Challenges in the Diagnosis of (Micro)Invasive Carcinoma

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Overview

- Microinvasion
  - Helpful clues
  - Immunostains and pitfalls in interpretation
  - Clinical significance
- Invasive ca that mimics benign
- Invasive ca that mimics in situ
- Benign that mimics invasive ca

Microinvasion

2010 AJCC Staging Manual

- T1mi
- “Extension of cancer cells beyond the basement membrane…as an invasive ca with no focus measuring >1 mm”
- Not connected with CIS
- No need to subtype
- **!!** If multiple foci, should ***not*** be added together
- An attempt to quantify them should be included
- Prognosis is generally quite favorable
- Clinical impact of multifocality is not well understood

Always r/o microinvasion if…

- High grade or comedo-type DCIS
  - Other DCIS types can also have it
- Comedo-type or pleomorphic LCIS
- Extensive CIS
- Periductal lymphoid infiltrates
- Mucocele-like lesions

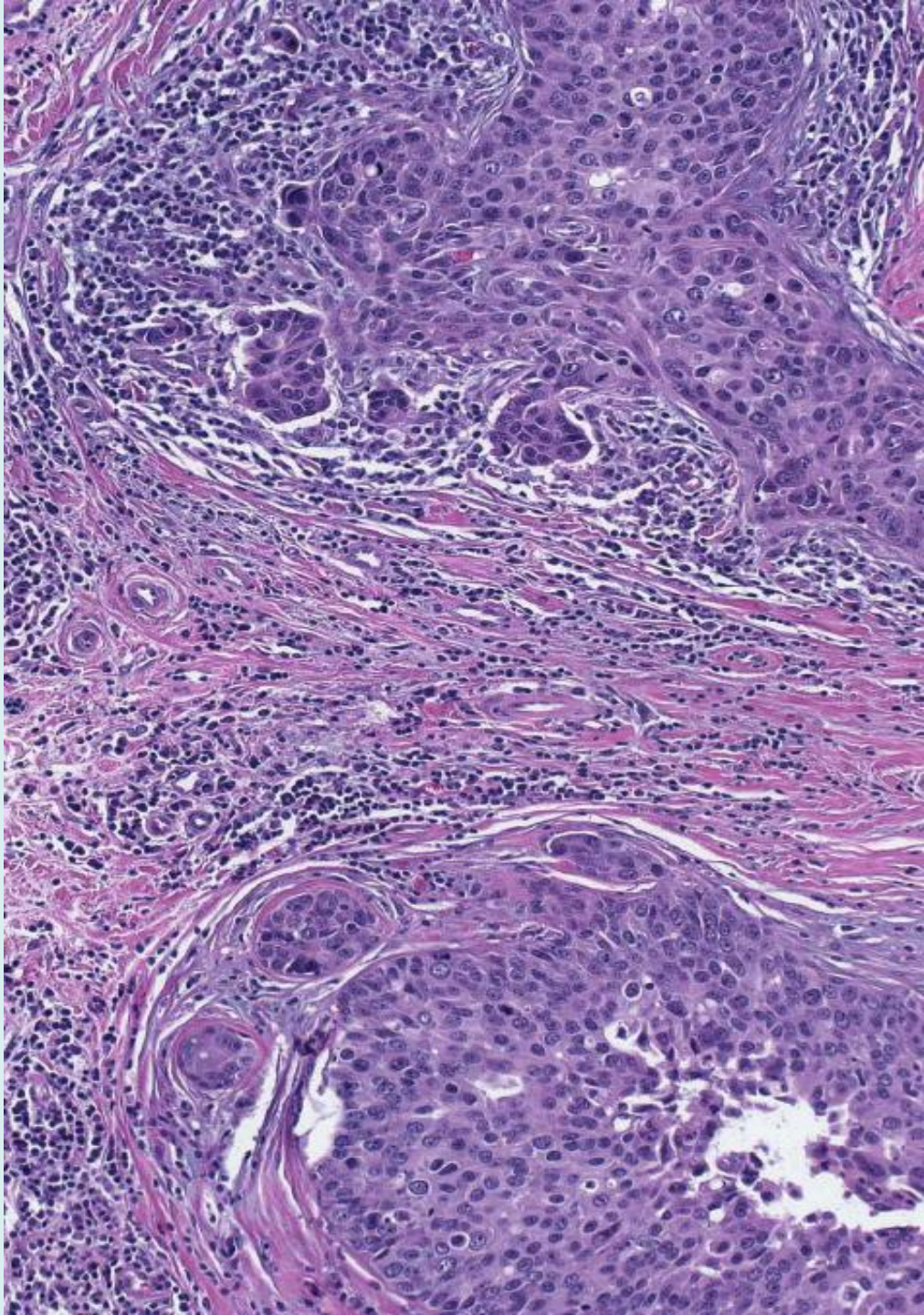
Useful lower-power field tools

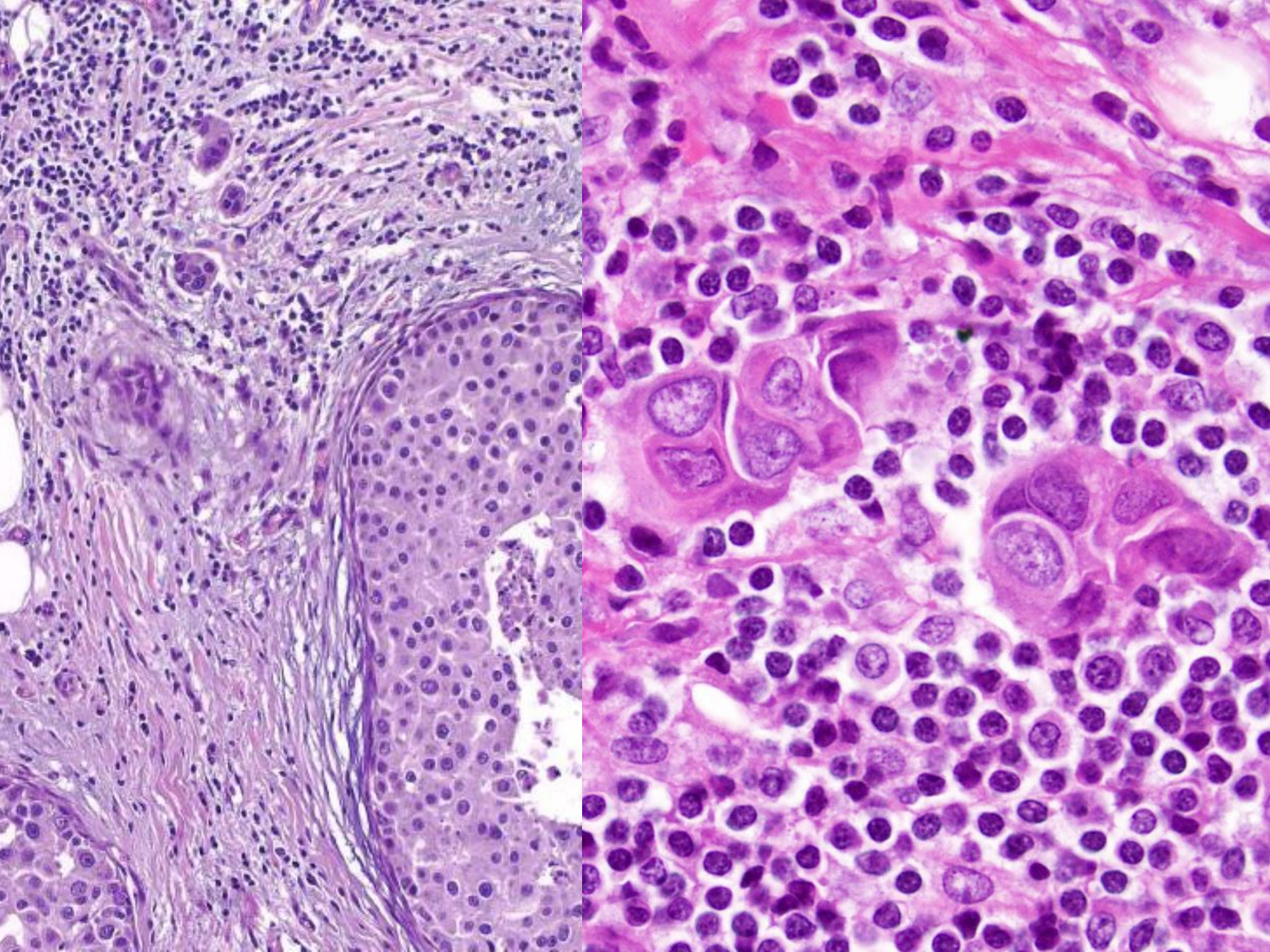
- Irregularity of the contour of the nests/glands
- Retraction around the invasive nests
- Tumor nests/glands without a lobulocentric organization
- Chronic inflammation
- Reactive stroma
- Increased stromal cellularity
- DCIS: blurred edges of the duct wall due to tangential sectioning

Useful higher-power field tools

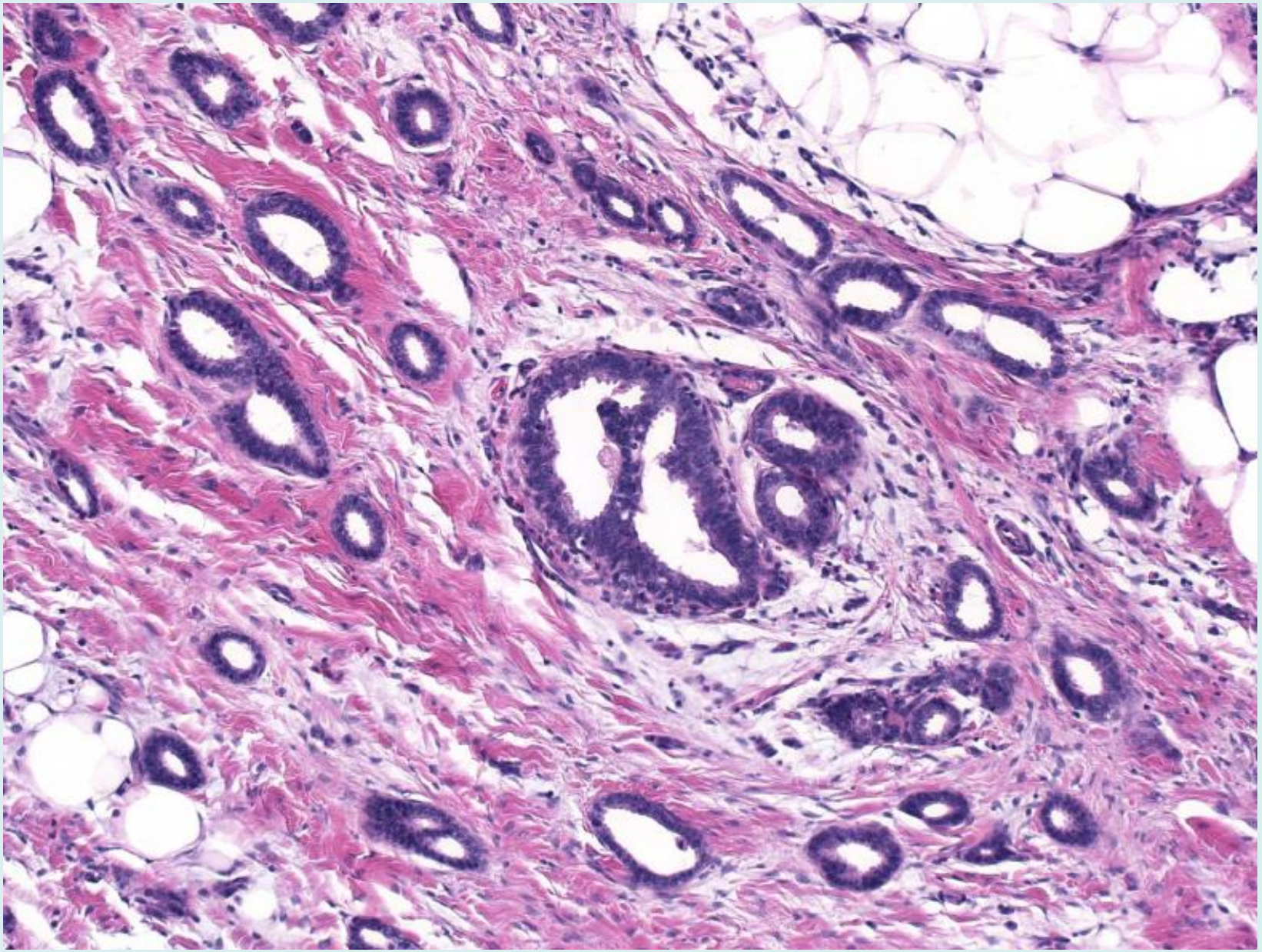
- Irregularity of the contour of the nests/glands
- No basement membrane (BM): tumor cells directly abut the stroma/adipose tissue
- No myoepithelial cells on H&E
- Retraction around the invasive nests

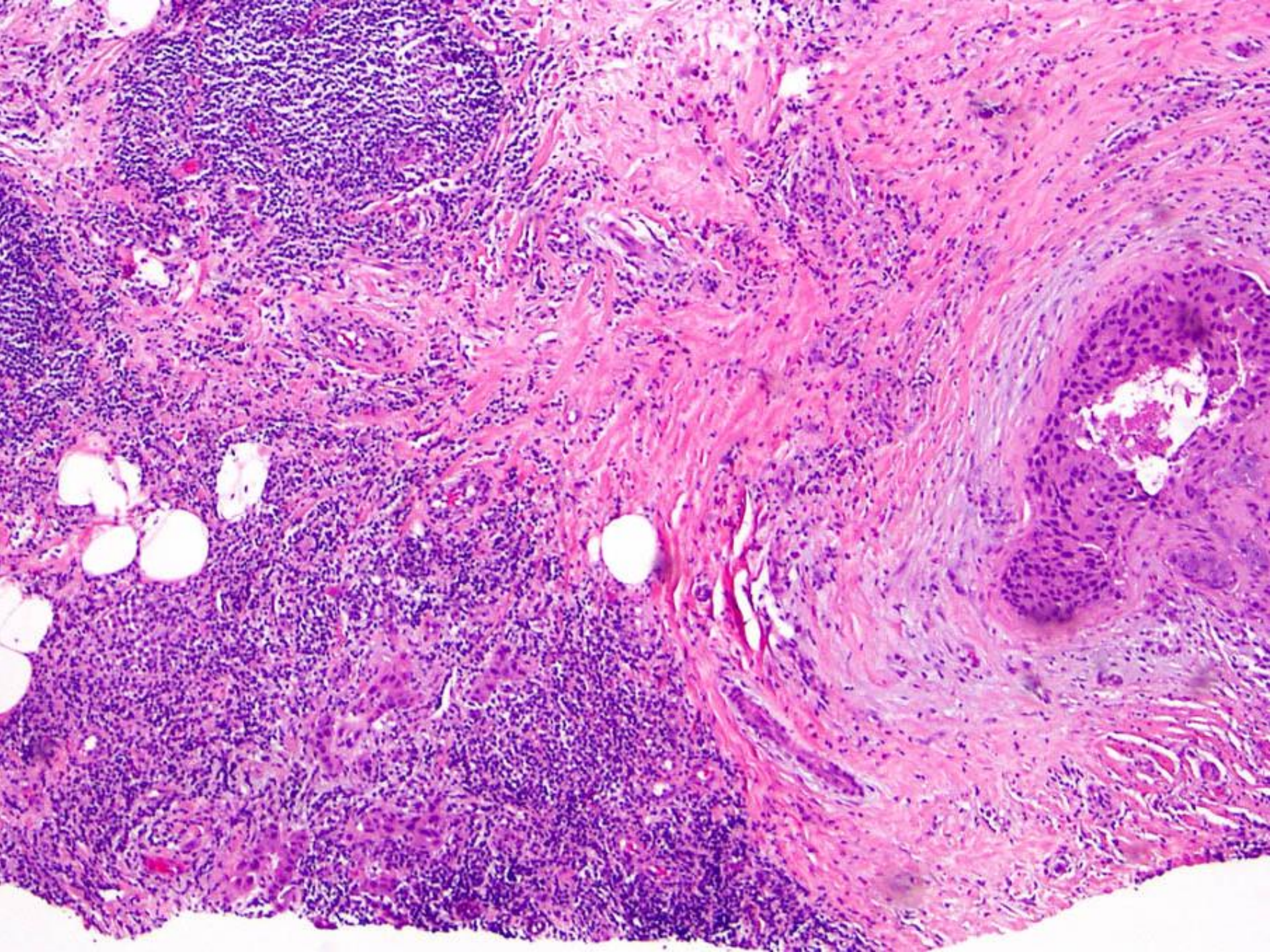
- **DCIS** with smooth contours (below)
- **Microinvasive** carcinoma with irregular contours (above)



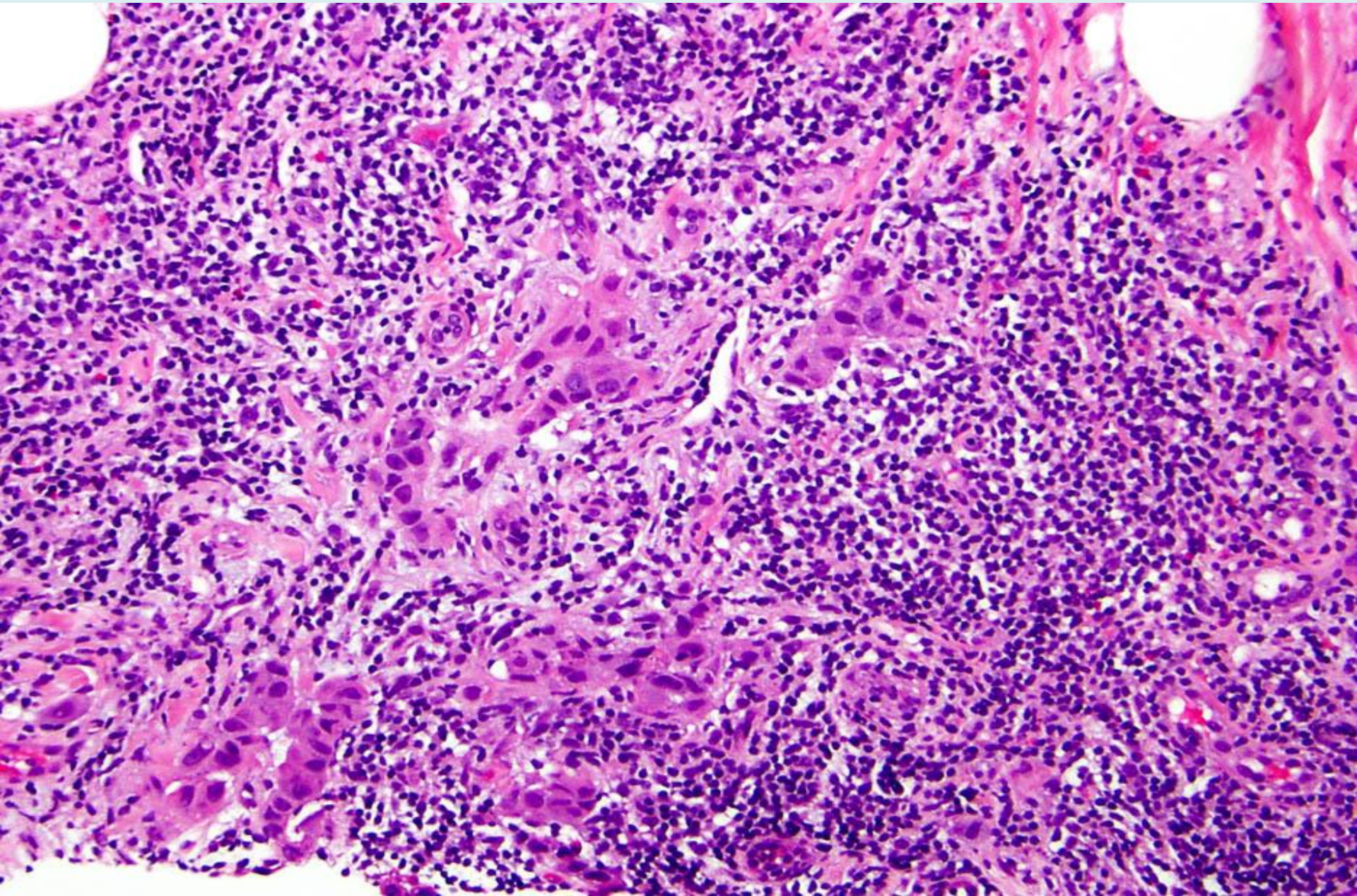


IDC: absent lobular arrangement around benign

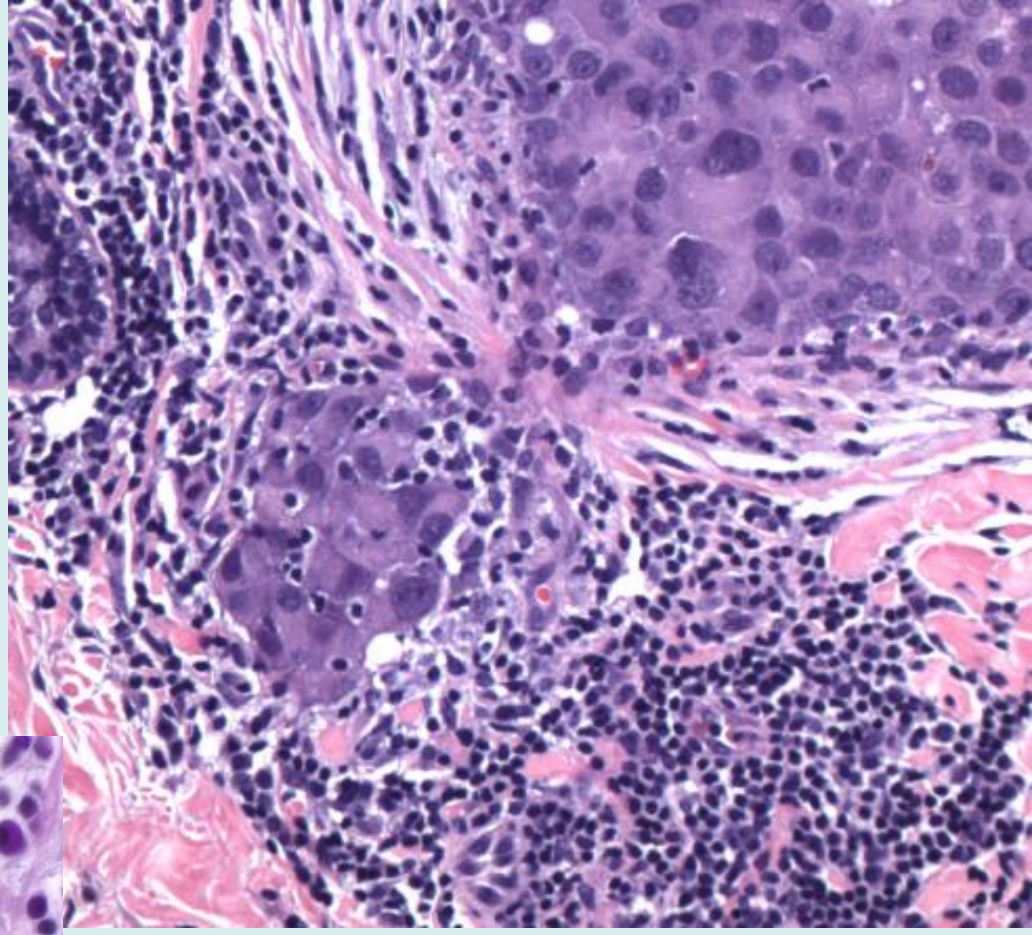


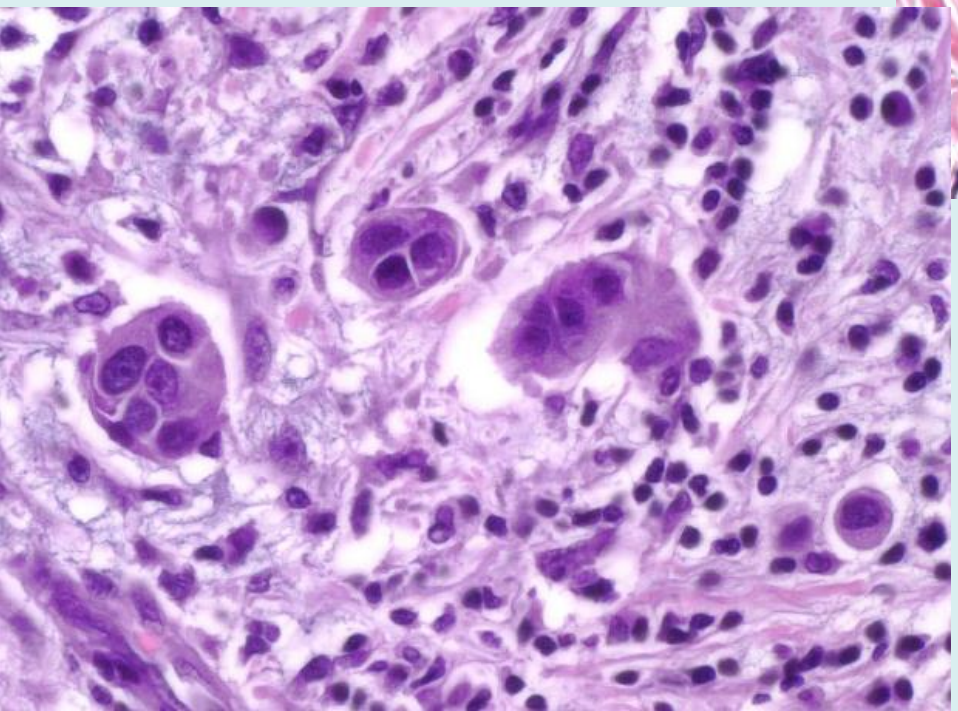


Invasion

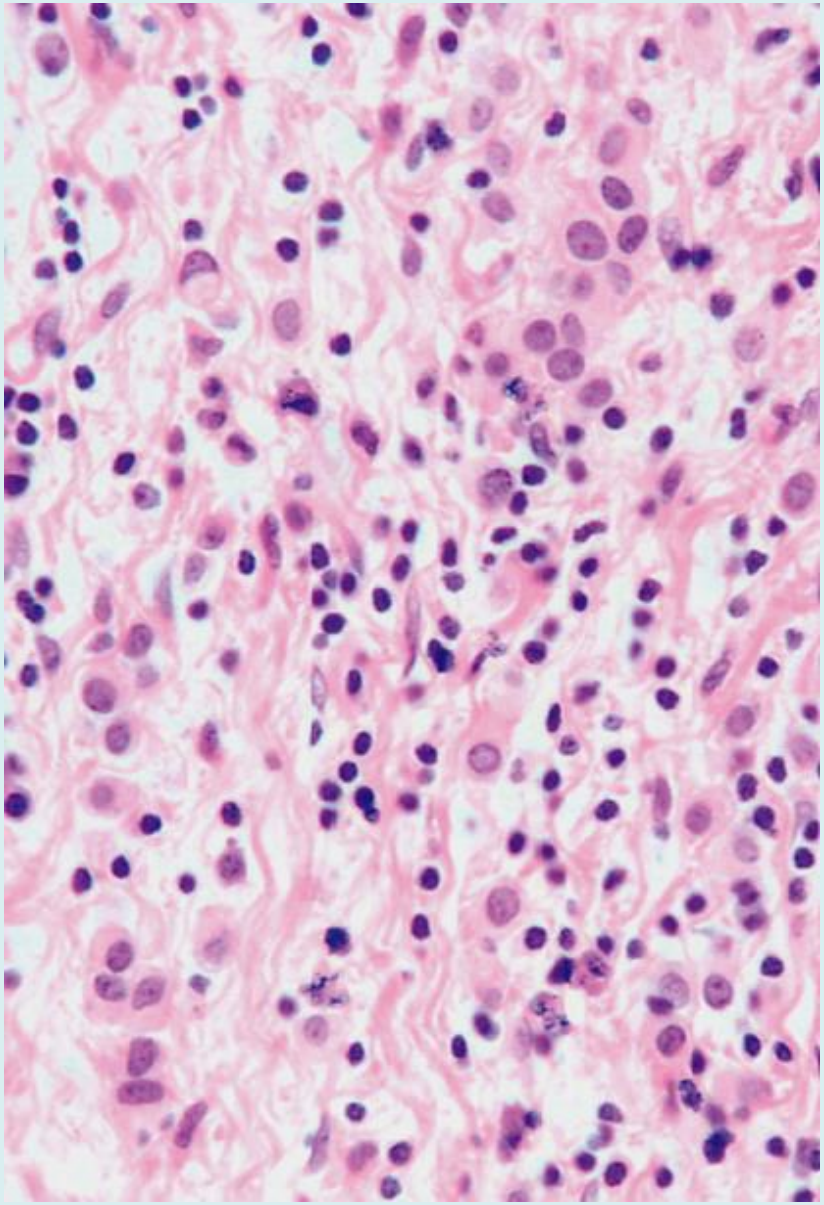


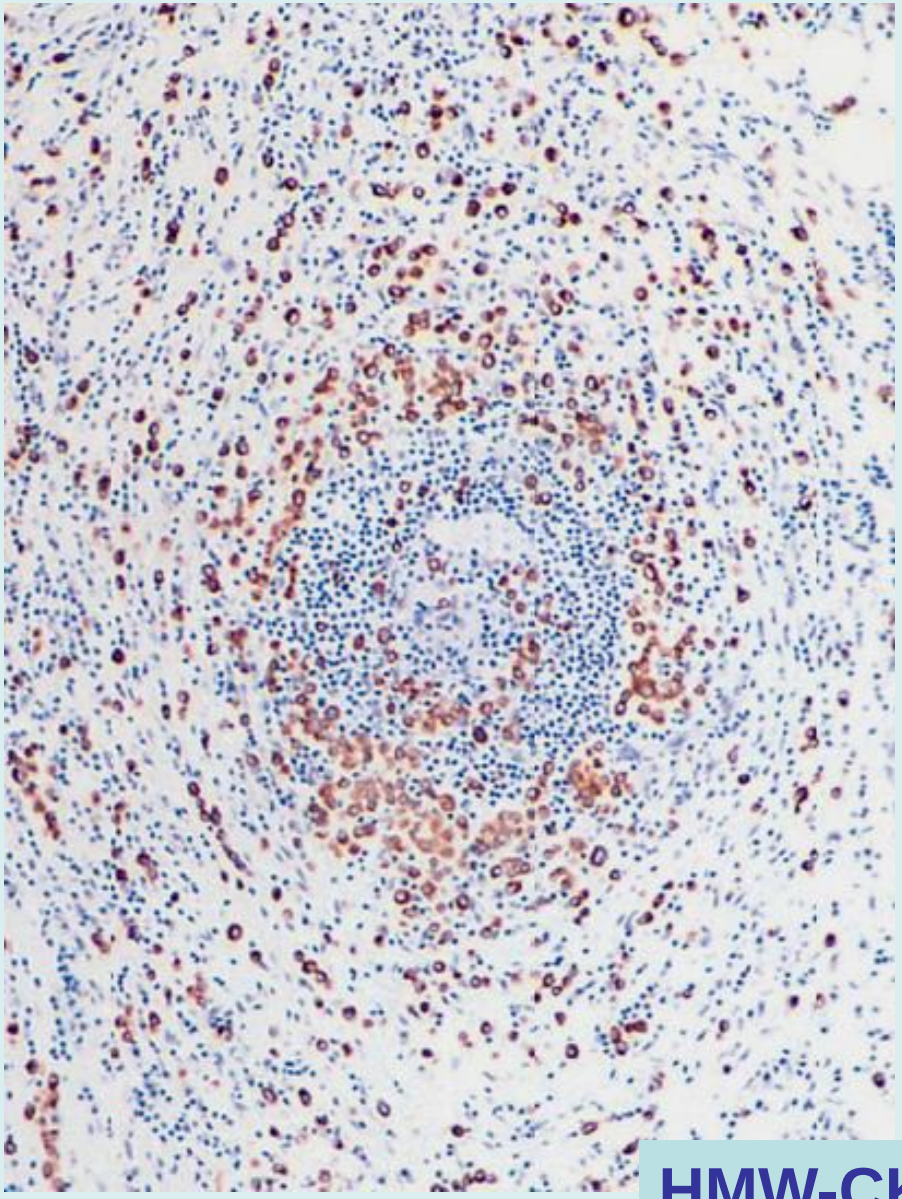
- Stromal (periductal) chronic inflammation needs closer evaluation
- **!!** Useful: at final margins → levels!



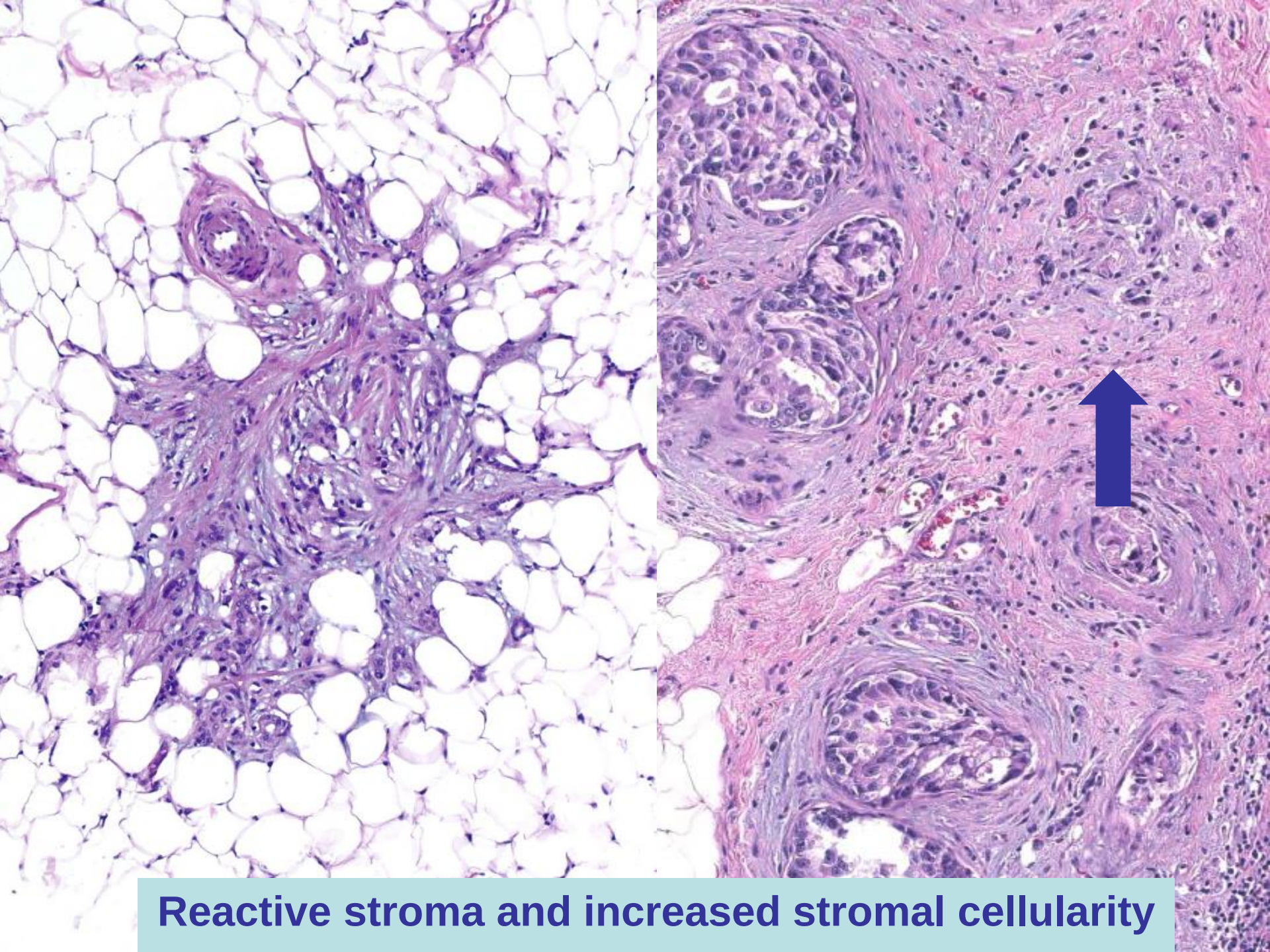


Invasive lobular carcinoma with lymphocytes



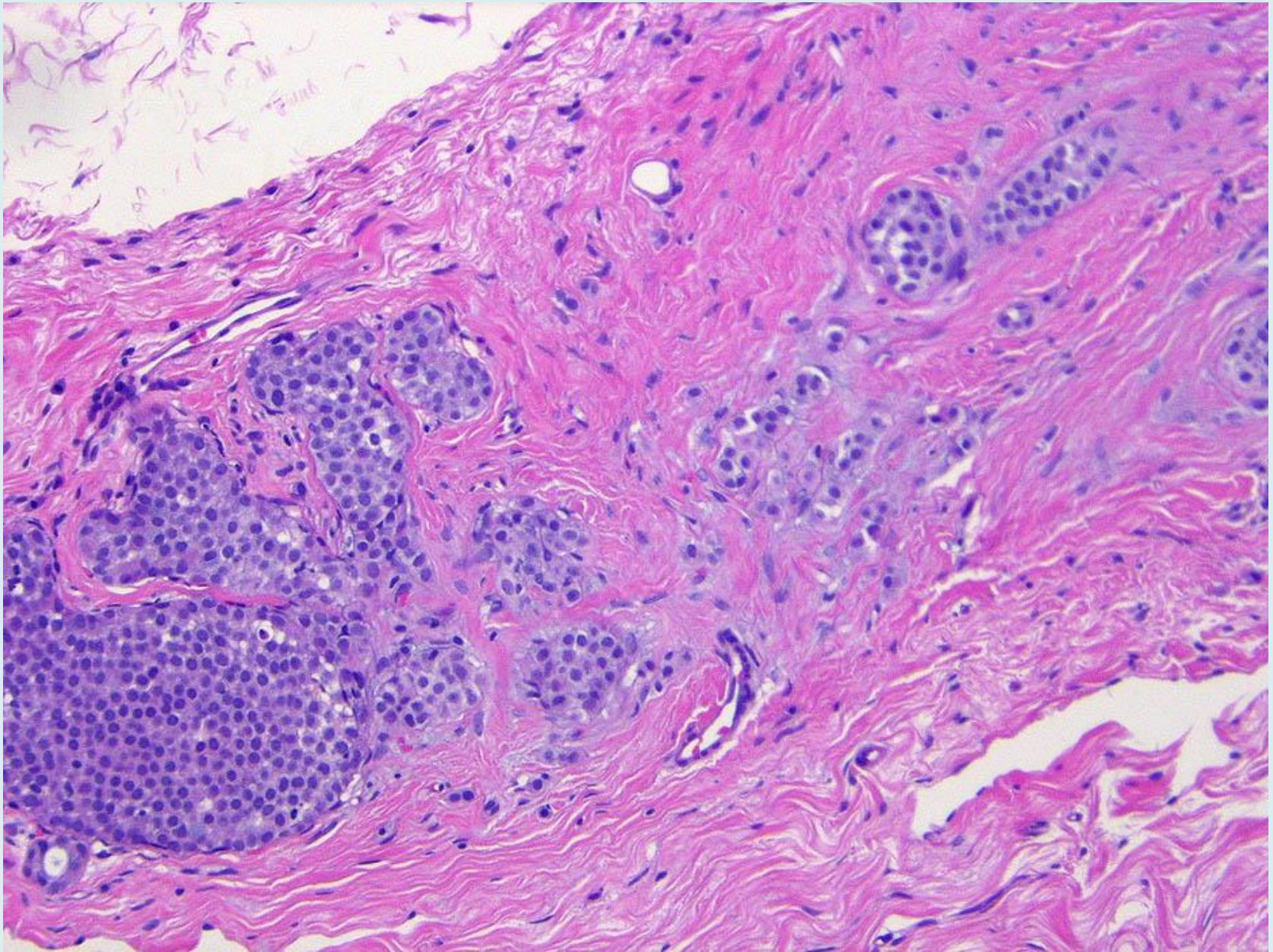


HMW-CK

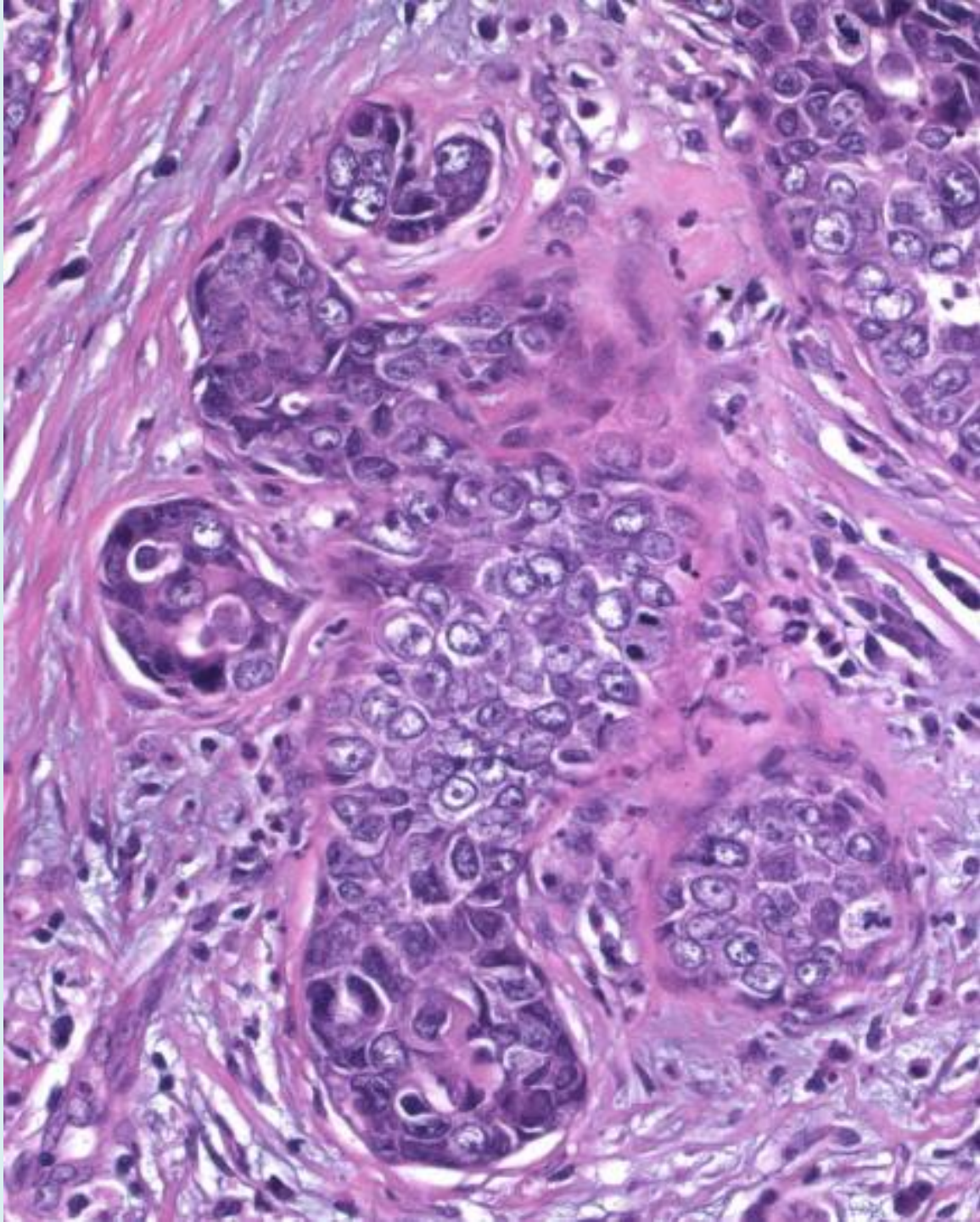


Reactive stroma and increased stromal cellularity

Microinvasive lobular simulates lymphocytes



DCIS: tangential sectioning of the duct wall will create a blurred edge



Helpful studies

- Definitive diagnosis is not always possible on H&E
- **!!** Most useful adjunctive studies:
  - IHC: at least **2** myoepithelial markers

Assessing invasion by IHC

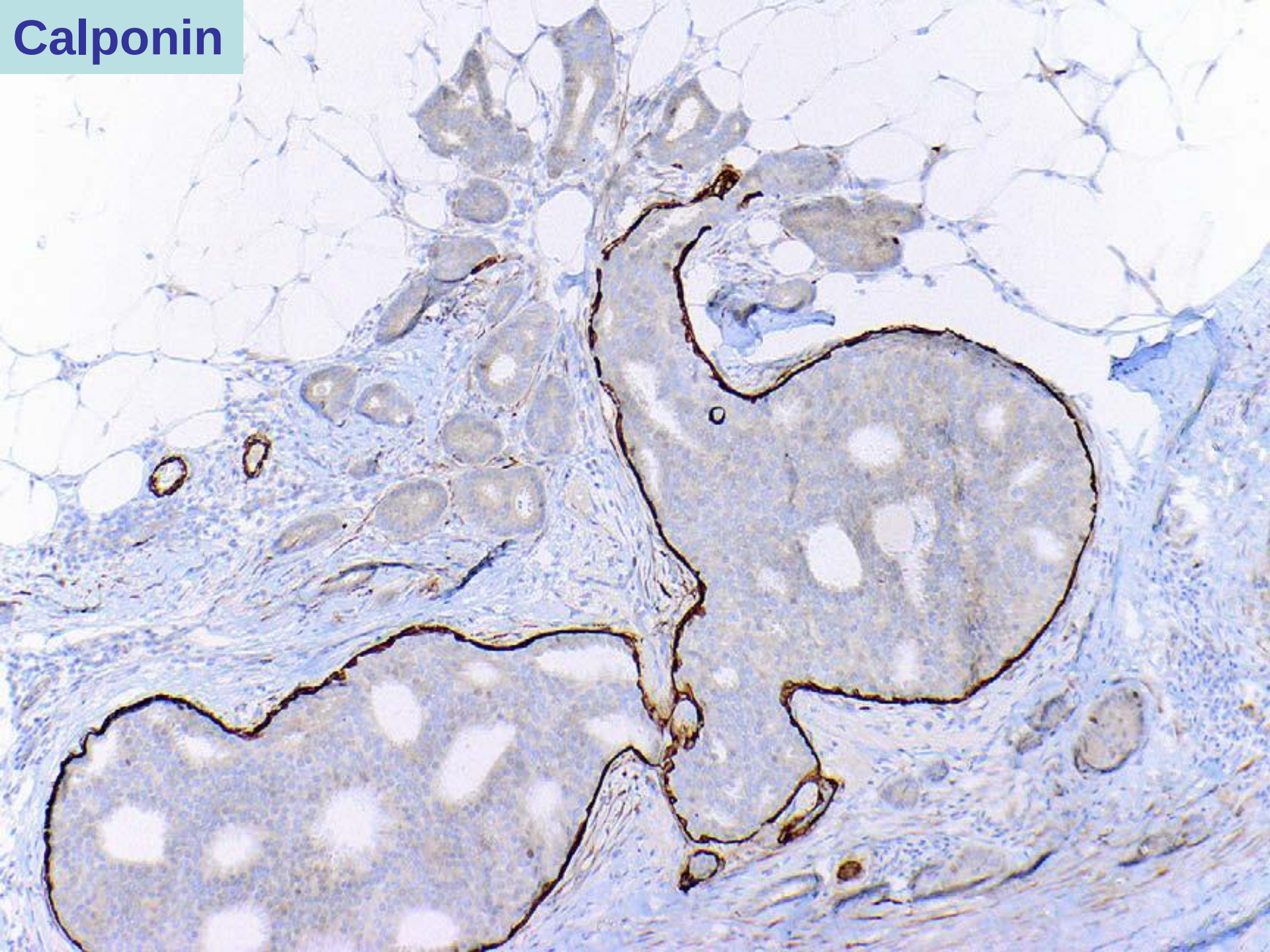
- Invasive carcinoma:
  - *Lack* of both basement membrane and myoepithelial cells
- Benign and in situ lesions:
  - *Presence* of both basement membrane and myoepithelial cells

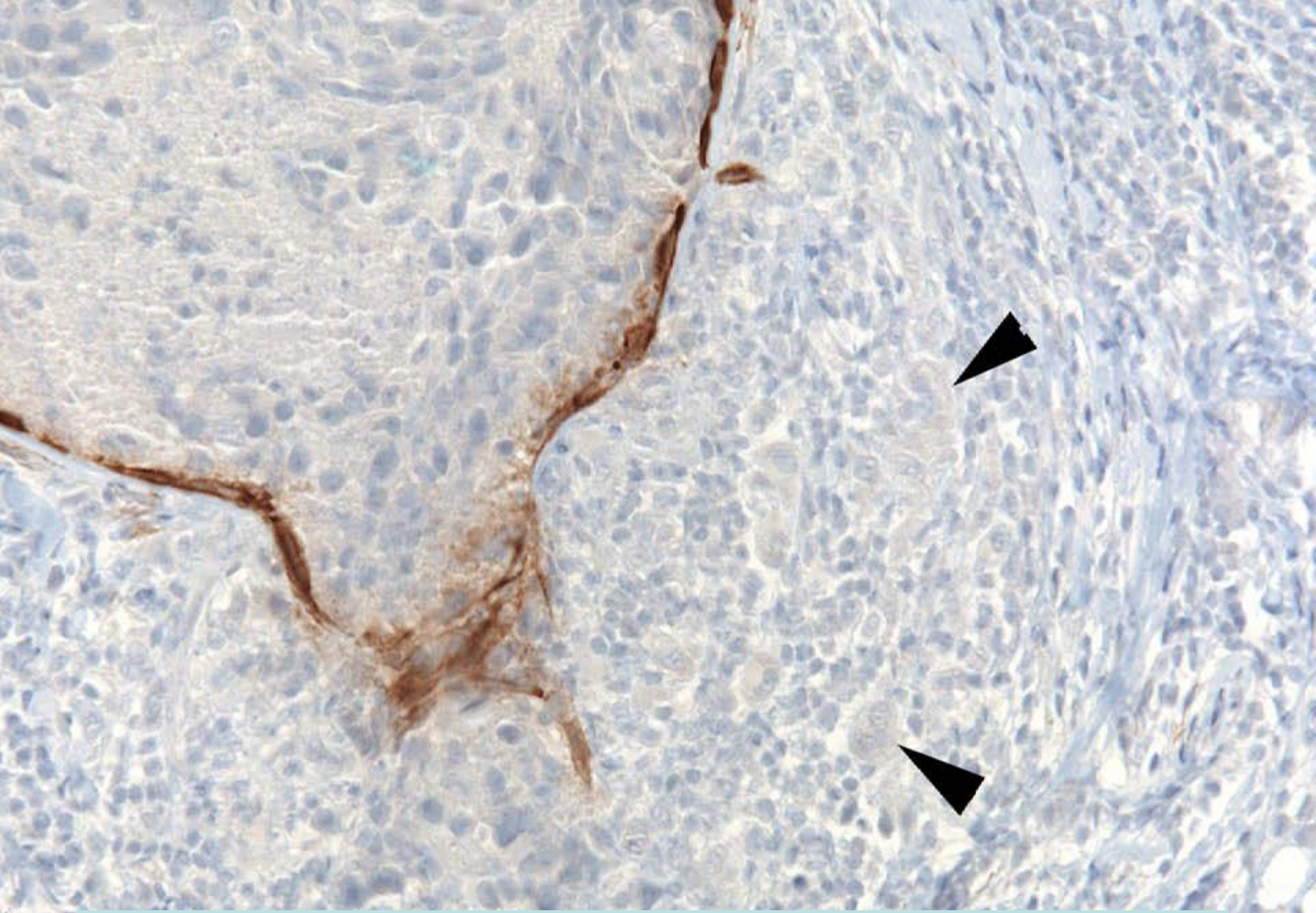
Myoepithelial cell markers

Marker	Sensitivity	Specificity
S-100	Good	Unacceptable
Actin	Good	Poor
SMMHC	Good	Excellent
Calponin	Excellent	Very good
HMW-CK	Very good	Poor

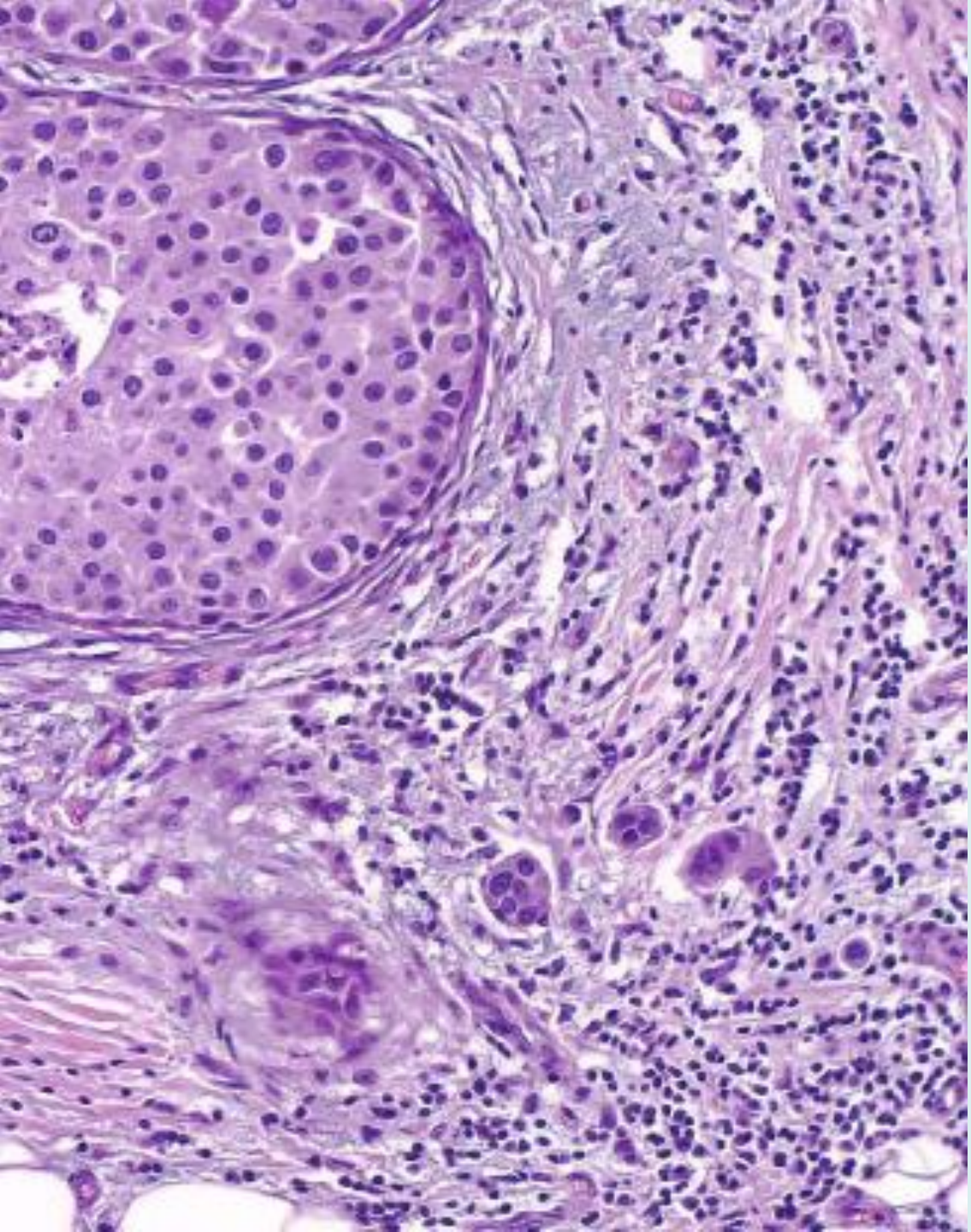
Adapted from Yaziji, et al. Adv Anat Pathol 2000, 7:100-109

Calponin





Calponin: easily overlooked microinvasive carcinoma

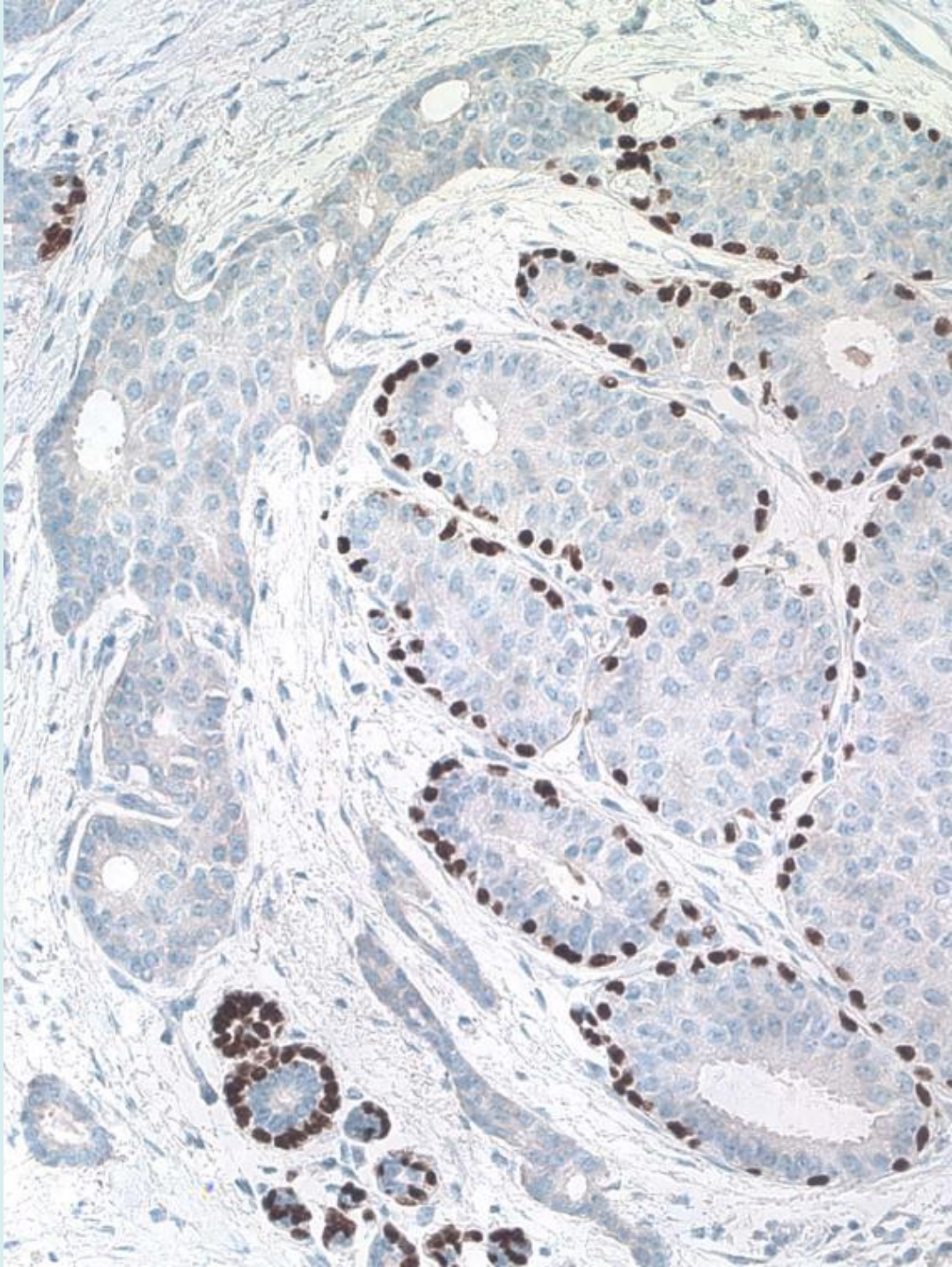


An **H&E section** paired with 2 myoepithelial cell markers is critical

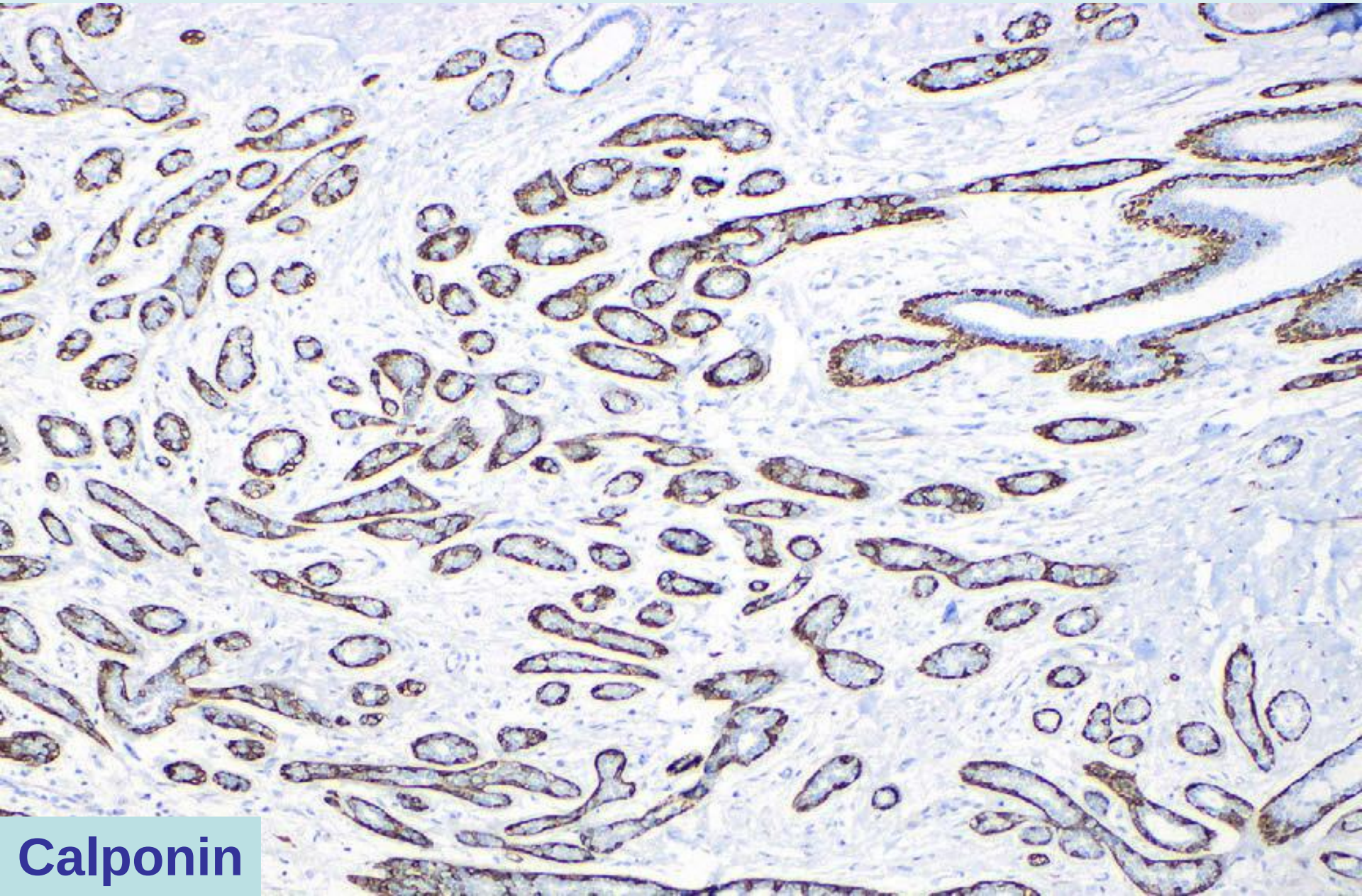
MOST COMMONLY USED	USED	RARELY USED
CALPONIN	CK5/6	S100
SMMHC	CD10	
SMA	34B12	
p63		

p63

- p53 family
- Nuclei only
- High sensitivity
- High specificity
- No myofibroblast staining
- Positive in some DCIS and IDC (metaplastic)

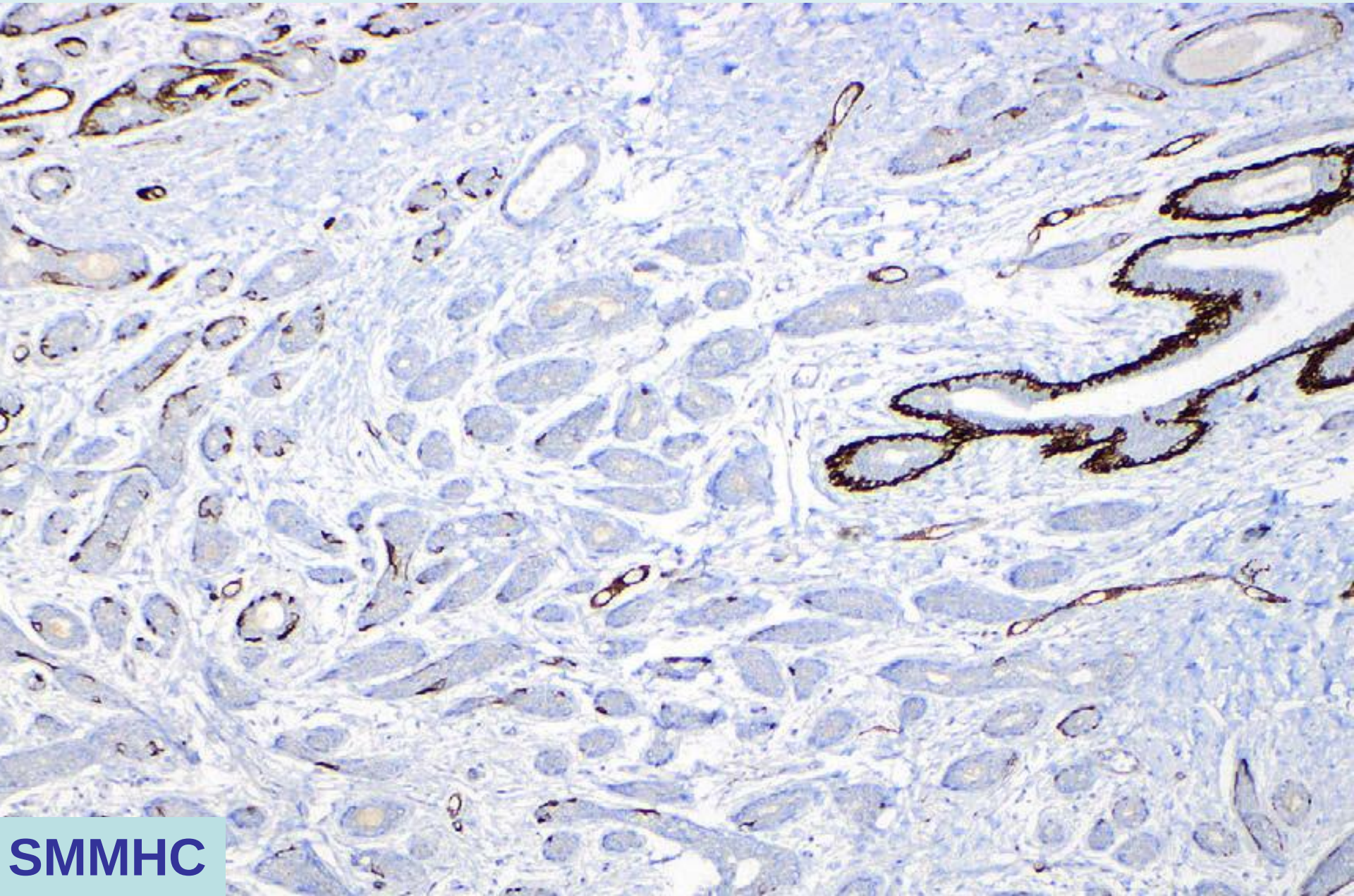


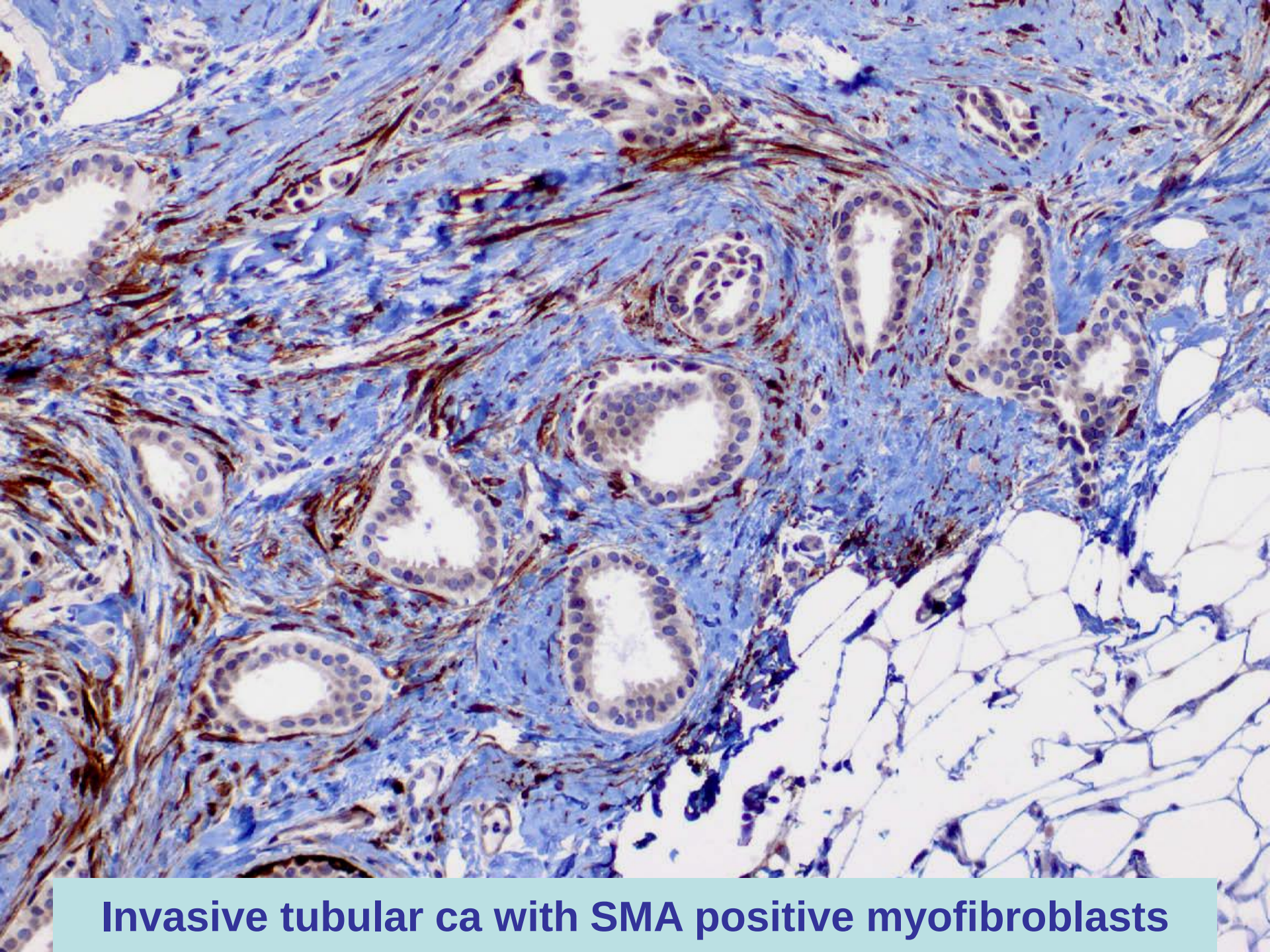
Tubular adenosis



Calponin

Tubular adenosis

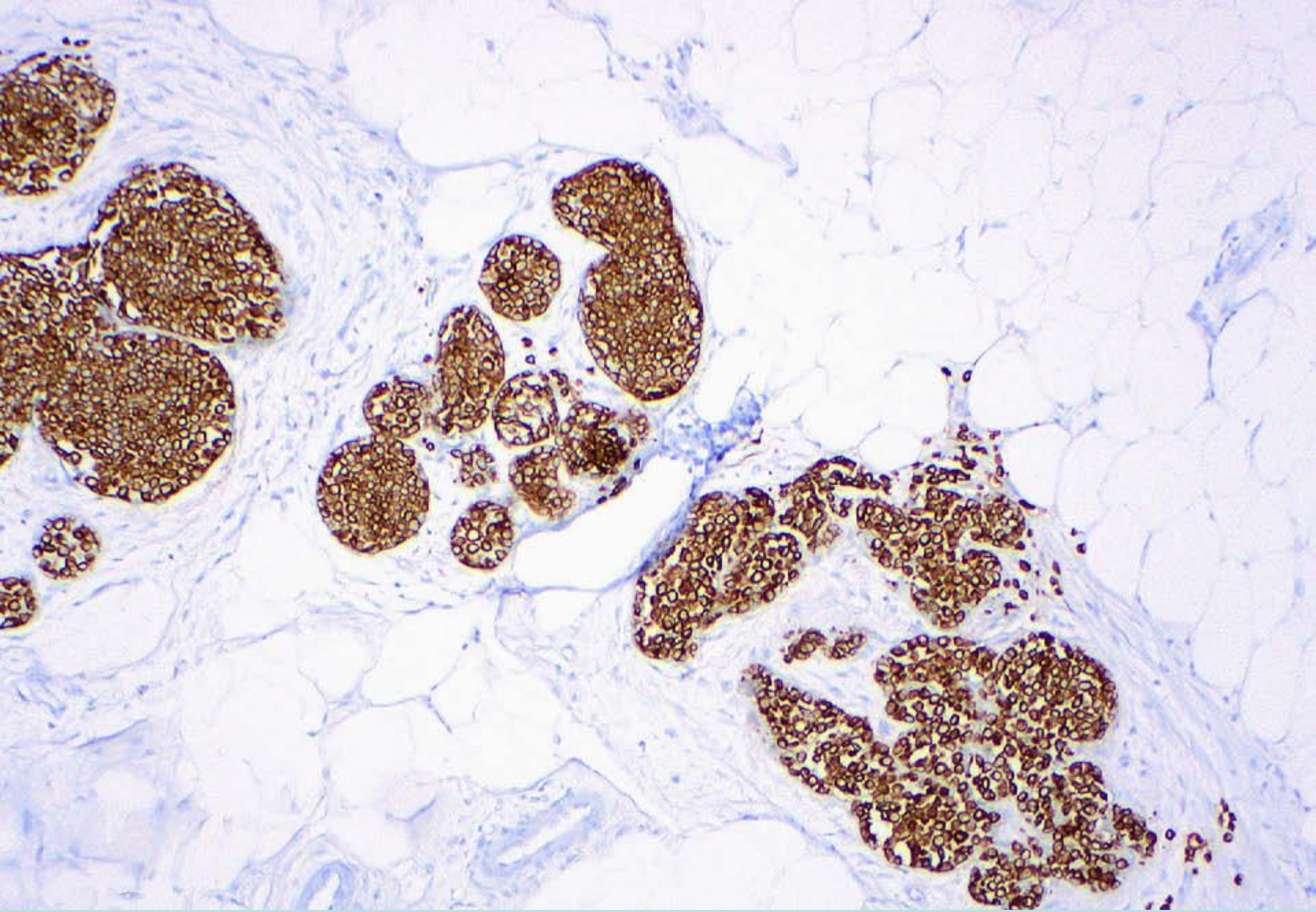




Invasive tubular ca with SMA positive myofibroblasts

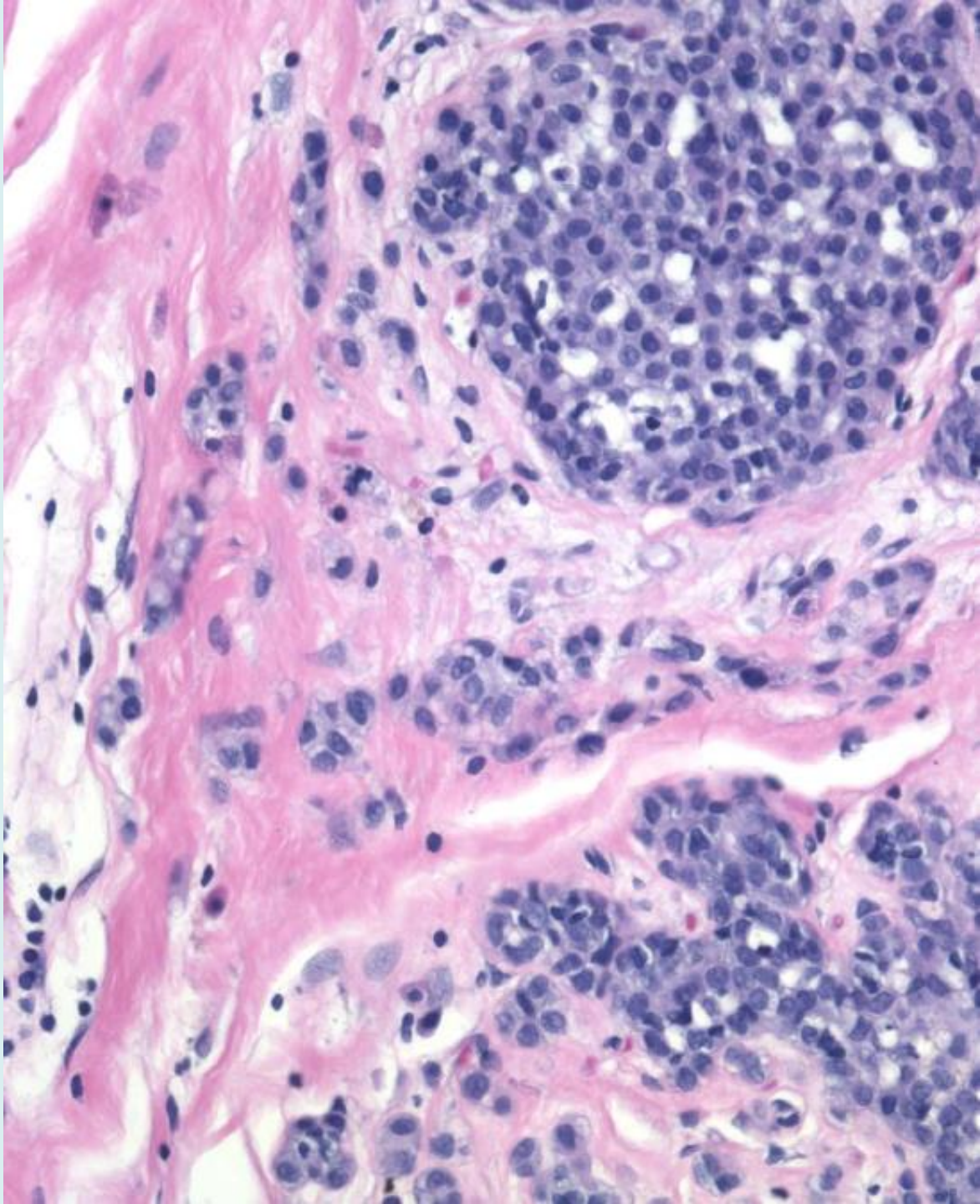
Myofibroblast cross-reactivity of myoepithelial cell markers

SMA	+++
Calponin	++
SMMHC	+
p63	-

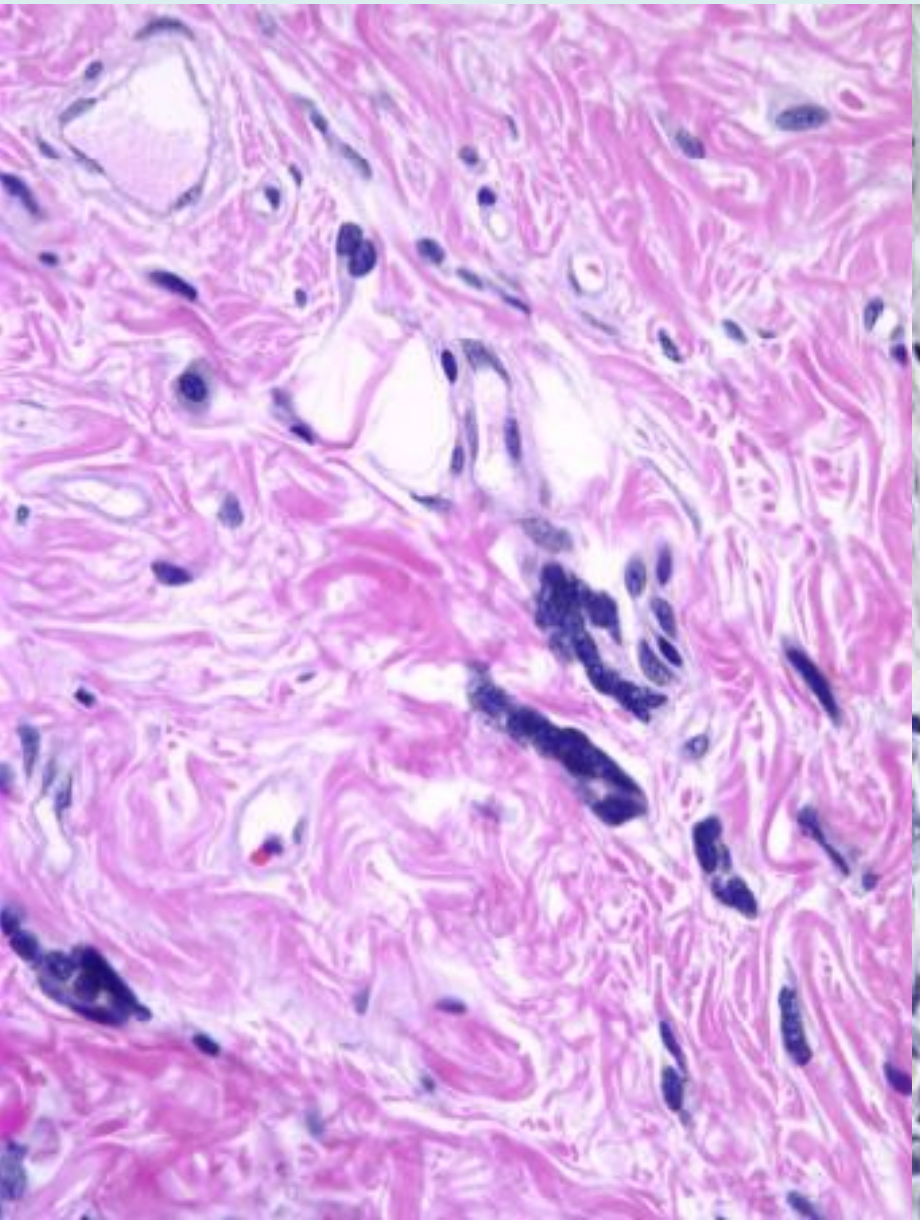


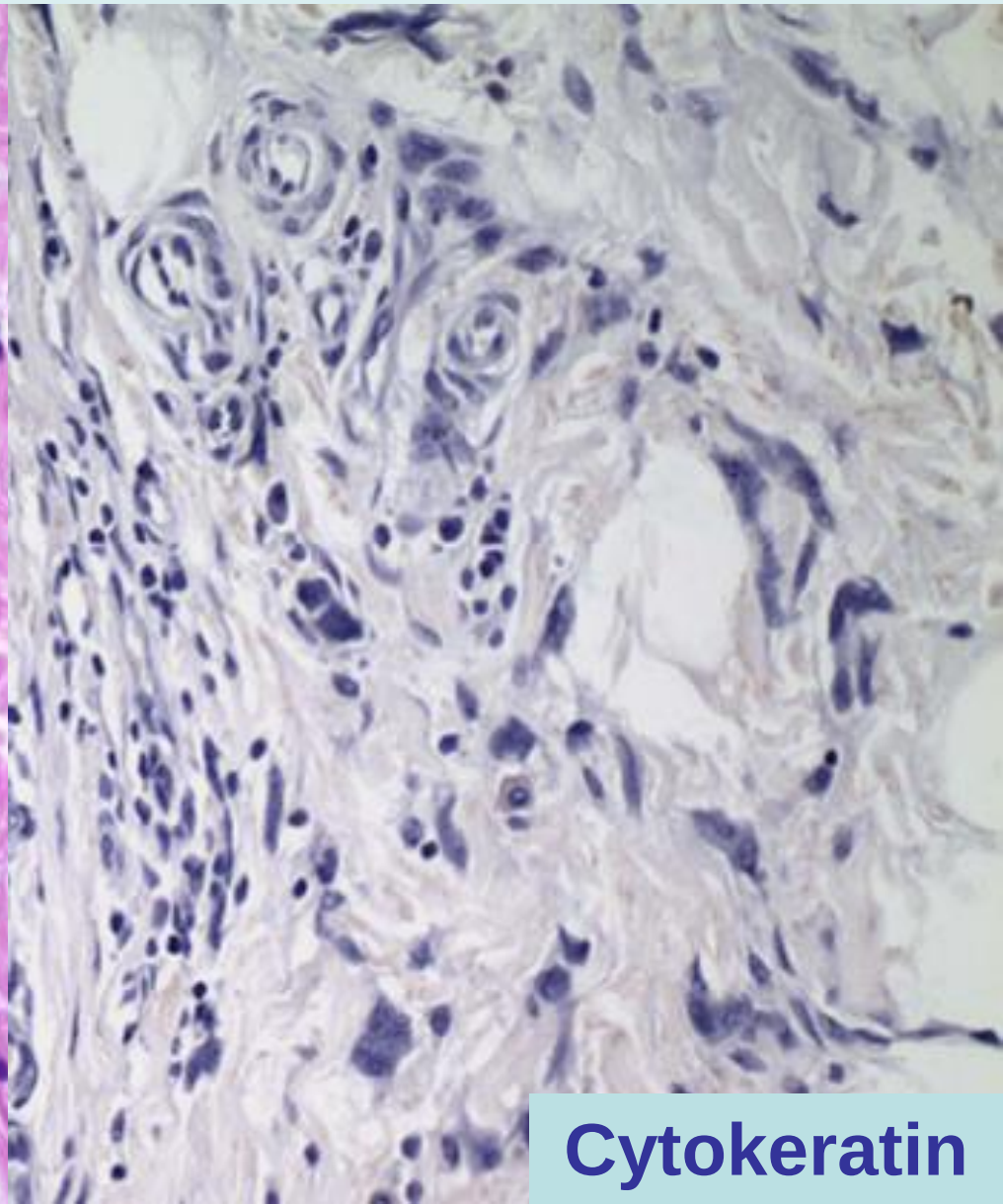
A HMW-CK paired with 2 myoepithelial cell markers is critical

Lobular carcinoma cells invade the interlobular collagenous stroma



Multinucleated stromal giant cells





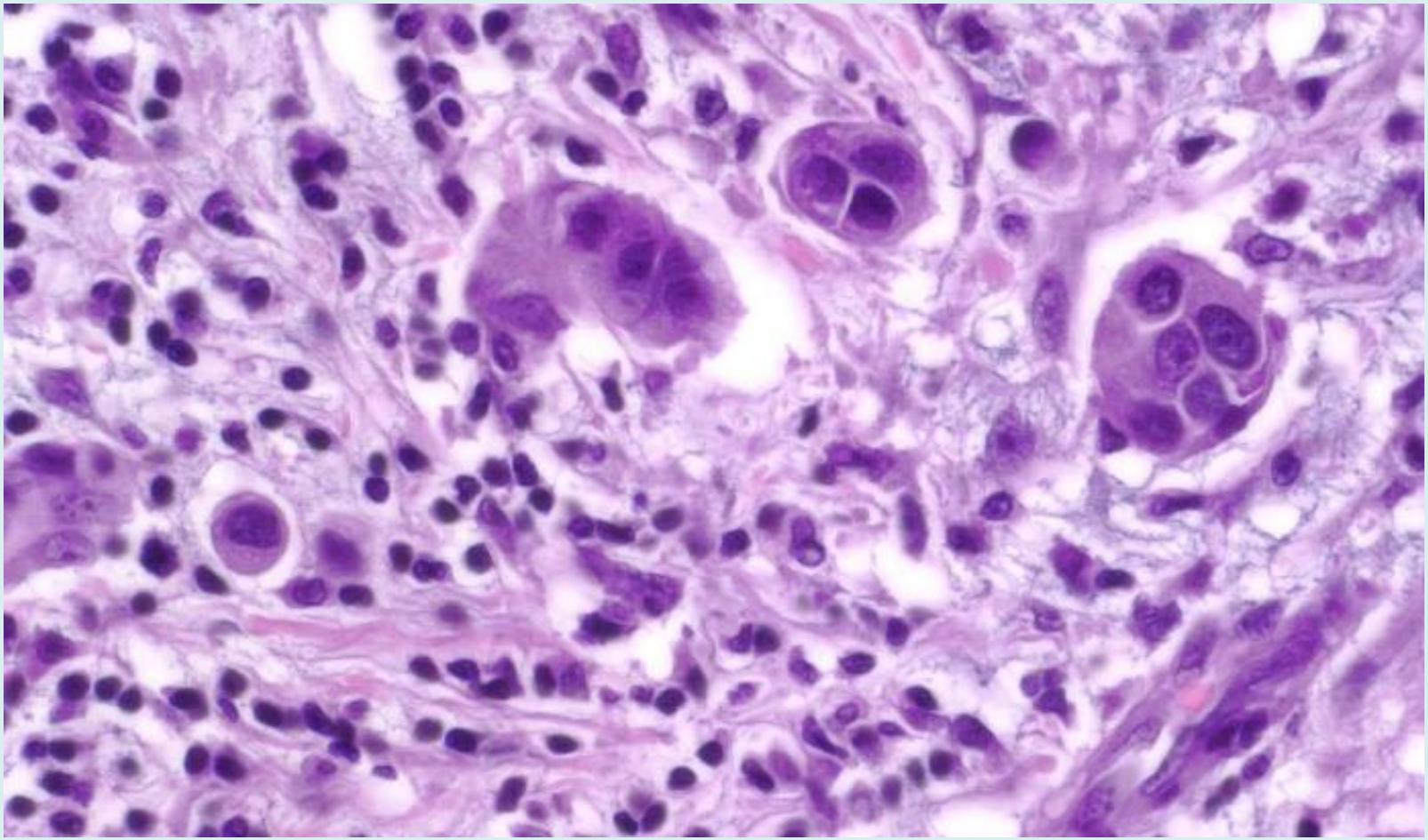
Cytokeratin

Clinical significance of microinvasion

- Studies in the past:
  - small numbers
  - varying definitions
  - varying degrees of tissue sampling
- No clear differences from pure DCIS
- Clinical significance is unclear

Single cells in the stroma: what do they mean?

De Mascarel, Cancer 2002; 94:2134



Axillary LN involvement and 10 yrs outcome

	#pts	%node+
DCIS	722	1.4%
DCIS + single cells in stroma	72	0

De Mascarel, Cancer, 2002

	DDFS	OS
DCIS	98%	96.5%
DCIS + single cells in stroma	97%	96.3%

Single cells in the stroma: what do they mean?

- **No evidence** that:
  - Is associated with axillary LN +
  - Has adverse clinical outcome
- In practice, we consider them **microinvasion**

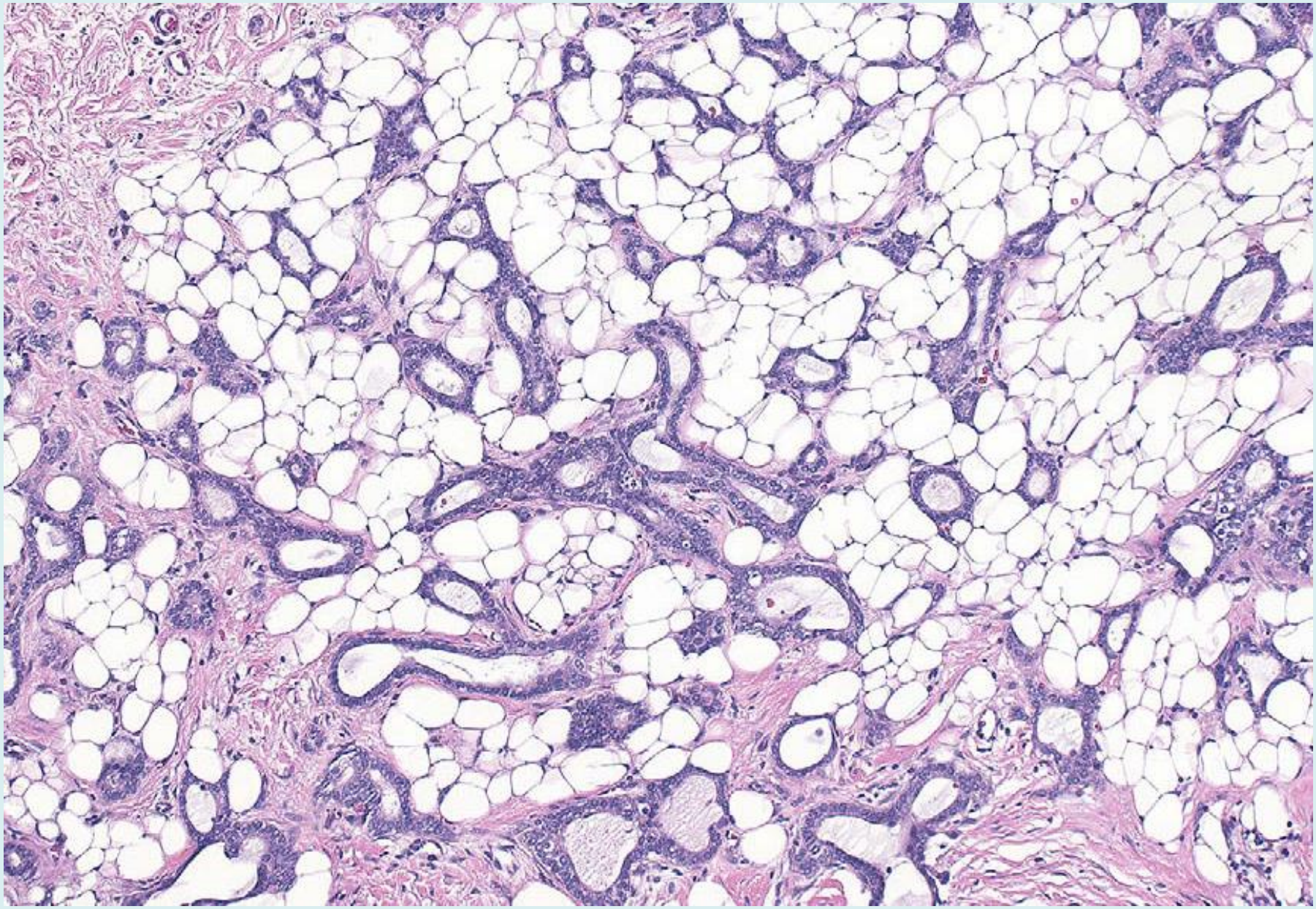
- By using **AJCC definition** pts will likely have:
  - Very low rate of ALNM
  - Cure rate approaching 100% with good local treatment
- Goal: **identify** this subset of **pts**

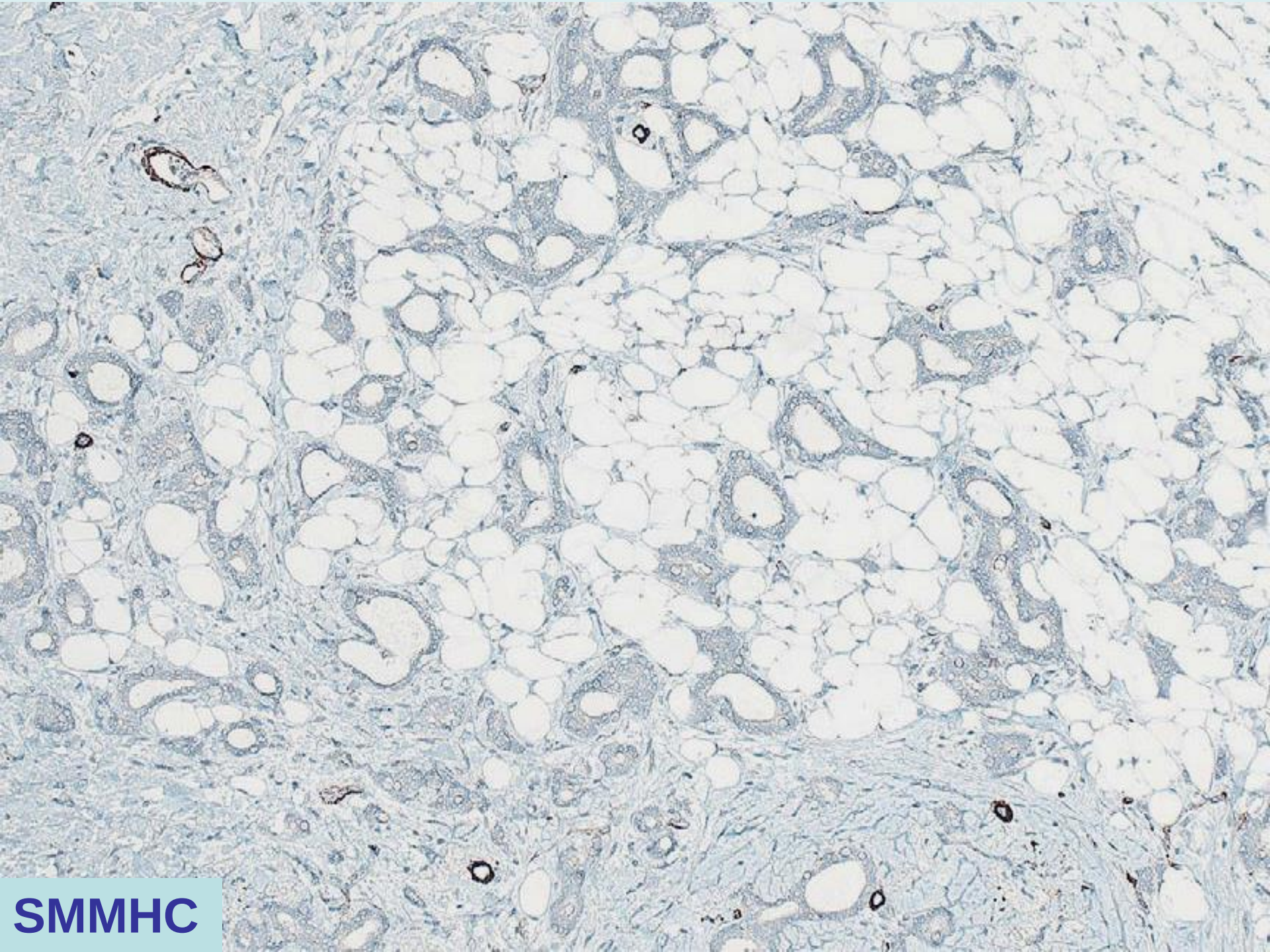
Invasive Carcinoma that Mimics Benign

Useful clues

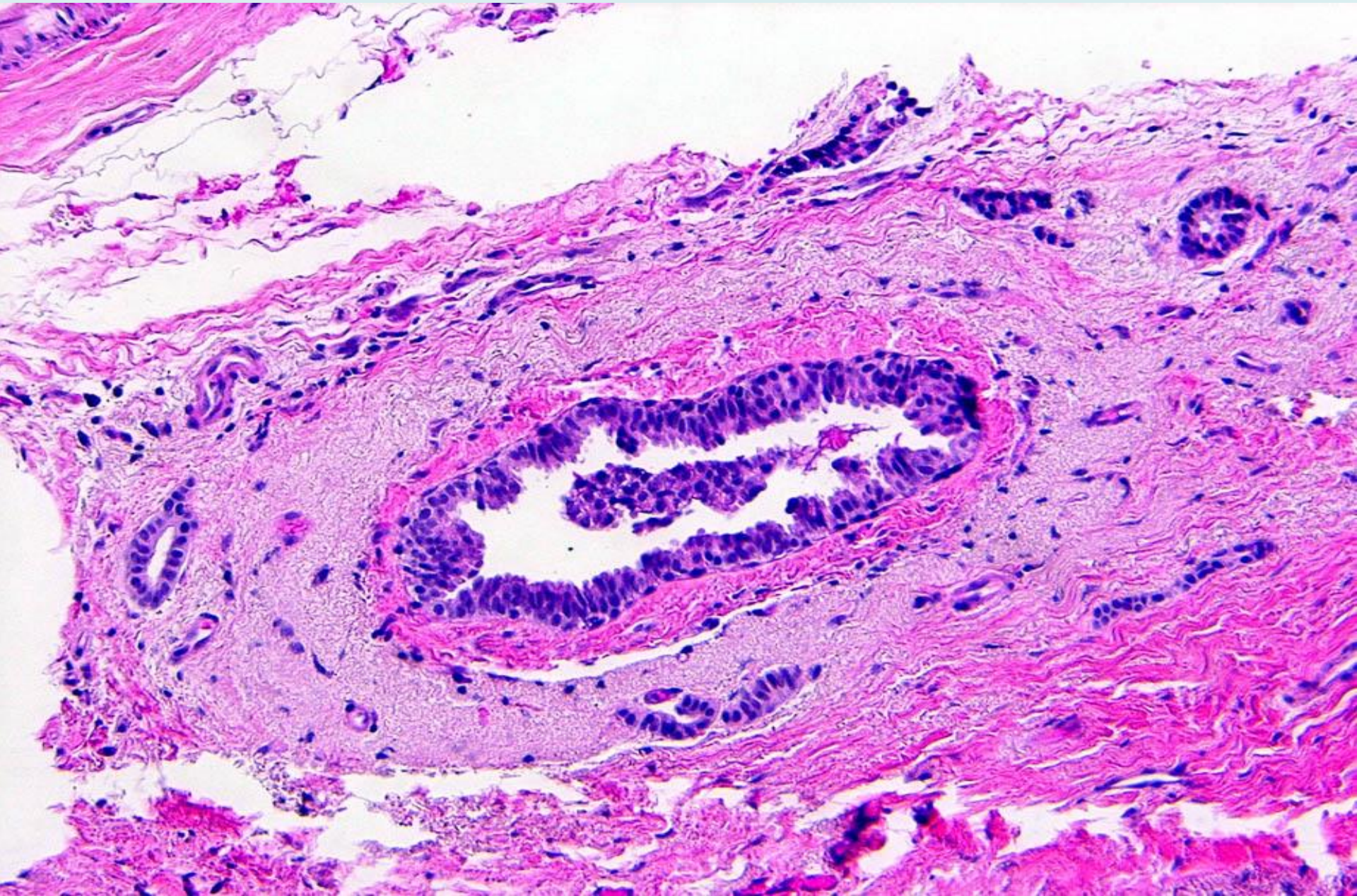
- Glandular disarray
- Irregular tubules/glands of variable size/shape/orientation
- Infiltration around benign
- Open glandular lumina
- Lack of BM and myoepithelium
- Stromal hypercellularity
- Stromal desmoplasia

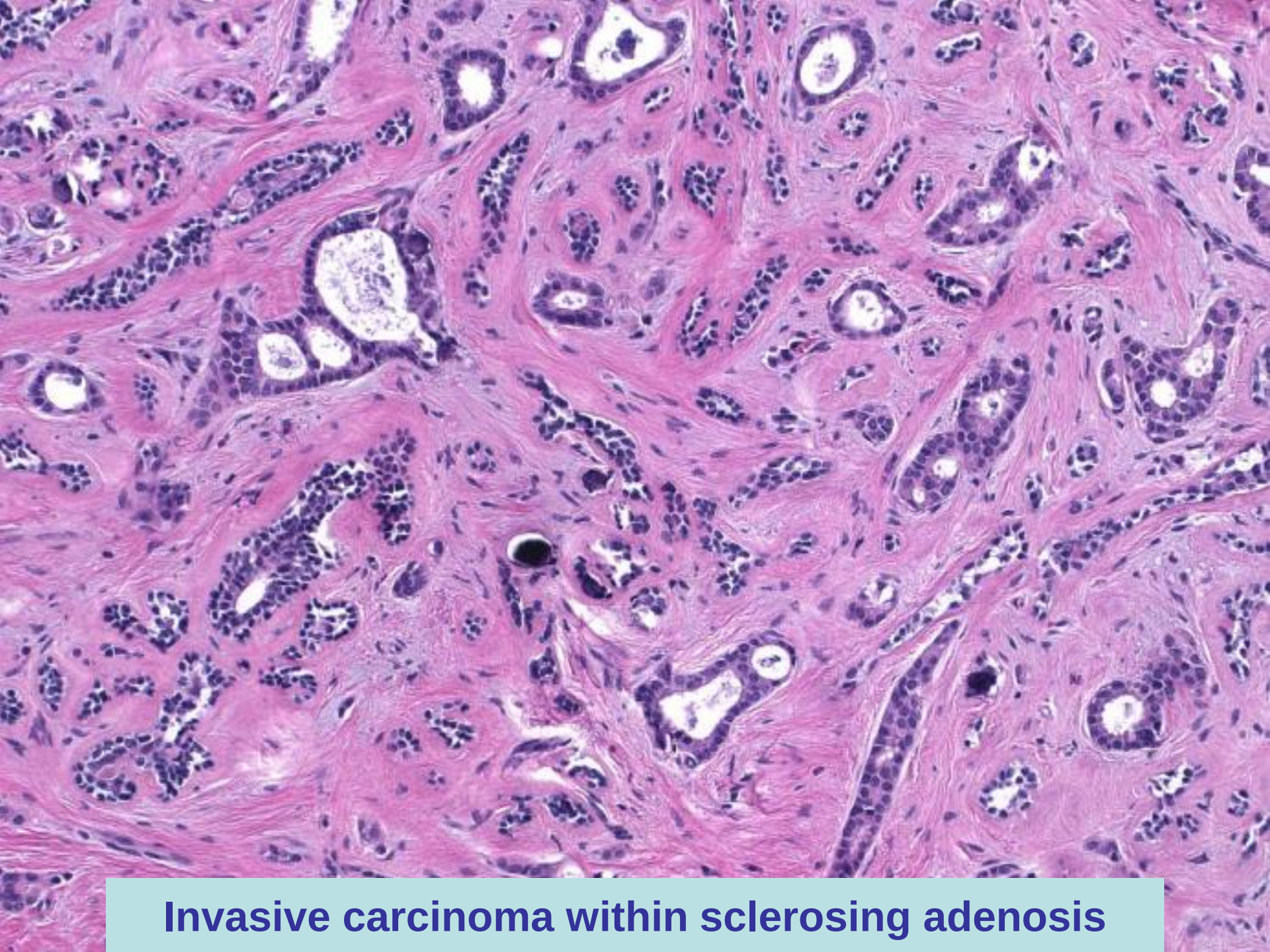
IDC mimicking benign adenosis



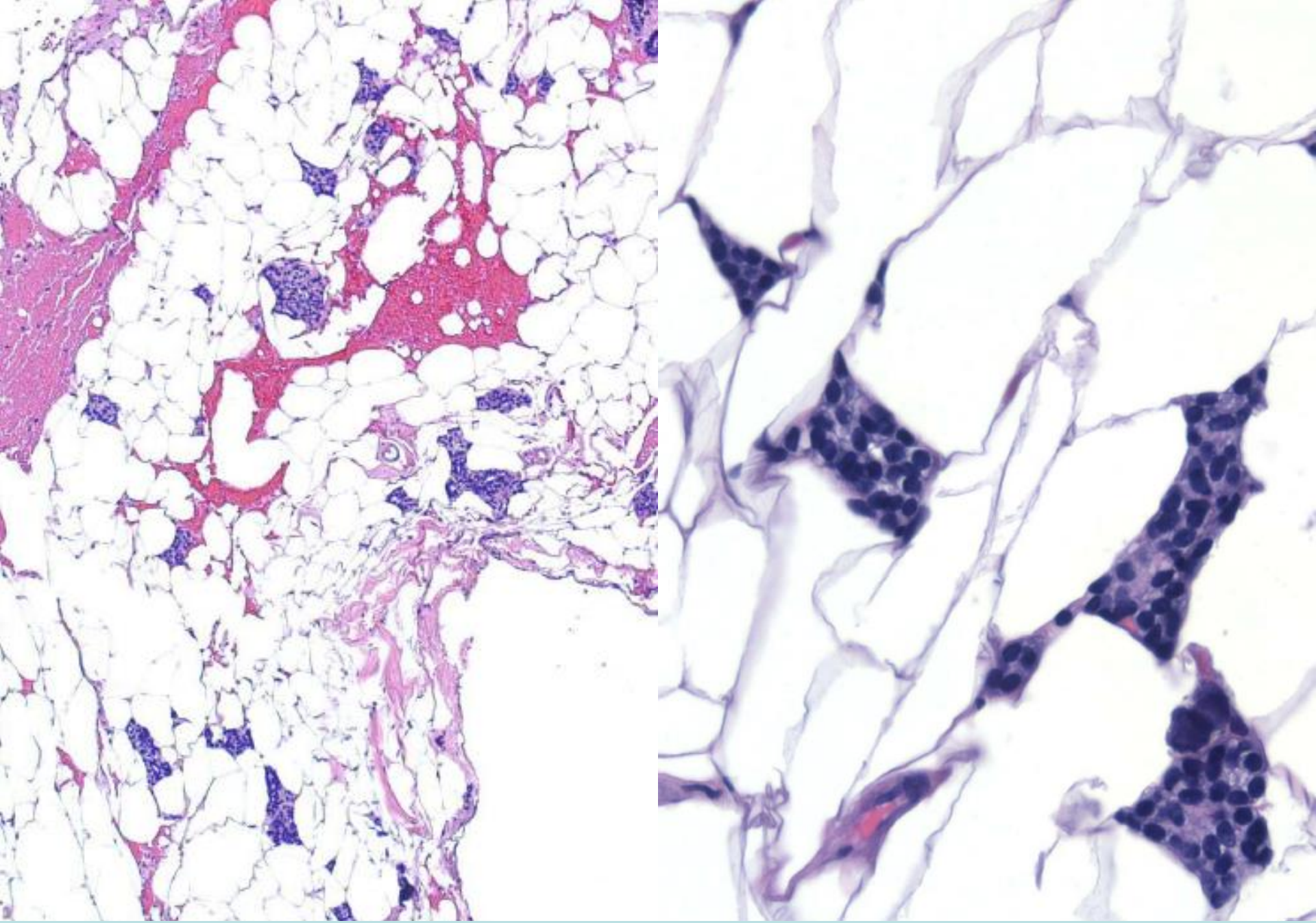

SMMHC

Invasive ductal carcinoma surrounding DCIS

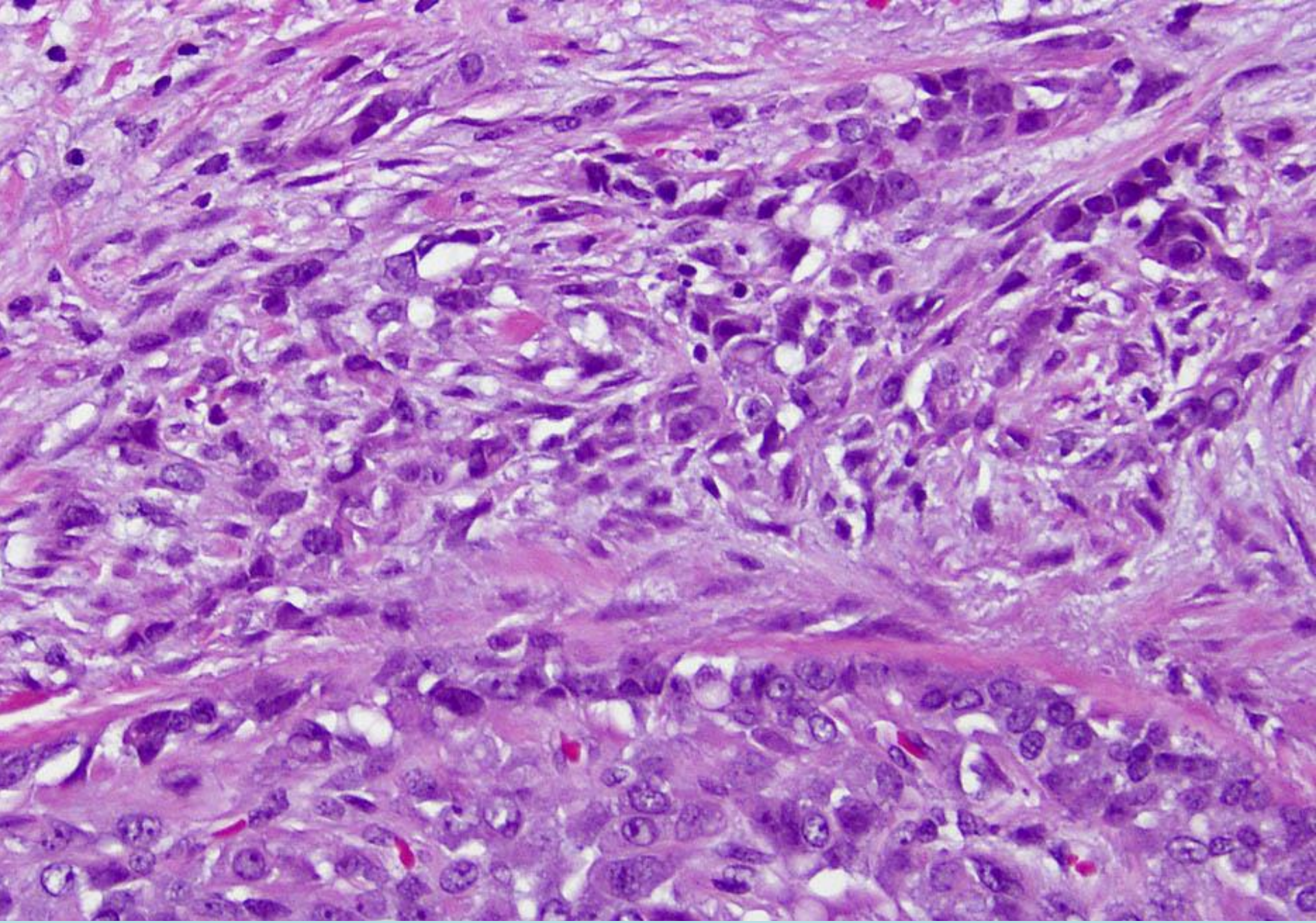




Invasive carcinoma within sclerosing adenosis



IDC mimics benign breast, but no BM and myoepithelium



Suspect ILC: Stromal hypercellularity and desmoplasia

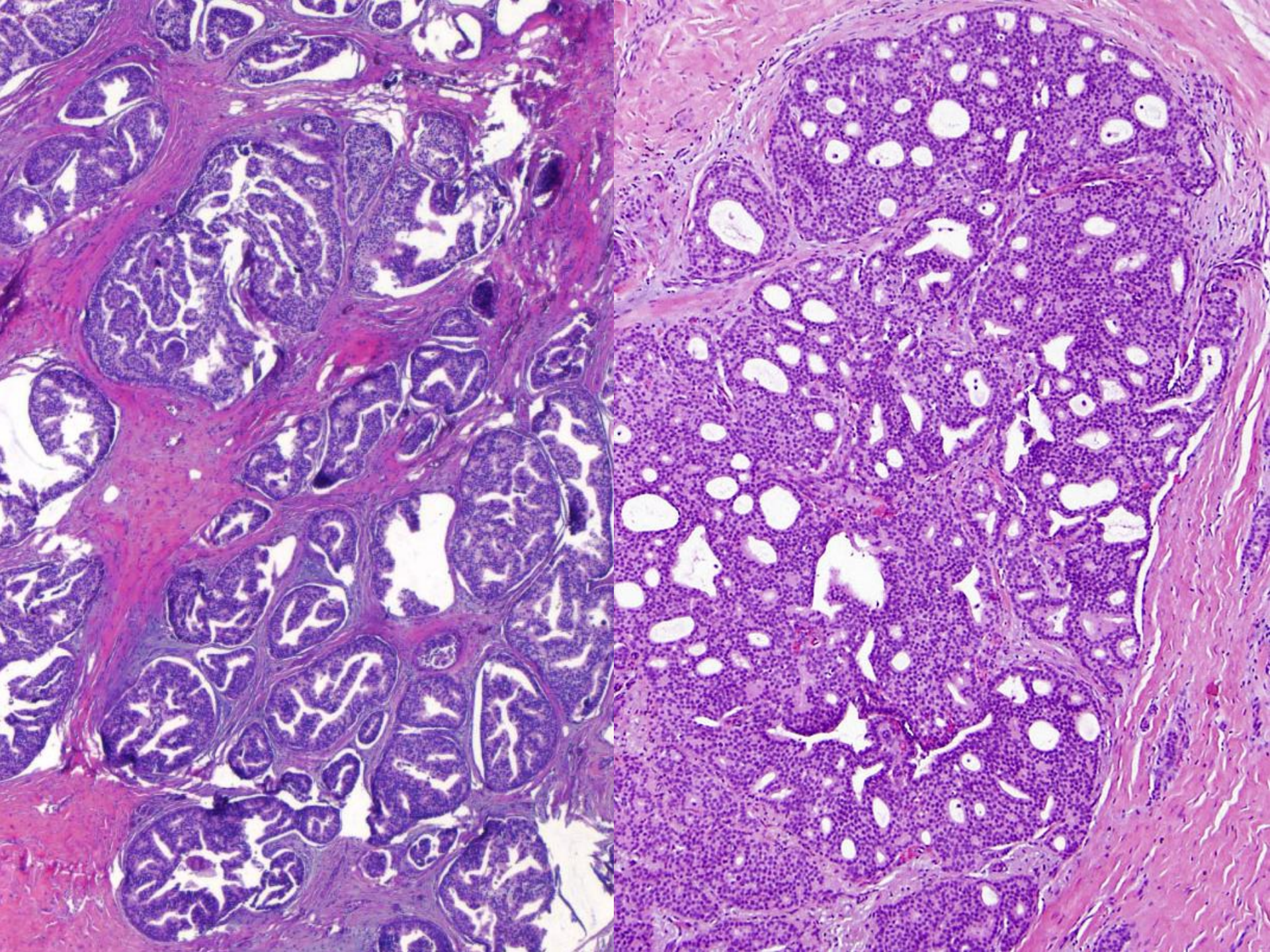
Invasive carcinoma that mimics in situ

Problematic patterns

- Nested invasion
- Blunt invasion
- Occlusive LVI

Clues for nested invasion

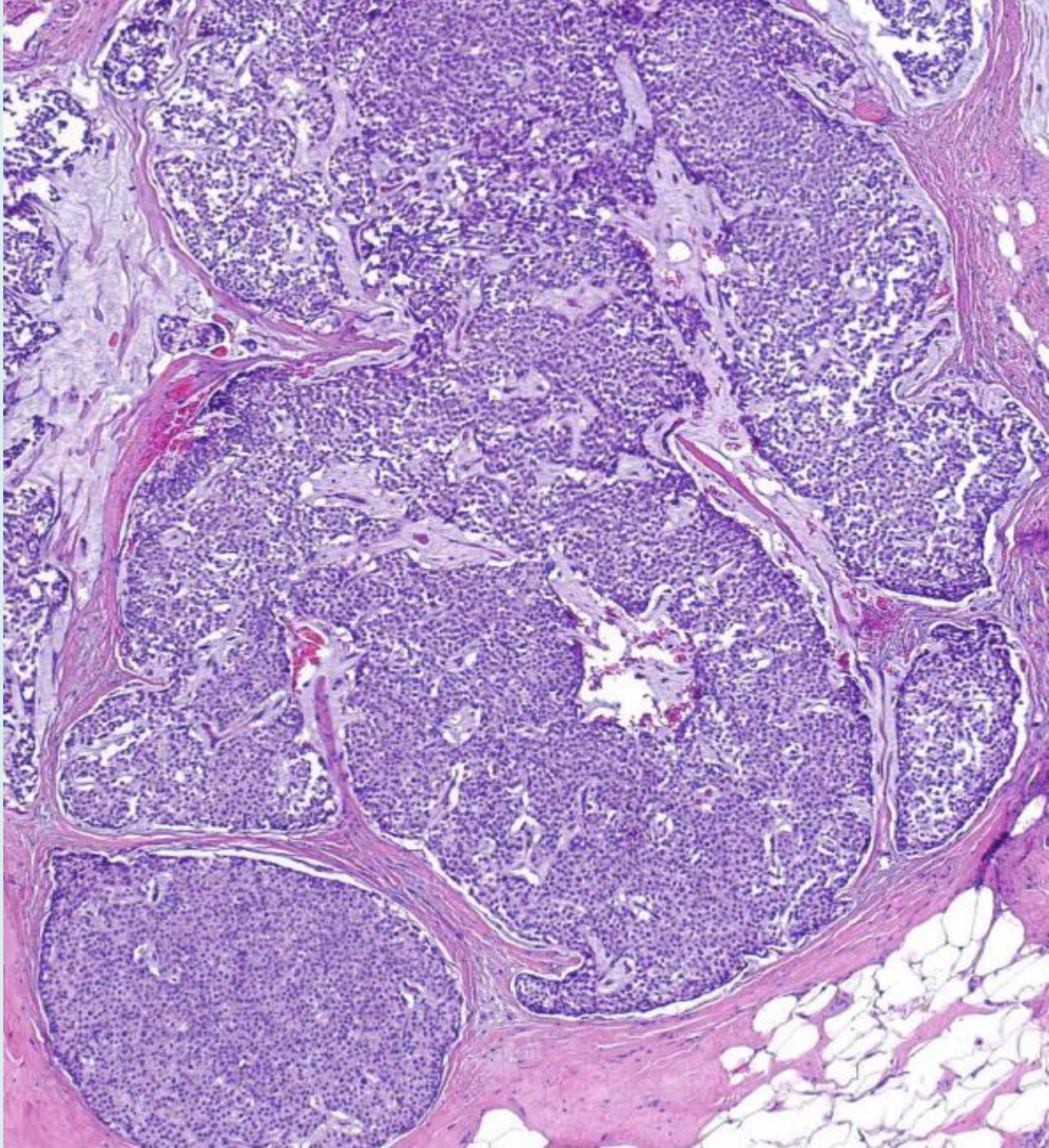
- Too confluent and/or haphazard distribution
- Large nests adjacent to completely normal lobules
- Irregularities in the contour of the nests
- Reactive stroma (if present)
- The following two pictures show how IDC can mimic DCIS



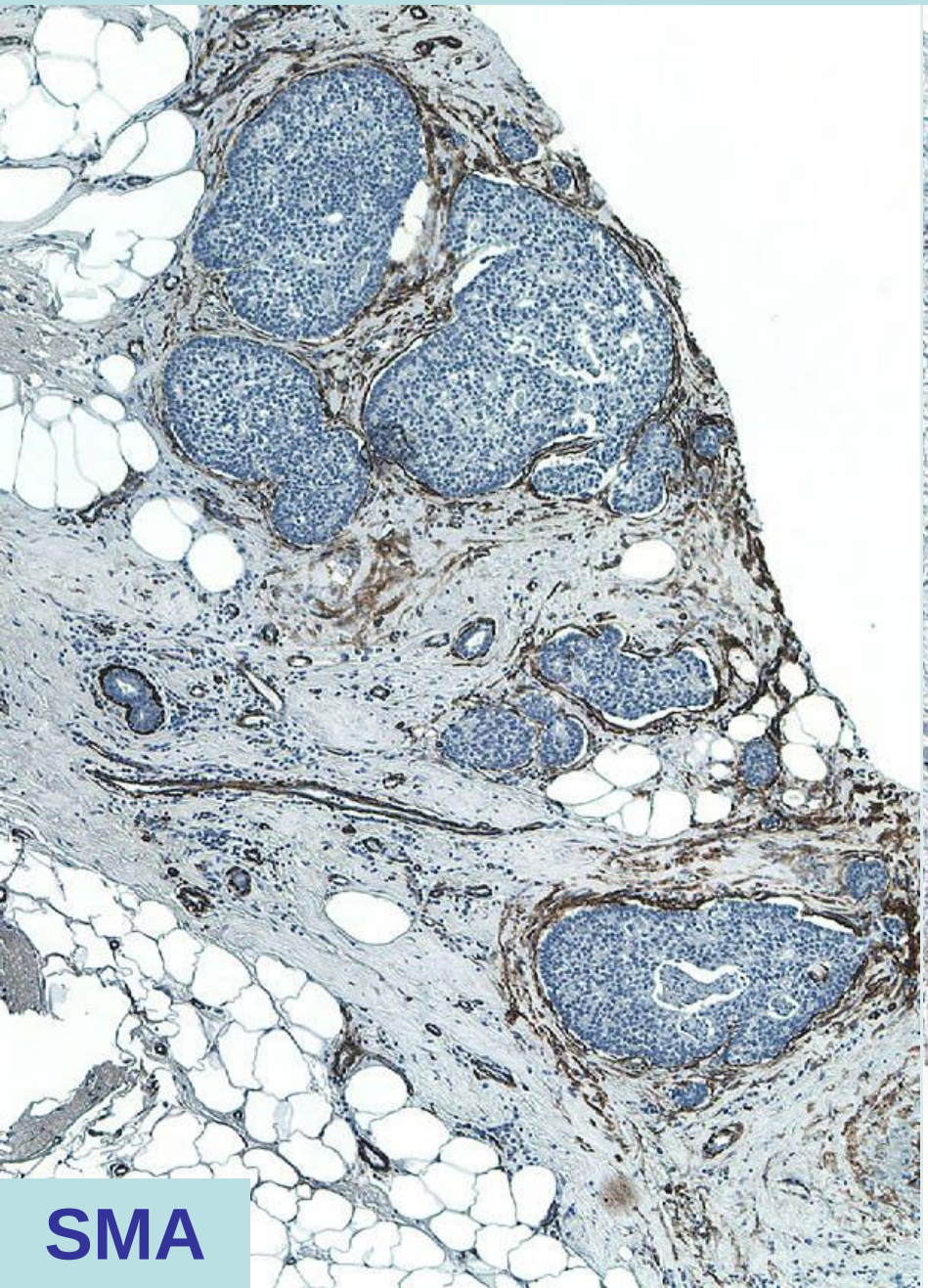
Clues for blunt invasion

- Common in solid papillary carcinoma and papillary carcinoma
- Too large nests
- Discontinuity along the periphery of the nests
- Fat, collagen, large vessels or benign glands entrapped

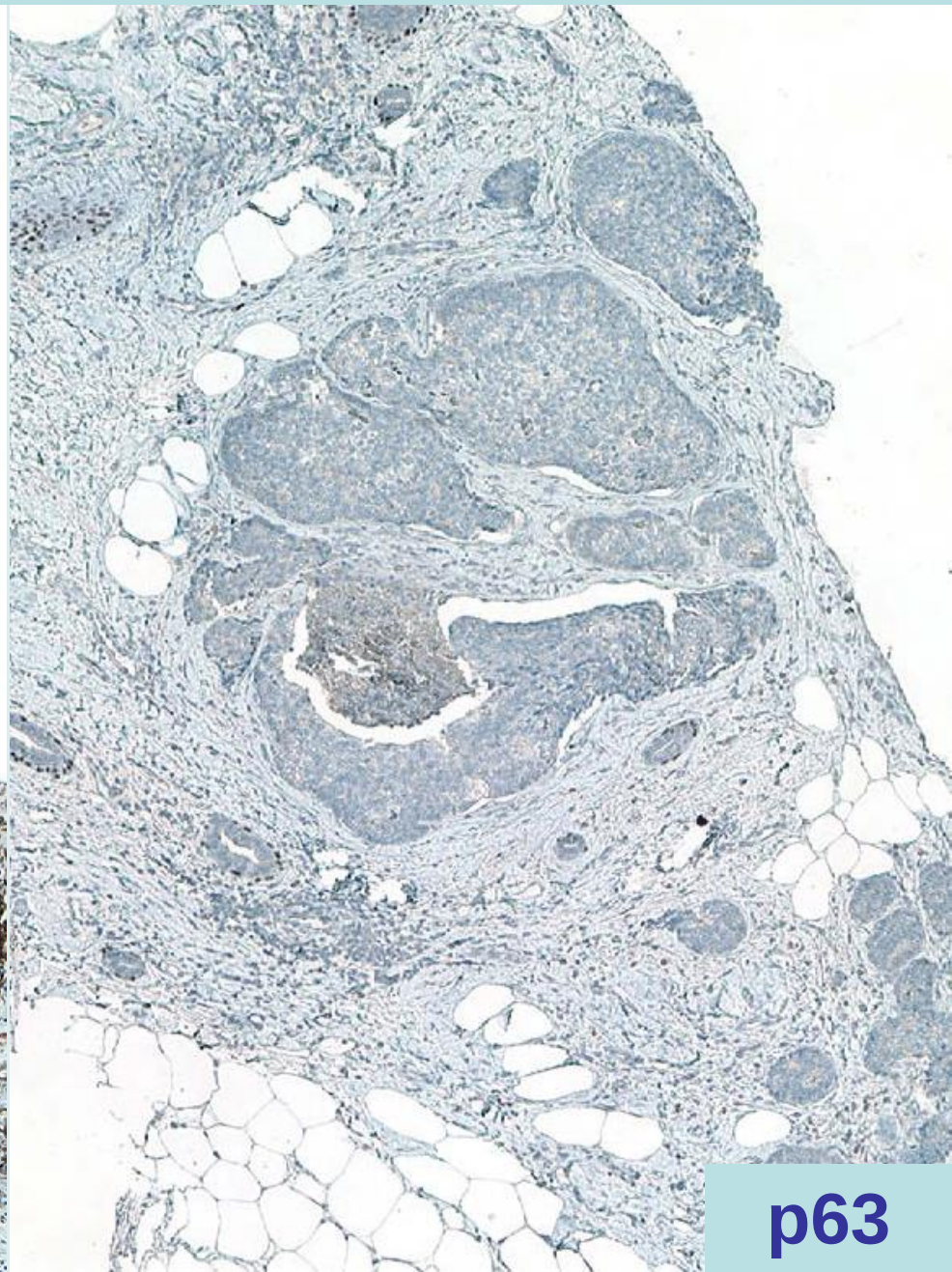
Large size of the nests raises concern of blunt invasion



Case initially misdiagnosed as DCIS

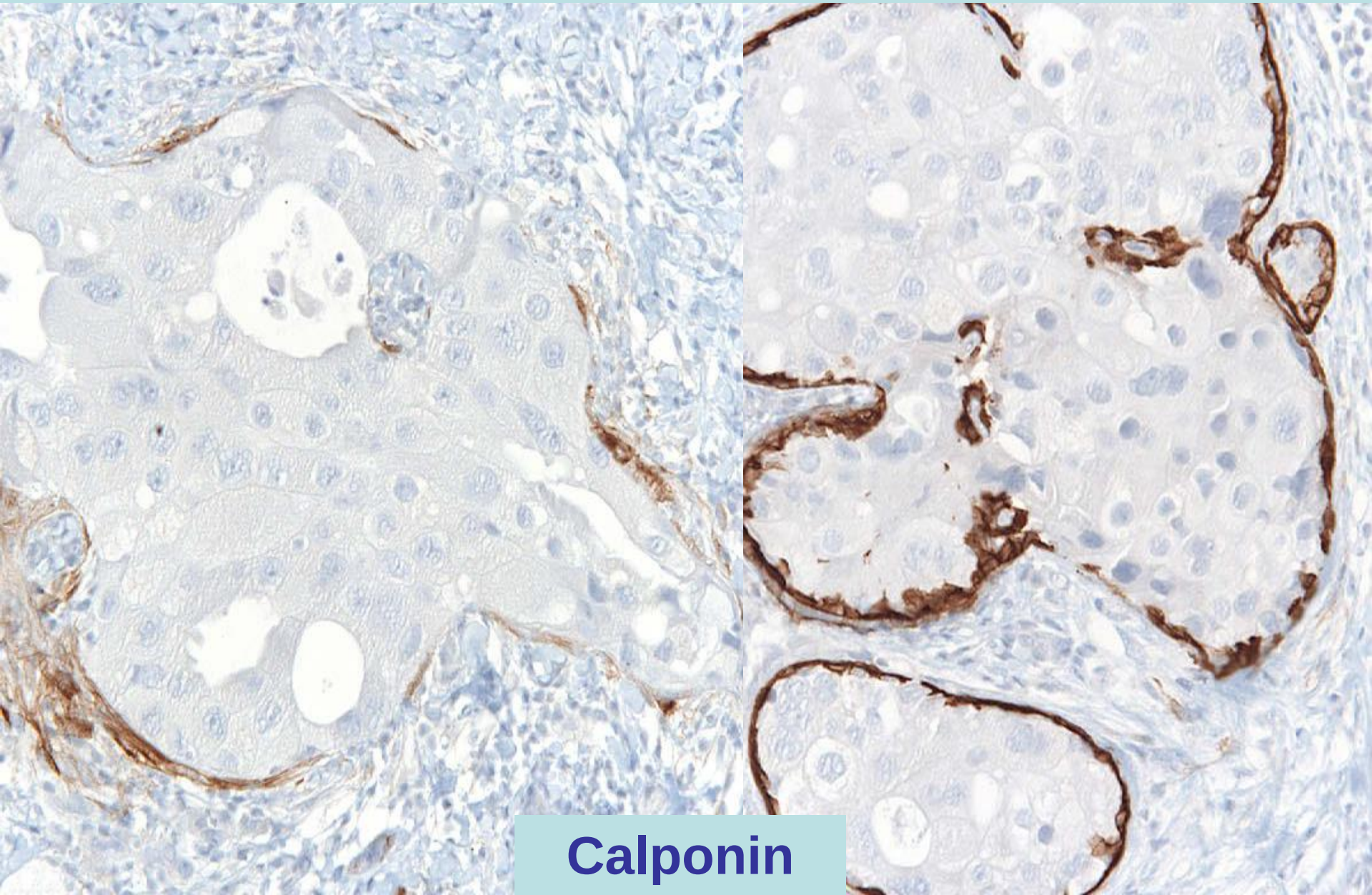


SMA



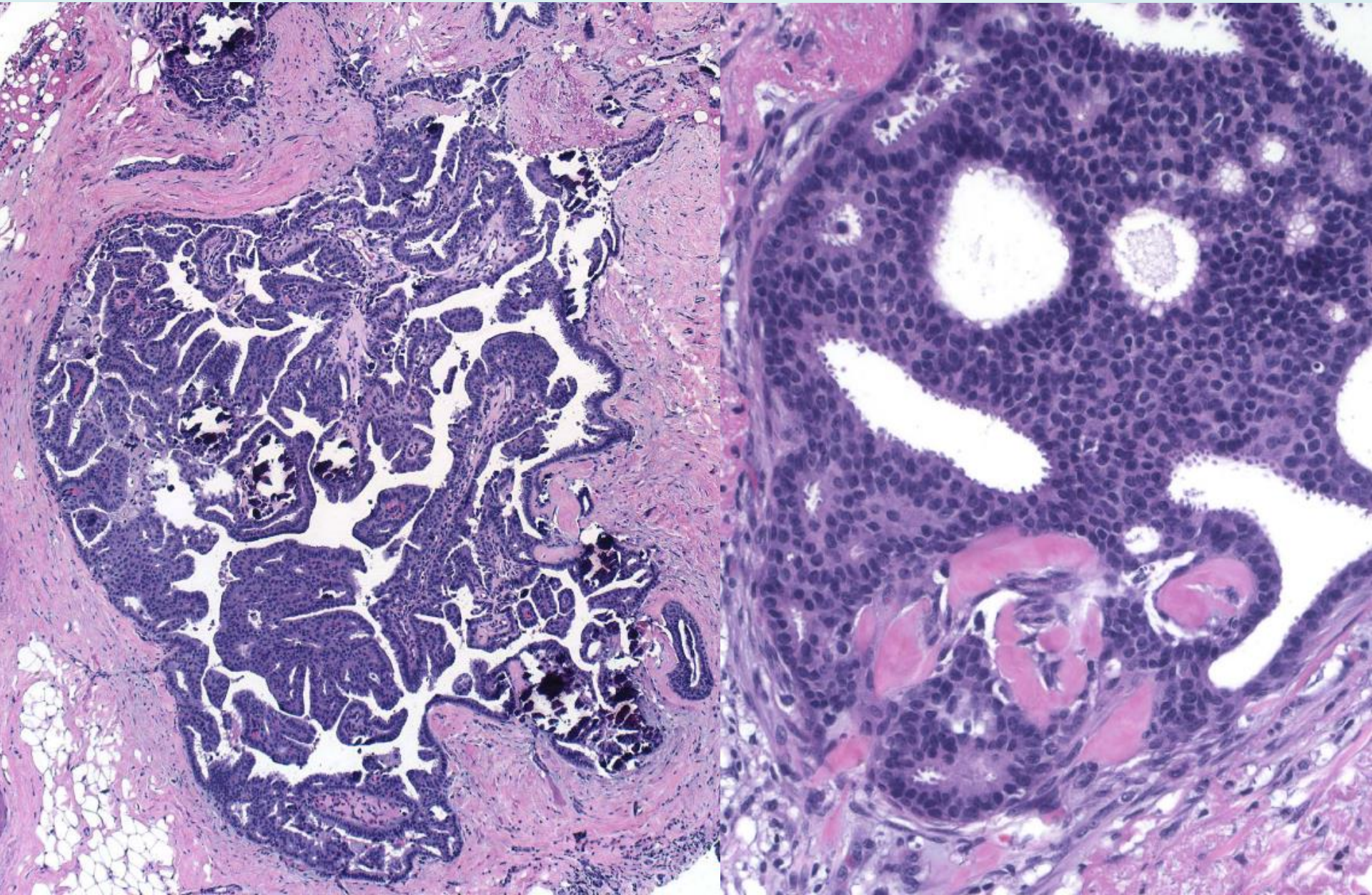
p63

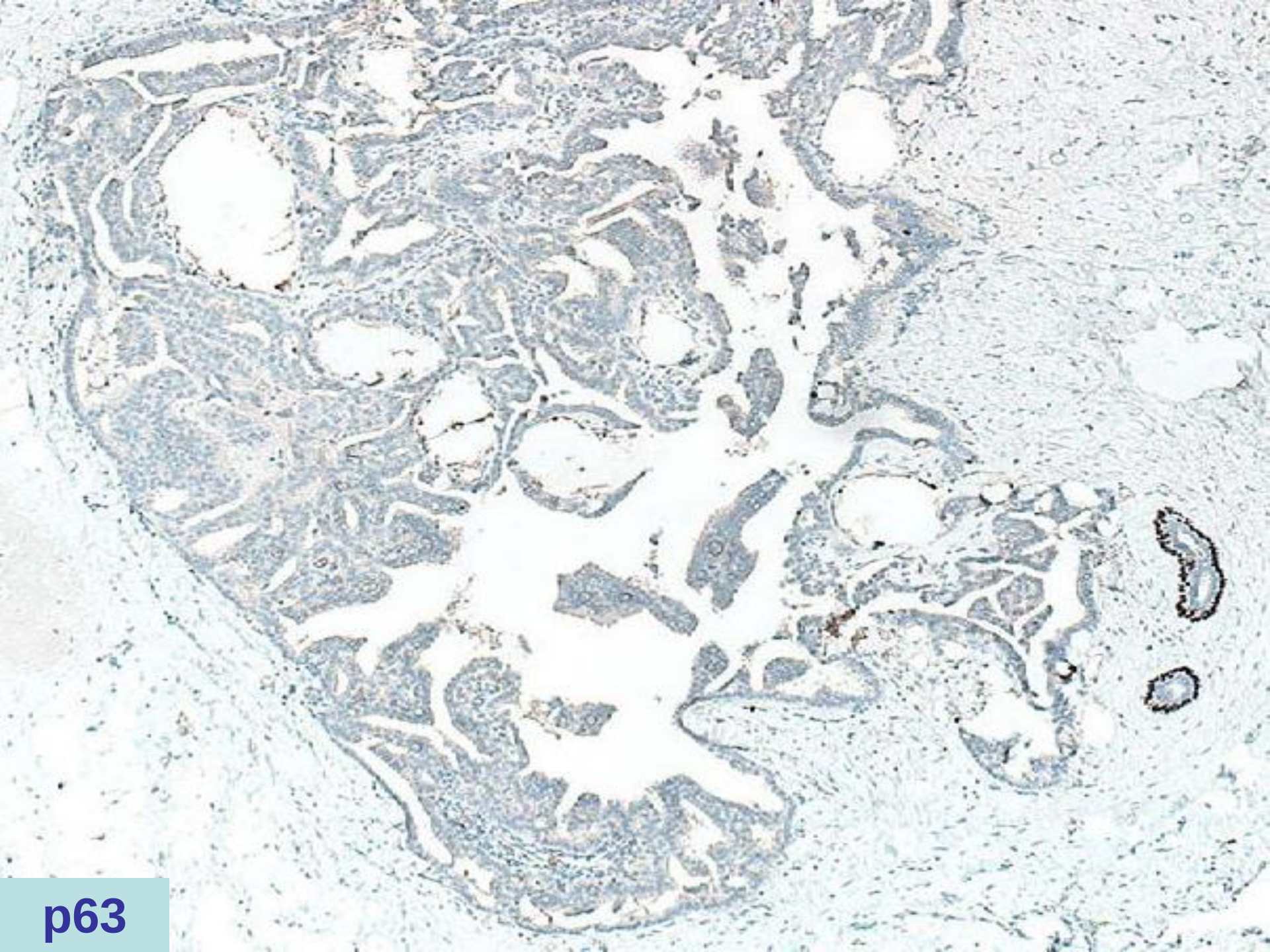
IDC vs DCIS



Calponin

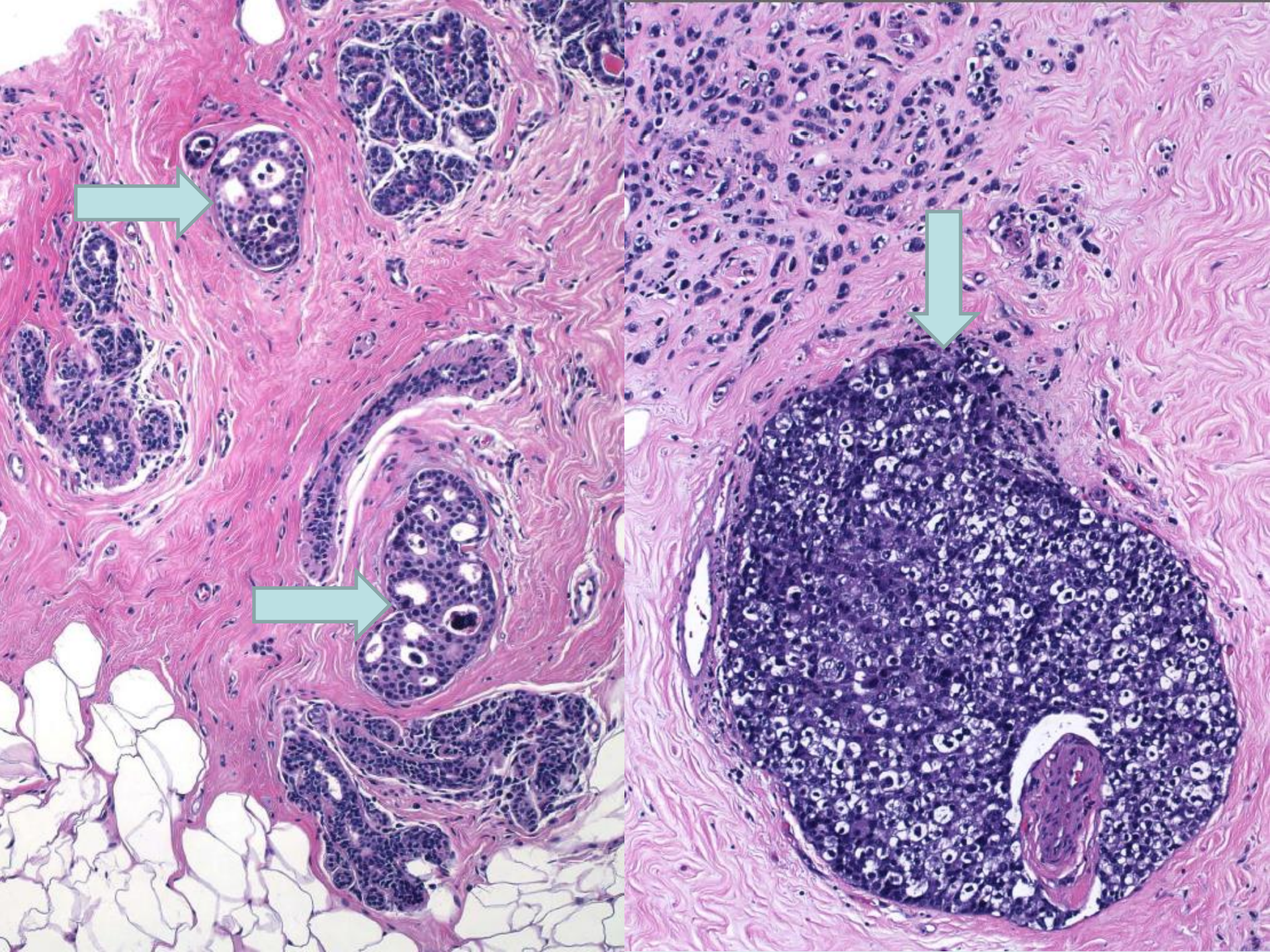
Invasive Papillary Carcinoma

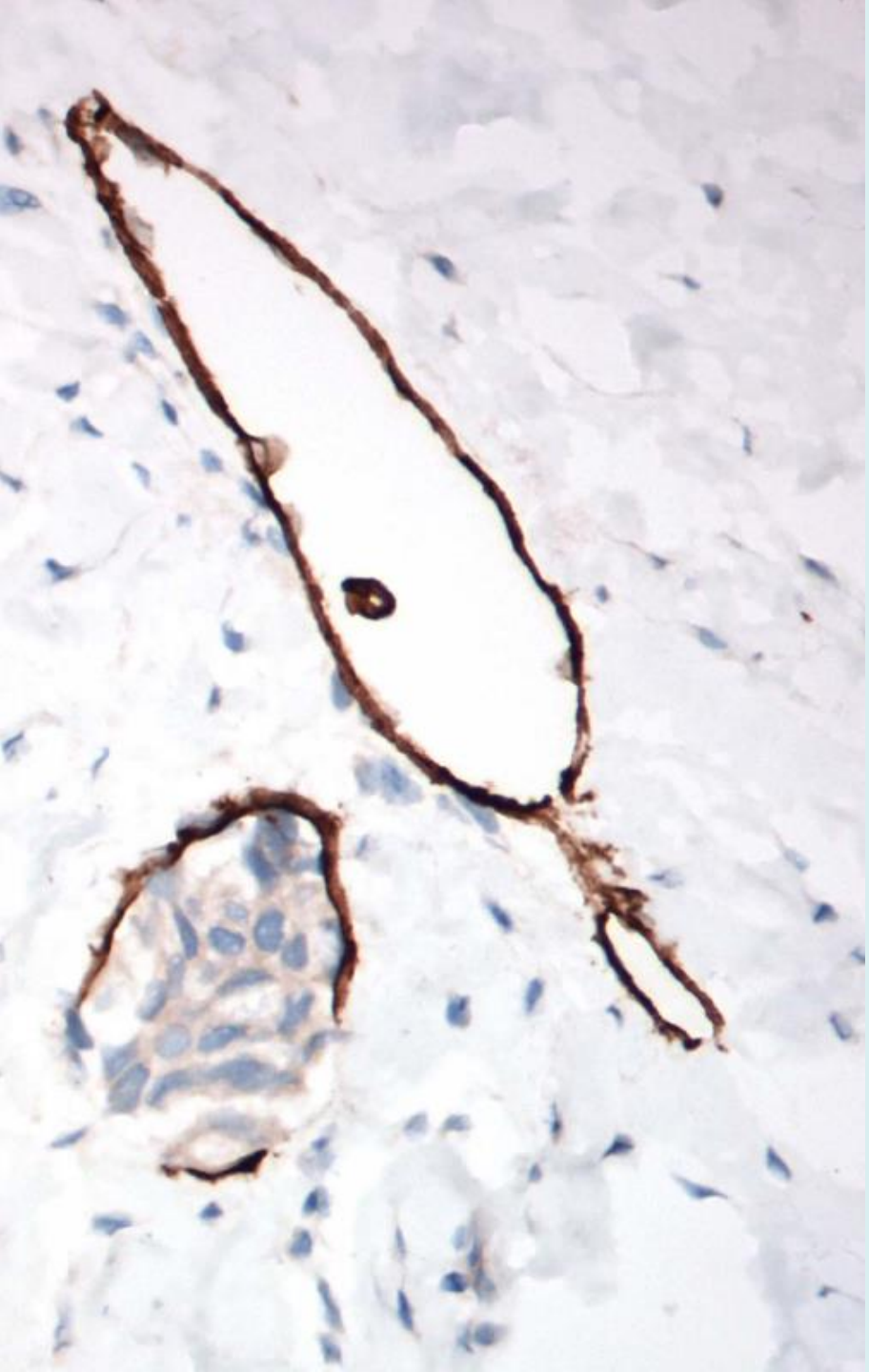



p63

Clues for occlusive LVI

- Buckshot distribution
- In arteries and veins
- Carcinoma associated with vascular bundle
- D2-40 + and p63 –
- **!!** Issue: foci near margins
- The next 2 pictures show occlusive LVI mimicking DCIS





D2-40

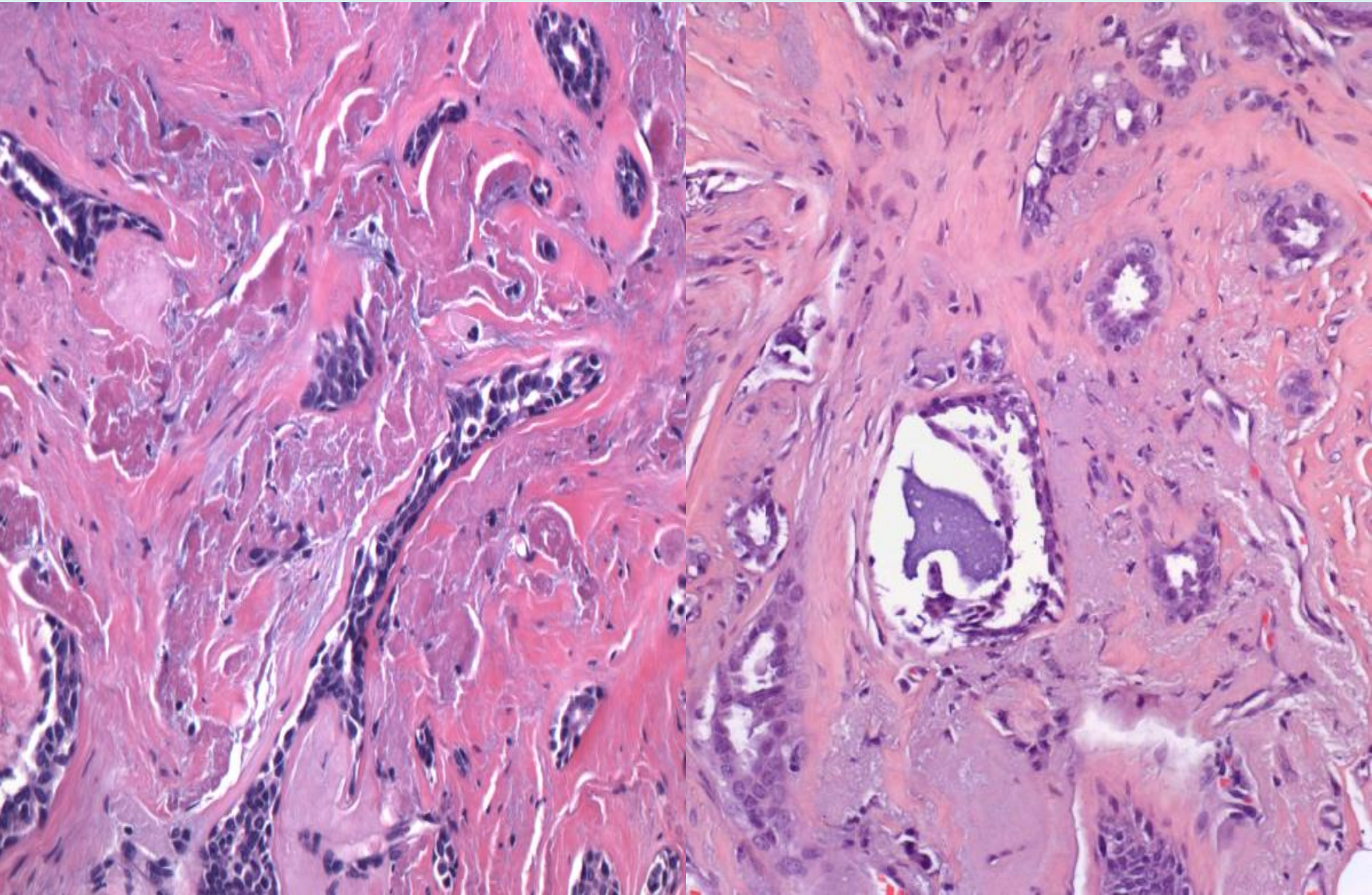
- Ab to human podoplanin
- Used to identify lymphatic vessels
- Less myofibroblast staining
- **!!** DCIS or LCIS with retraction could be misinterpreted as LVI (and viceversa)

Benign lesions that mimic invasive carcinoma

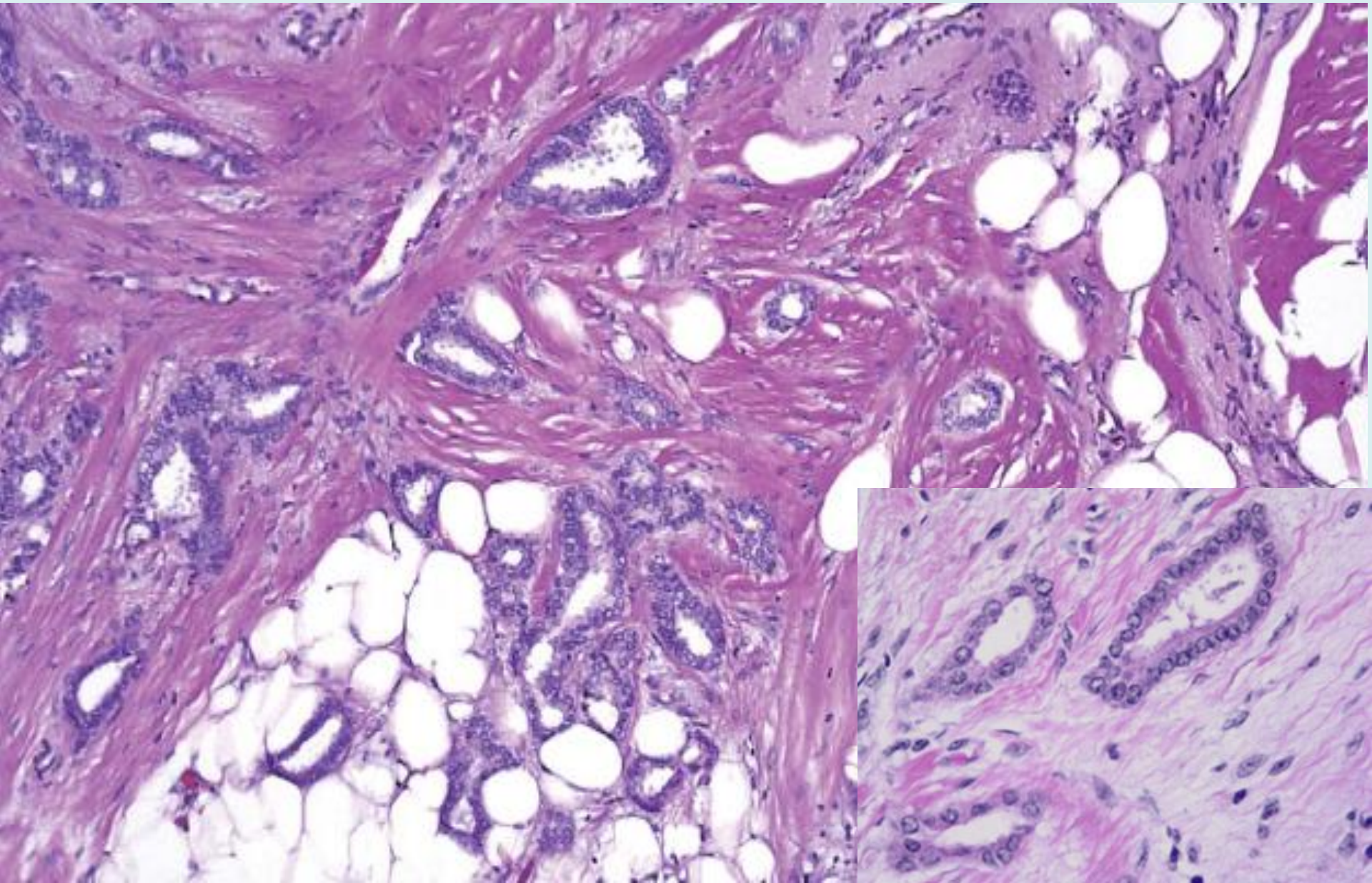
Sclerosing and pseudoinvasive lesions

- Radial scar/complex sclerosing lesion
- Sclerosing adenosis
- Involvement of benign lesions by CIS
- Microglandular adenosis (MGA)
- Multinucleated stromal giant cells
- Mucocele-like lesions
- Sclerosing papillary lesions

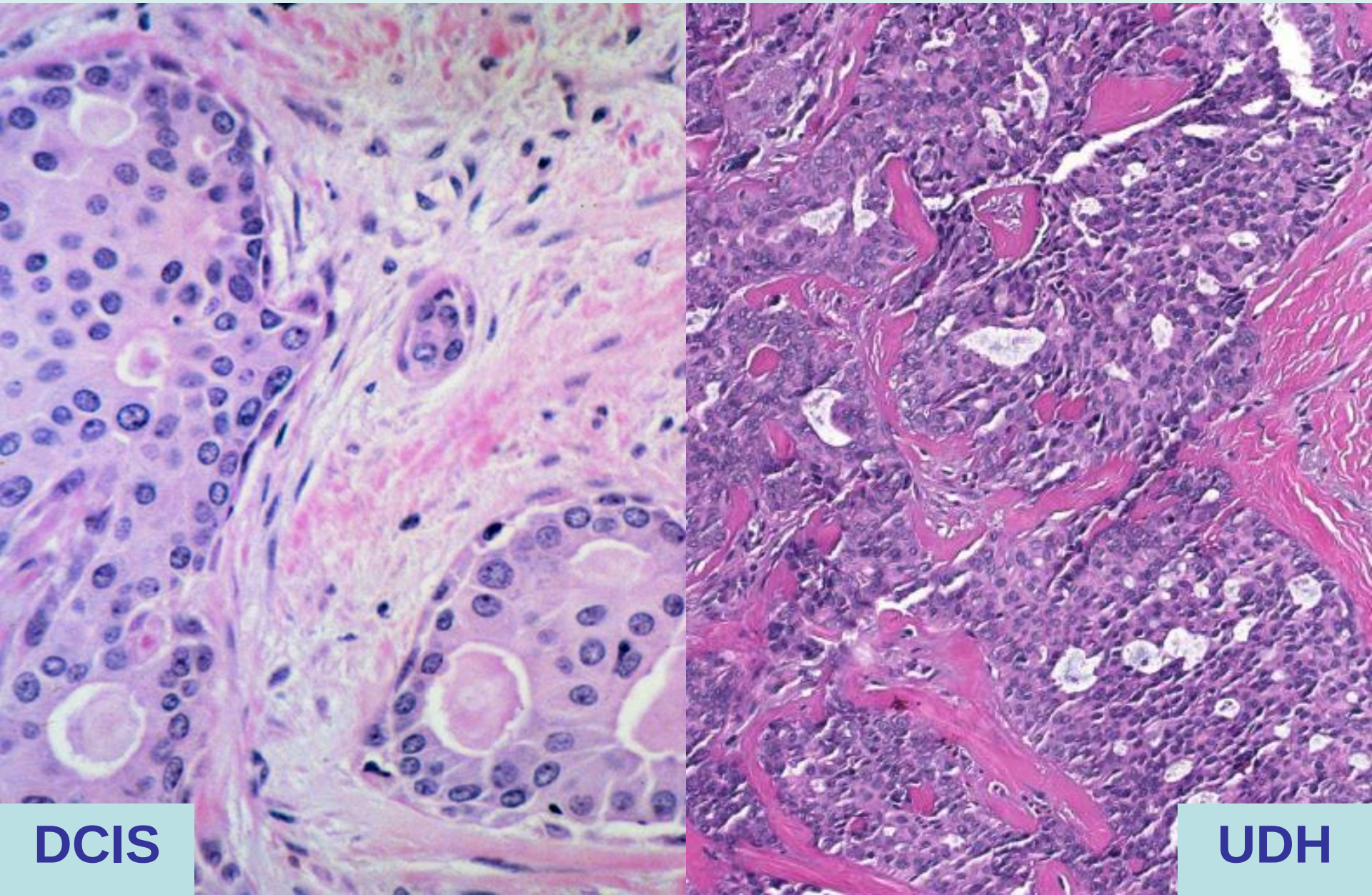
Radial Scar Nidus



Tubular Carcinoma



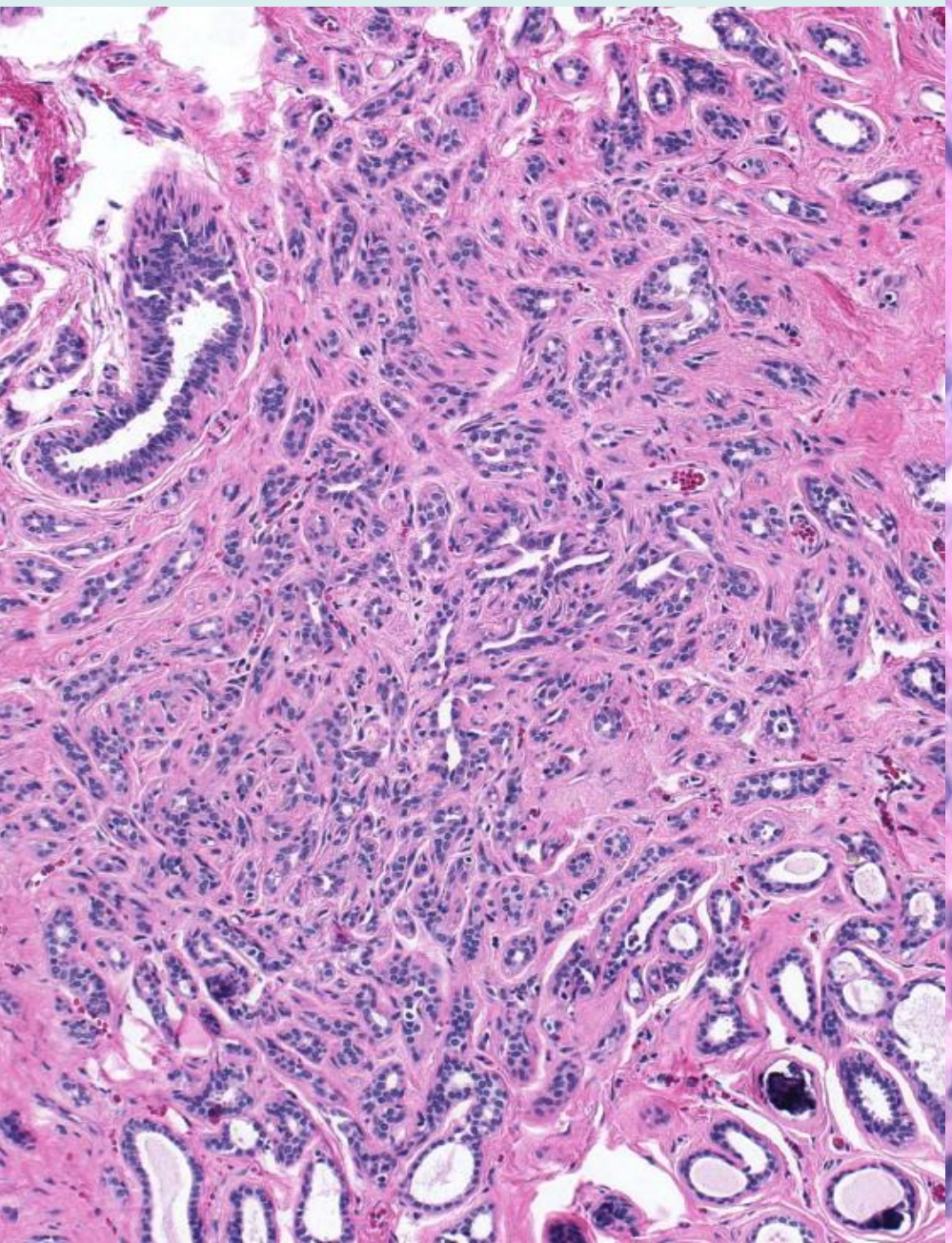
Radial Scar Nidus

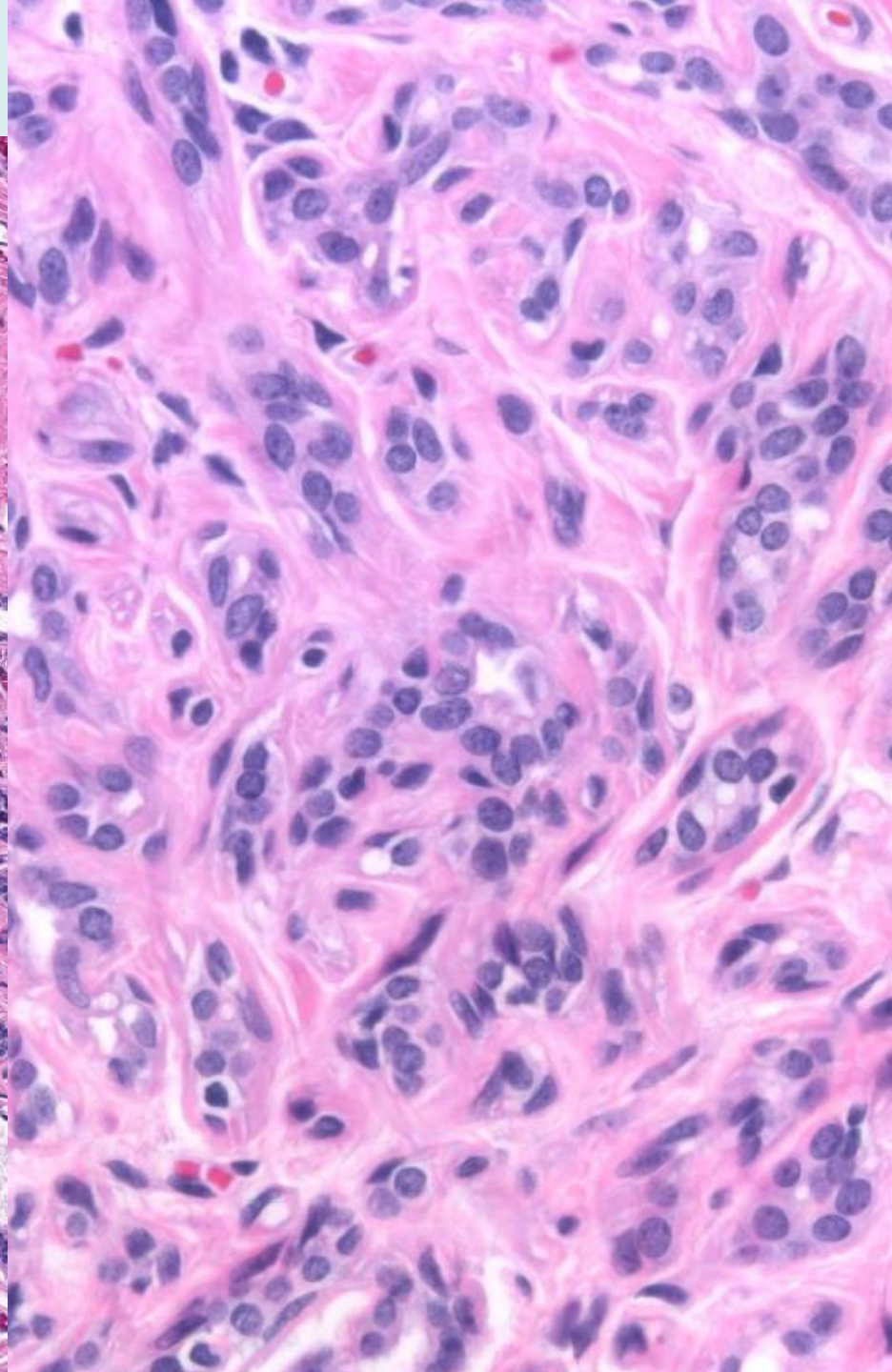


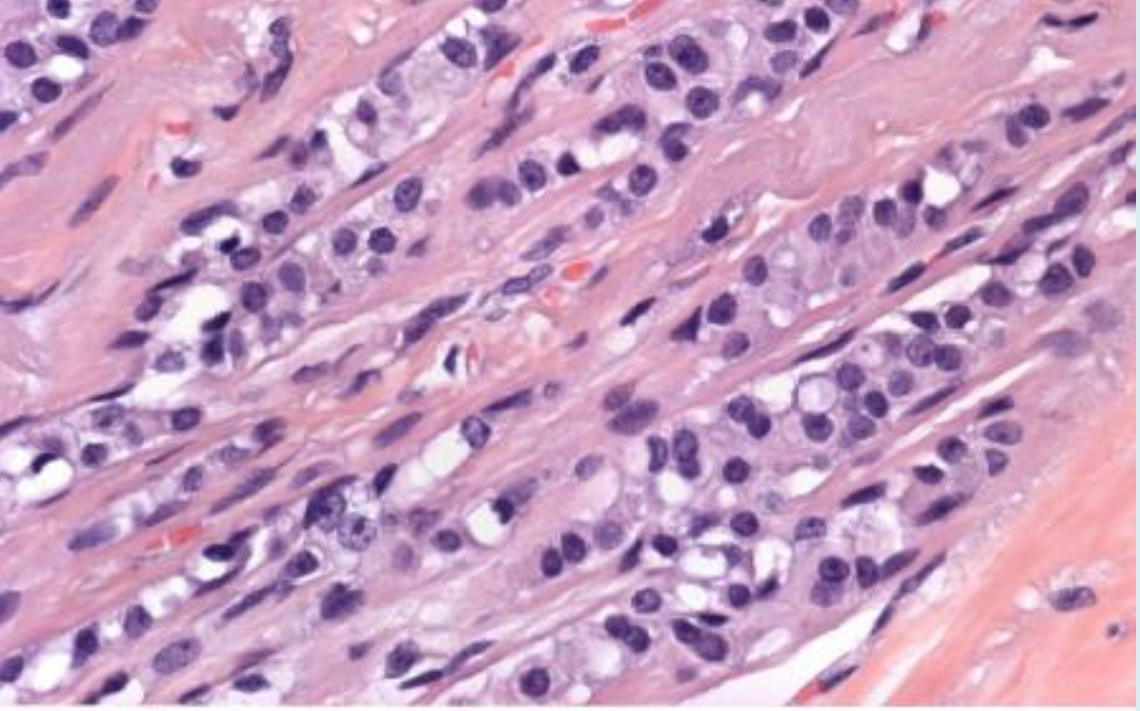
DCIS

UDH

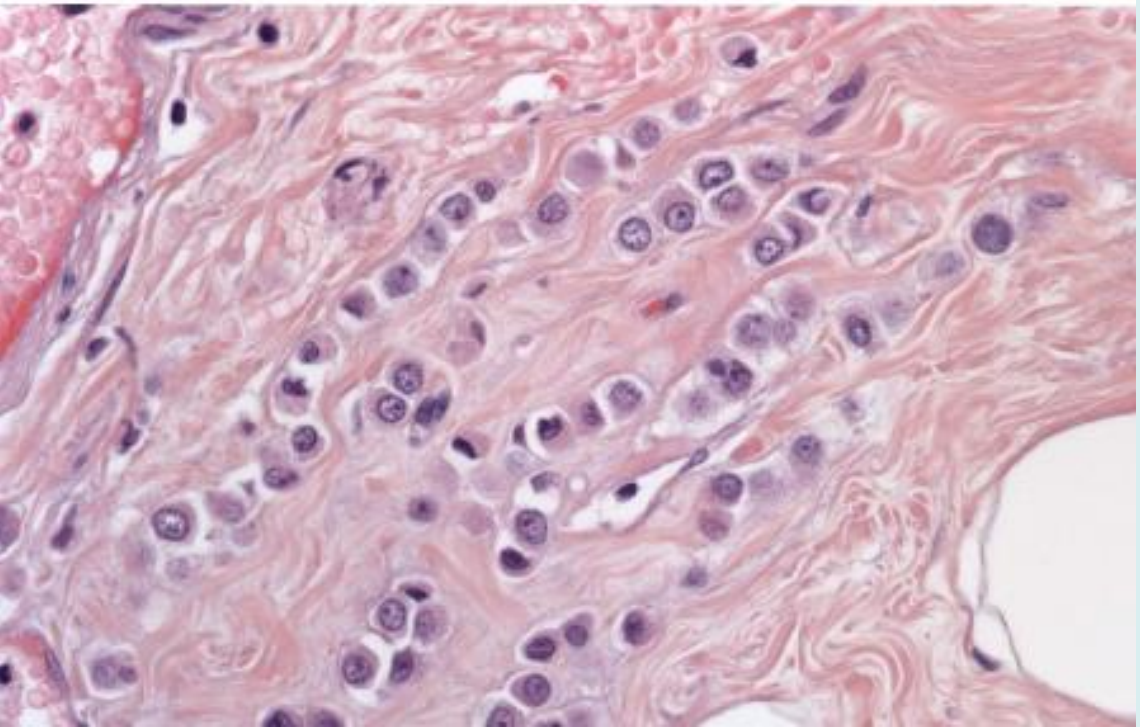
Sclerosing adenosis





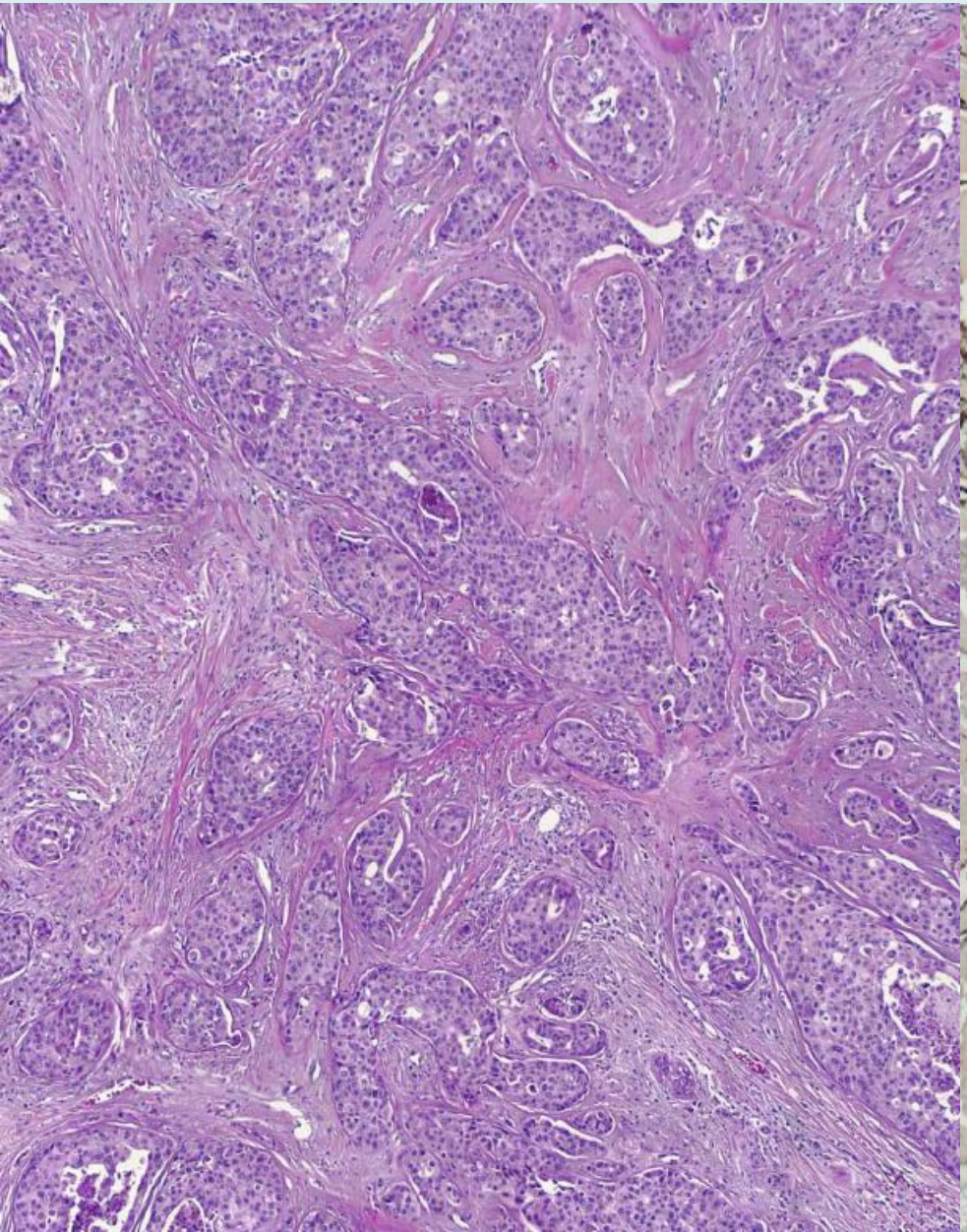


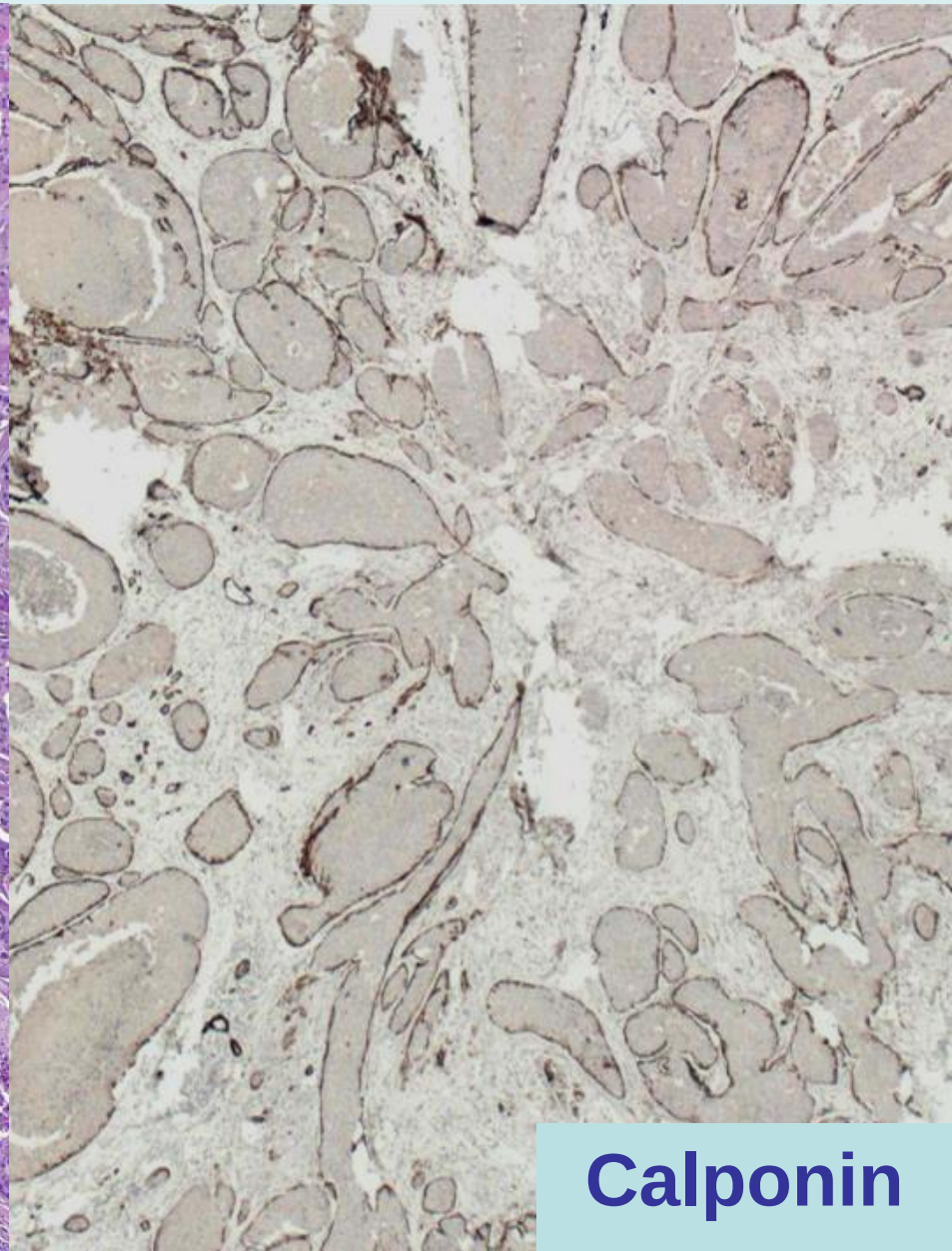
ALH in sclerosing adenosis



Invasive lobular carcinoma

DCIS involving a sclerosing lesion

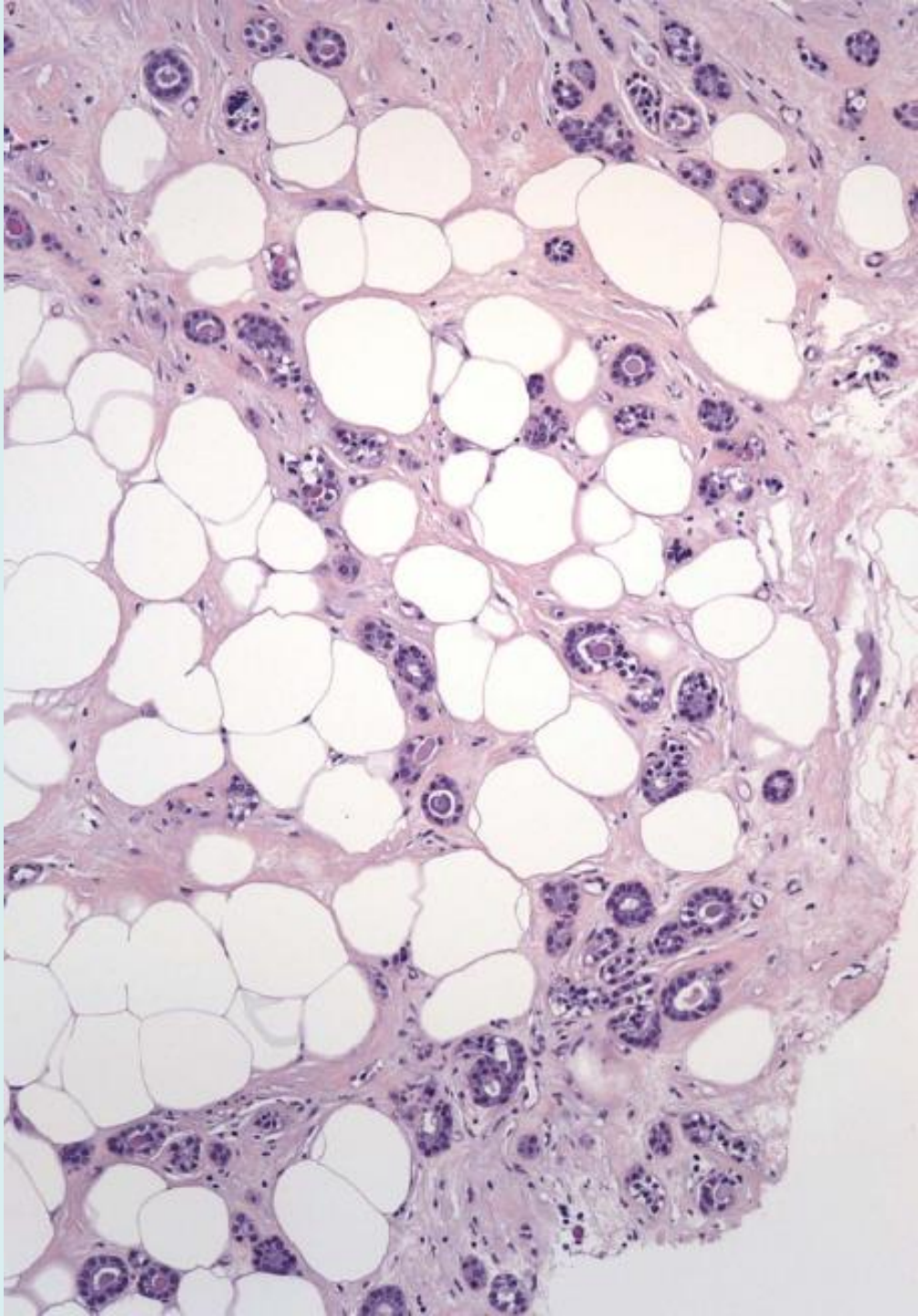




Calponin

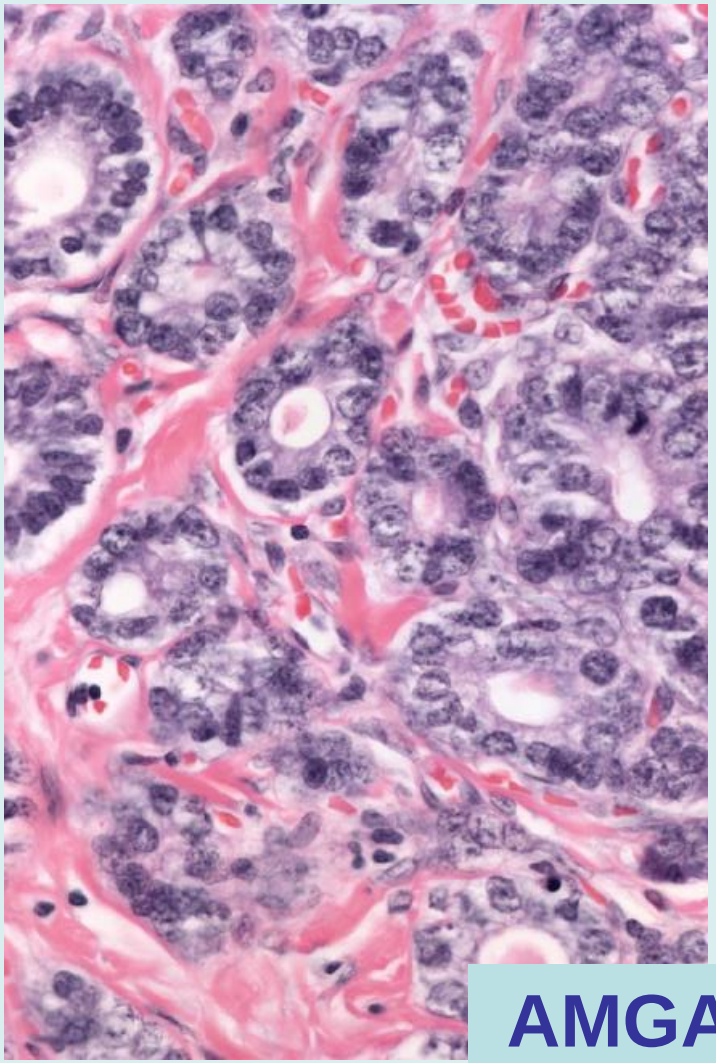
MGA vs Tubular ca:

- Fibrotic stroma
- Uniform, round tubules
- No snouts
- Eosinophilic colloid-like secretion
- Prominent BM
- ER negative
- S100 positive
- **!!** Myoep negative



MGA reported associated with ca in up to 25% of cases

- *Rosenblum Am J Surg Pathol 1986;10:237*
- *James Am J Clin Pathol 1993;100:507*
- *Acs Am J Surg Pathol 2003;27:1052*
- *Resetkova Arch Pathol Lab Med 2003;127:77*
- *Salarieh, Sneige Arch Pathol Lab Med 2007;131:1397*

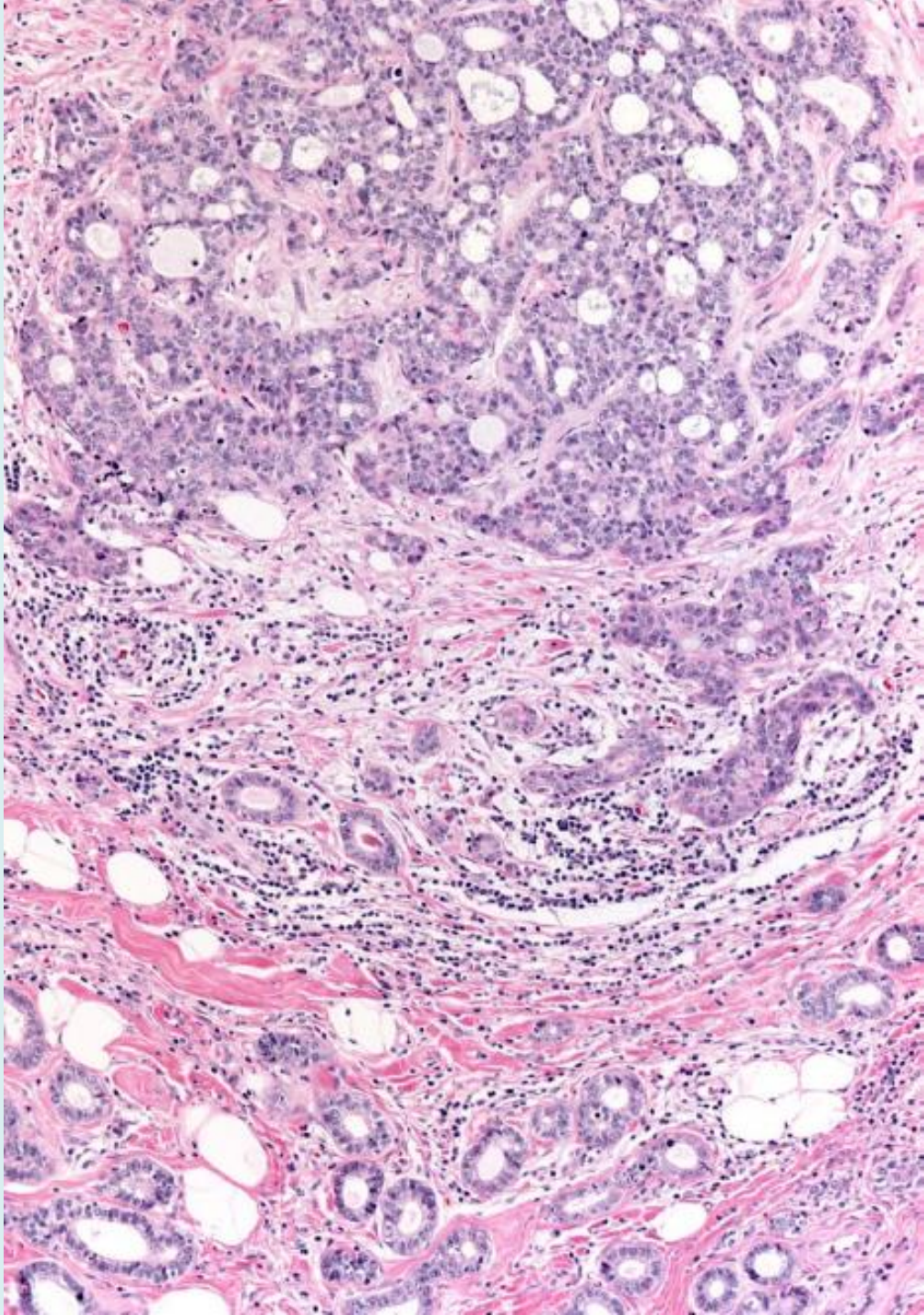


AMGA

MGA and Carcinoma

- Similar immunoprofile
  - ER -
  - Myoeps -
  - S100 +
- Overlapping genetic alterations
- Suggested transition as a non-obligate precursor

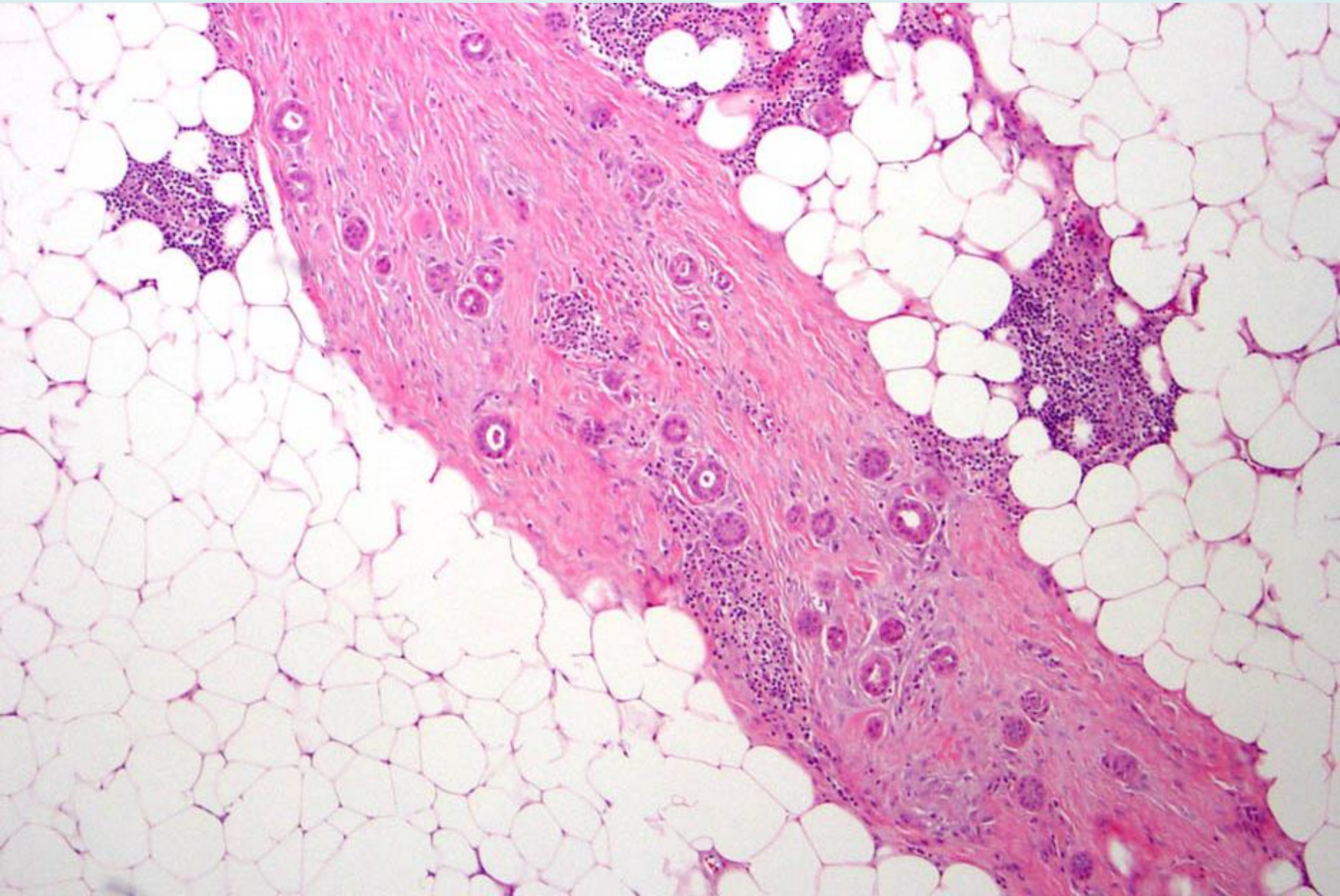
Shin S, et al. Am J Surg Pathol 2009;33;496



Recurrent issues with MGA

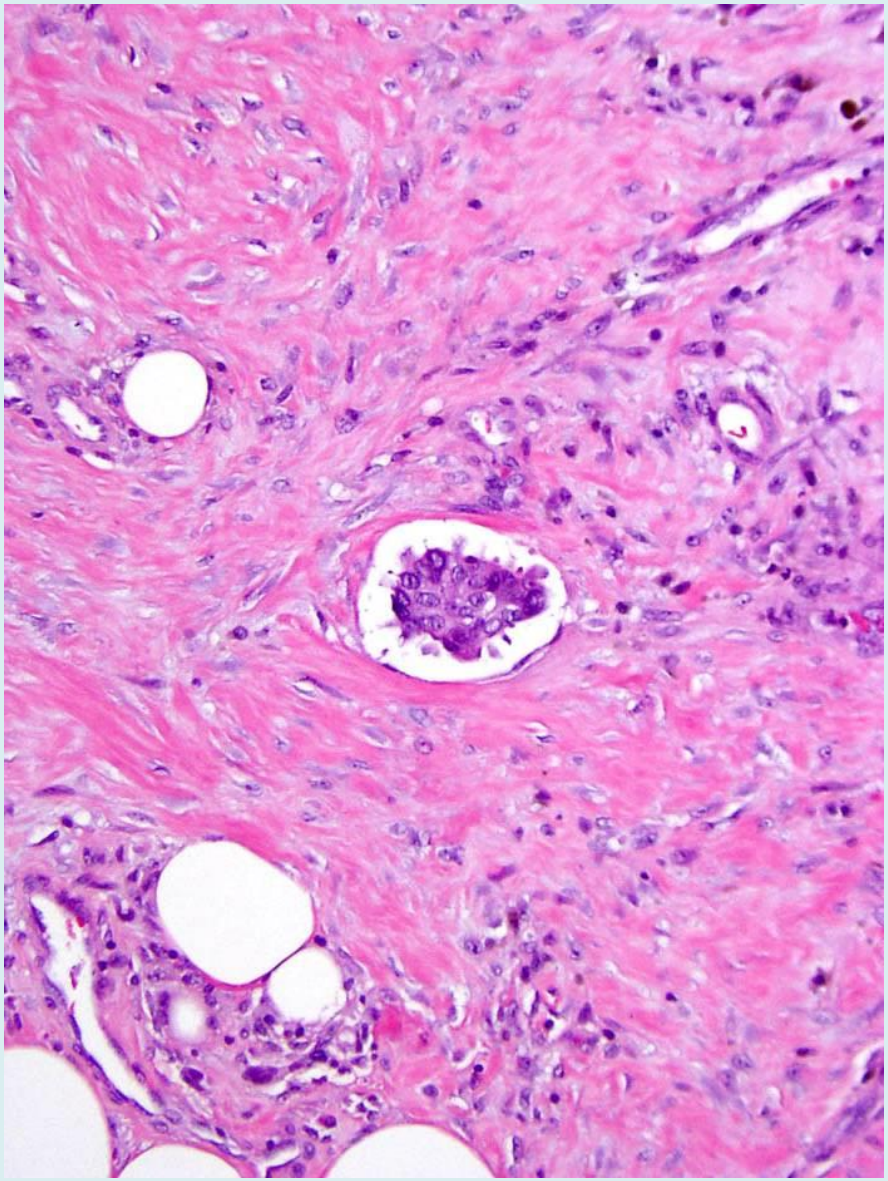
- Core biopsy
  - Difficult to recognize
  - Recommend excision
- Surgical specimen
  - MGA at margin → complete excision

Artifactual displacement



Artifactual displacement

- Epithelium confined to biopsy site
- Benign cytology with round and “shrunken” glands
- Benign primary lesion
- Myoepithelial cells may or may not be retained
  - More useful, if positive
  - p63 more specific



Summary

- Microinvasion
  - Helpful clues
  - Immunostains and pitfalls in interpretation
  - Clinical significance
- Invasive ca that mimics benign
- Invasive ca that mimics in situ
- Benign that mimics invasive ca