The challenge

- Diagnostic thresholds for ADH vs. LG DCIS can be subjective even with provided definitions
- No ancillary studies that can guide diagnostic distinction
- WHO advises a conservative approach to diagnosis in the setting of CNB

WHO 2019

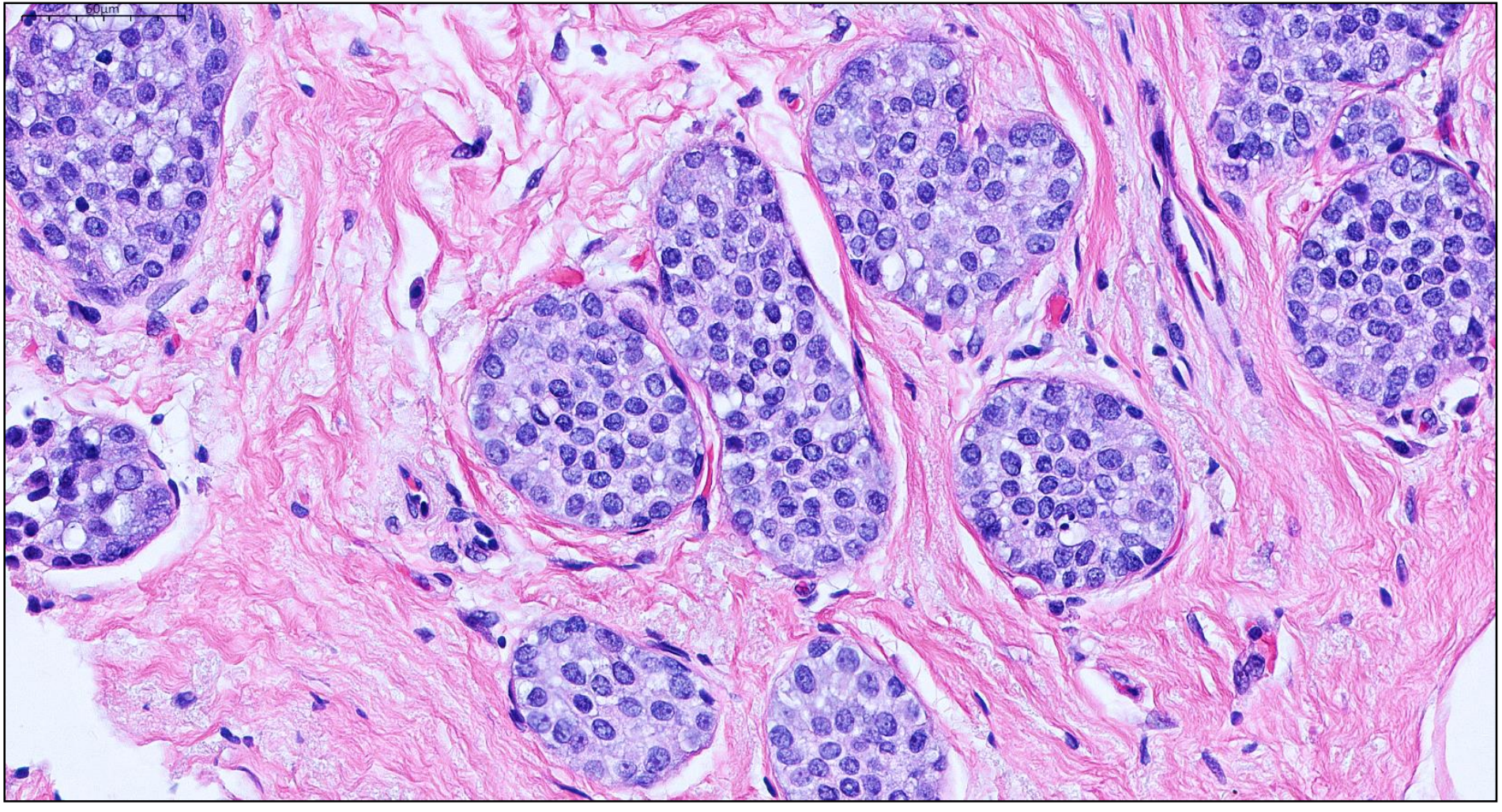
Current Management

- Upgrade rates to DCIS or invasive carcinoma remain ~20%
- Excision remains the standard of care for patients diagnosed with ADH on CNB
- [Becomes ineligible for clinical trials for LG DCIS]

ASBS Consensus Guideline, 2016
Schiaffino, Radiol, 2020
WHO 2019

LCIS and Atypical lobular hyperplasia (ALH)

Radiologic-pathologic concordant, incidental classic LCIS/ALH no longer require excision


60µm

Longstanding Practice for LN on CNB

- LN on CNB requires surgical excision to exclude a worse lesion (DCIS ± invasion)
- Upgrade rates reported range from 0-33%
- But classic LCIS/ALH is usually an incidental finding with no associated imaging target….

Classic LCIS/ALH on CNB

- More contemporary studies with careful radiologic-pathologic correlation demonstrate very low upgrade rates when classic LN is determined to be incidental

Table 2. Individual and pooled upgrade rates and 95% confidence intervals for studies included in the meta-analysis

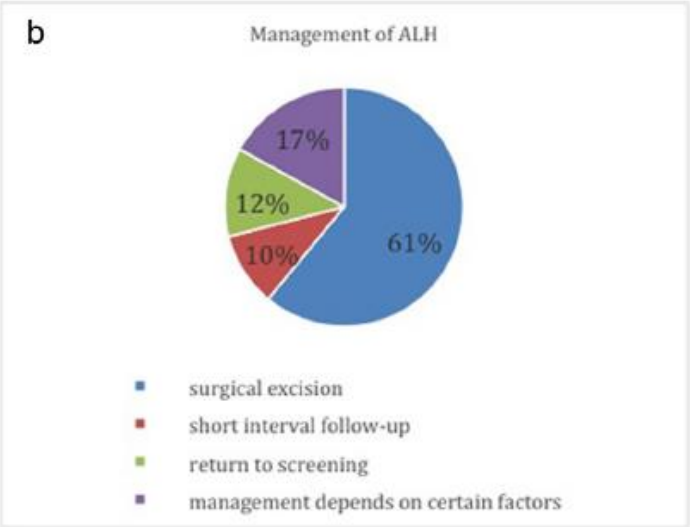
Study	All		ALH		LCIS*	
	Lesions Upgraded to Any Malignancy	Lesions Upgraded to Invasive Malignancy	Lesions Upgraded to Any Malignancy	Lesions Upgraded to Invasive Malignancy	Lesions Upgraded to Any Malignancy	Lesions Upgraded to Invasive Malignancy
Atkins et al 2013	0% (0/50)	0% (0/50)	0% (0/8)	0% (0/8)	0% (0/29)	0% (0/29)
Chaudhary et al 2013	3% (3/87)	2% (2/87)	0% (0/22)	0% (0/22)	5% (3/65)	3% (2/65)
Holbrook et al 2019	0% (0/79)	0% (0/79)	NR	NR	NR	NR
Hwang et al 2008	0% (2/221)	0% (0/221)	NR	NR	NR	NR
Menon et al 2008	11% (5/44)	5% (2/44)	NR	NR	NR	NR
Mooney et al 2016	14% (10/74)	4% (3/74)	7% (3/43)	2% (1/43)	23% (7/31)	6% (2/31)
Muller et al 2018	3% (3/87)	0% (0/87)	3% (3/87)	0% (0/87)	NA	NA
Murray et al 2013	3% (2/80)	0% (0/80)	7% (2/30)	0% (0/30)	0% (0/42)	0% (0/42)
Nakhlis et al 2016	3% (2/77)	1% (1/77)	0% (0/49)	0% (0/49)	12% (2/17)	6% (1/17)
Niell et al 2012	9% (4/47)	4% (2/47)	6% (1/16)	0% (0/16)	10% (3/31)	6% (2/31)
Purdie et al 2010	16% (7/45)	NR	NR	NR	NR	NR
Rendi et al 2012	4% (3/67)	1% (1/67)	2% (1/47)	0% (0/47)	5% (1/20)	0% (0/20)
Schmidt et al 2018	3% (5/173)	1% (2/173)	NR	NR	NR	NR
Sen et al 2016	4% (17/442)	2% (8/422)	2% (8/335)	1% (2/335)	8% (9/107)	6% (6/107)
Shah-Khan et al 2012	1% (2/166)	NR	1% (1/124)	0% (0/124)	3% (1/32)	0% (0/32)
Susnik et al 2016	1% (2/222)	NR	NR	NR	NR	NR
Pooled percentage (95% CI)	3.1% (1.8%-5.2%)	1.3% (0.7%-2.4%)	2.5% (1.6%-3.9%)	0.4% (0.0%-4.2%)	5.8% (2.9%-11.3%)	3.5% (2.0%-5.9%)

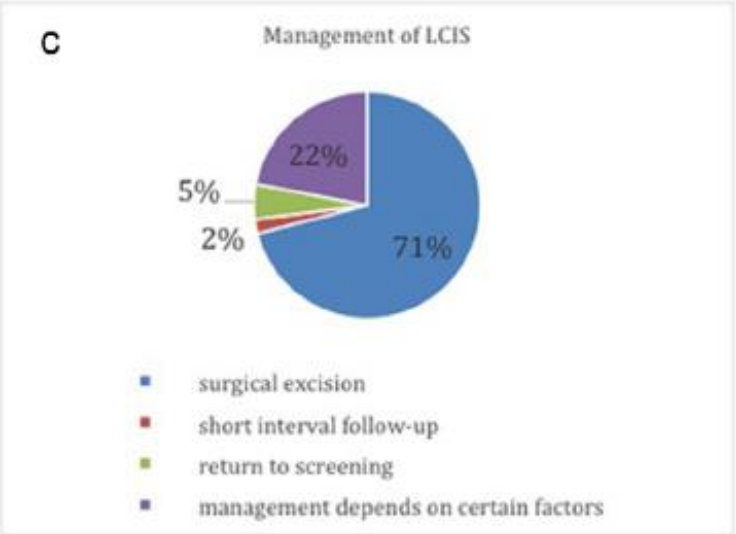
Note: Upgrade rates for each study were calculated for all reported imaging-concordant classic lobular neoplasia lesions managed with either surgical excision or clinical or imaging follow-up. Pooled rates were estimated from a random-effects meta-analysis. ALH = atypical lobular hyperplasia; CI = confidence interval; LCIS = lobular carcinoma in situ; NA = not applicable; NR = not reported (or unable to calculate from provided data).

*Includes lesions identified as "lobular neoplasia unspecified" and mixed "ALH + LCIS" lesions.

Shehata, J Am Coll Radiol, 2020

Variability in the Management Recommendations Given for High-risk Breast Lesions Detected on Image-guided Core Needle Biopsy at U.S. Academic Institutions





41 of 59 academic institutions contacted responded (69%)

Falomo, Curr Prob Diag Radiol, 2019

Current Management

- Upgrade rates to DCIS or invasive carcinoma are low in cases of incidental classic LCIS/ALH (0-~3%)
- When present, carcinomas tend to be small, low grade lesions
- No excision needed
- Consideration of chemopreventive therapy
- Excision performed when LCIS is the imaging target (usually the variant forms)

ASBS Consensus Guideline, 2016
Schiaffino, Radiol, 2020
NCCN, 2020

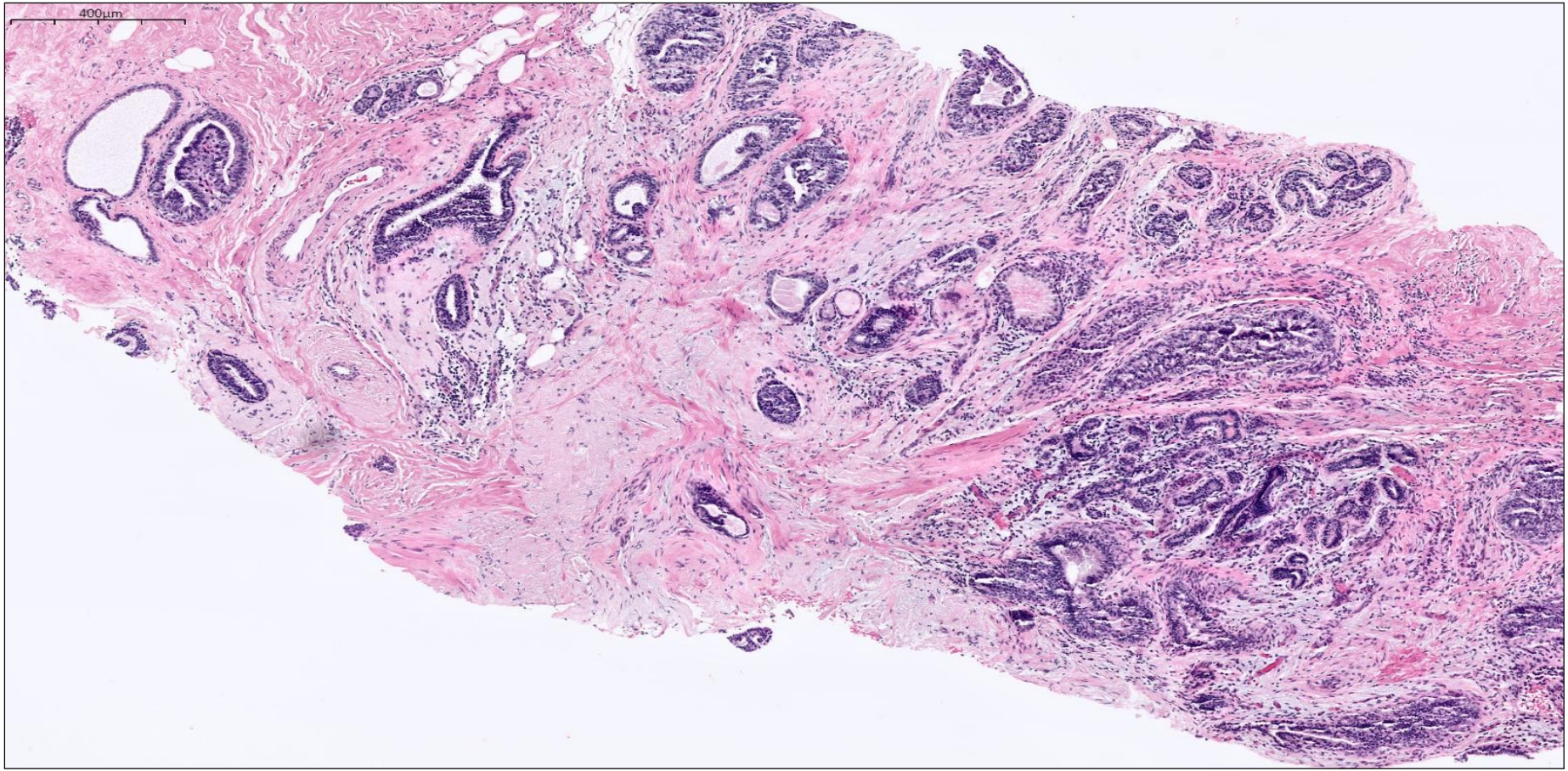
Radial scar/Complex sclerosing lesion

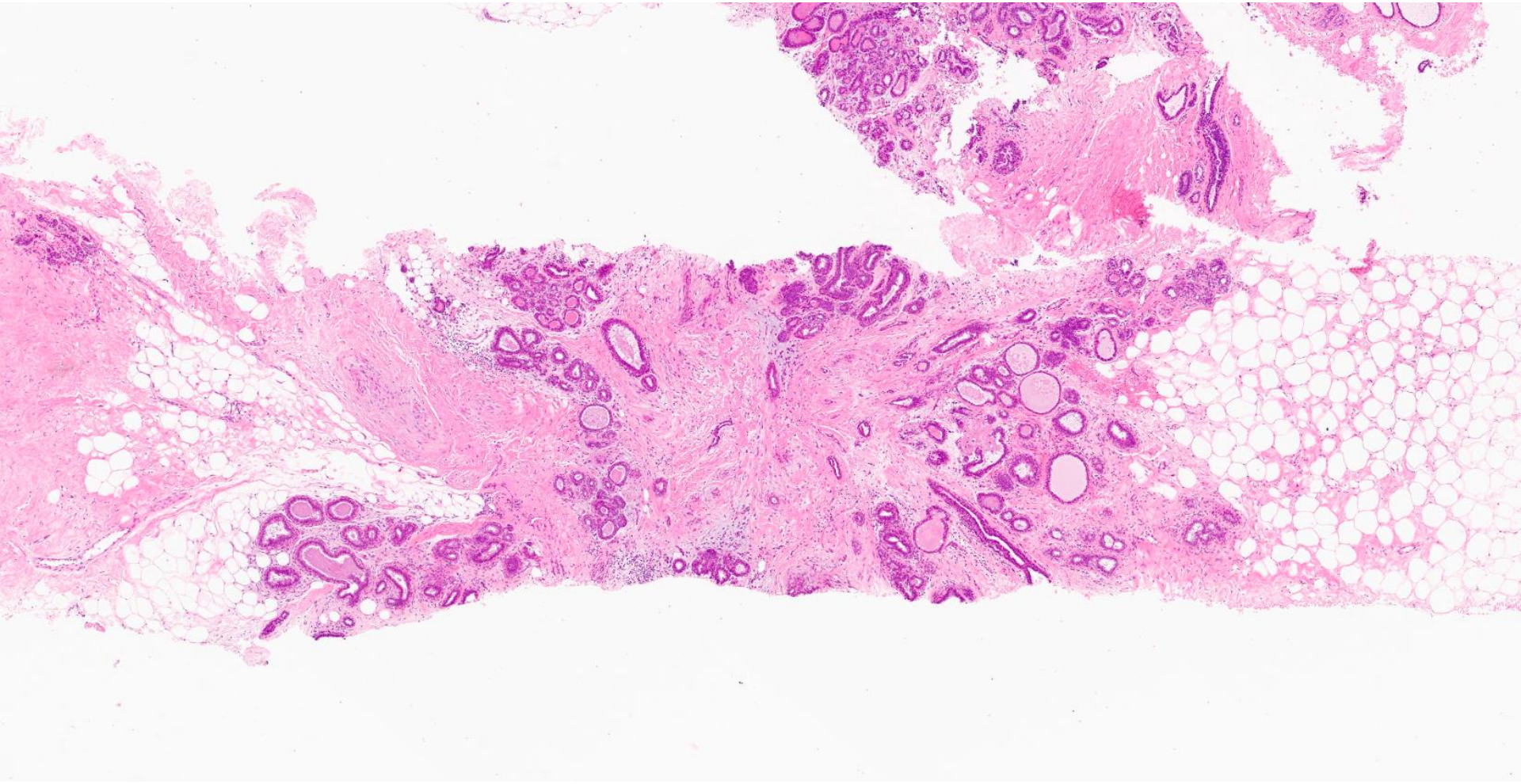
Incidental radiologic-pathologic concordant radial scars do not require excision

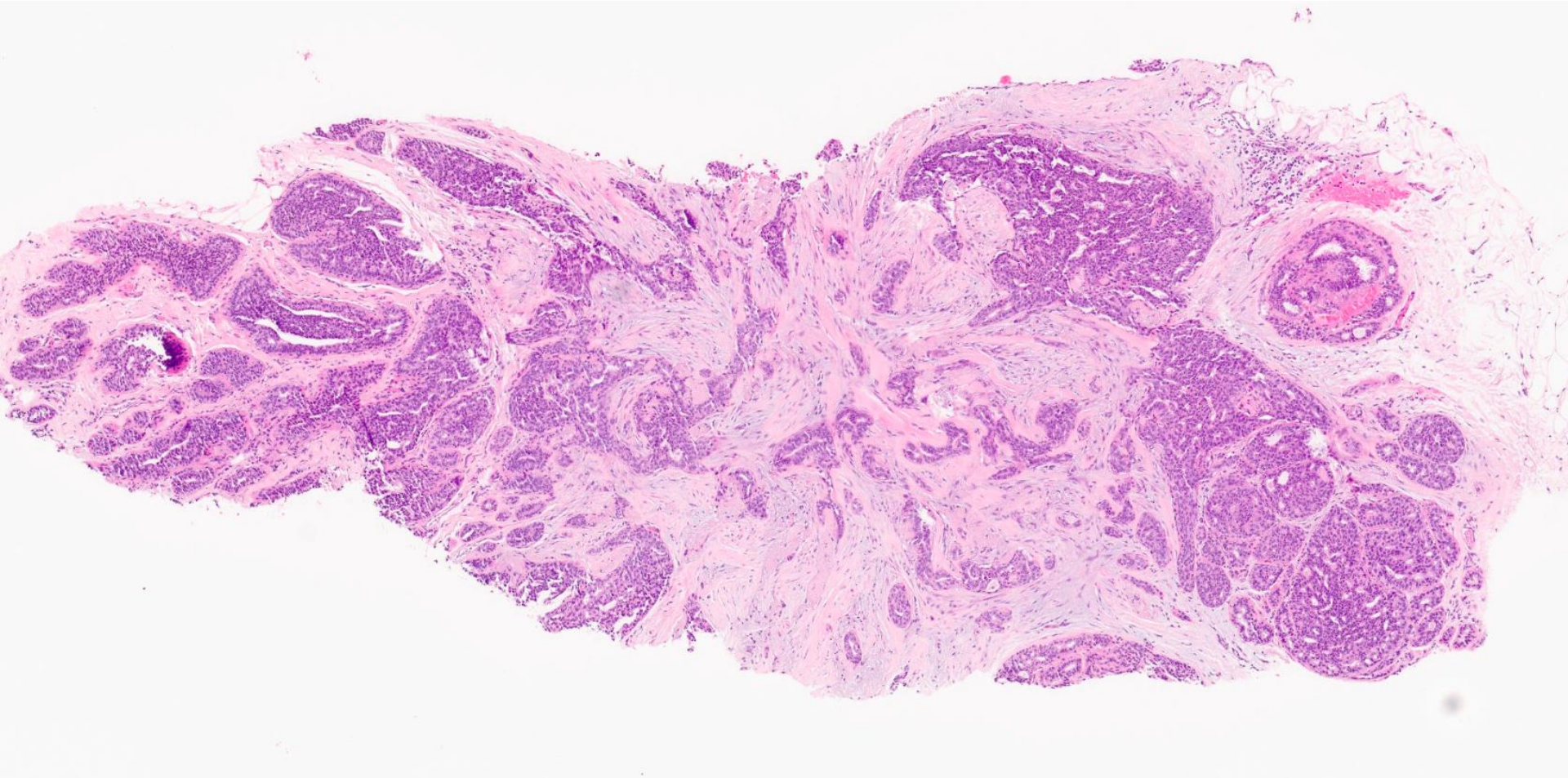
Excision remains standard of care for most image detected radial scars/CSLs

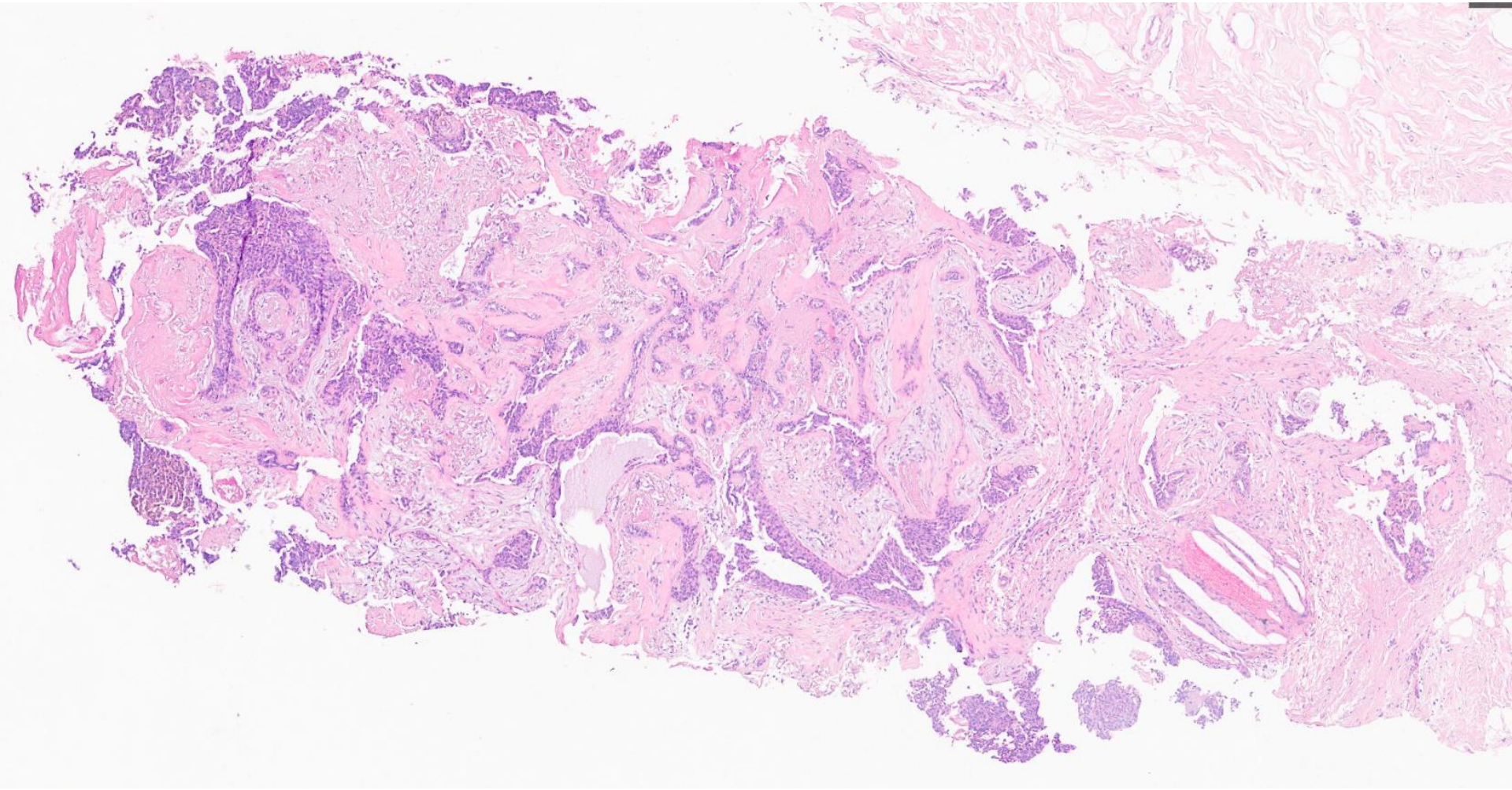
The challenge

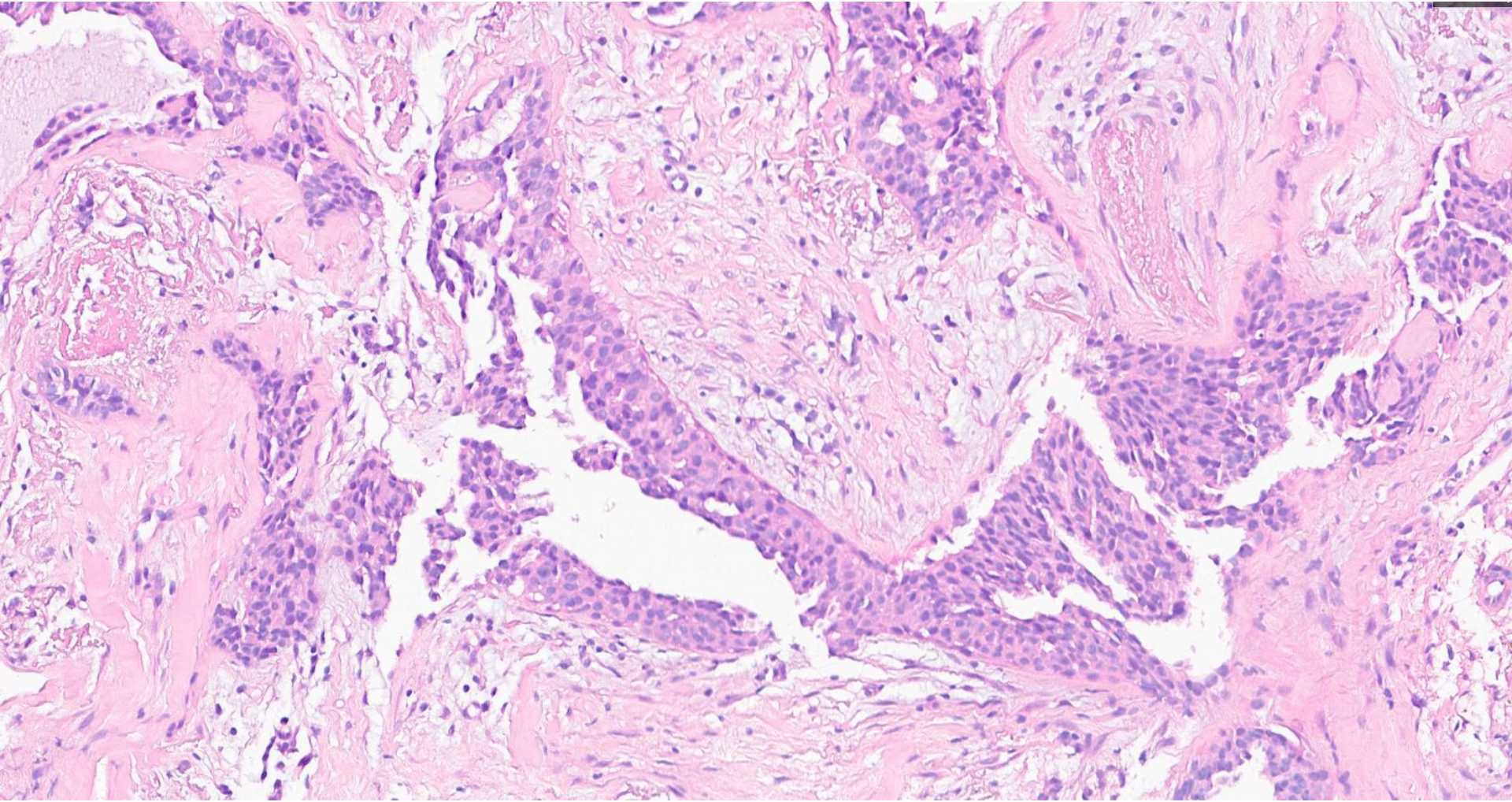
- RS/CSL can mimic carcinoma clinically, radiologically and pathologically
- Some imaging features favor RS, e.g. lucent center, greater reach of “stellate” features
- Pathologically, lobulocentric pattern and elastotic stroma favor a benign process
- Use of IHC to highlight myoepithelial cell layer helpful

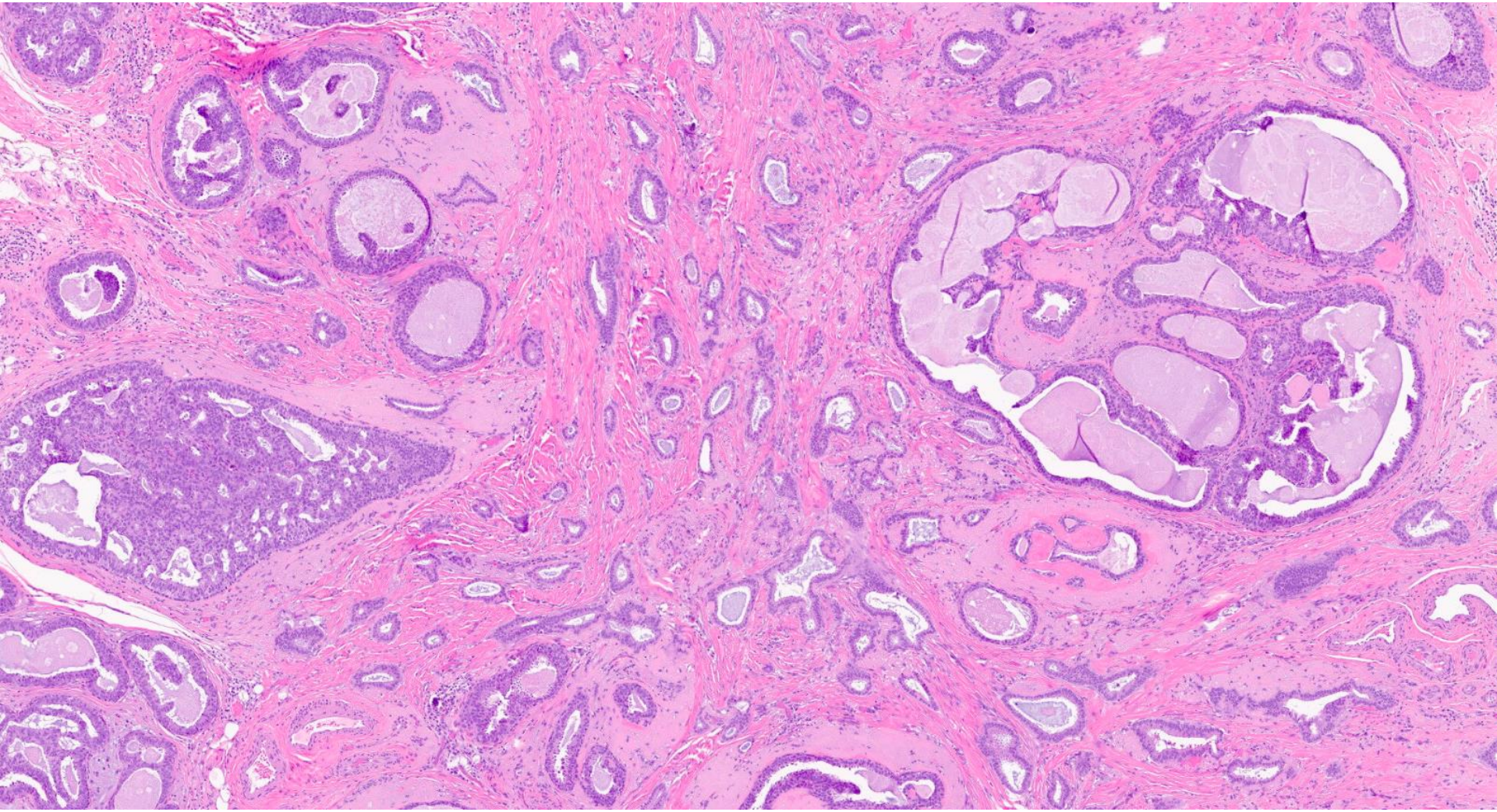

400µm



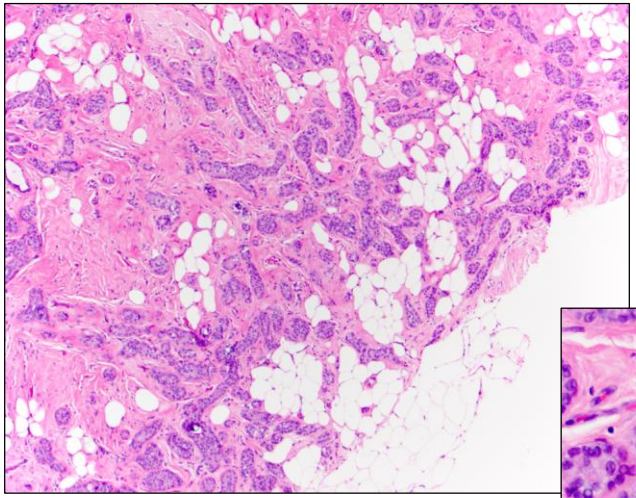


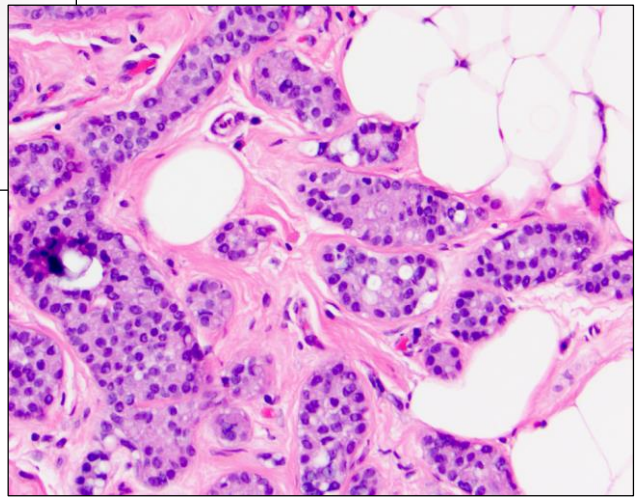


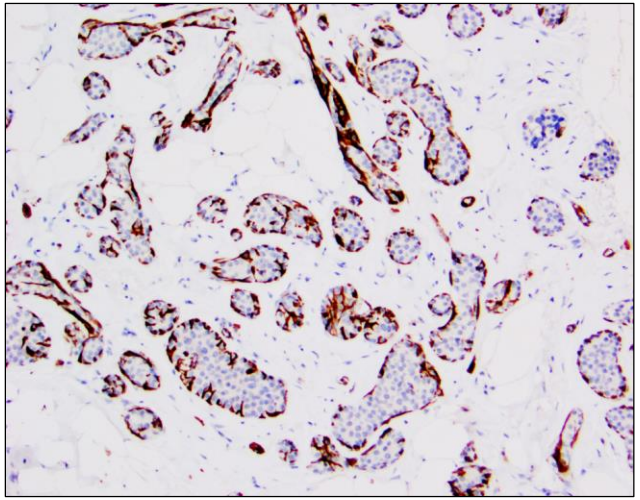




LCIS in adenosis



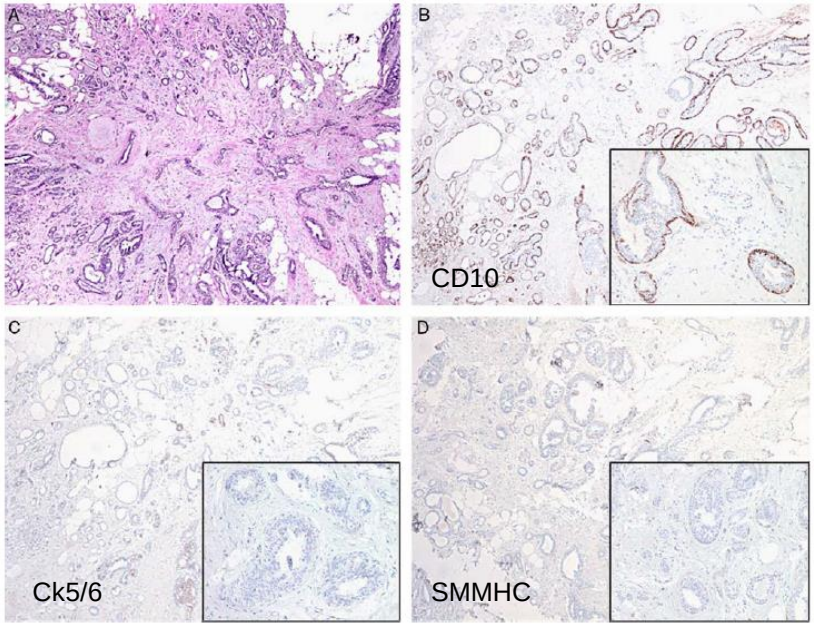




Phenotypic Alterations in Myoepithelial Cells Associated With Benign Sclerosing Lesions of the Breast

Justin B. Hilson, MD, Stuart J. Schnitt, MD, and Laura C. Collins, MD

Reduced expression of MEC markers is seen in some benign sclerosing lesions



Current Management

- Upgrade rates to DCIS or invasive carcinoma while lower than in the past, remain high enough (~5%) that excision is generally indicated for image detected lesions
- Excision required if there is involvement by carcinoma in situ

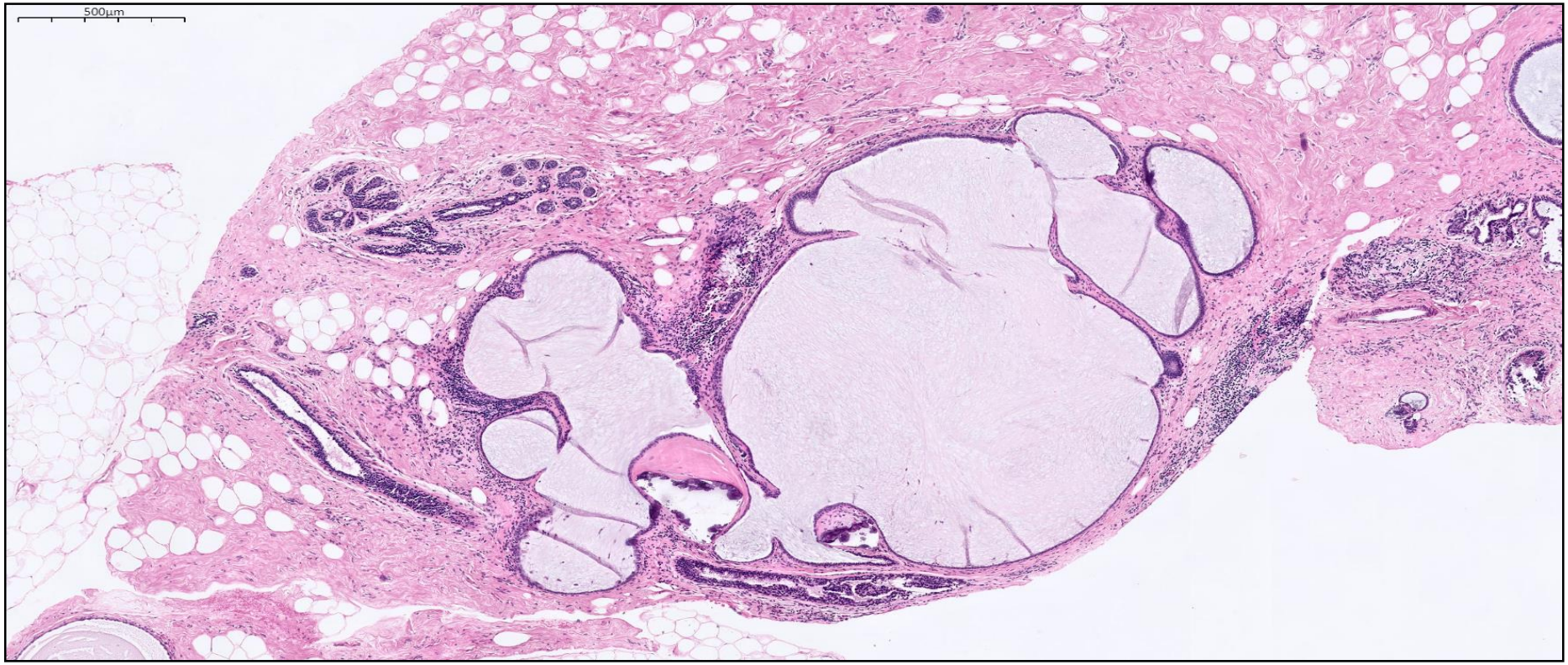
ASBS Consensus Guideline, 2016
Schiaffino, Radiol, 2020
NCCN, 2020

Mucocele-like lesion

Radiologic pathologic concordant MLL without atypia no longer require excision

Mucocele-like lesion

- As with other lesions discussed, older data is confounded by including cases with radiologic-pathologic discordance, the presence of atypia on histology, selection bias in cases undergoing excision etc.



Mucocele-like Lesion

Differential Diagnosis

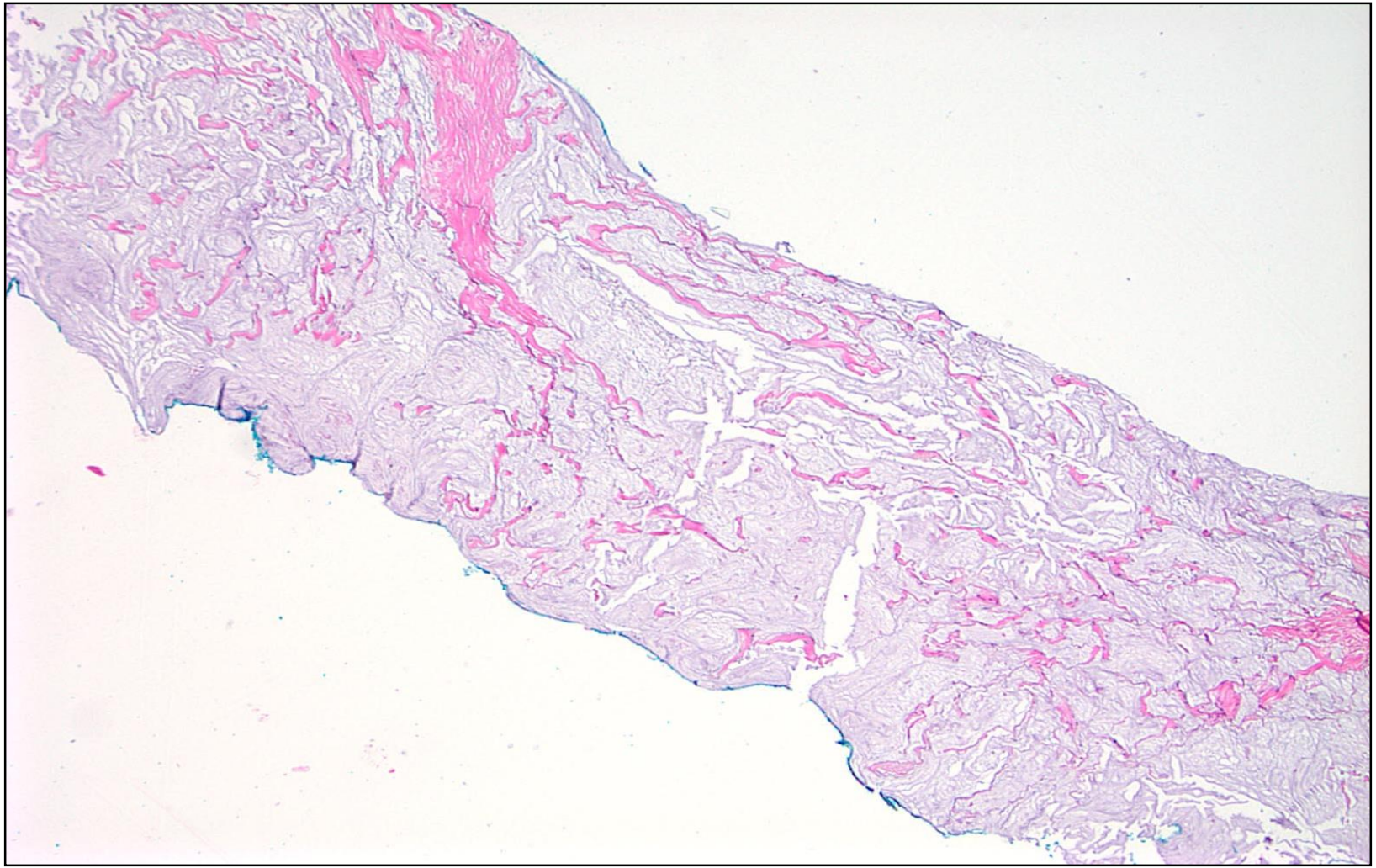
Beth Israel Deaconess Medical Center

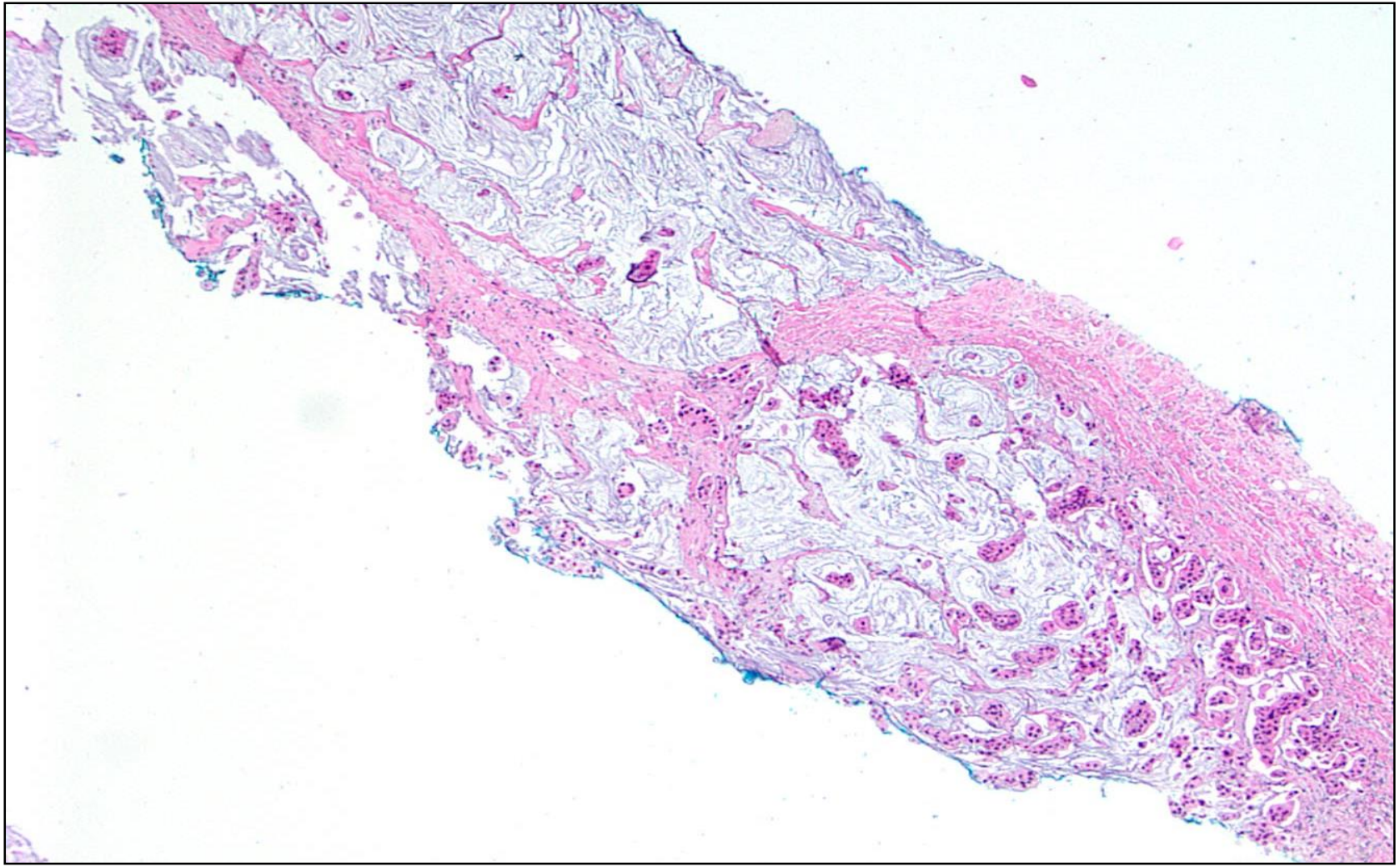
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Mucinous carcinoma

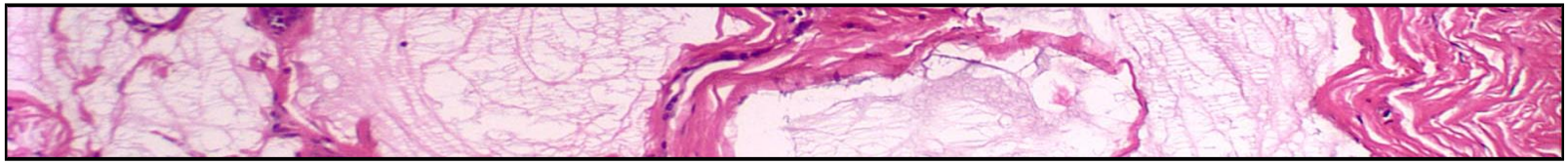
Mucin pools s/p neoadjuvant systemic therapy

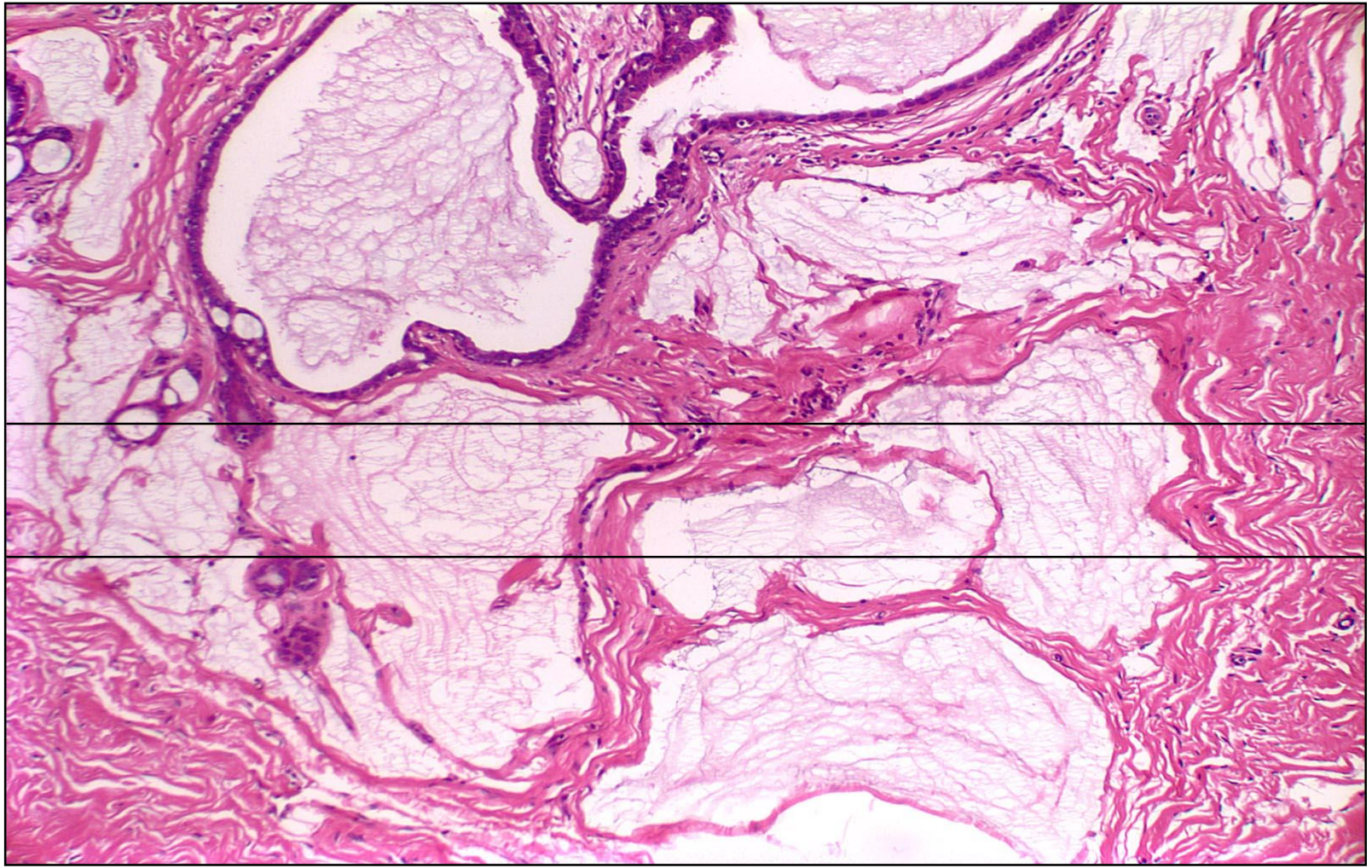
Metastasis



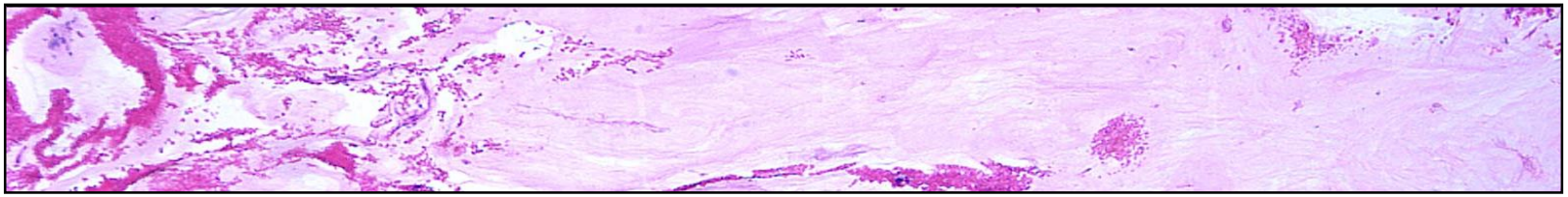


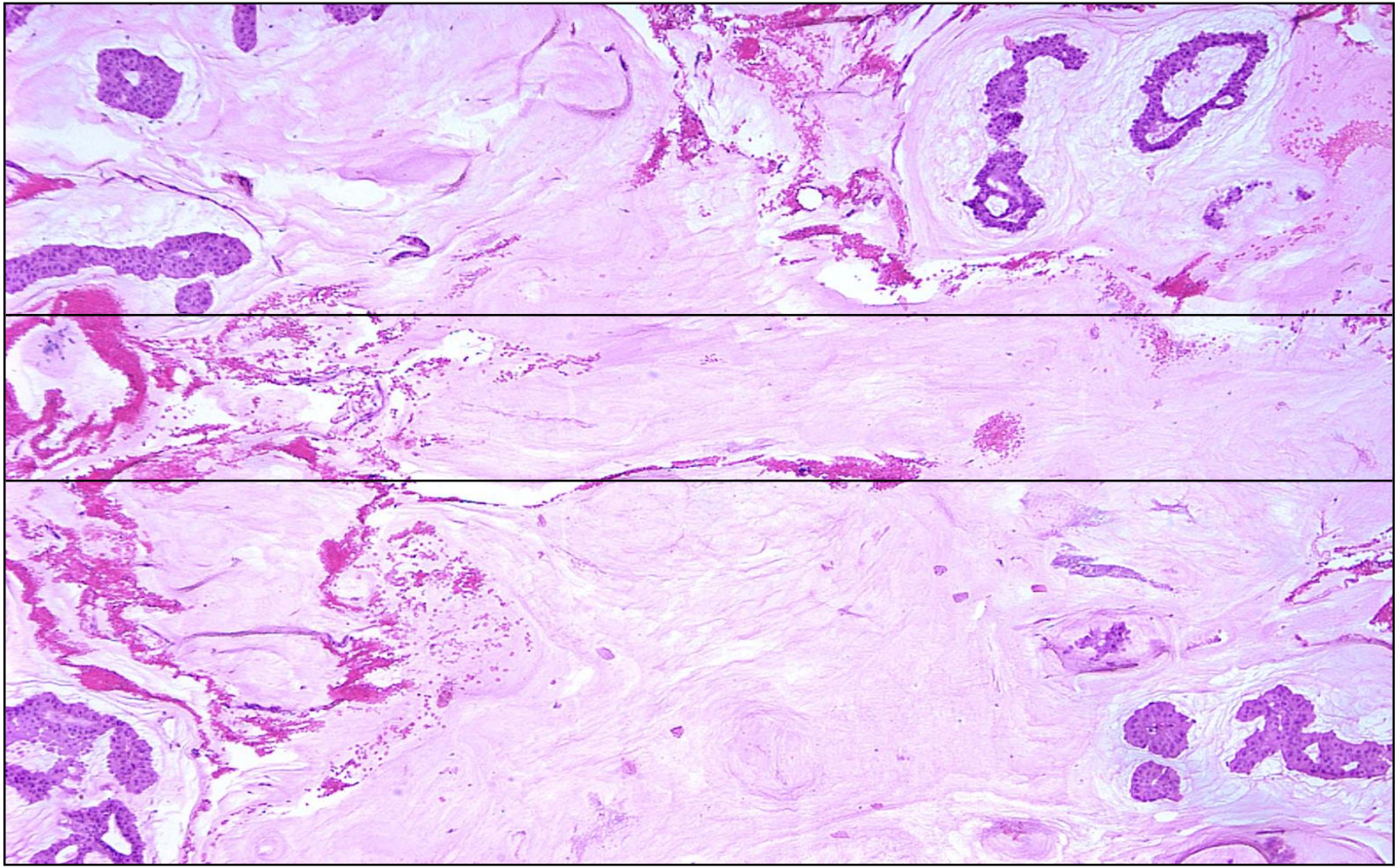
Example 1





Example 2





Mucocele-Like Lesions Stratified by Atypia

Beth Israel Deaconess Medical Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

441 cases without atypia reported over a 20 year period

- 15 upgrades to DCIS or invasive carcinoma (3.4%)

117 MLL with atypia; 17.9% upgrade rate

Rakha, Histopathol, 2013
Gibreel, Ann Surg Oncol, 2016
Dash, Clin Radiol, 2017
Ylagan, Mod Pathol A, 2019
Moseley, Ann Surg Oncol, 2019

Current Management

- Upgrade rates to DCIS or invasive carcinoma are low in cases of MLL without atypia (0-~3%)
- Excision performed for MLL with atypia or cases of radiologic discordance

ASBS Consensus Guideline, 2016
Schiaffino, Radiol, 2020
Bahl, Radiol Clin N Am, 2021

SUMMARY	Upgrade rate (%): CNB to excision
Atypical ductal hyperplasia	~20
Atypical lobular hyperplasia/LCIS	0–4
Flat epithelial atypia	0–4
Papilloma	~3
Radial scar/complex sclerosing lesion	~5
Mucocele-like lesion without atypia	0-4

In the presence of radiologic-pathologic concordance, and in the absence of clinical or radiologic concerns the following lesions no longer require routine excision

- Incidental ALH/LCIS
- Small asymptomatic papillomas/micropapillomas
- Mucocele-like lesions without atypia
- Incidental radial scars
- Columnar cell lesions
- FEA-depends on imaging findings/extent of calcifications

CONSEQUENCES OF CORE NEEDLE BIOPSY

Consequences, Complications and Artifacts Related to Core Needle Biopsies

- Hemorrhage, granulation tissue, scarring and bx site
- Infarction
- Epidermoid cysts
- The missing cancer
- Epithelial displacement

Epithelial Displacement

- Benign epithelium, ductal carcinoma in situ: stroma or vascular spaces
- Invasive carcinoma: vascular spaces
- Displacement/transport of benign epithelium, DCIS or invasive cancer to axillary nodes

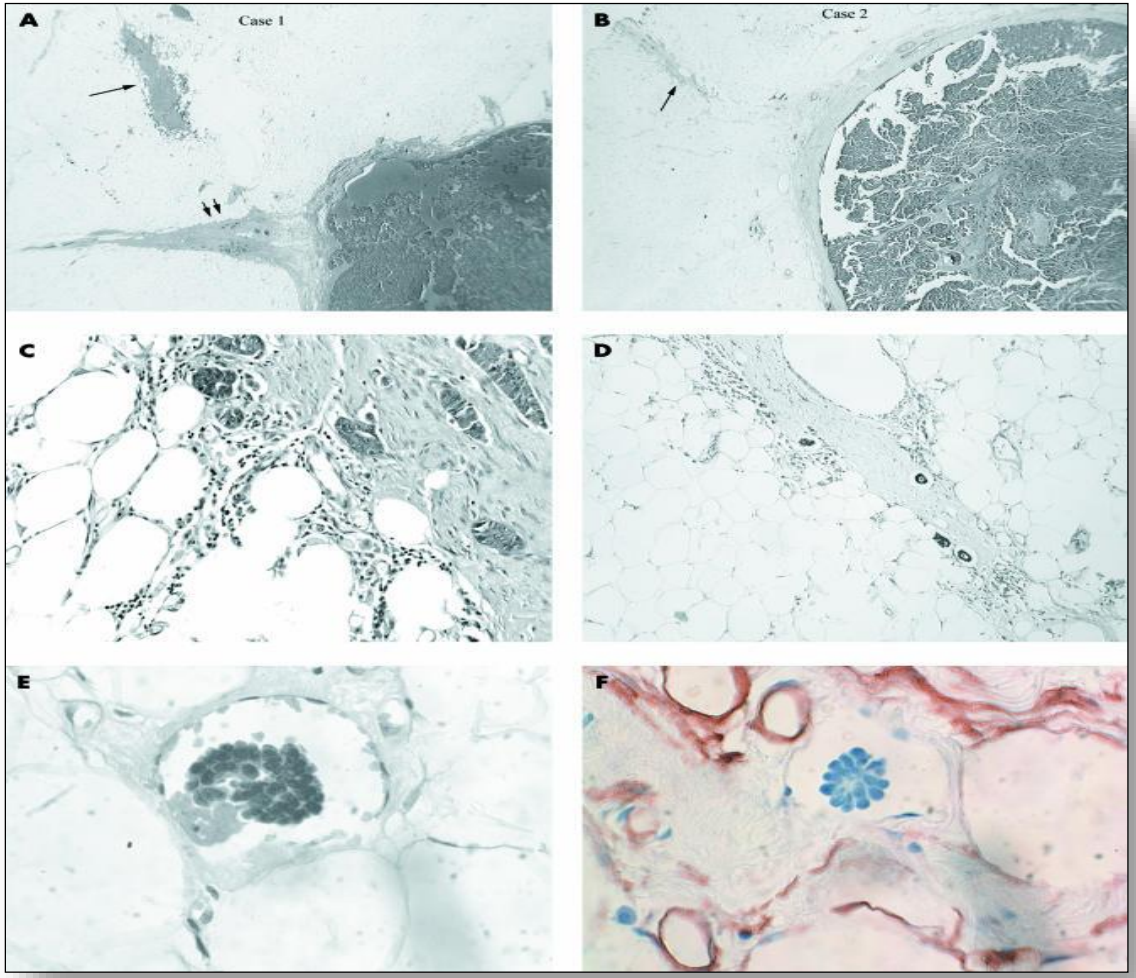
Displaced Epithelium Following Core Needle Biopsy

Inversely related to CNB interval

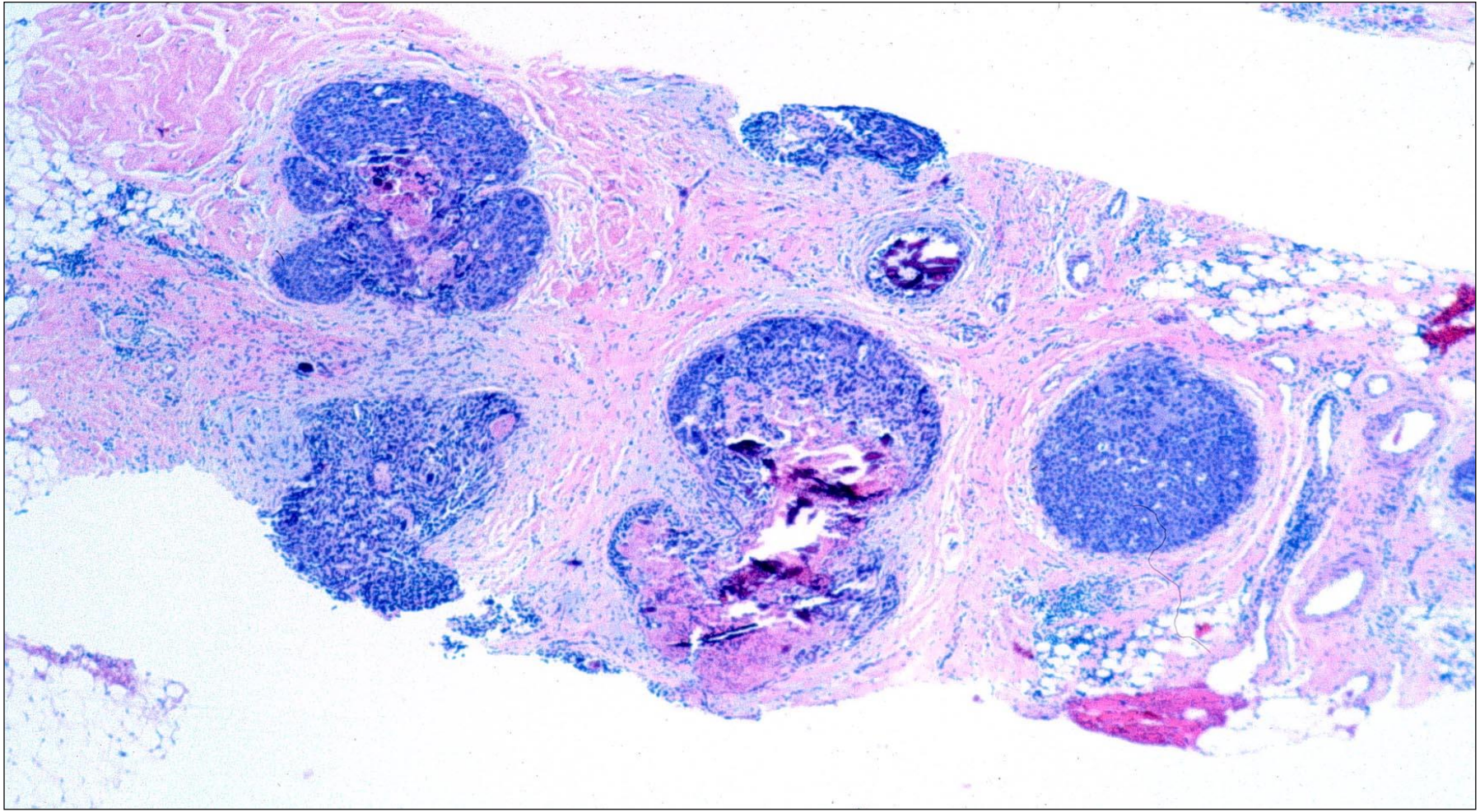
Increased with papillary lesions

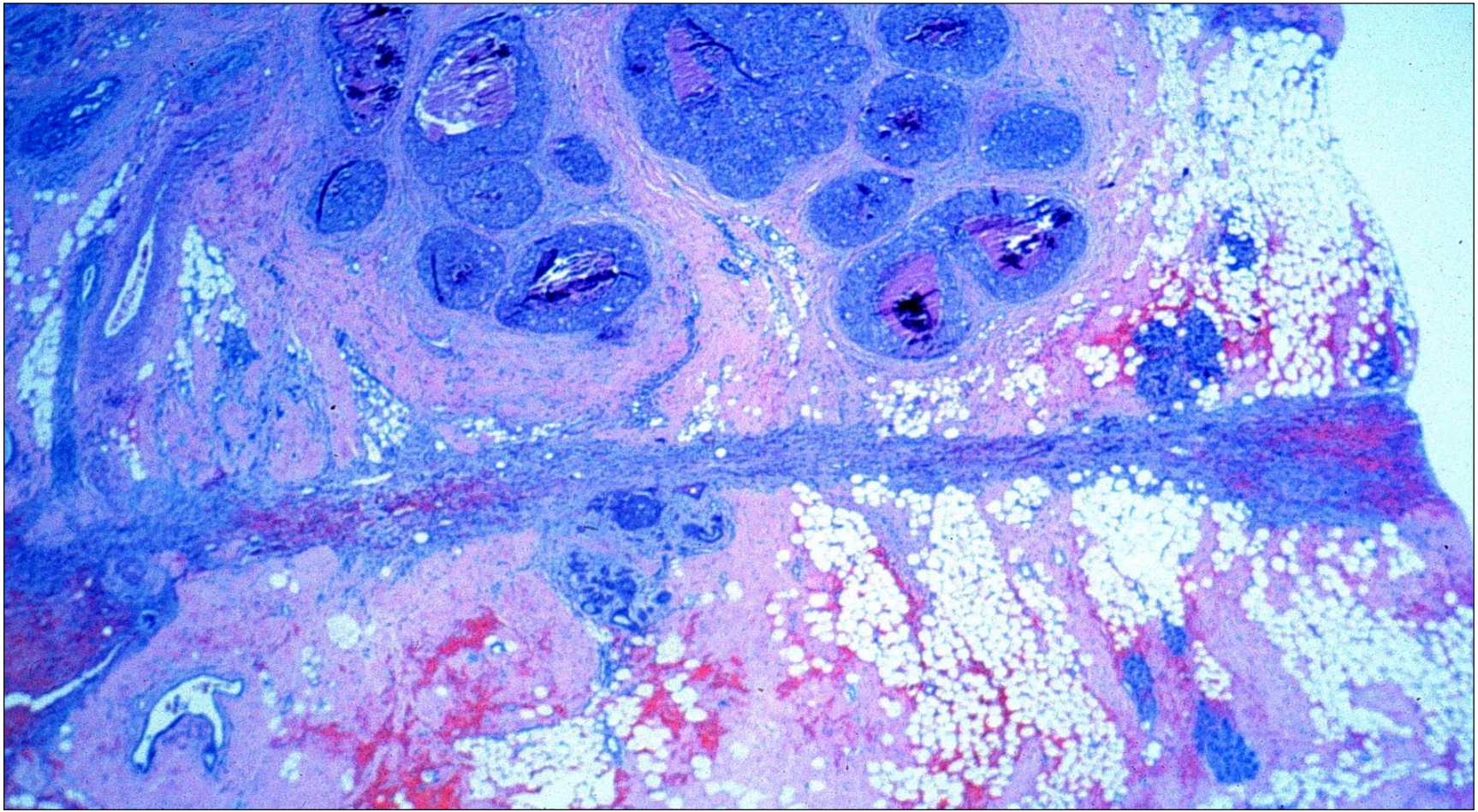
(May occur following liposuction)

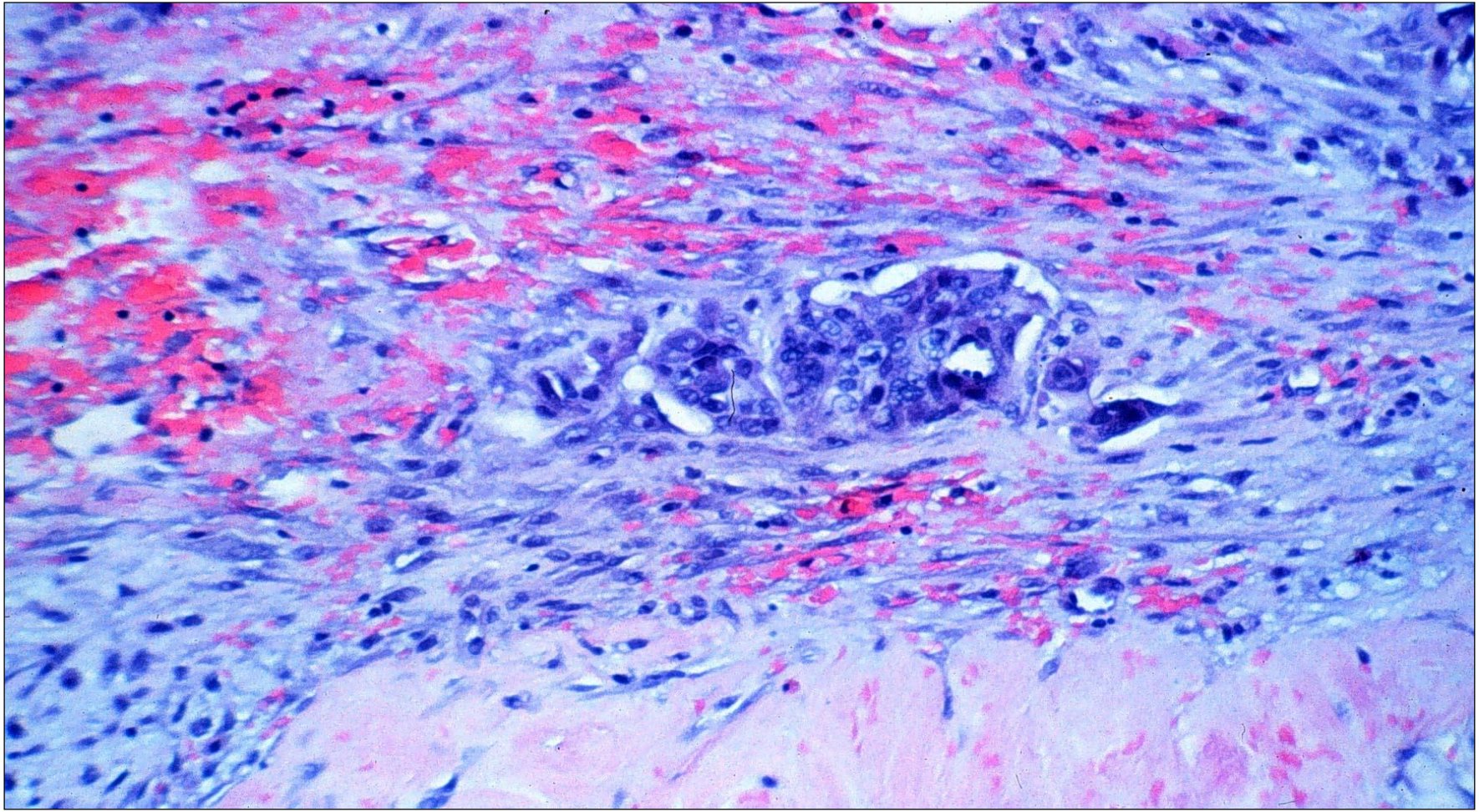
Diaz, 1999;
Nagi, 2005;
Phelan, 2007;
McLaughlin, 2011

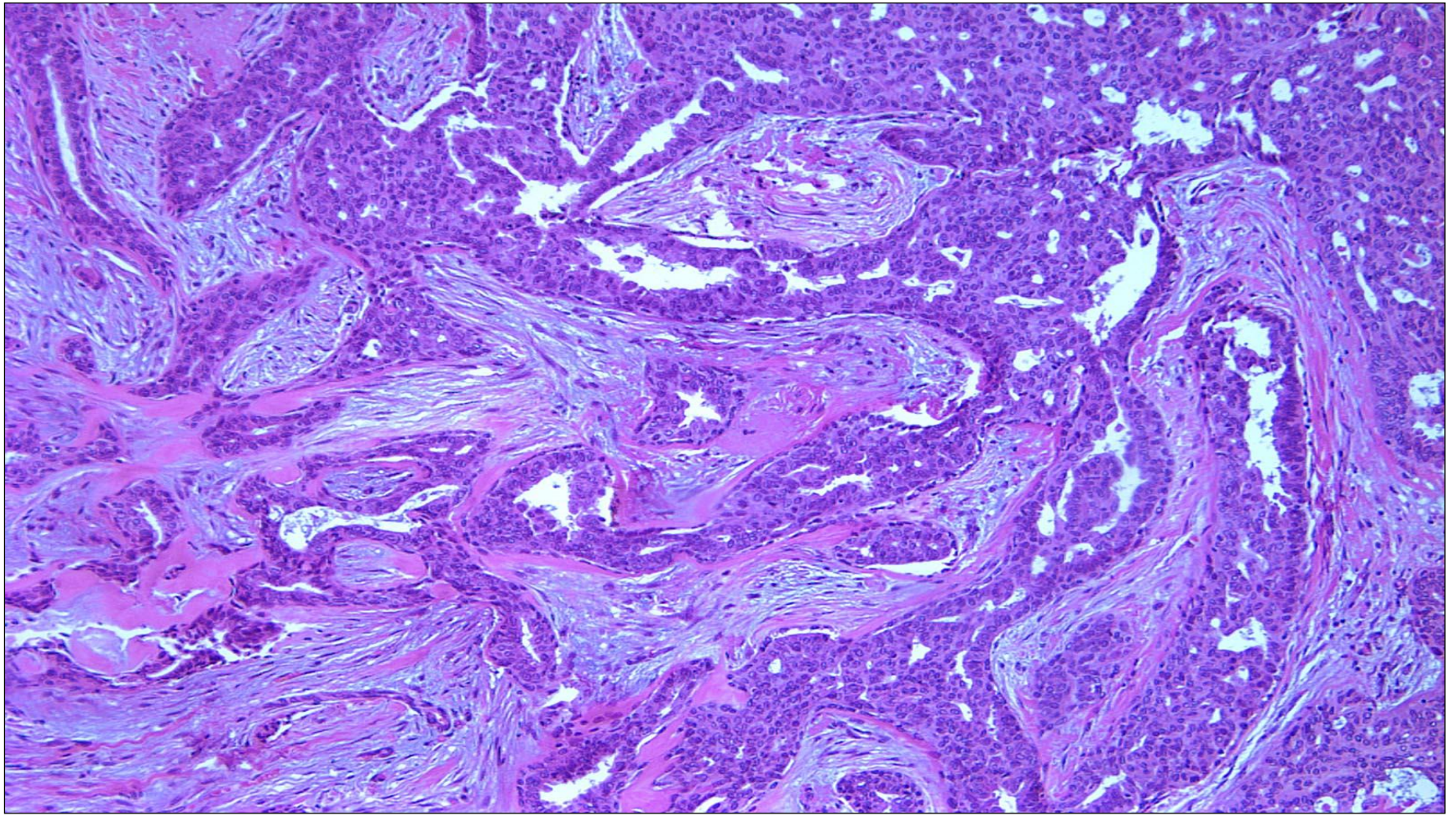


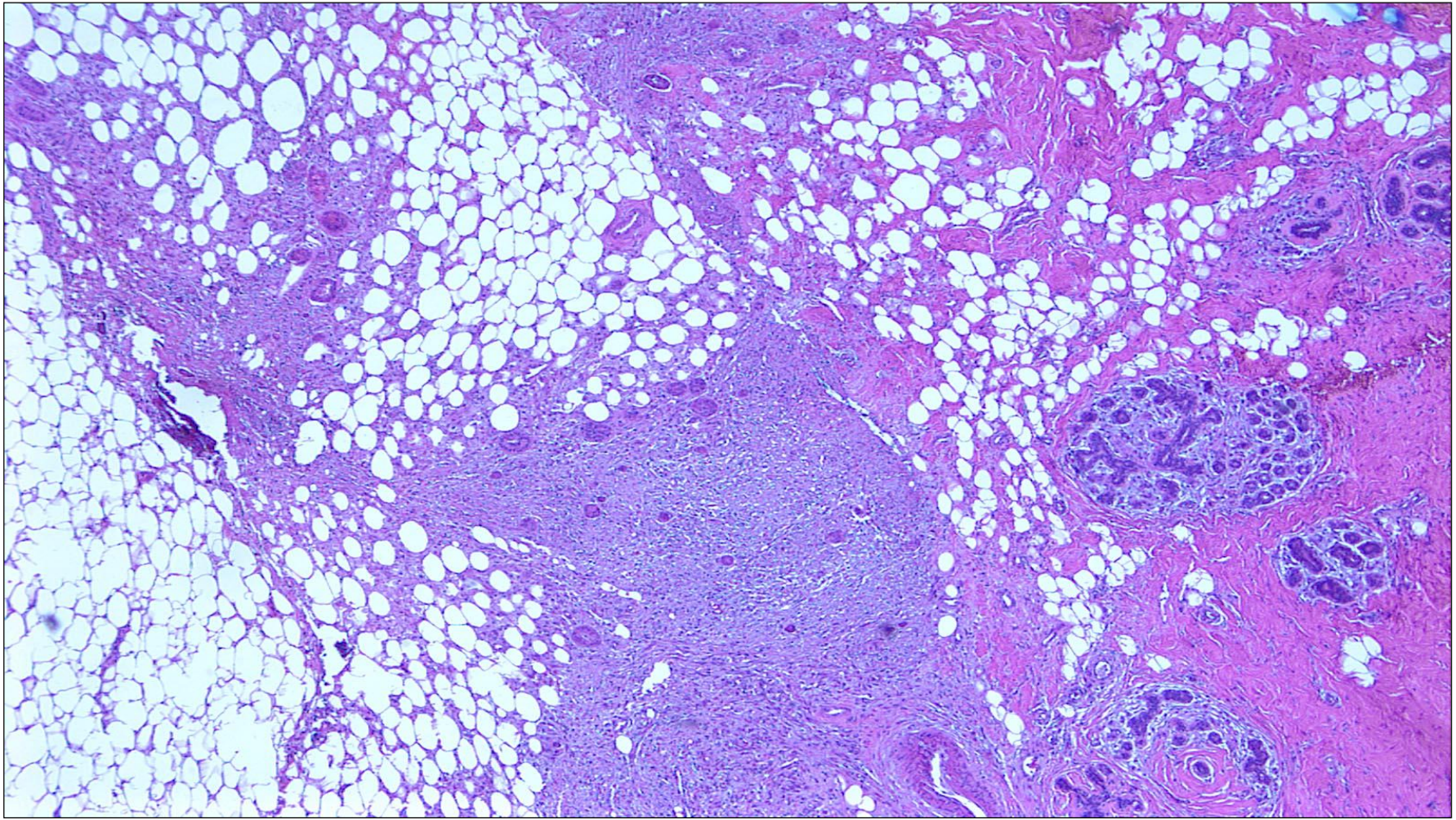
Douglas-Jones, J Clin Pathol, 2002
Encapsulated papillary carcinoma, 2 cases, with displaced epithelium

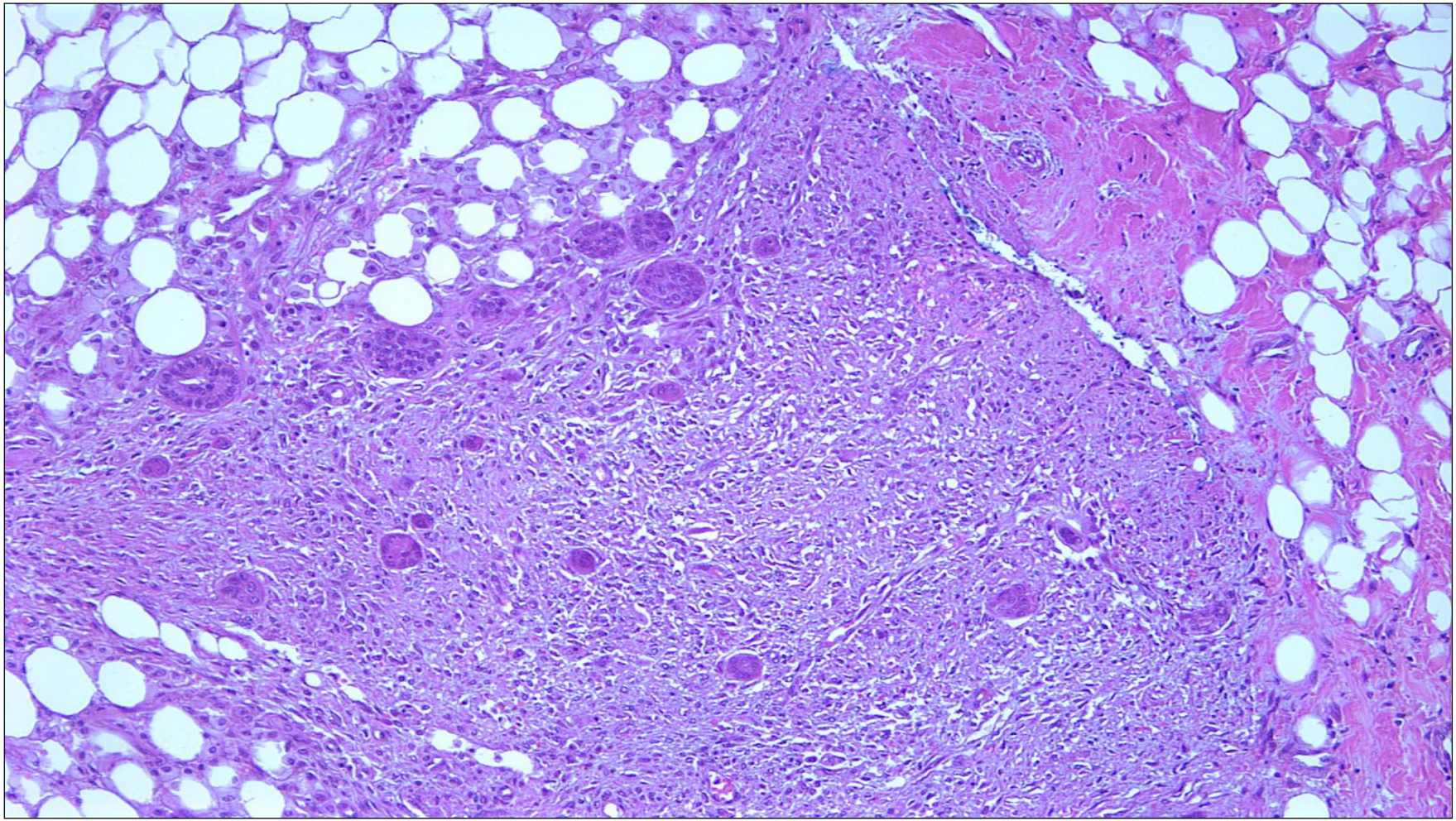


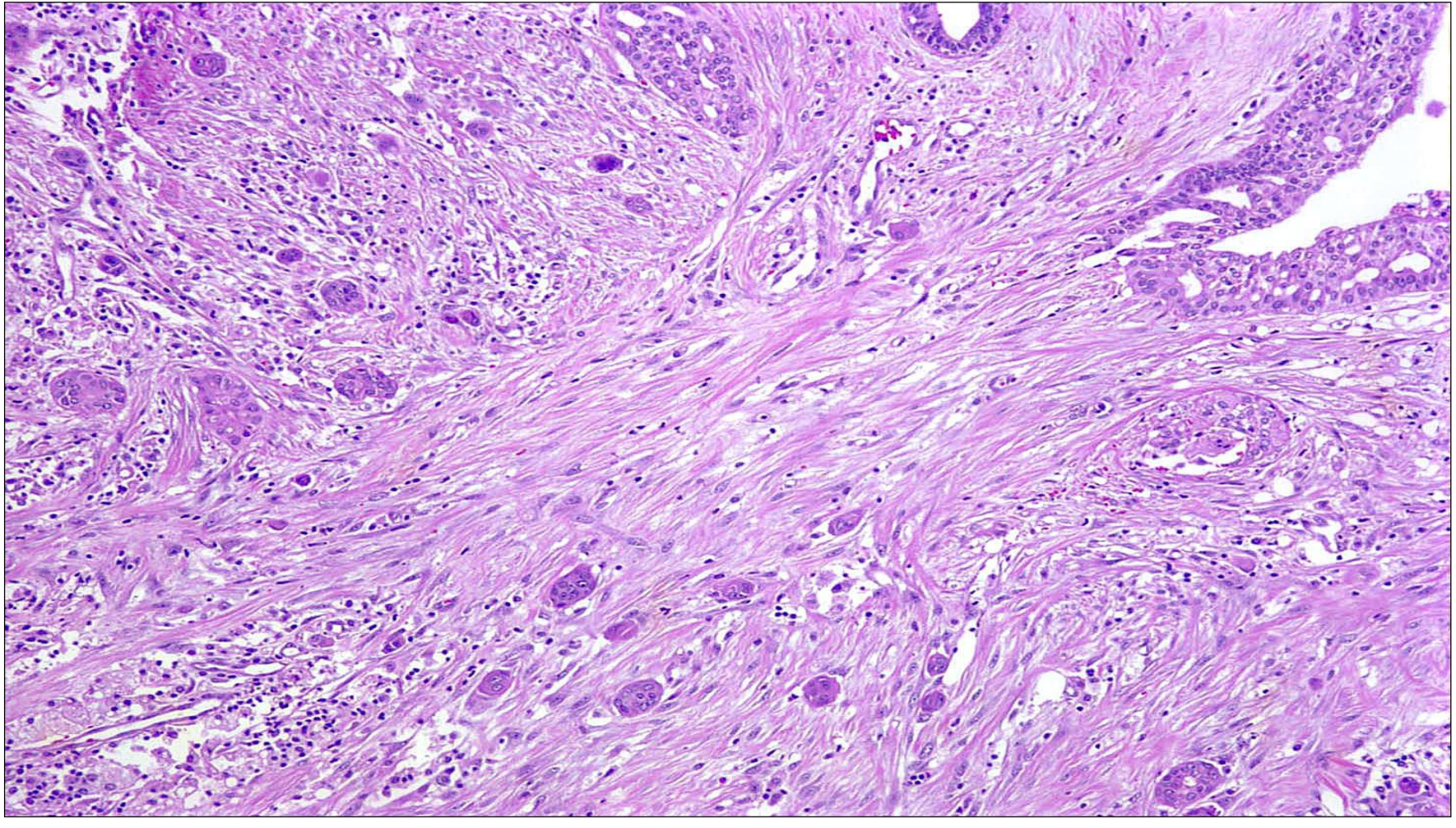


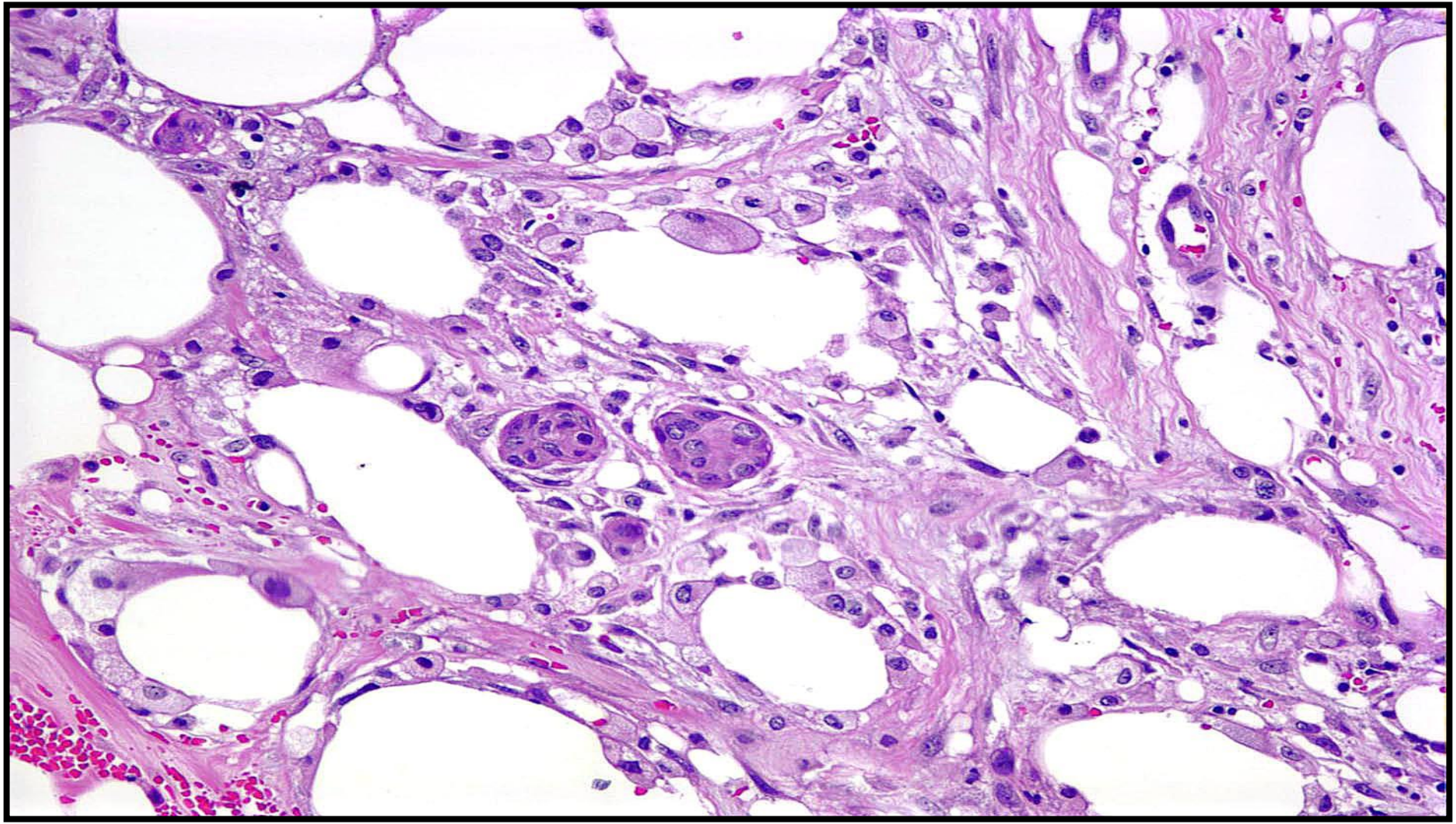


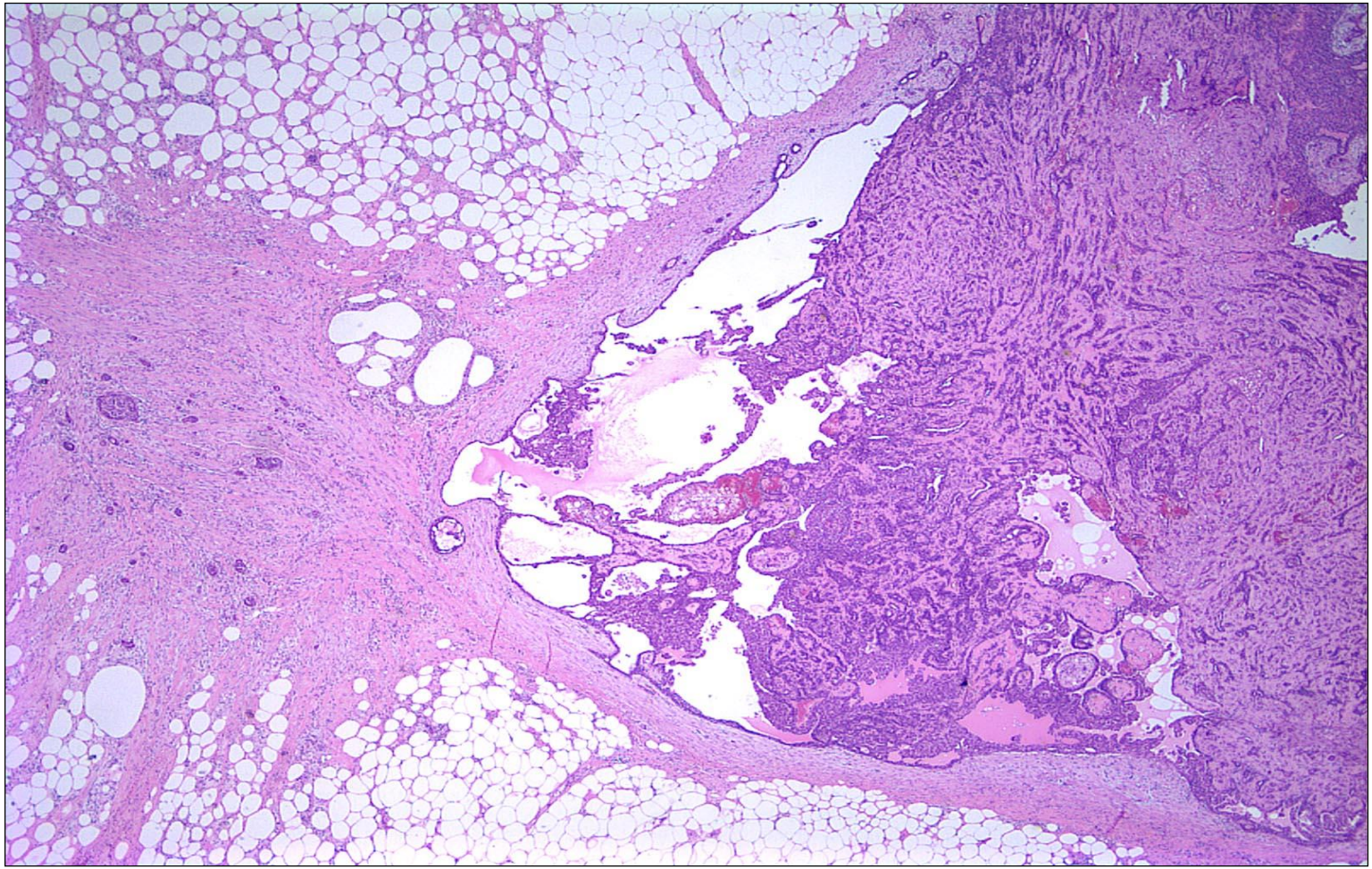


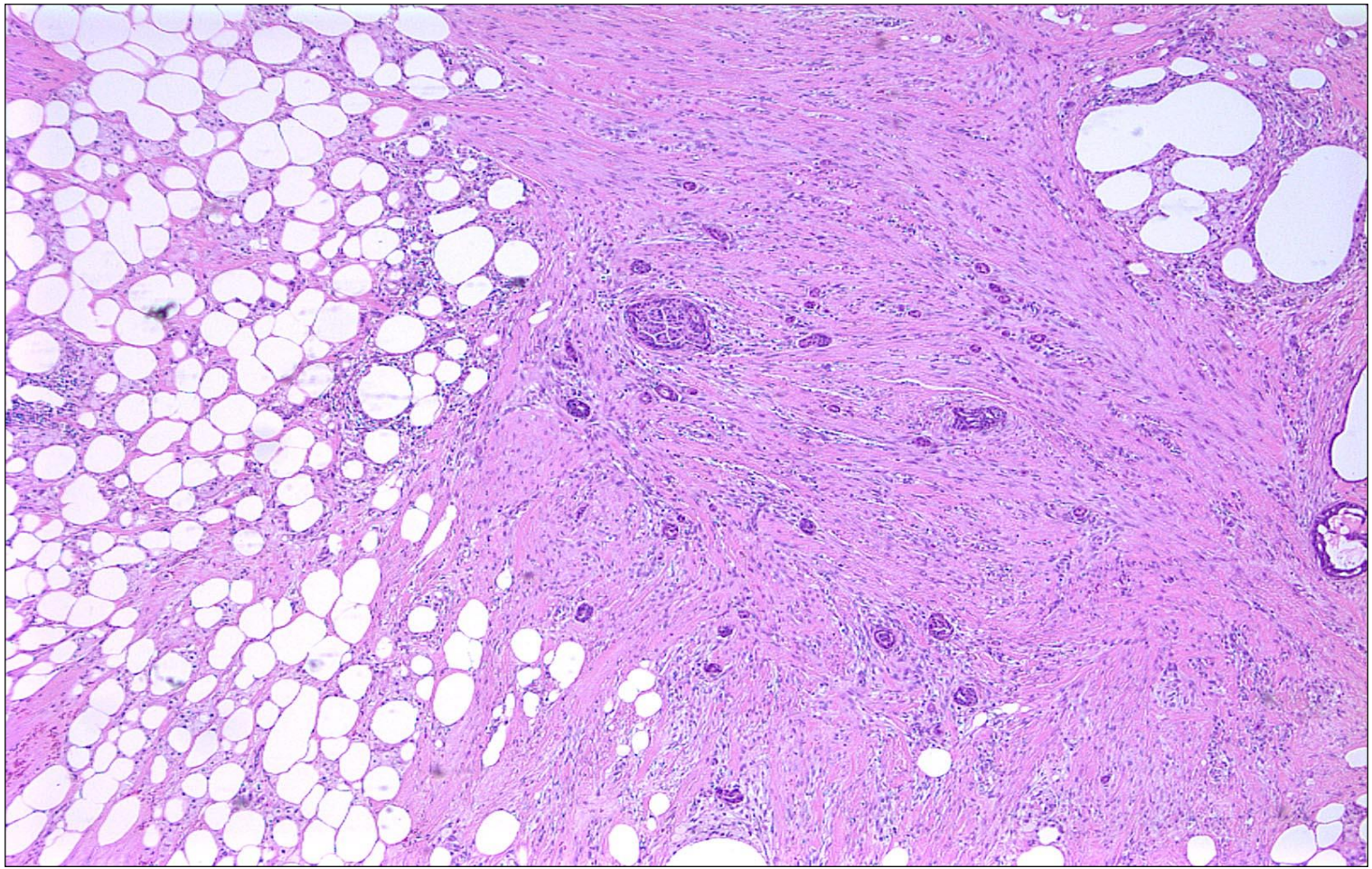


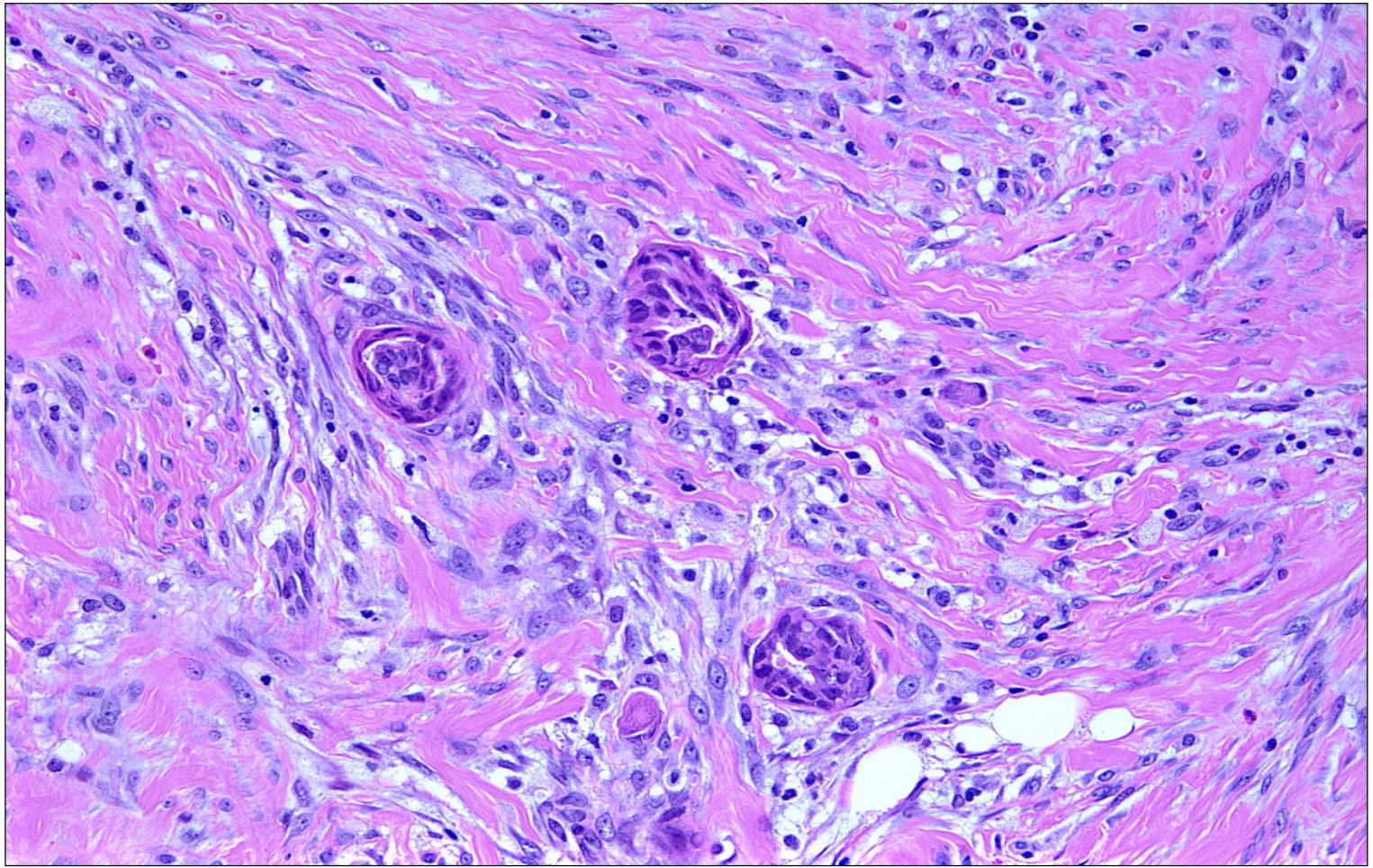


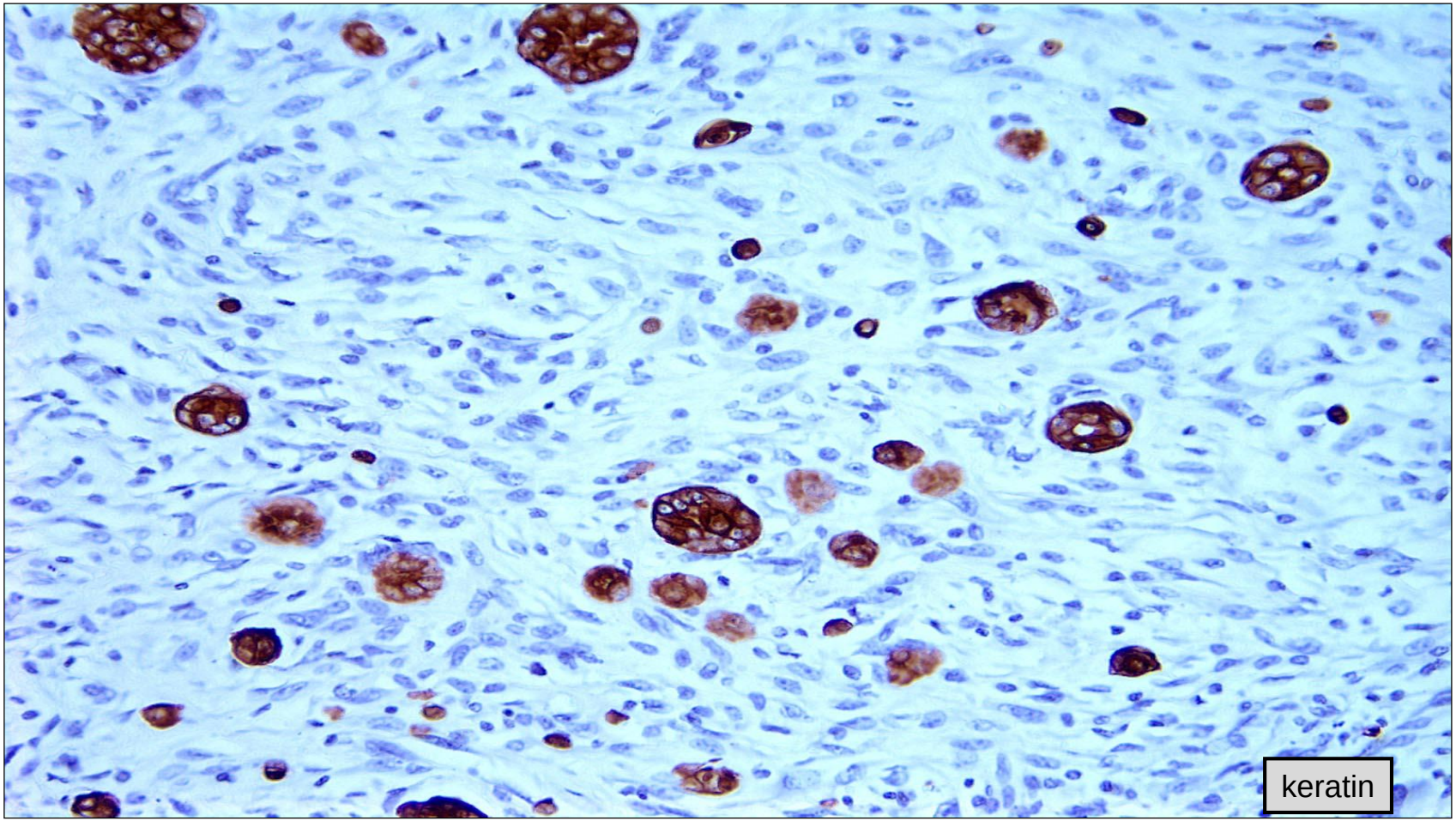


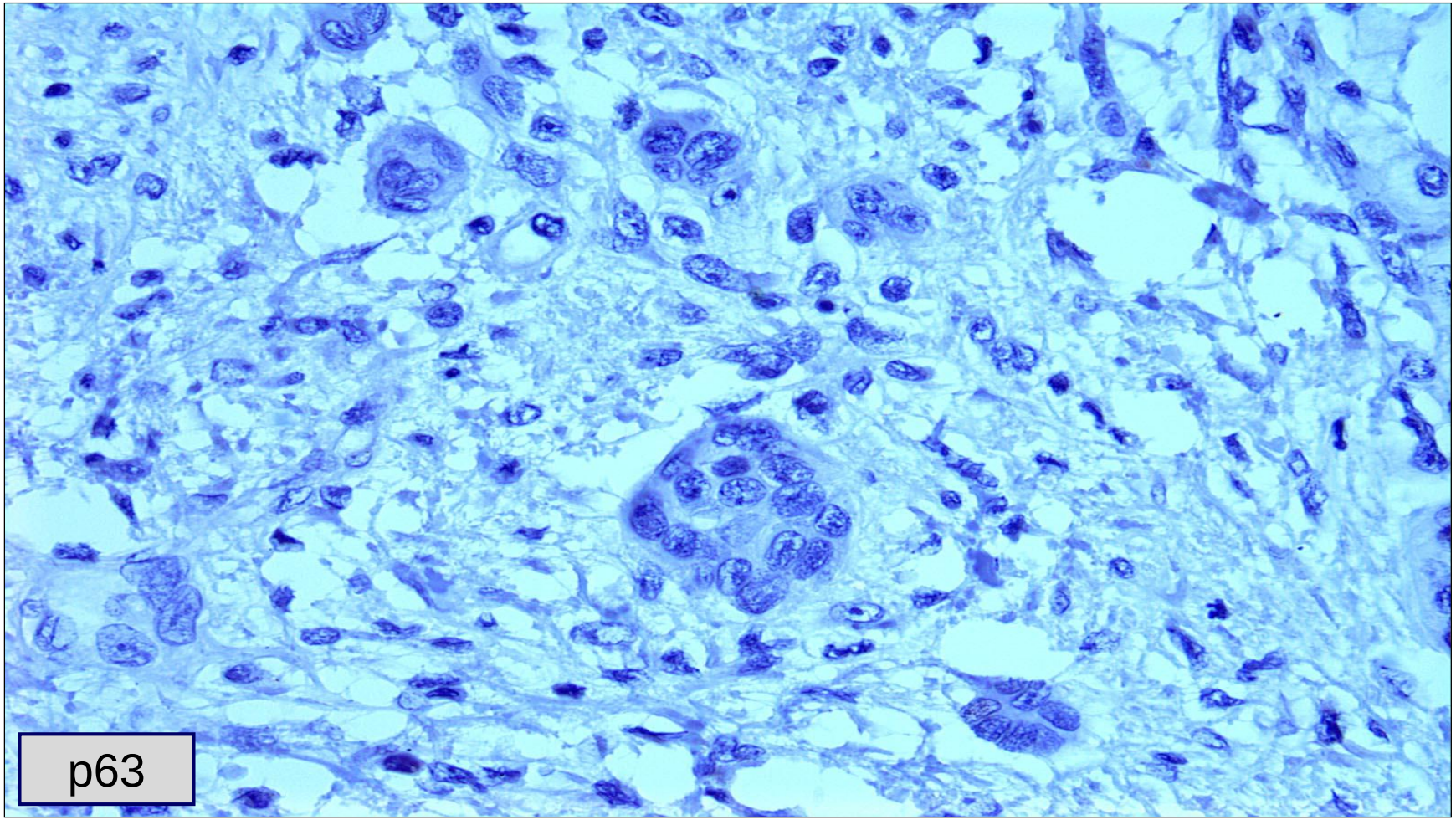


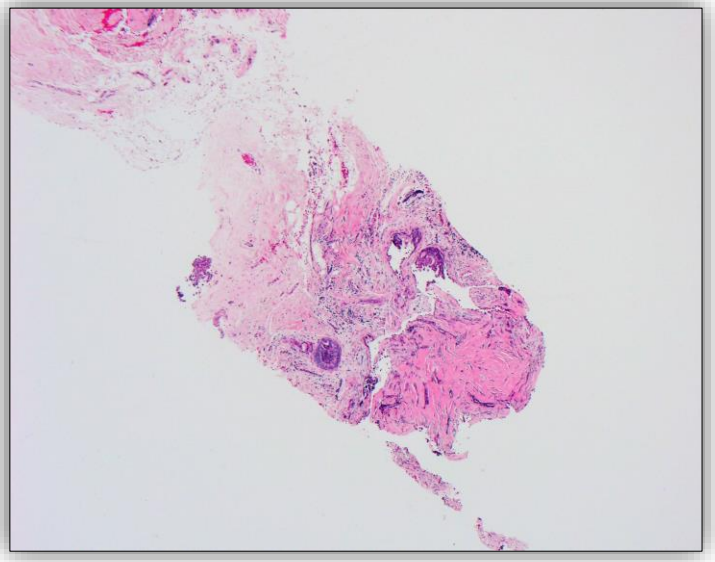


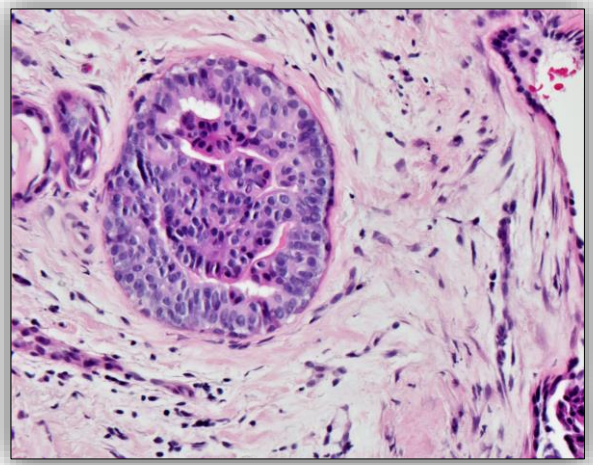


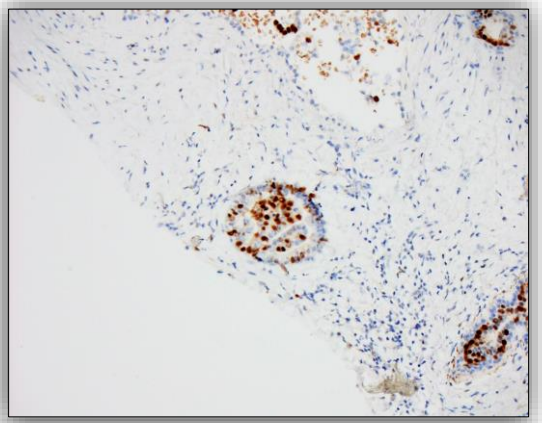


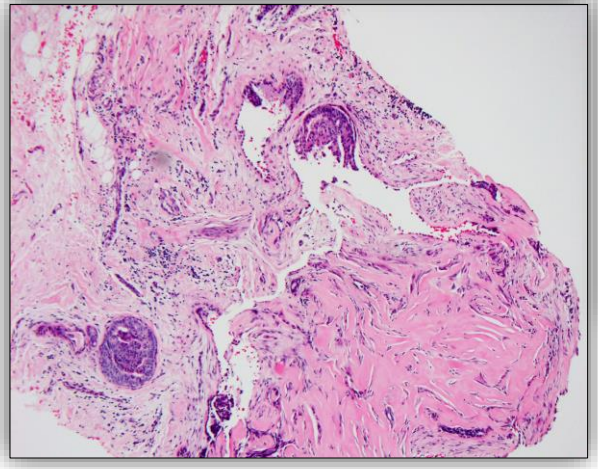

keratin

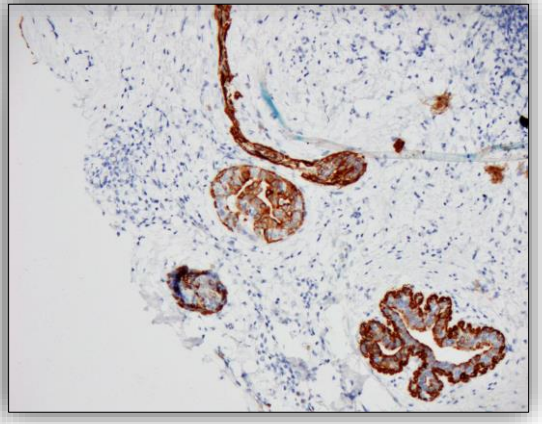

p63

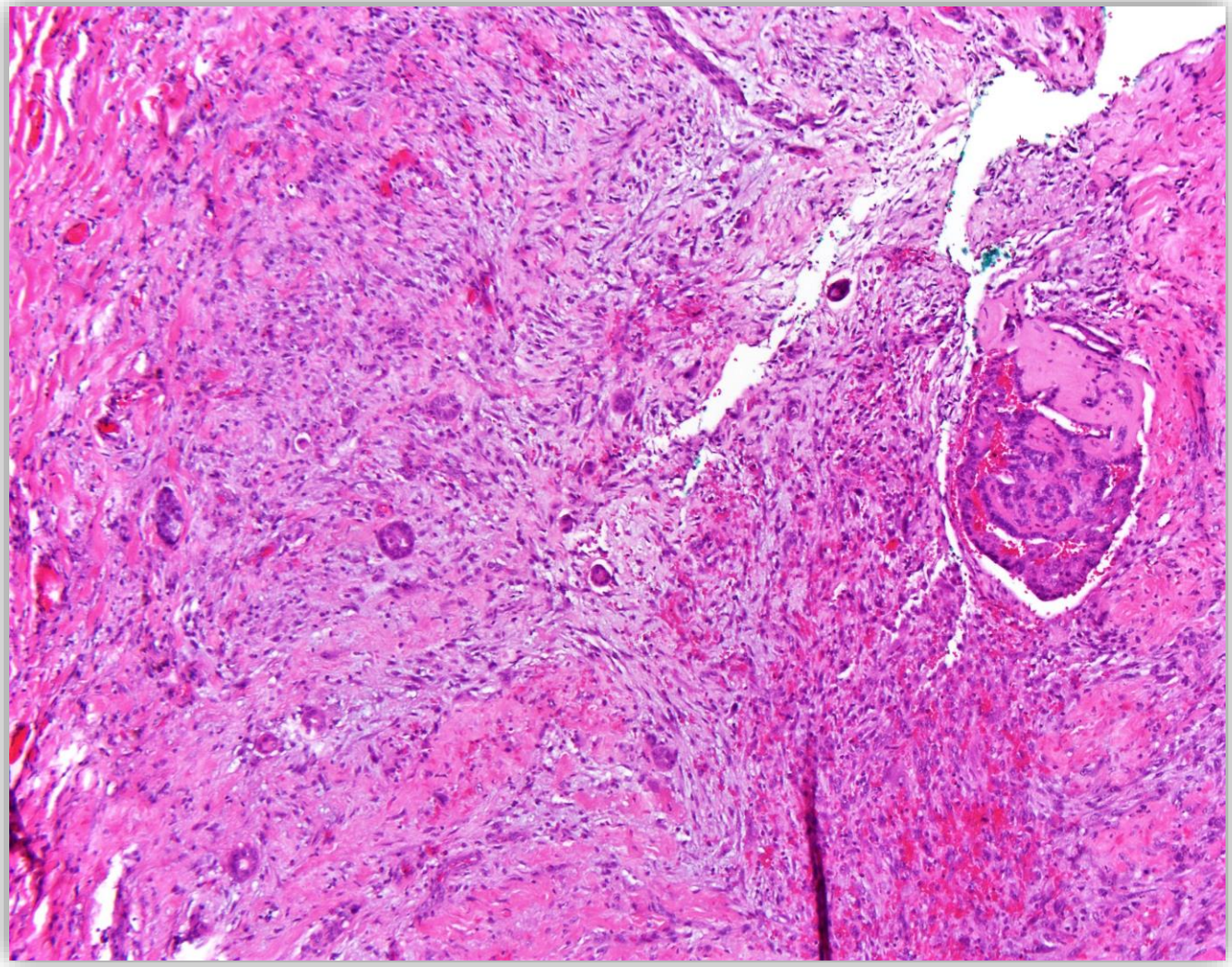


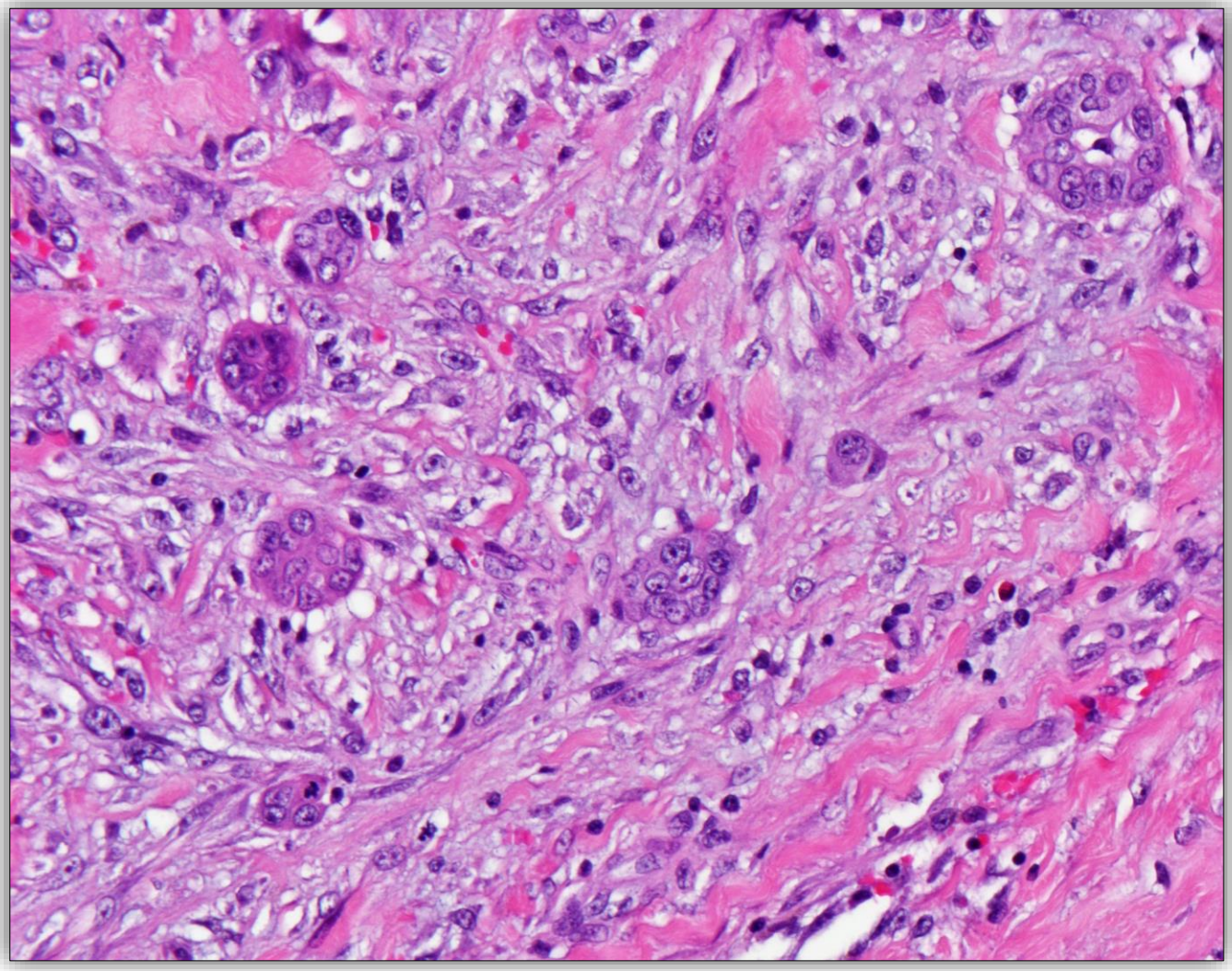


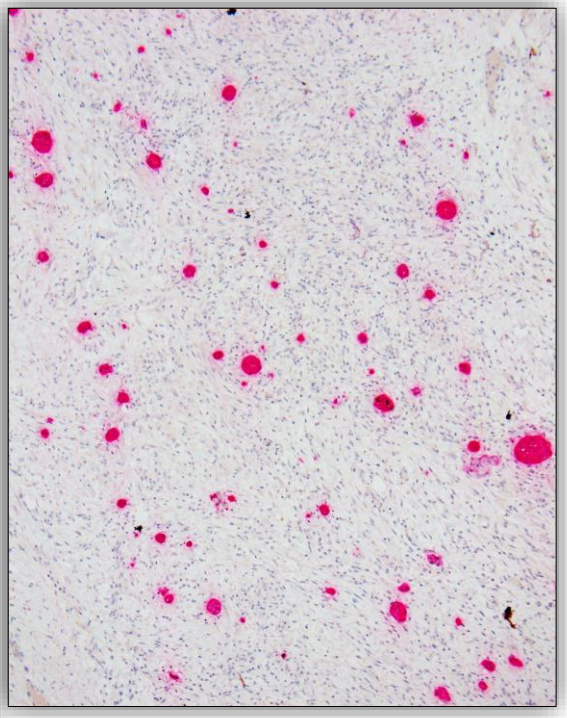












CKAE1/3 and p63

To Avoid Overdiagnosis

- Look for invasion away from biopsy site
- Look for recognized type of invasive cancer
- For LVI, be extremely conservative if there is only DCIS or a benign lesion
- Look for vascular involvement away from biopsy site

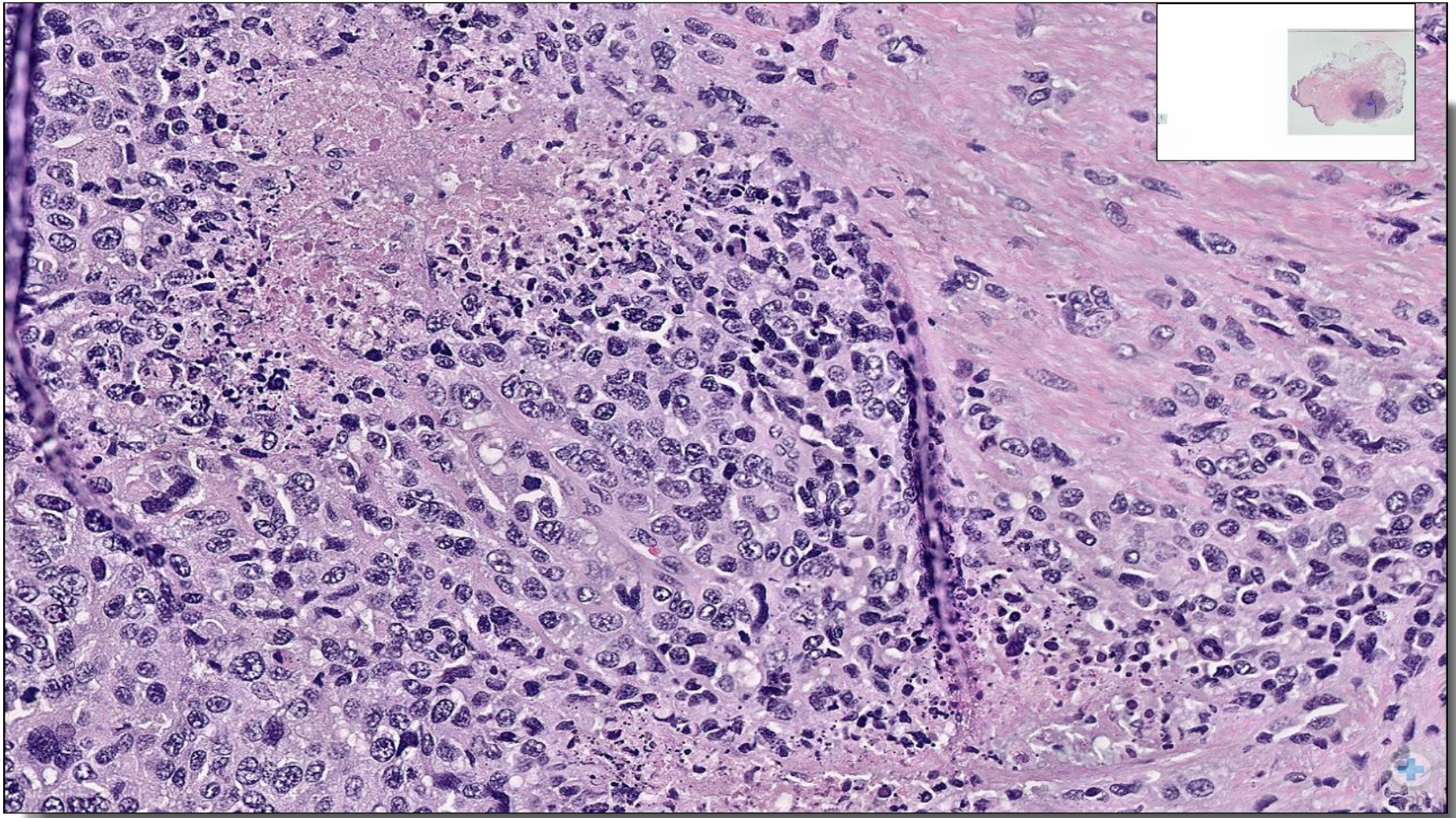
OTHER HIGH RISK SITUATIONS

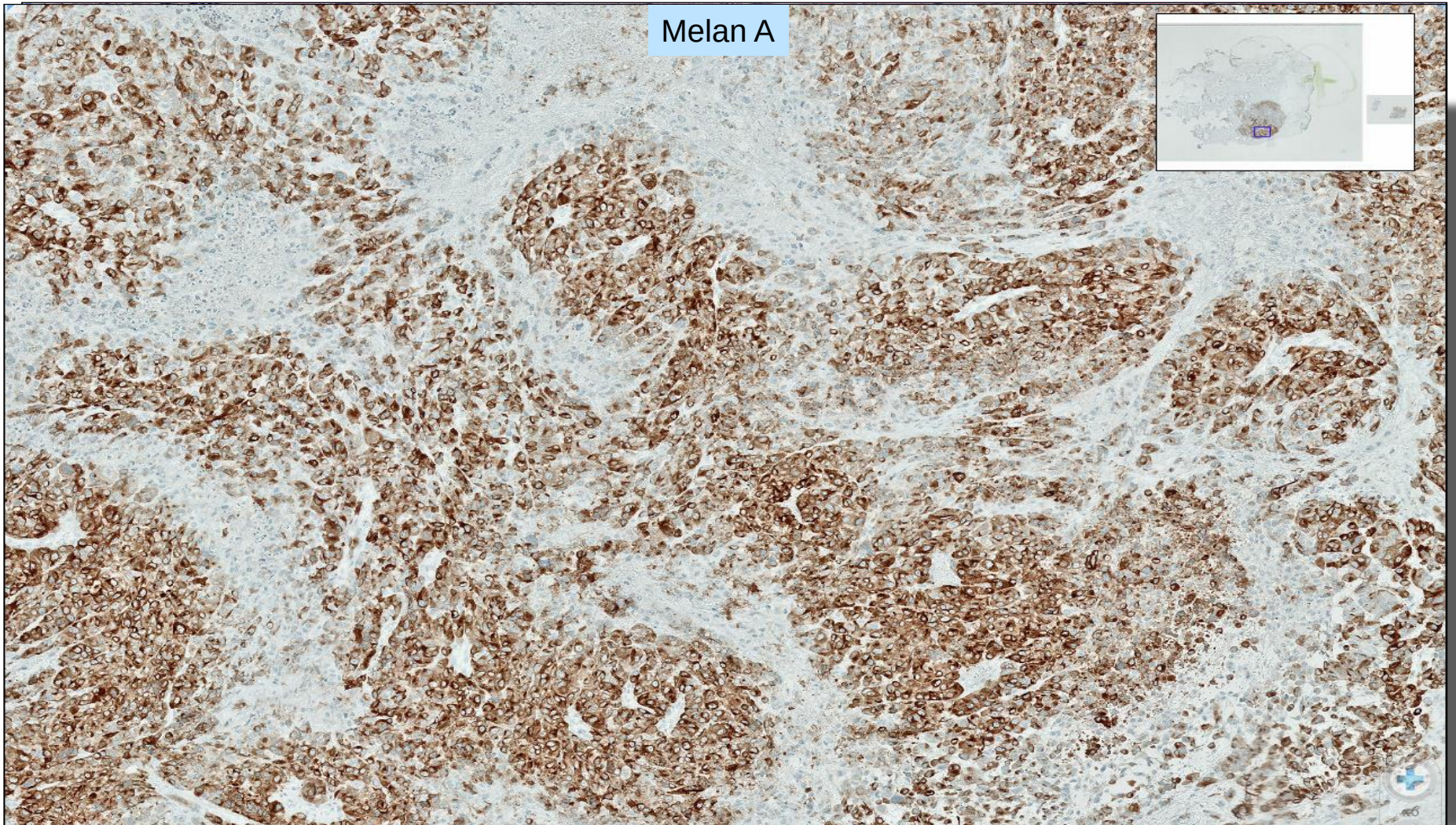
Era of Neoadjuvant Systemic Therapy

In an era of NAST, it is particularly prudent to review the H&E slide at the time of receptor s/o especially for TNC

- Confirm that morphology is c/w breast carcinoma
- Ensure there is no prior history of another cancer
- Consider further IHC work up, if findings are atypical and/or in the setting of h/o cancer

Triple Negative Breast Carcinoma




Melan A

Lesions Metastatic to the Breast

- Don’t forget that not all cancers in the breast are breast cancer
- Consider this when morphology is atypical
- Absent in situ component-with caveats
- History of other cancer
- Triple negative cancers

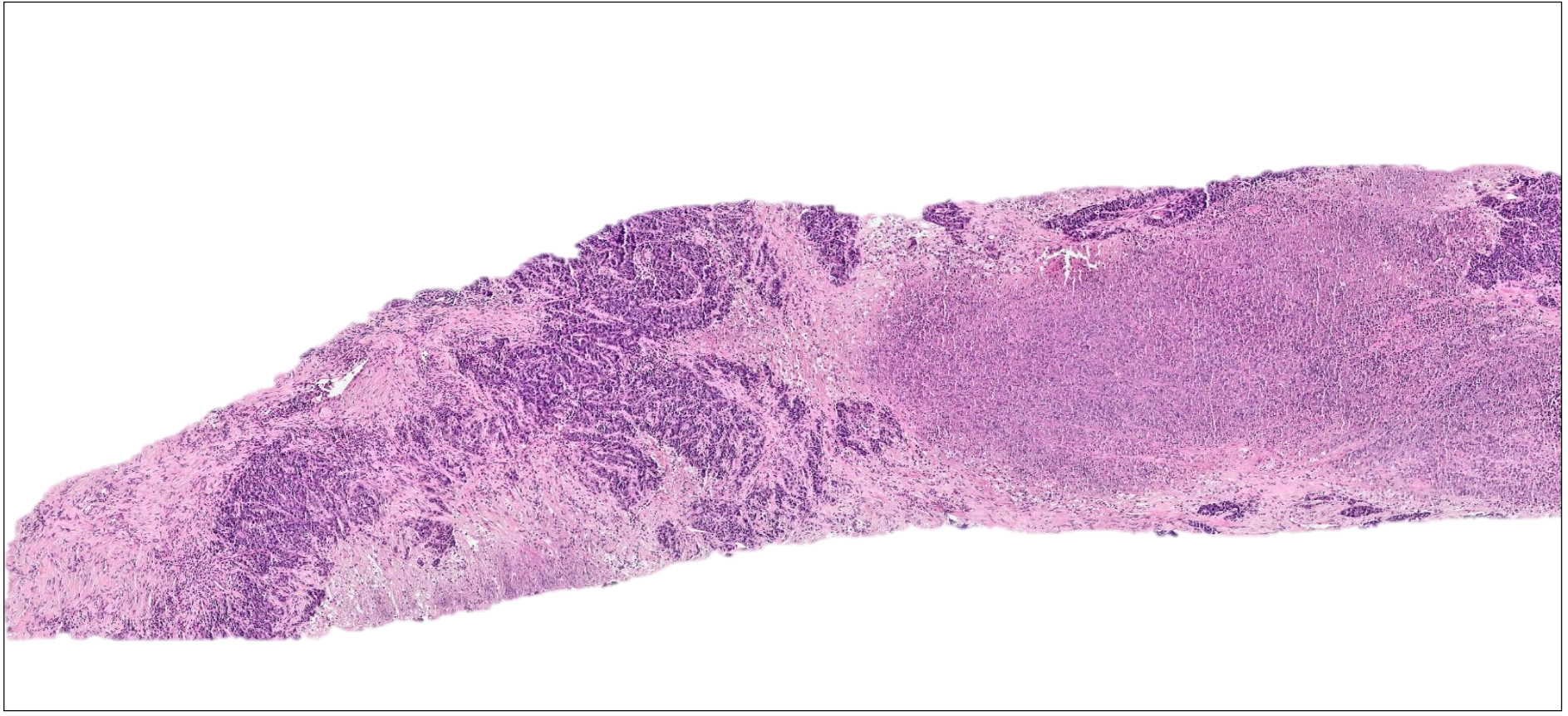
Lesions Metastatic to the Breast

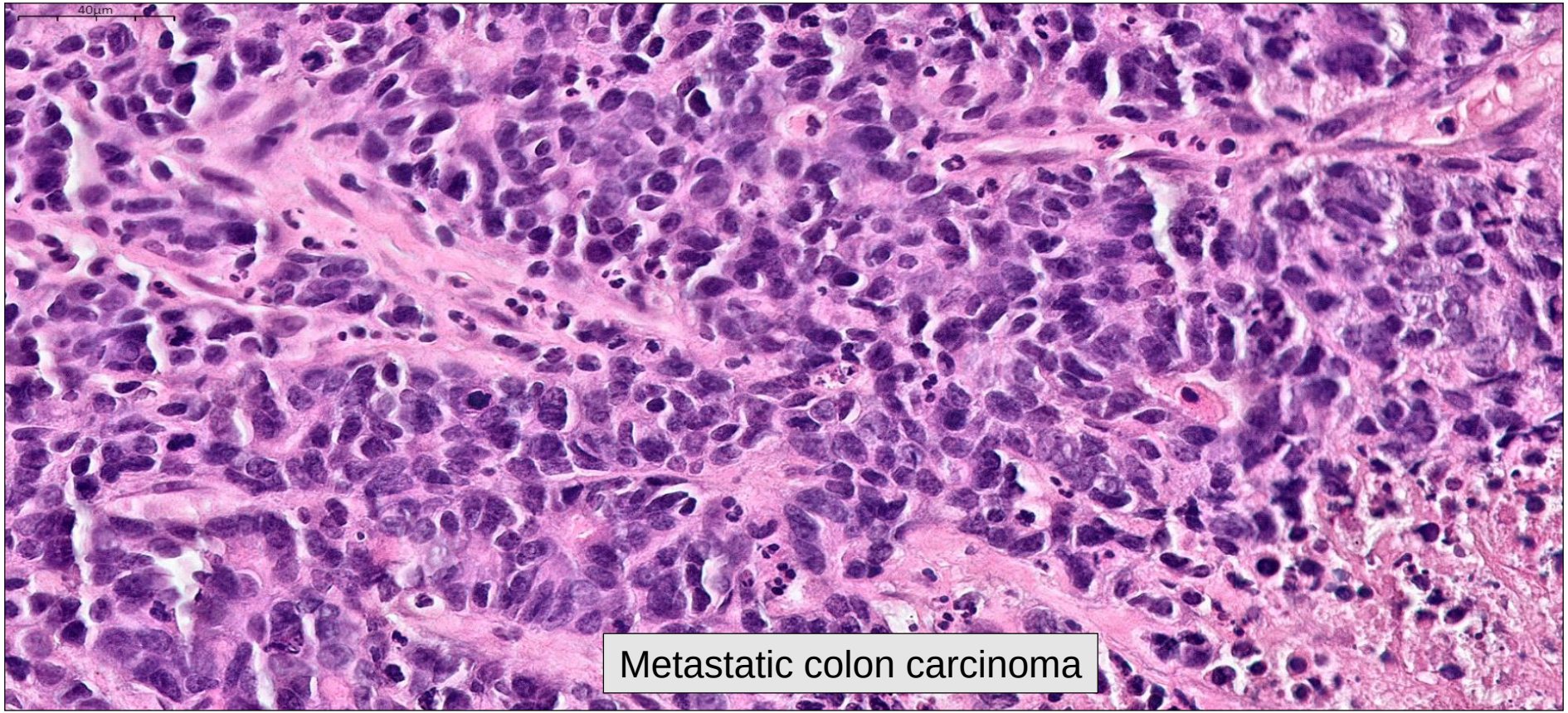
Malignancies metastatic to the breast are rare (0.2-2%)

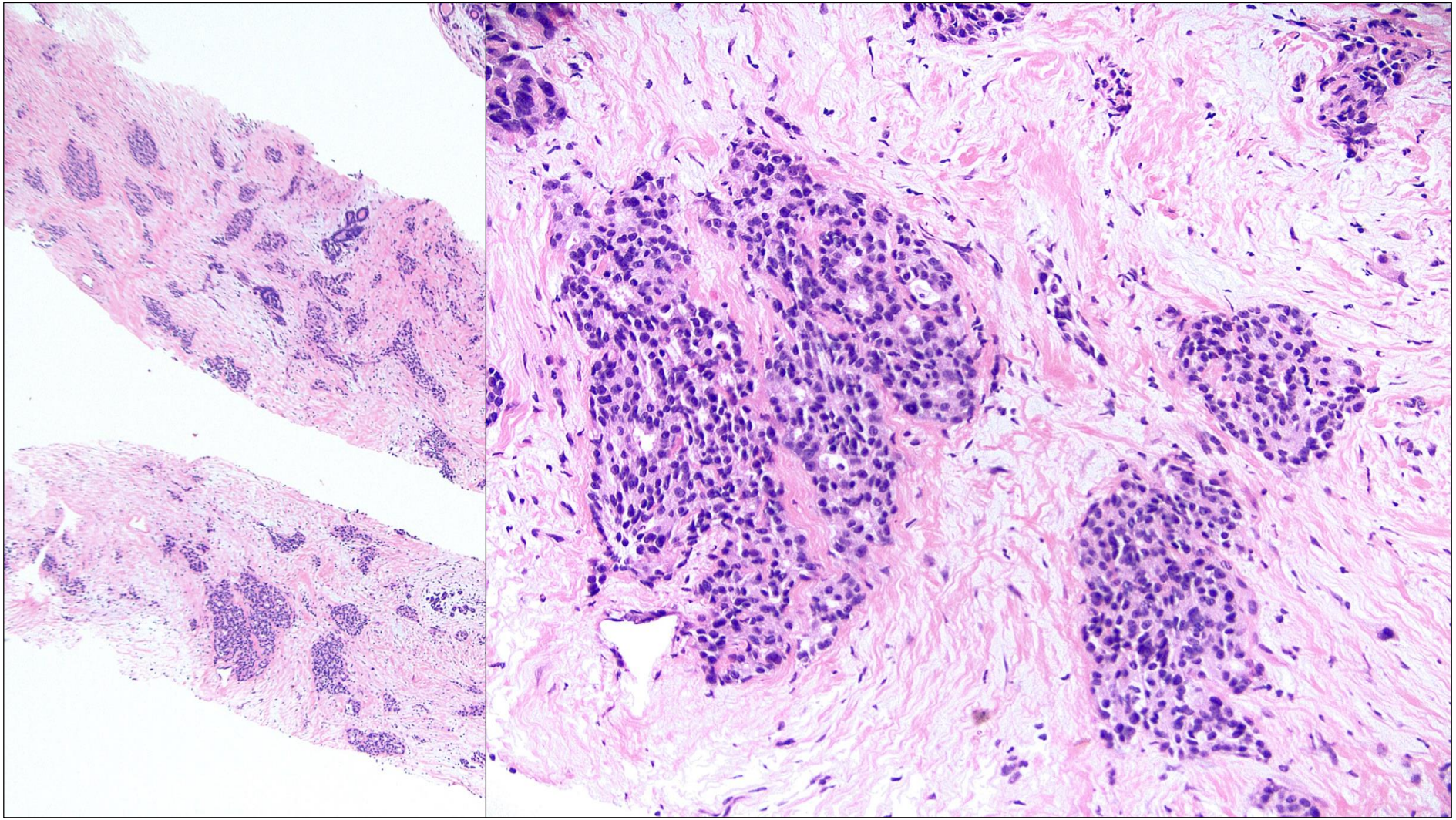
Common primary tumors:

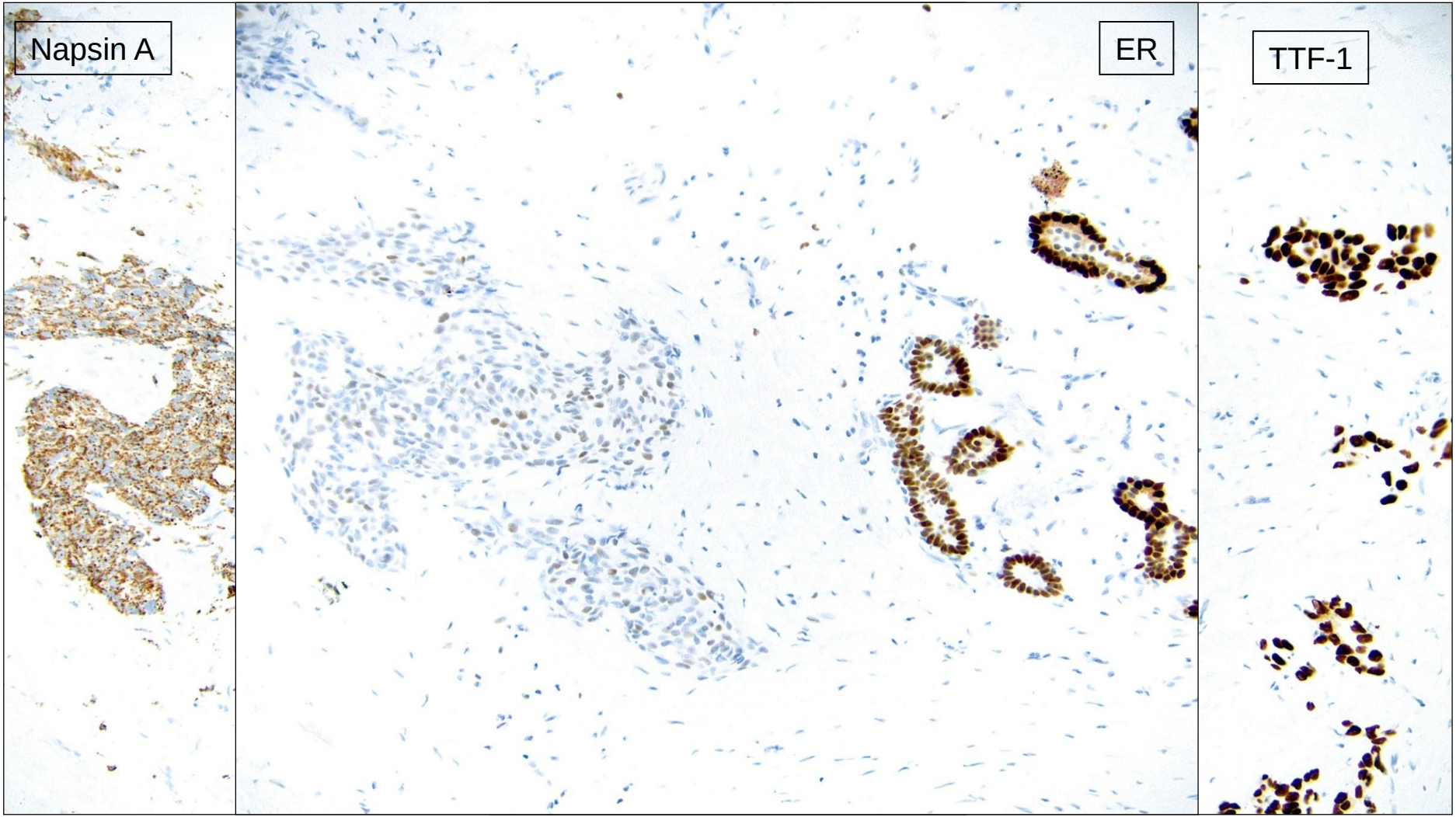
- Melanoma
- Ovarian carcinoma
- Lung carcinoma
- Lymphoma

Klingnen, Tumor Biol, 2009
DeLair, Mod Pathol, 2013
Yang, Arch Pathol Lab Med, 2017




40µm
Metastatic colon carcinoma




Napsin A
ER
TTF-1

IHC in metastatic lesions-LUNG

Some lung cancers (~10%) show focal ER expression (frequency appears to be antibody clone-related)

Some lung cancers (~5%) are focally GCDFP positive, and these are usually also TTF-1 negative

Some breast cancers (~2%) are TTF-1 positive

Use caution when interpreting small biopsies

Wang, Appl Immuno Mol Morph, 2009
Robens, Am J Surg Pathol, 2010
Abd El-Maqsoud, Tum Biol, 2016

IHC in Metastatic Lesions-Breast markers

ER, PR, HER2

GATA3, GCDFP-15, mammaglobin, TRPS1

Combination improves sensitivity

Caveats:

- ER, also seen in lung, thyroid, NE and gyn tract
- HER2 may be seen in lung and gastric cancers
- GATA3, also seen in skin and urothelial cancers
- GCDFP-15, also seen in skin, salivary gland and prostate
- Mammaglobin, also seen in endometrial, ovarian and melanomas
- Absence does not exclude breast origin

IHC in Metastatic Lesions

TRPS1

Trichorhinophalangeal syndrome type 1 (TRPS1)

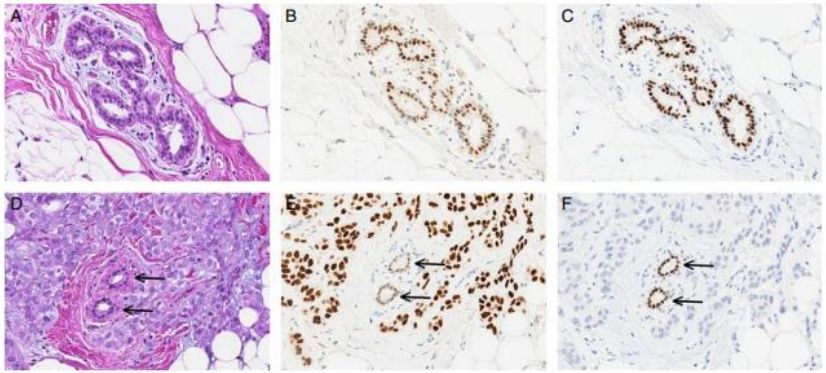
High sensitivity and specificity for breast, especially useful in TNBC

Caveats:

- May be seen in other tumors e.g. lung, bladder, but expression usually low/weak
- Serous carcinoma may express TRPS1, therefore combination with PAX8 recommended
- Salivary gland carcinoma most problematic with ~15% of cases demonstrating strong expression with TRPS1

Ai, Mod Pathol, 2021
Parkinson, AJSP, 2022

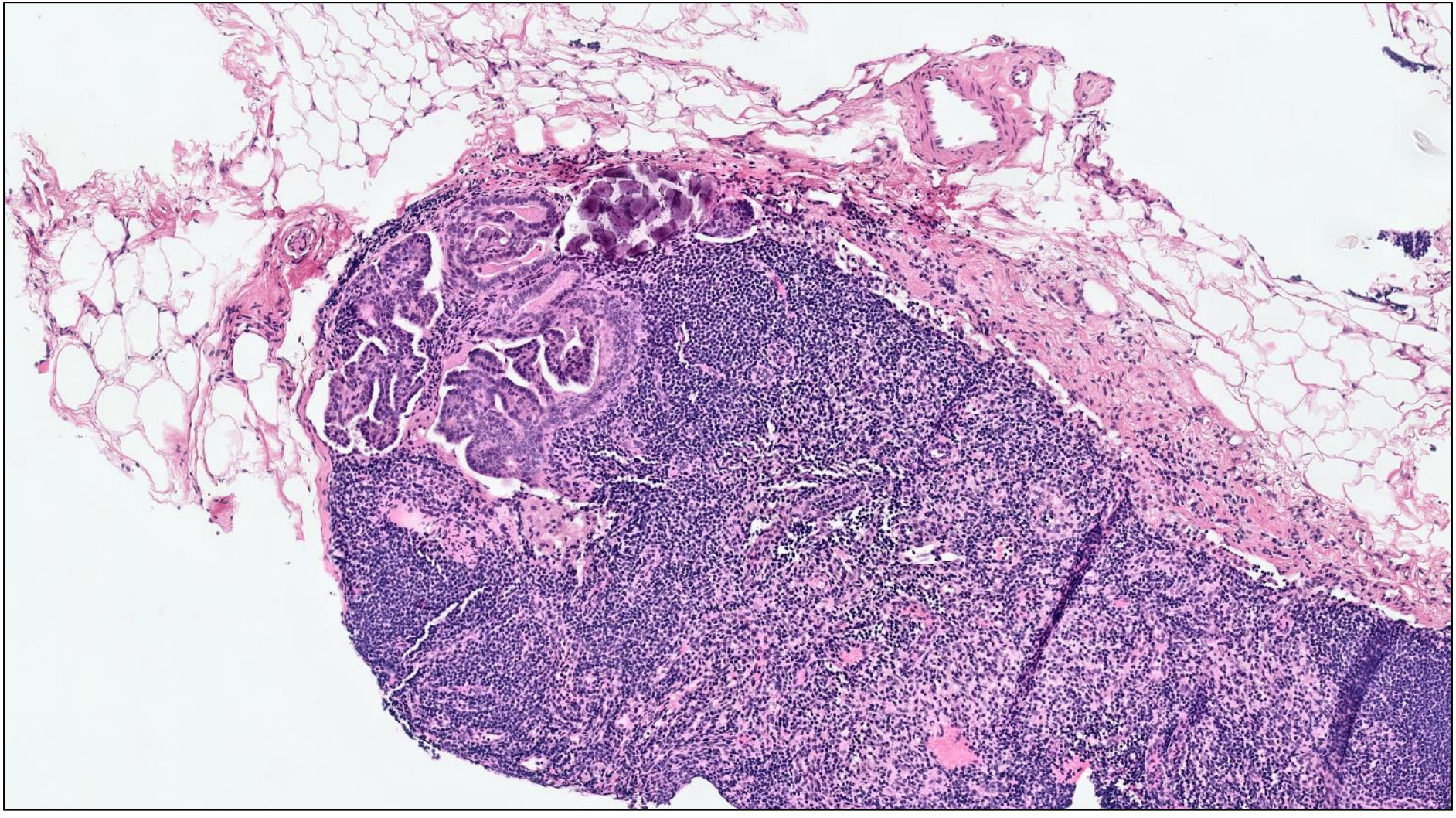
Breast carcinoma		Negative	Positive			Total
			Low	Intermediate	High	
TRPS1						
ER/PR+		3 (2%)	5 (3%)	22 (12%)	146 (83%)	176
HER2+		9 (13%)	5 (8%)	14 (21%)	39 (58%)	67
TNBC	Metaplastic	7 (14%)	3 (5%)	12 (23%)	30 (58%)	52
	Nonmetaplastic	26 (14%)	8 (5%)	41 (22%)	109 (59%)	184
GATA3						
ER/PR+		8 (5%)	7 (4%)	27 (15%)	131 (76%)	173
HER2+		8 (12%)	8 (12%)	22 (33%)	29 (43%)	67
TNBC	Metaplastic	41 (79%)	7 (13%)	3 (6%)	1 (2%)	52
	Nonmetaplastic	90 (49%)	20 (11%)	48 (26%)	26 (14%)	184

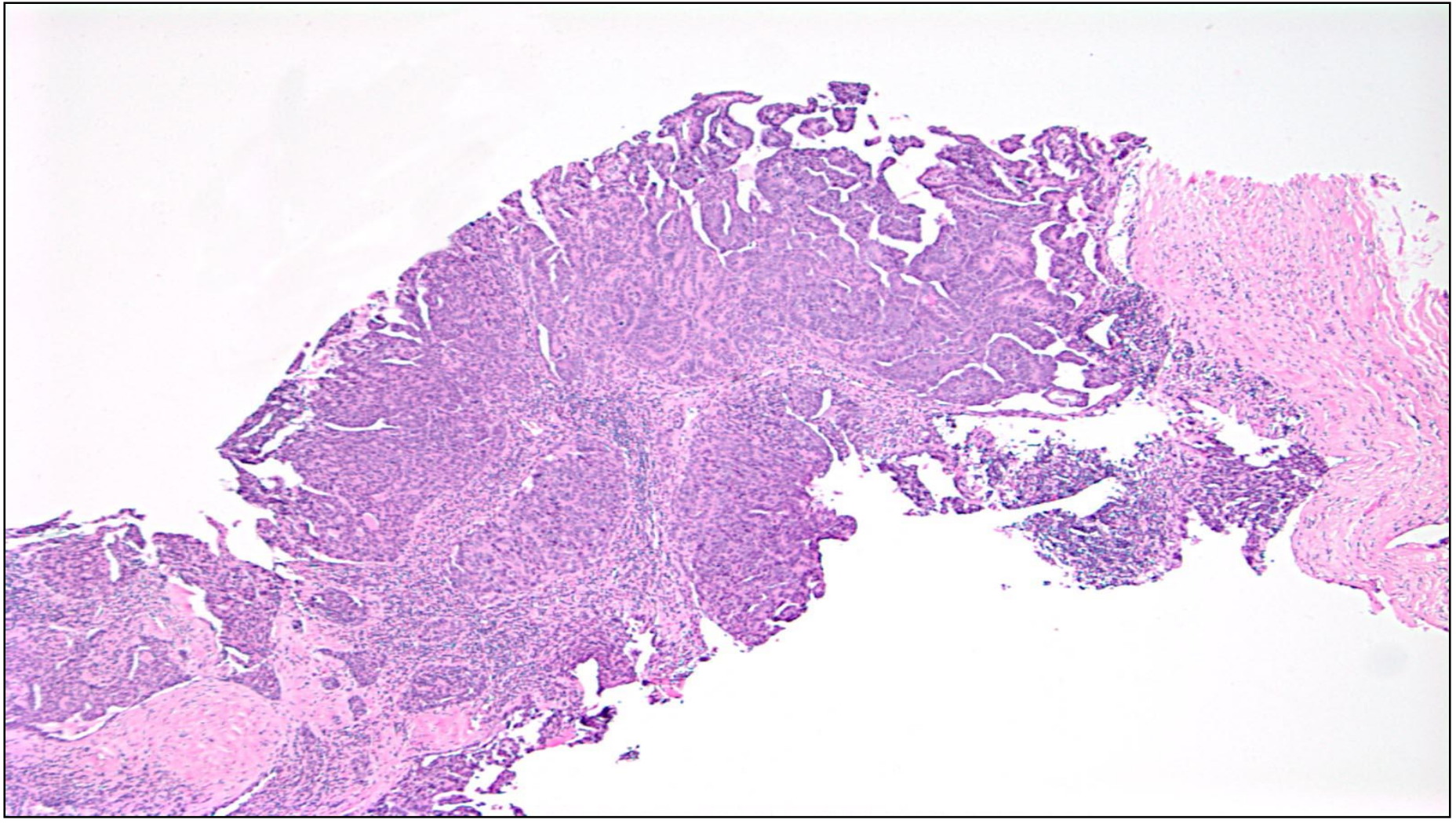


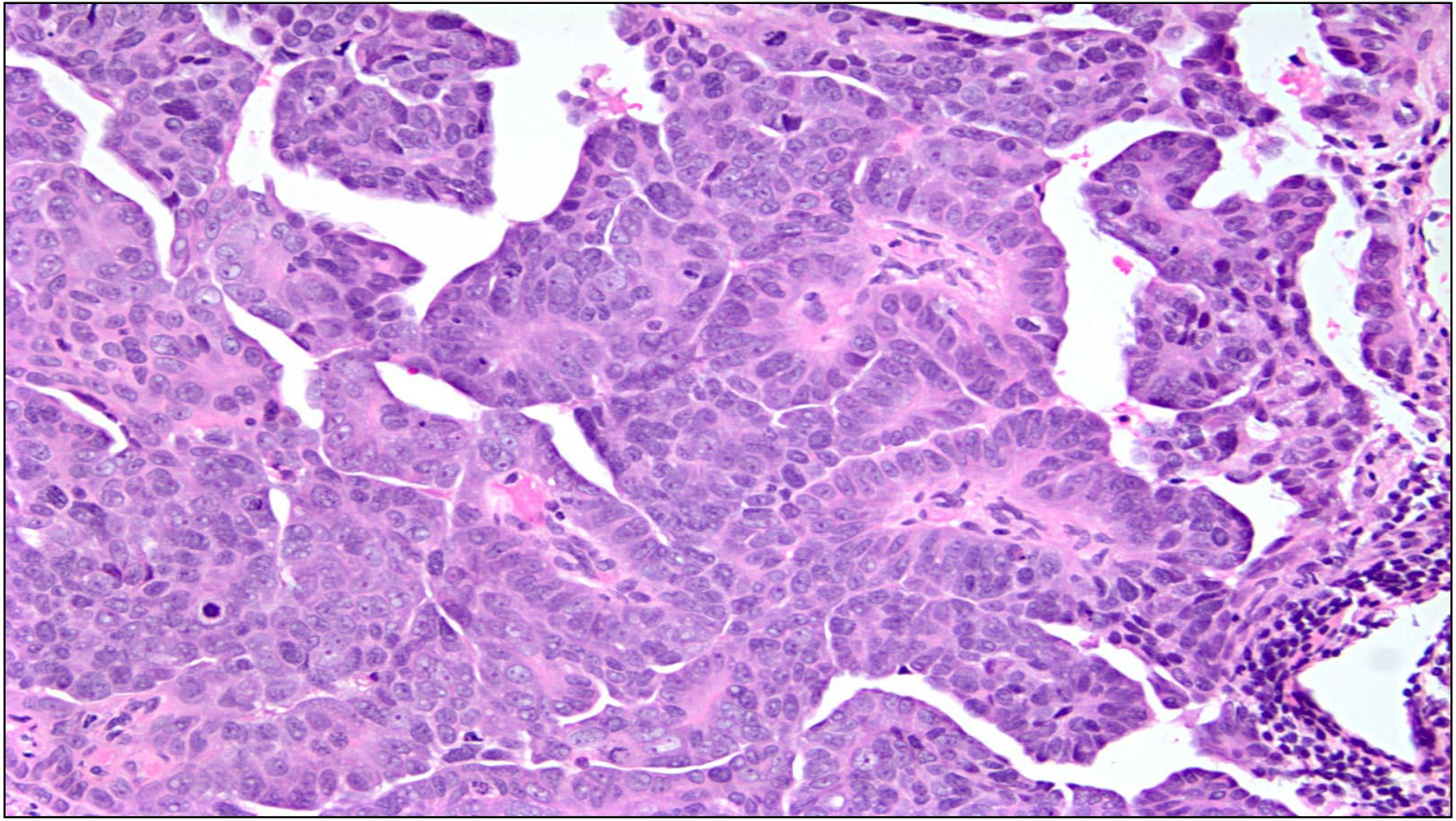
IHC in Metastatic Lesions, SOX10

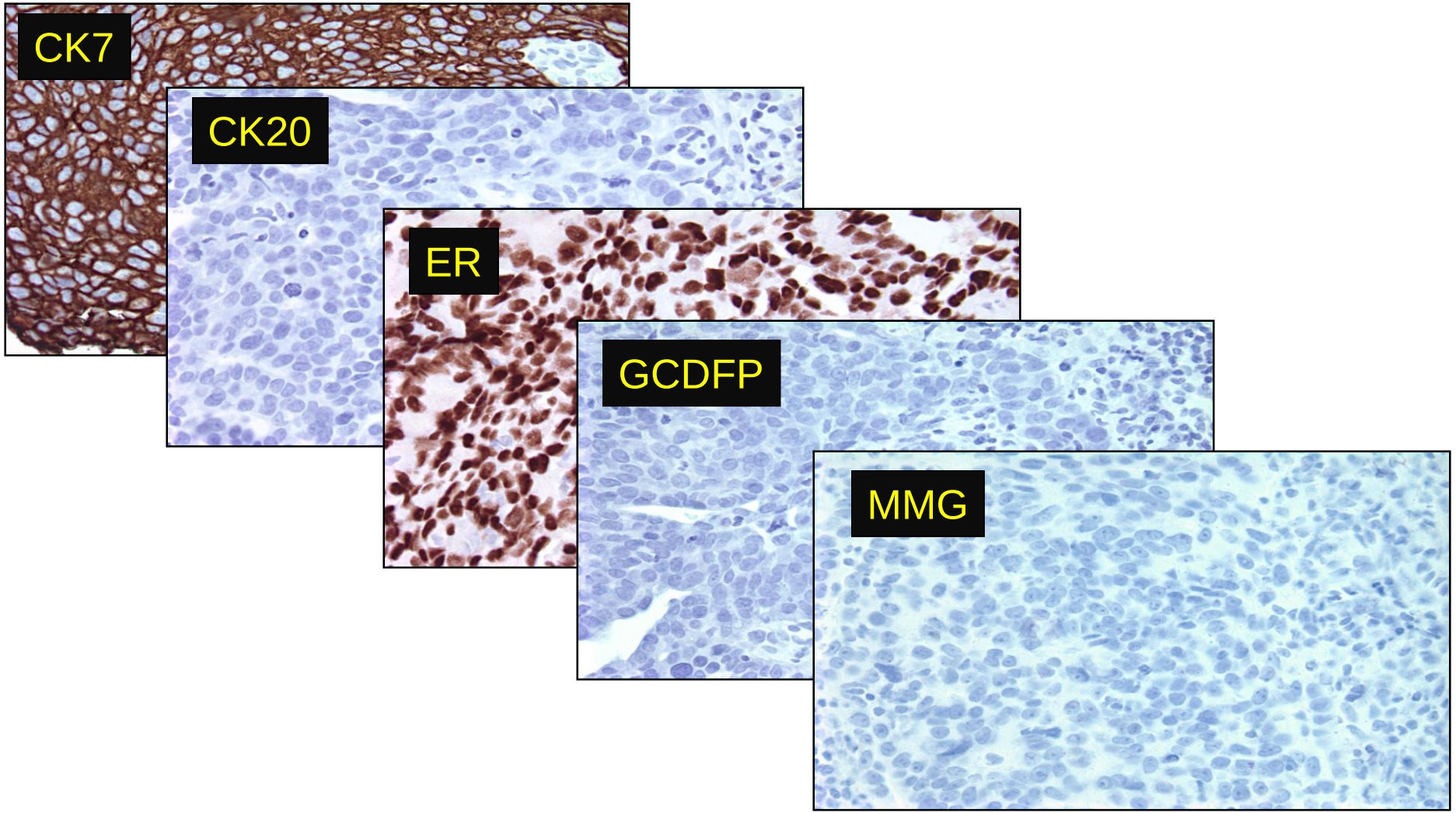
- Mediates differentiation of neural crest-derived cells
- Expressed in ~40% of TNBC and metaplastic carcinomas, rarely seen in ER+ or HER2+ tumors
- Useful in the differential with lung adenocarcinoma, even TTF1 negative tumors
- Consider in the differential with S100+ epithelioid malignant neoplasm

Cimino-Mathews, Human Pathol, 2013
Nelson, Hum Pathol, 2017
Laurent, Am J Surg Pathol, 2019

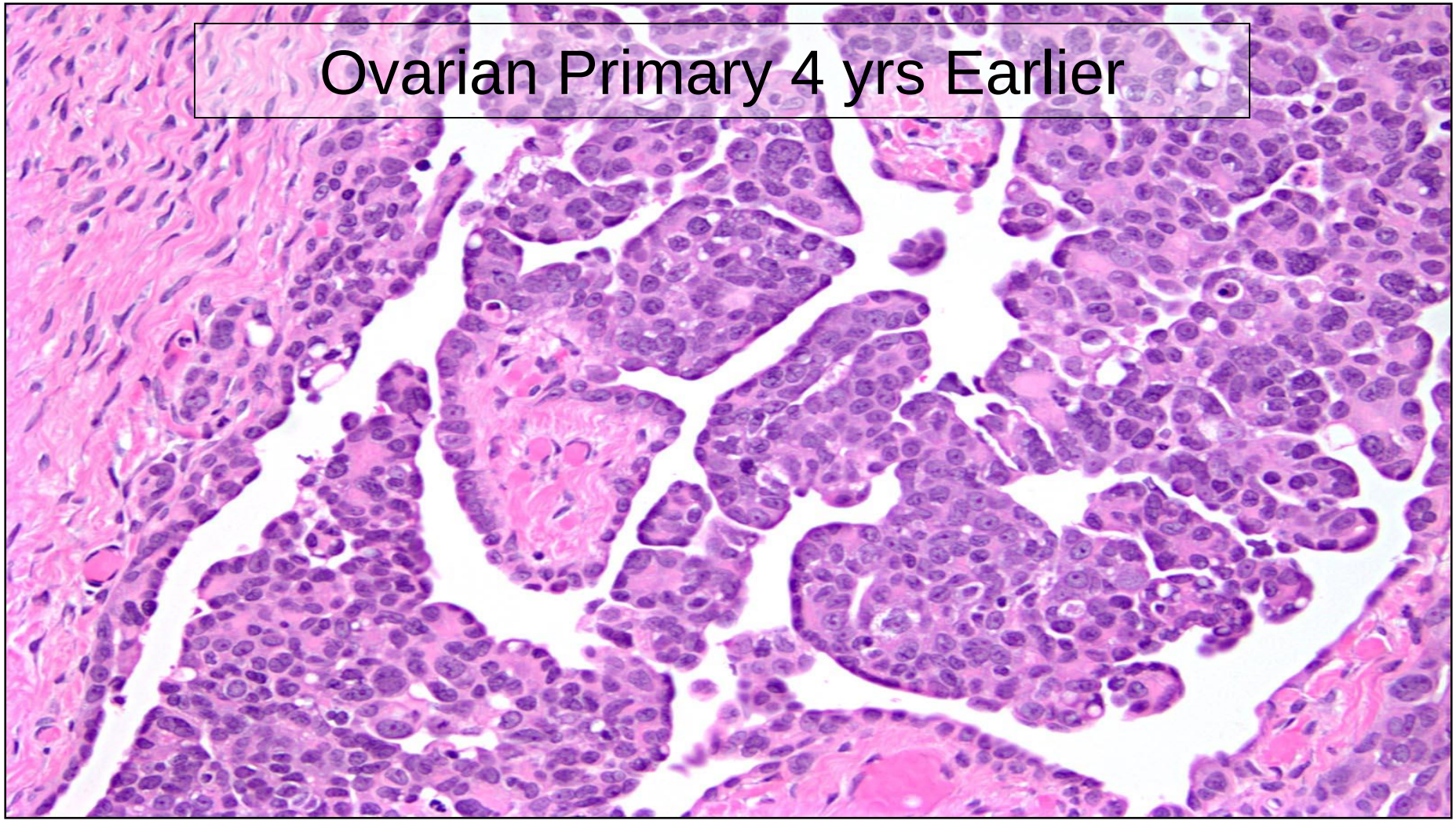




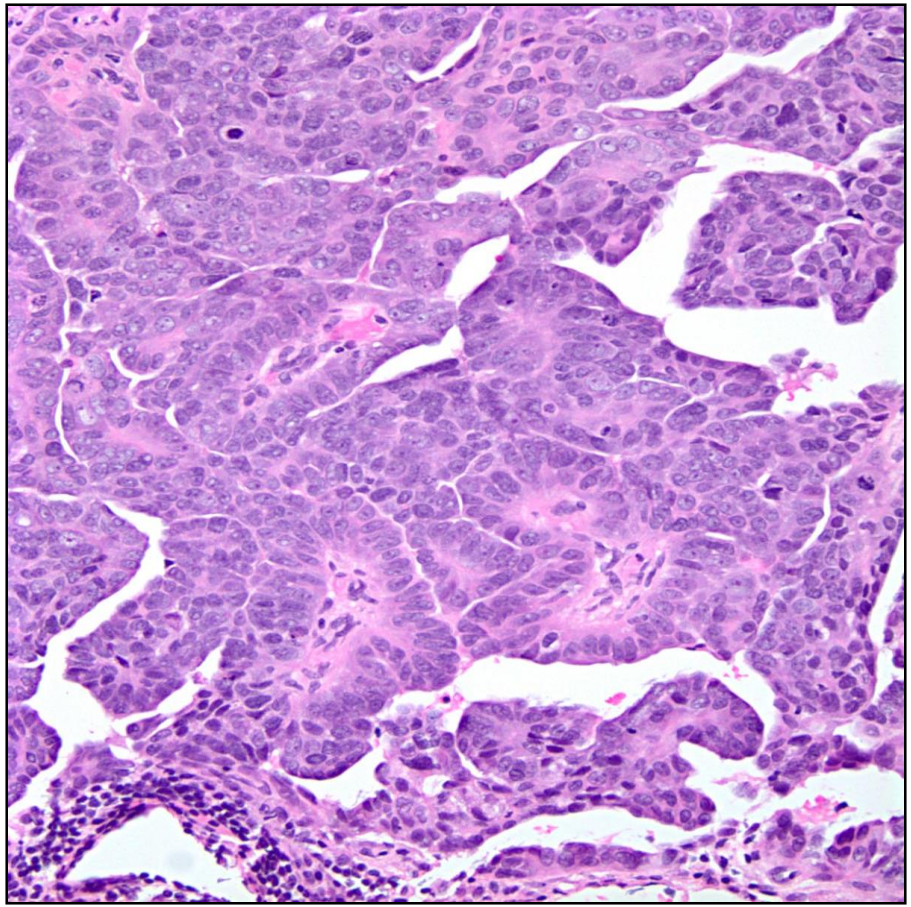



CK7
CK20
ER
GCDFP
MMG

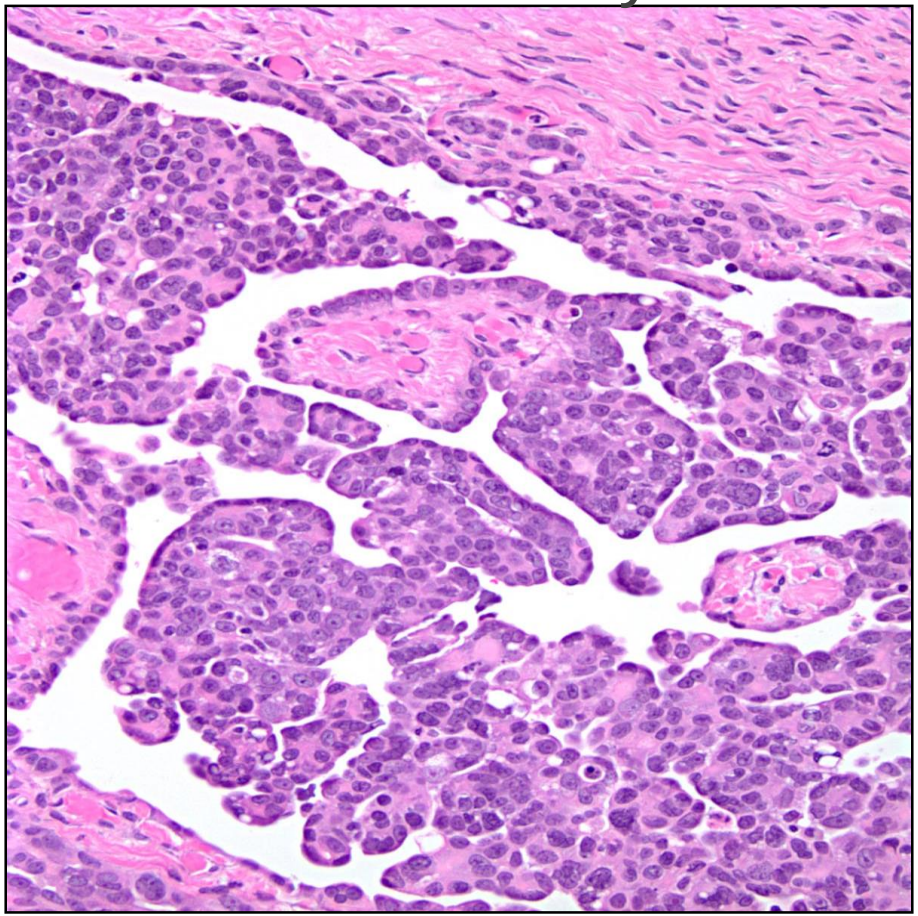
Ovarian Primary 4 yrs Earlier

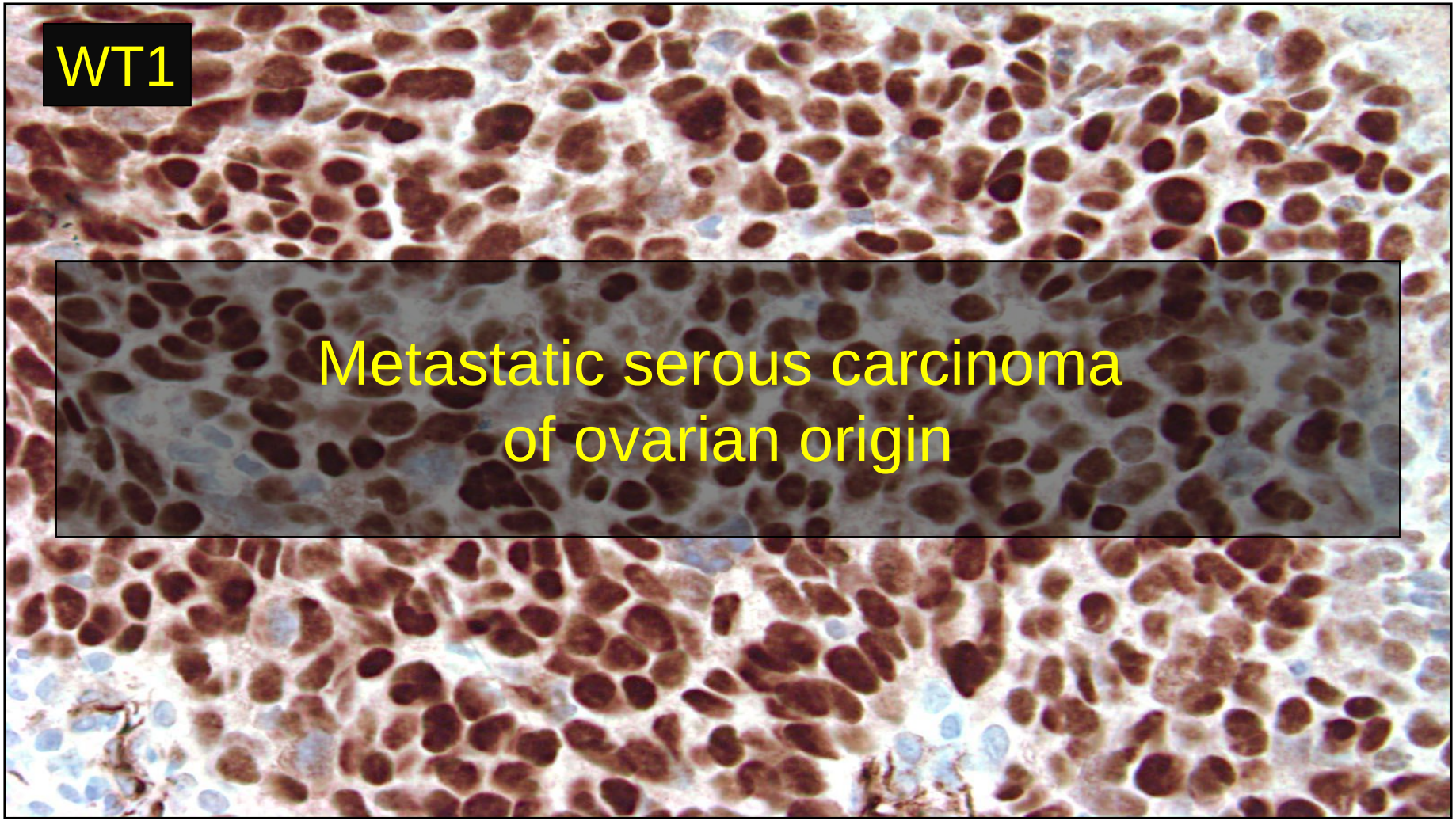


Breast CNB



Ovarian Primary




WT1
Metastatic serous carcinoma
of ovarian origin

IHC in Metastatic Lesions, Ovary

Most commonly misdiagnosed

Often ER/PR positive

PAX8 and WT1 most useful

PAX8+ in 87% of ovarian (96% if mucinous excluded) and ~3% breast

WT1+ in 85% of ovarian and 2% of breast

EMA useful if micropapillary breast carcinoma in the DDX

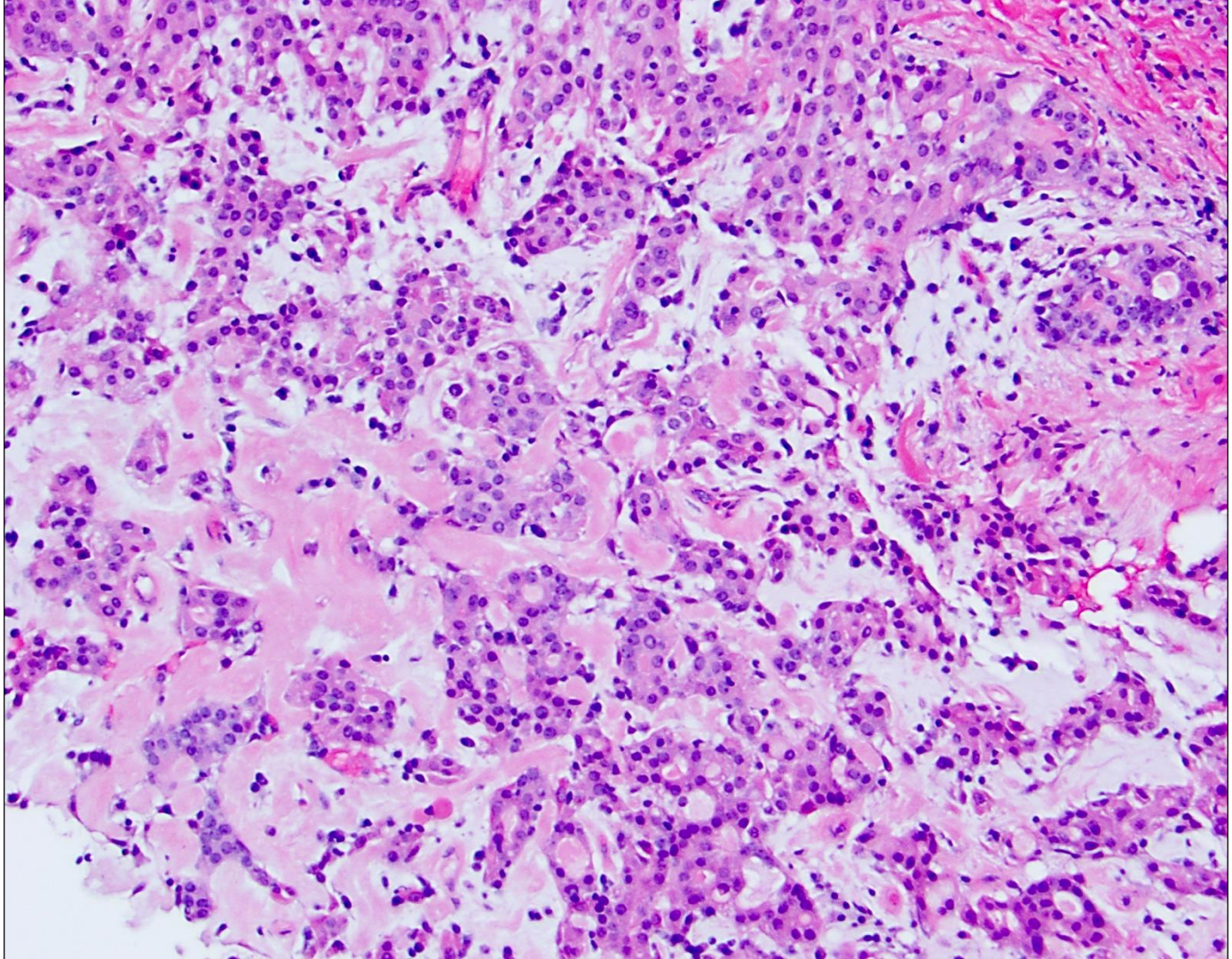
Beware!

- Mucinous breast carcinomas can be WT1+
- Up to 64%, though weak and focal

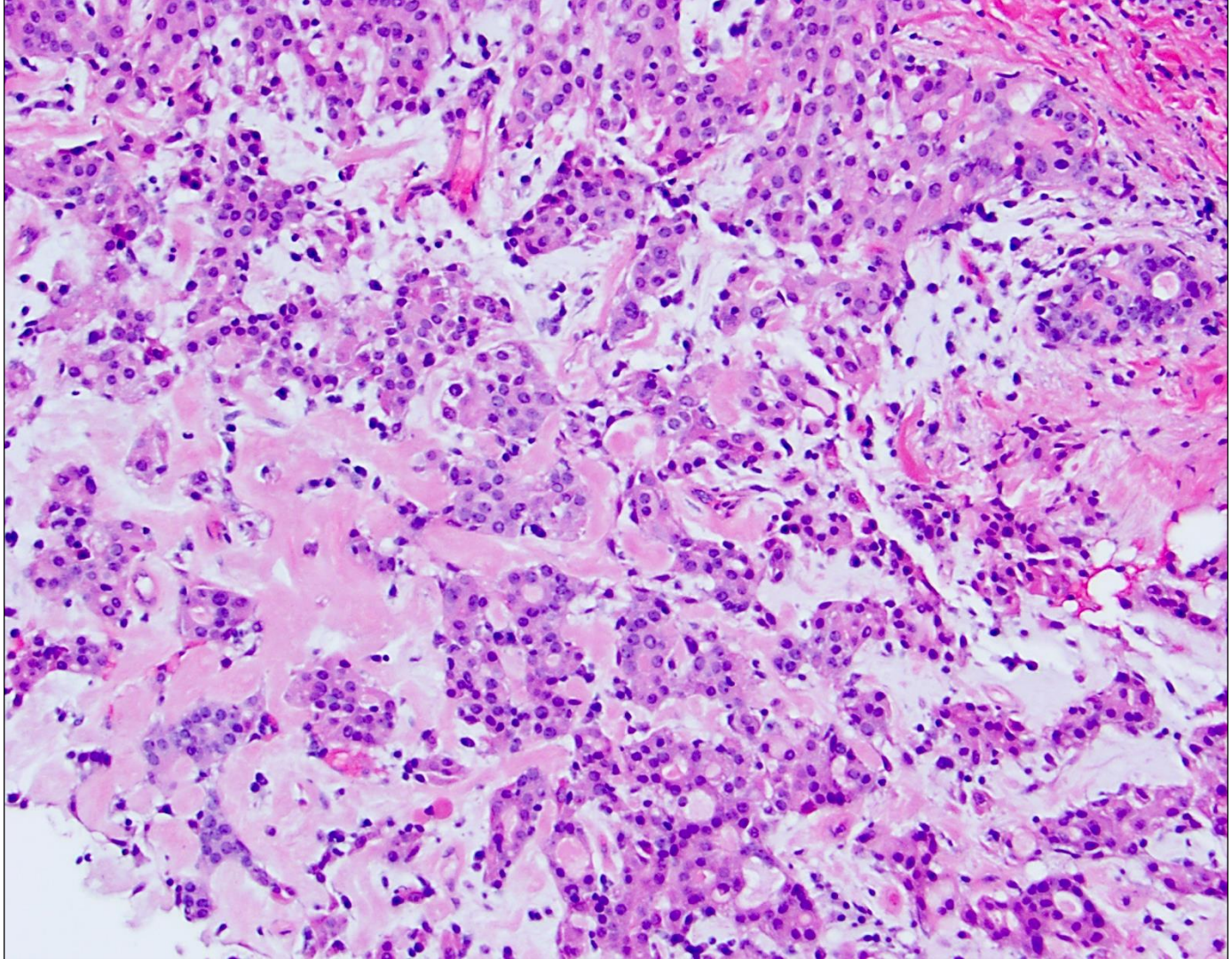
Nonaka, AJSP, 2008
Domfeh, Mod Pathol, 2008
DeLair, Mod Pathol, 2013
Singh, Mod Pathol A, 2019

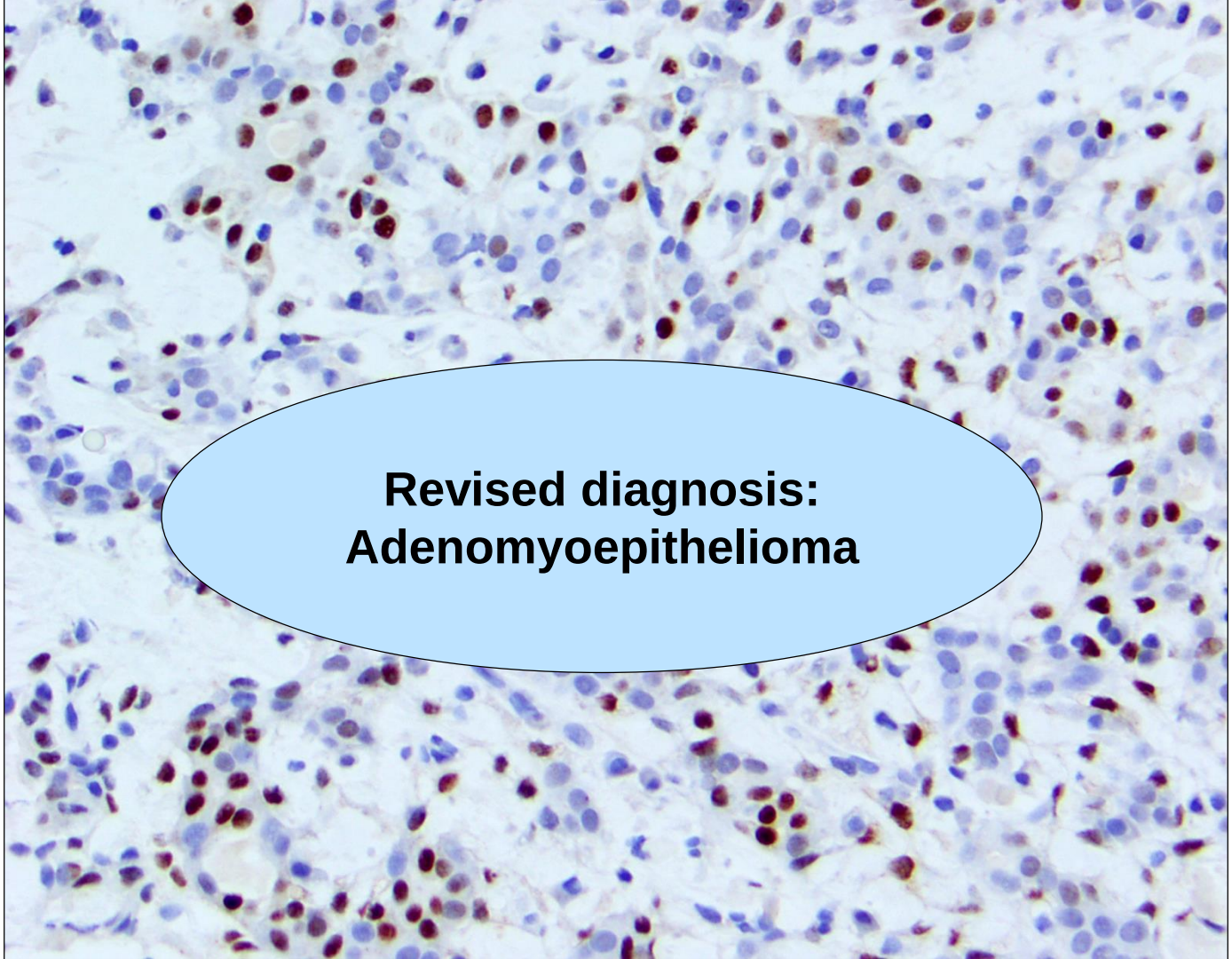
ER AS A SAFETY CHECK

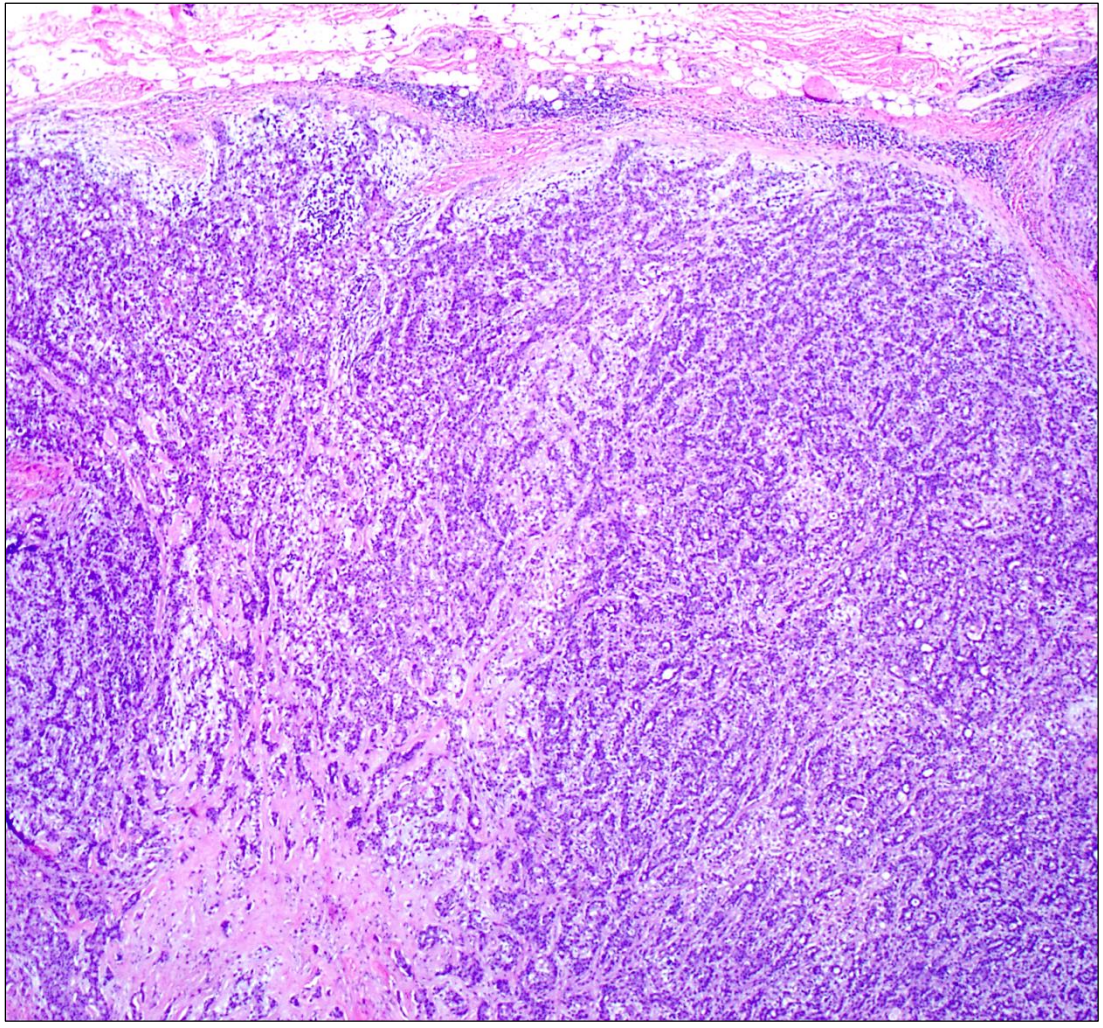
Heterogeneous expression of ER is not typical for invasive ductal carcinoma (grade 1 or 2), review the slides to exclude misdiagnosis (UDH or less likely metastasis)

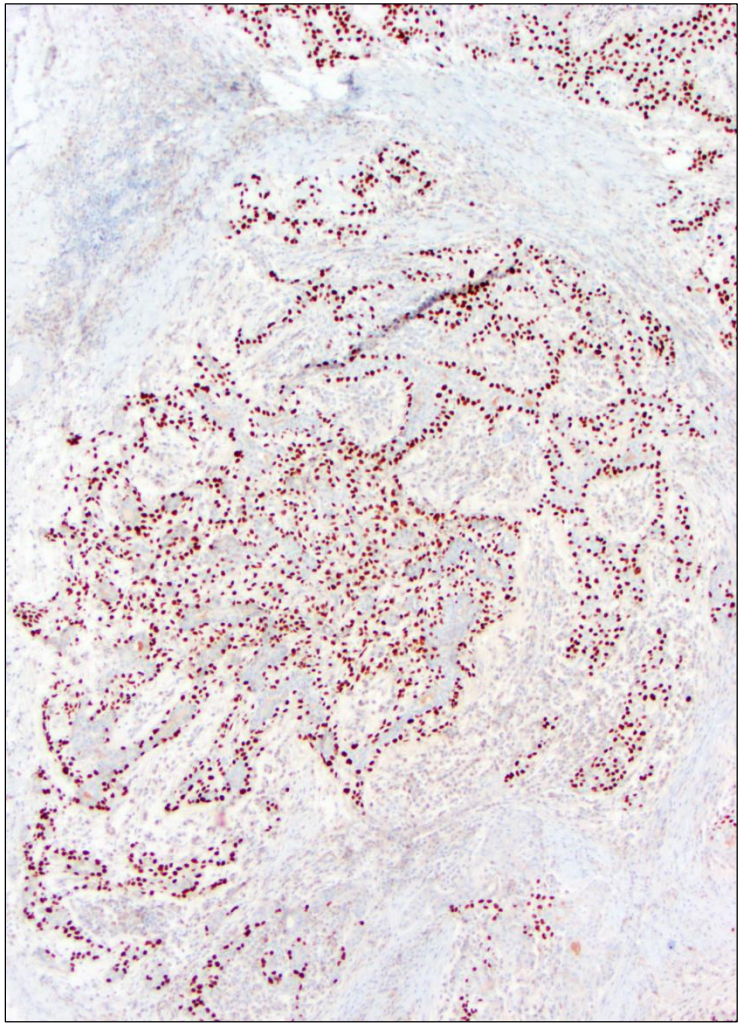


75 year old with large, palpable breast mass




Revised diagnosis:
Adenomyoepithelioma





BE MINDFUL OF UNUSUAL LOOKING TUMORS AND TRIPLE NEGATIVE CANCERS

Don’t Need to Work-up Every Case to Rule Out Metastasis

Just Pause and Consider

Ensure Receptor Status is Concordant with H&E Findings

ER low positive tumors, usually high grade

- Be accurate with % positivity
- Otherwise may exclude patients from triple negative therapies/trials
- Ensure low grade tumors are strongly and diffusely positive

Ensure Receptor Status is Concordant with H&E Findings

Be careful about HER2 2+ vs. 3+ and 0 vs. 1+

- FISH not mandated for IHC 3+ tumors
- Patients with palpable HER2 overexpressing tumors are often candidates for chemotherapy; whereas ER+, HER2 negative patients may not be
- Ensure morphology is compatible with HER2 positivity (apocrine histology; abundant eosinophilic cytoplasm; high grade tumors)

Re-review and Consider Further IHC Work Up

- If findings are unusual
- Receptor status is discordant
- In the setting of h/o cancer

Summary

- Reviewed how core needle biopsy diagnosis guides next management steps in radiology, surgery and oncology, and discussed the importance of radiologic-pathologic correlation
- Discussed management of high risk lesions diagnosed on breast core needle biopsy
- Discussed the importance of considering non-breast primaries and the need for careful correlation and accurate reporting of breast biomarker studies, particularly in an era of neoadjuvant systemic therapy