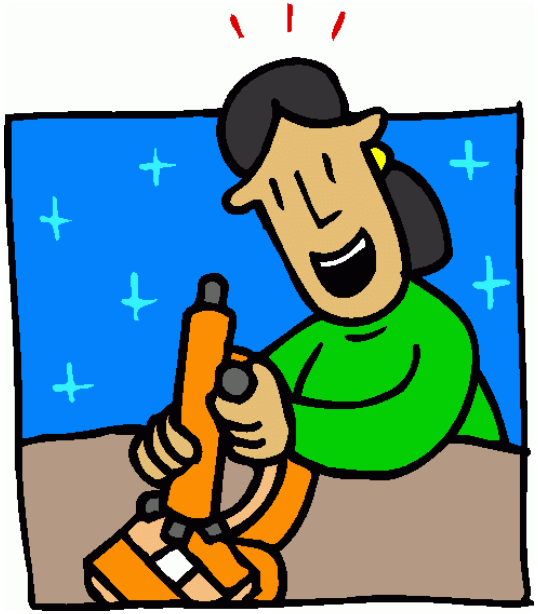


What's new in breast pathology?

Penny Barnes MD, FRCP(C)

May 17, 2016

Outline

- IHC markers of metastatic carcinoma of breast origin
- Uses and limitations of e-cadherin IHC
- Breast neoplasms with limited metastatic potential
- Sentinel node staging: changes in clinical management

1. IHC panels for metastatic carcinoma

- Work-up for metastatic carcinoma of unknown primary is common
  - Axillary lymph node metastasis
  - Carcinoma in other sites (liver, lung, bone marrow) with remote or no known primary
  - Breast tumors with atypical histologic features

‘Breast panel’

- CK7 +/CK 20 –
- ER
- GCDFP-15
- Mammoglobin
- GATA3

ER

- Metastatic setting, ERα is neither sensitive or specific for breast carcinoma
- Only ~50% of metastatic breast cancers express ER
- ER is expressed in non-breast carcinomas: endometrium, ovary, PTCa, adnexal tumors of skin
- ~10-20% of lung adenocarcinomas show weak/focal ER expression

GCDFP-15

- Ab derived against secretory glycoproteins
- Expressed in ~55% primary breast carcinomas
- Sensitivity in metastatic breast carcinoma only ~11%
- Dependent on histologic subtype: highly expressed in tumors with apocrine features and in lobular carcinoma with signet ring differentiation
- Often not expressed in high grade, triple negative tumors
- Expressed in non-breast primaries: cutaneous apocrine & eccrine carcinoma, salivary gland carcinoma, 5-10% of ovarian & endometrial carcinomas; ~5% lung adenocarcinomas

Mammaglobin

- Cytoplasmic protein
- Higher sensitivity than GCDFP-15
- Expressed in non-breast primaries: cutaneous adnexal carcinomas, salivary gland carcinoma, ~5-10% ovarian, endocervical & endometrial carcinomas
- Not expressed in lung ca

GATA3

- One of the 6 members of zinc finger transcription factor family
- Binds to the DNA nucleotide sequence GATA
- Involved in the differentiation of breast glandular epithelial cells, hair follicles, T cells, adipose tissue, kidney and nervous system
- Sensitivity in breast cancer >90%
- Expressed at lower levels in ER negative/triple negative tumors

GATA3

- Expressed in non-breast primaries: urothelial carcinoma, squamous cell tumors, BCC, cutaneous adnexal carcinomas, salivary gland carcinoma, chromophobe RCC, trophoblastic tumors
- ~5% thyroid carcinomas, ~8% lung adenocarcinomas, 58% mesotheliomas, 9% cholangiocarcinomas, 37% pancreatic carcinoma

GATA3

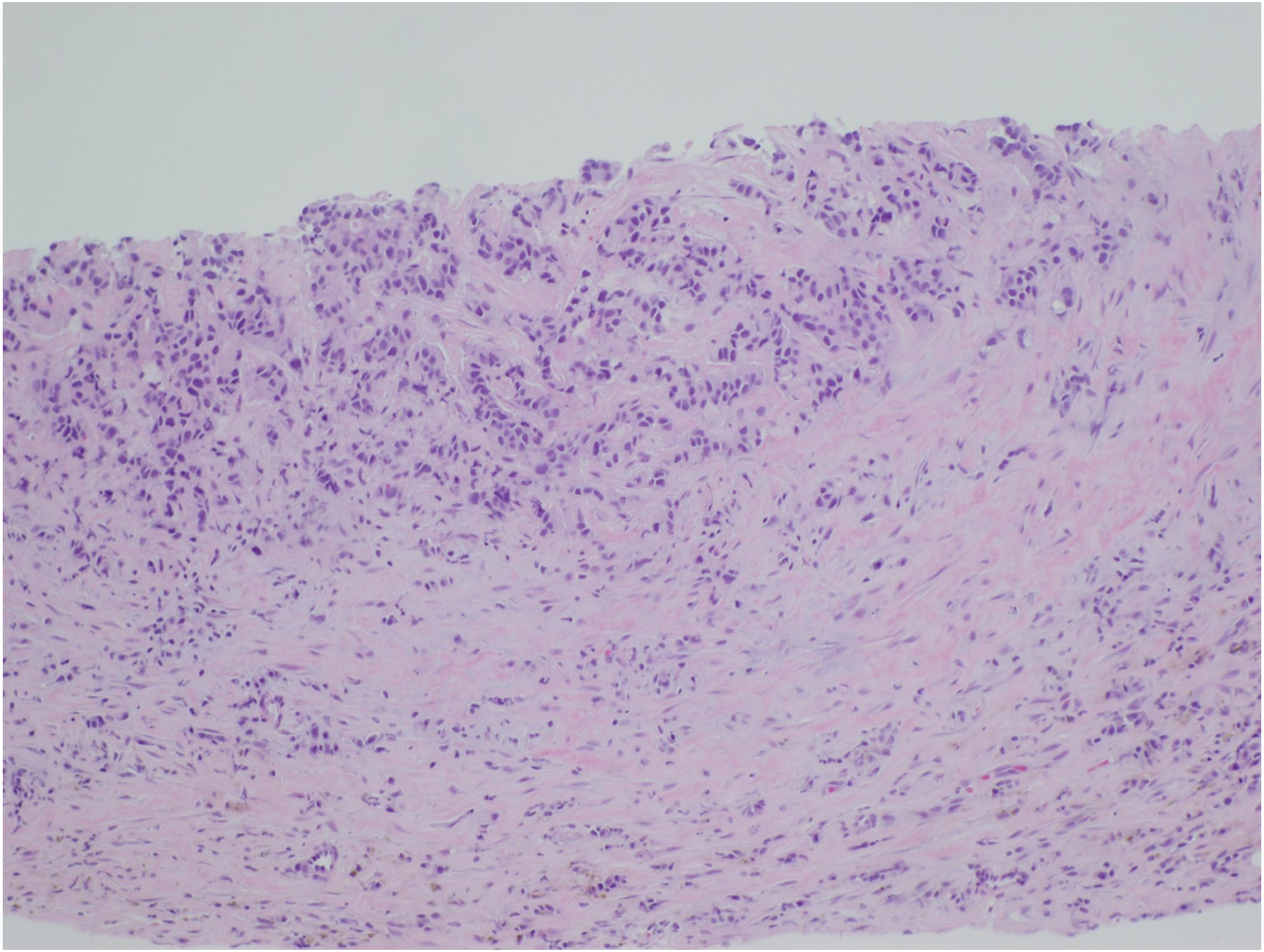
- GATA3 expression is frequently maintained between matched primary and metastatic carcinomas, including ER negative cases (90%)

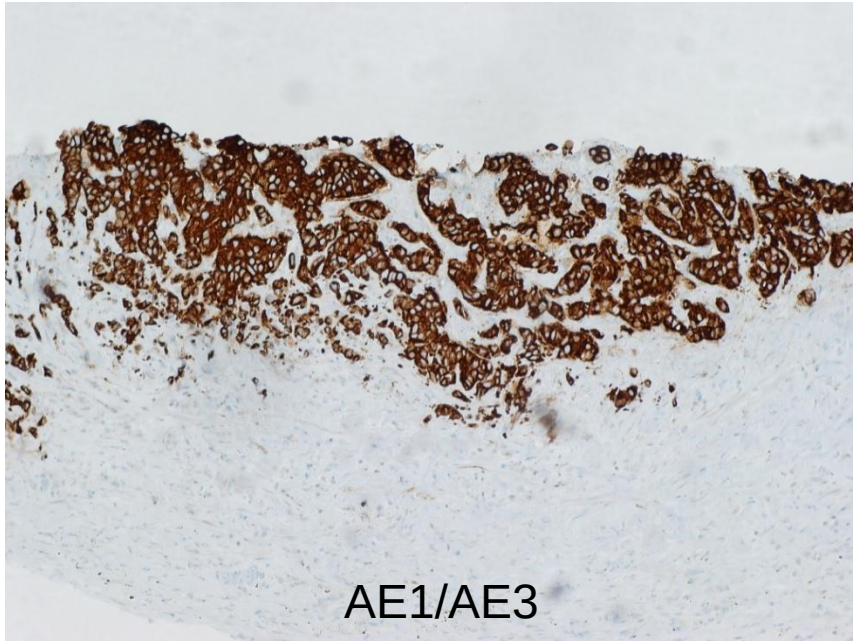
IHC panels for metastatic carcinoma

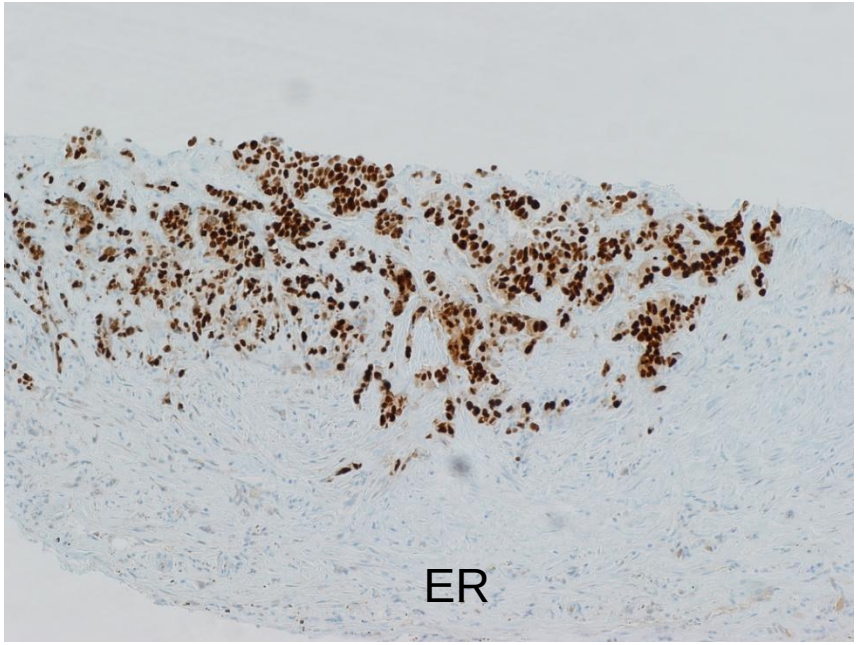
- Utilize a broad panel
- None of the markers available as yet have both high sensitivity and specificity
- All ‘breast markers’ have lower sensitivity in triple-negative breast cancers; GATA3 is the most useful in this context
- Incorporate clinical setting & imaging findings

Case 1

- 65 y.o. female
- Right axillary adenopathopathy
- Right breast mass; 2 previous core biopsies were benign
- PHx: contralateral invasive breast carcinoma 1997, invasive urothelial carcinoma, high grade, treated with radical cystectomy; no residual invasion seen cystectomy, 2009.




AE1/AE3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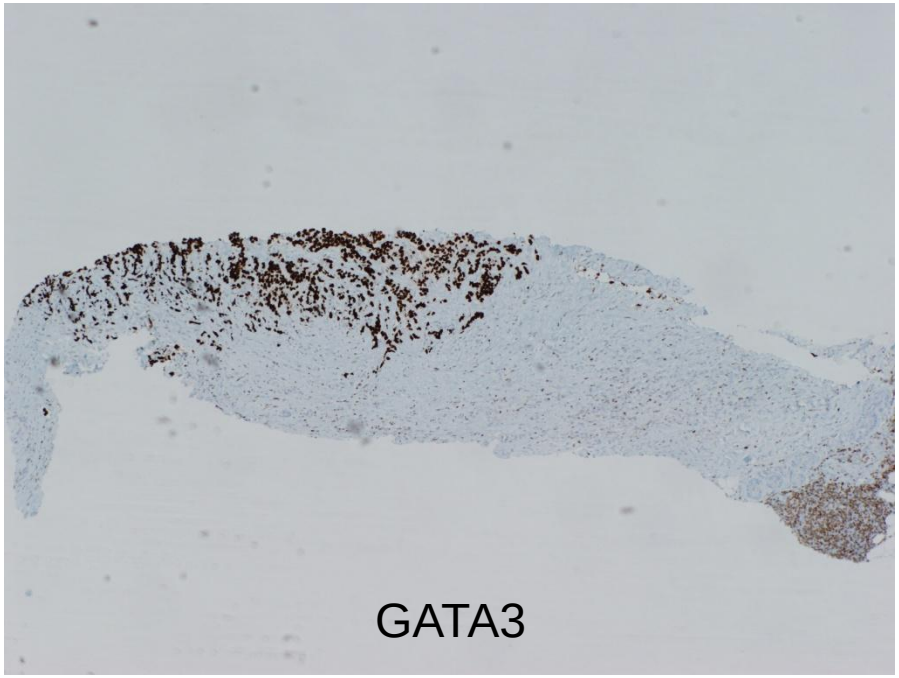
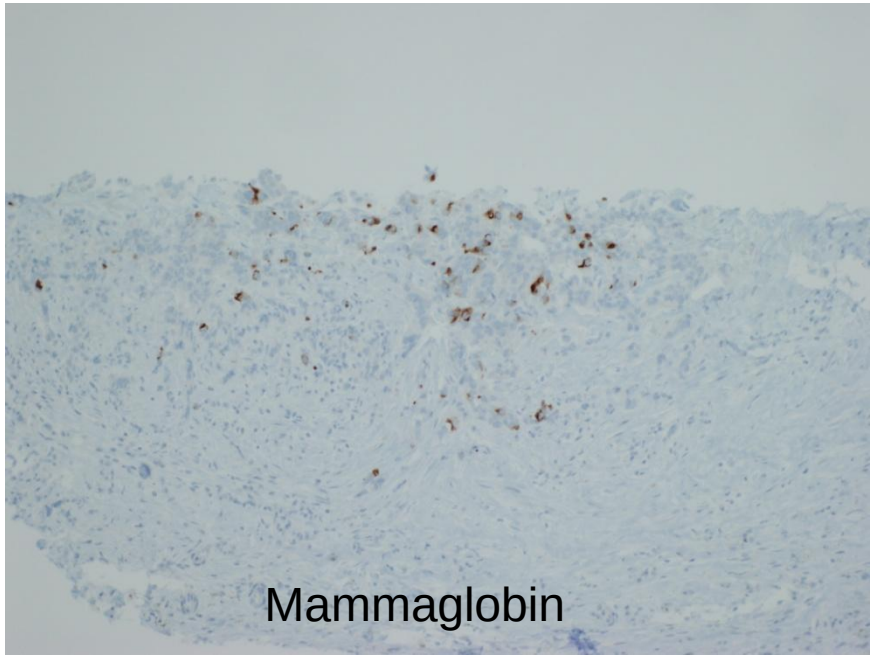

GATA3


Mammaglobin

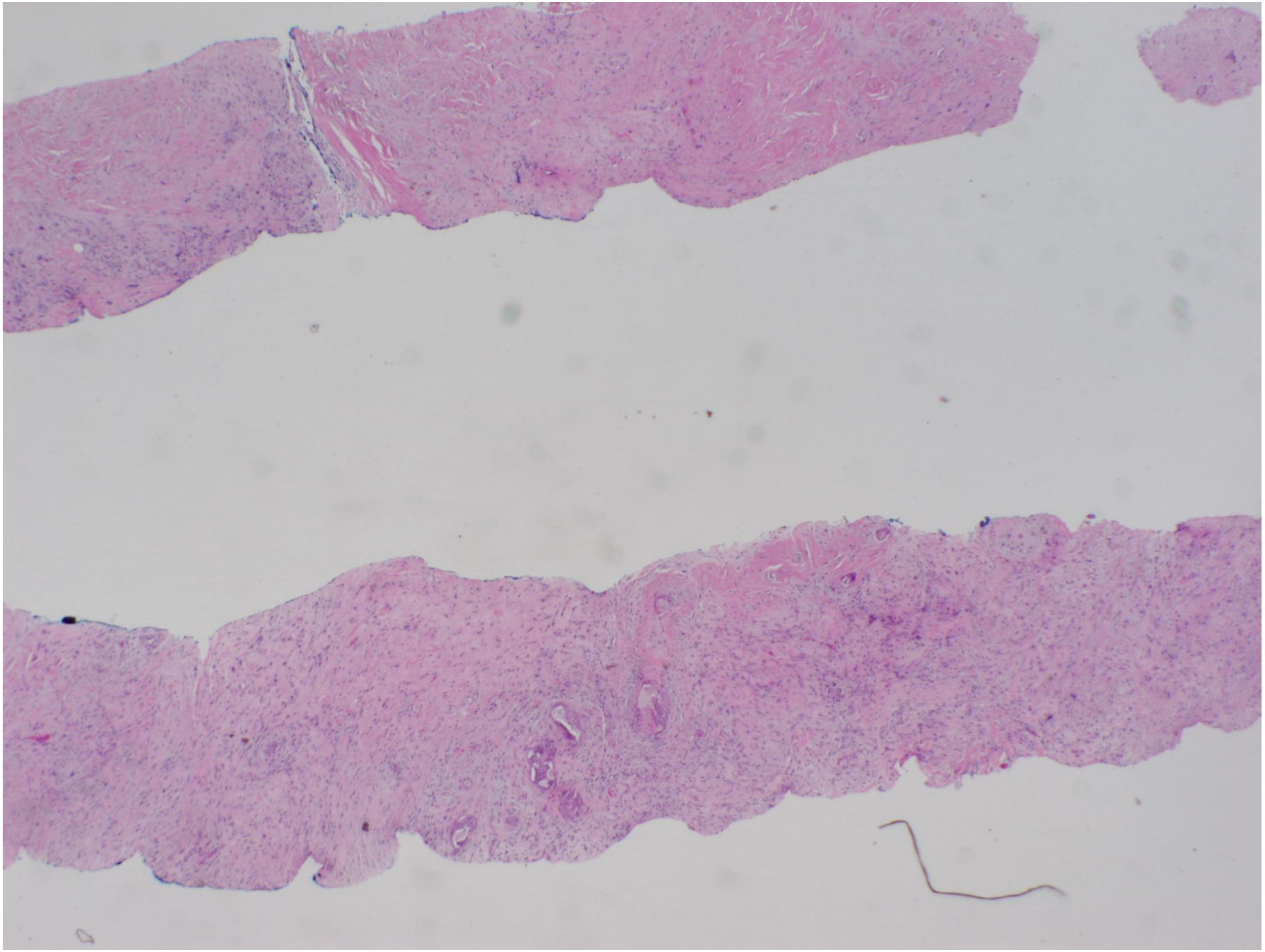
Case 1

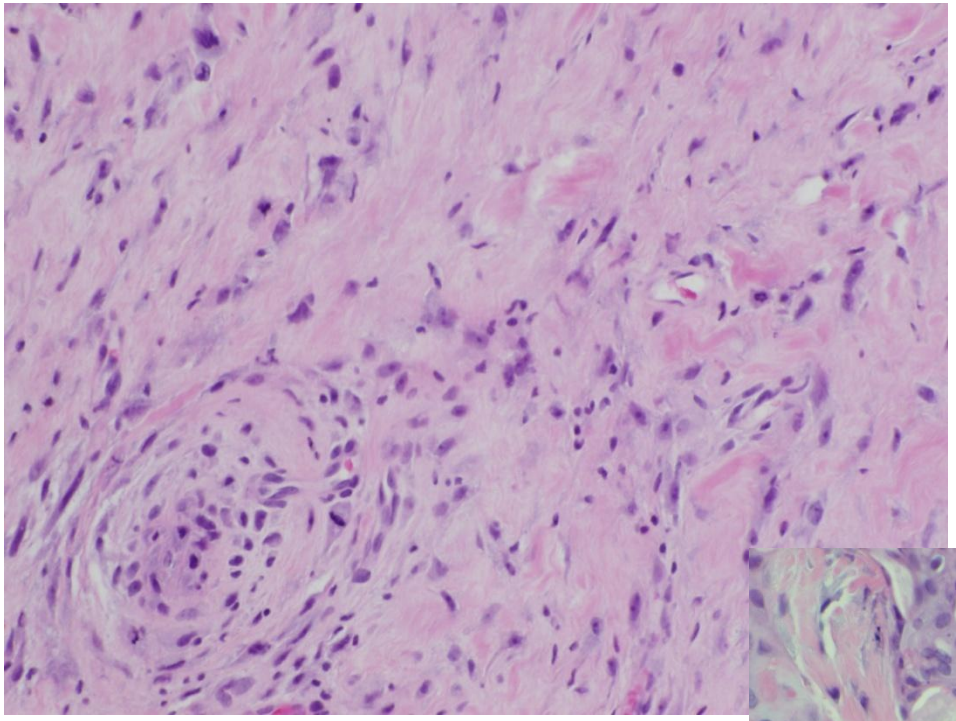
- IHC positive: PR, patchy GCDFP-15
- IHC negative: CK 7, CK 20, p63, HER2, TTF-1, napsin

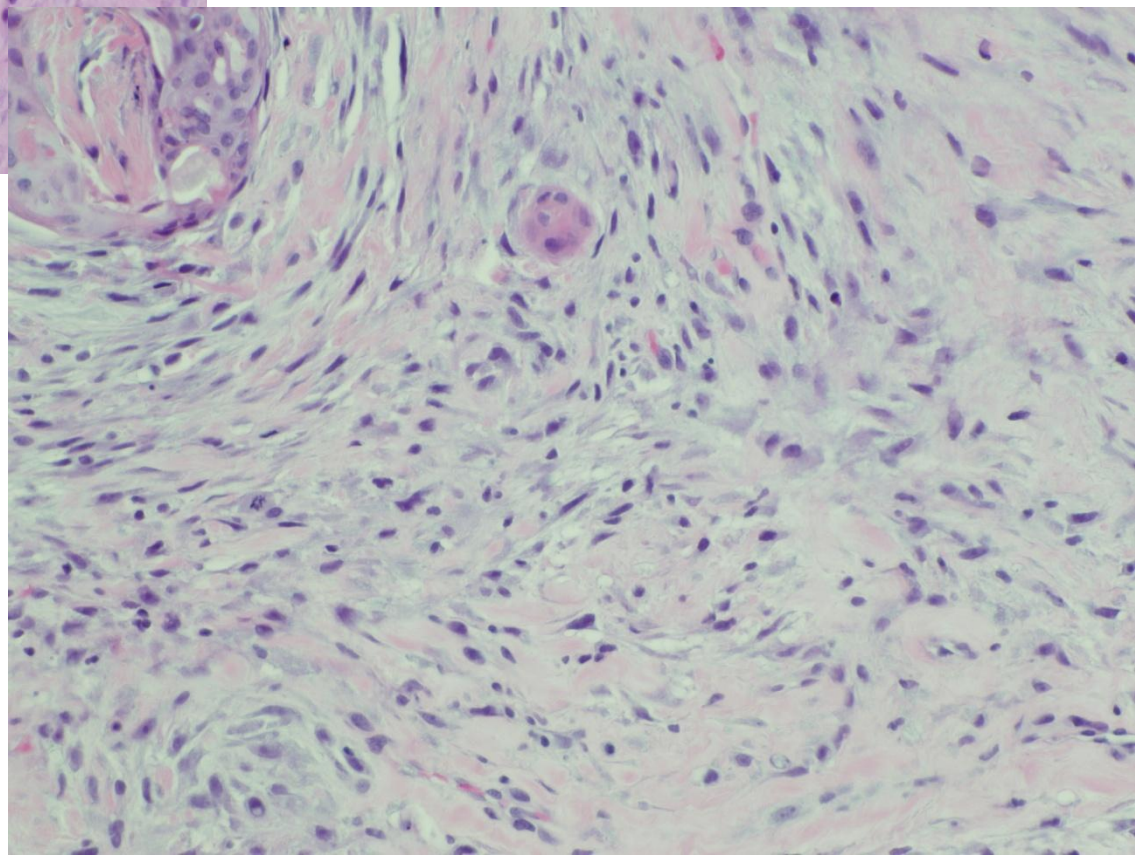
- Most consistent with metastatic adenocarcinoma of breast origin

Case 2

- 72 year old female
- History of stable breast mass x 10 years, now enlarging

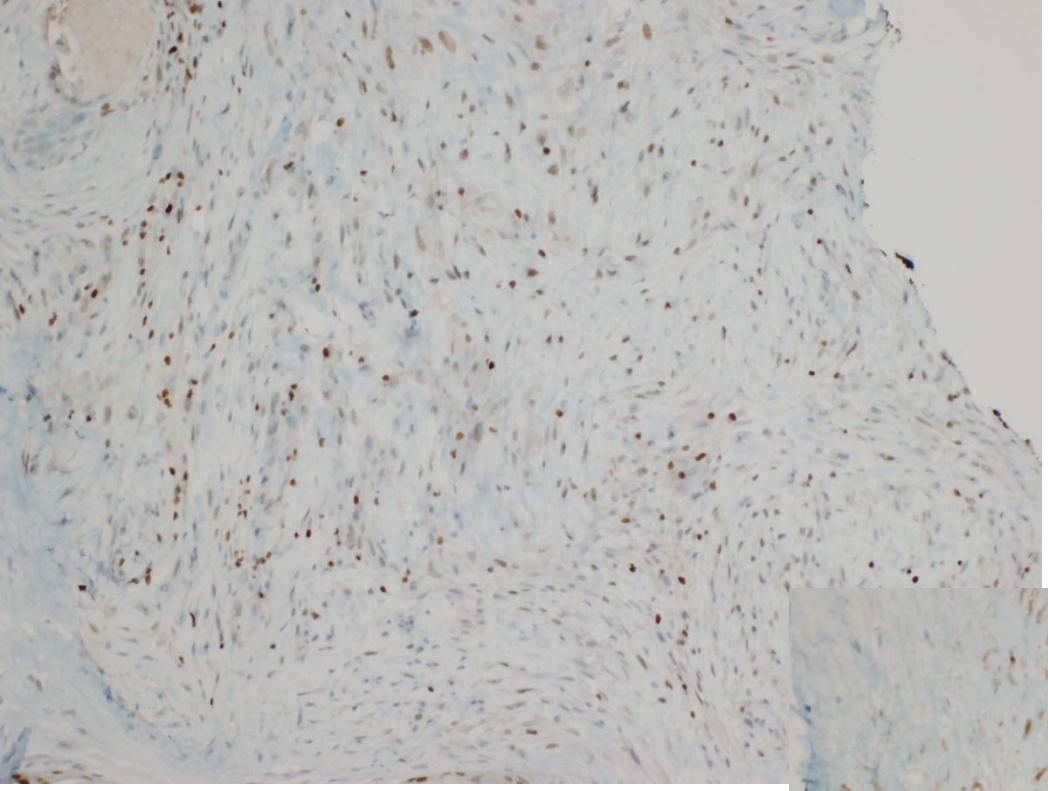




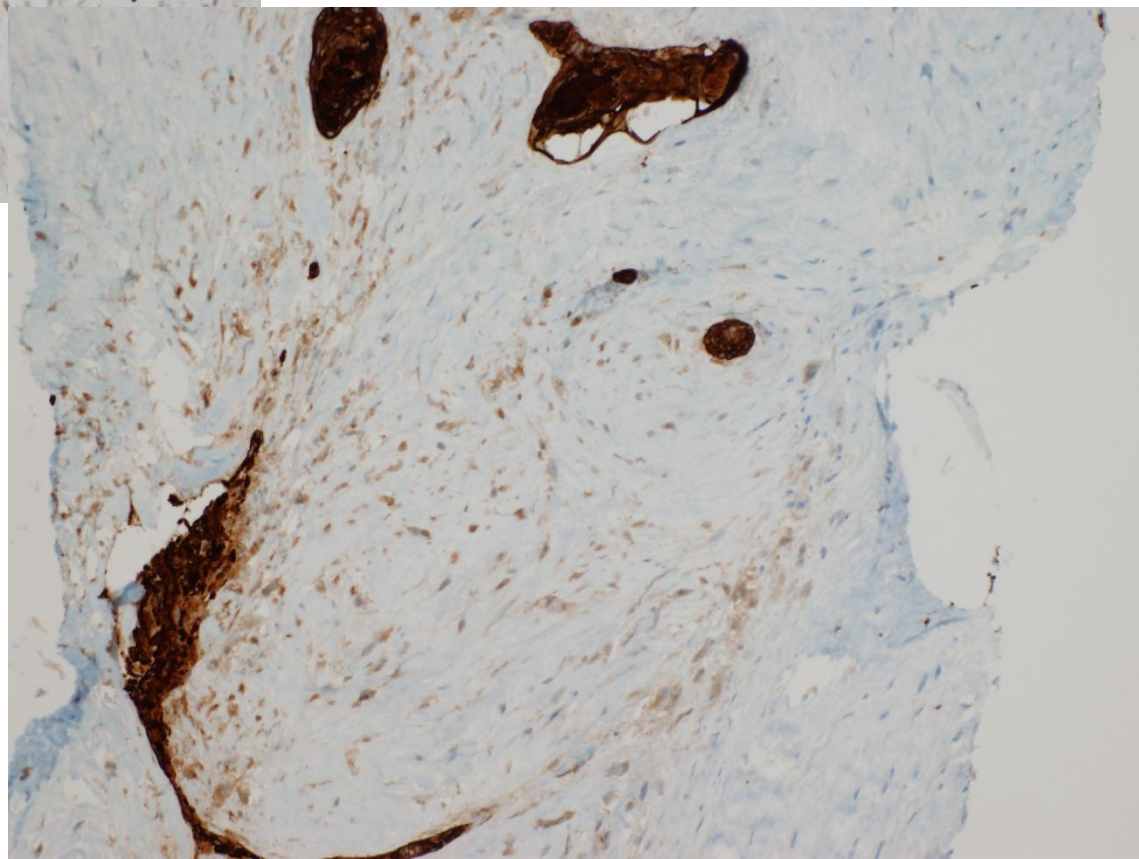


IHC panel

- Positive markers: GATA3, actin, focal weak expression of p63, CK5/6, AE1/AE3
- Negative: ER, PR, HER2, CD34, beta-catenin



GATA3



AEA1/AE3

GATA3 expression in triple negative and sarcomatoid carcinomas

- GATA3 expression seen in ~43% high grade triple-negative breast cancers
- GATA3 expression seen in ~56% of metaplastic carcinomas, weak-moderate
- Stromal GATA3 expression is rare in fibroepithelial neoplasms (~3%, 1 case of malignant PT)

Cimino-Mathews A, Subhawong AP, Illei PB et al. GATA3 expression in breast carcinoma: utility in triple negative, sarcomatoid, and metastatic carcinomas. *Human Pathology* 2013;44:1341-1349.

Malignant spindle cell neoplasms in core biopsies

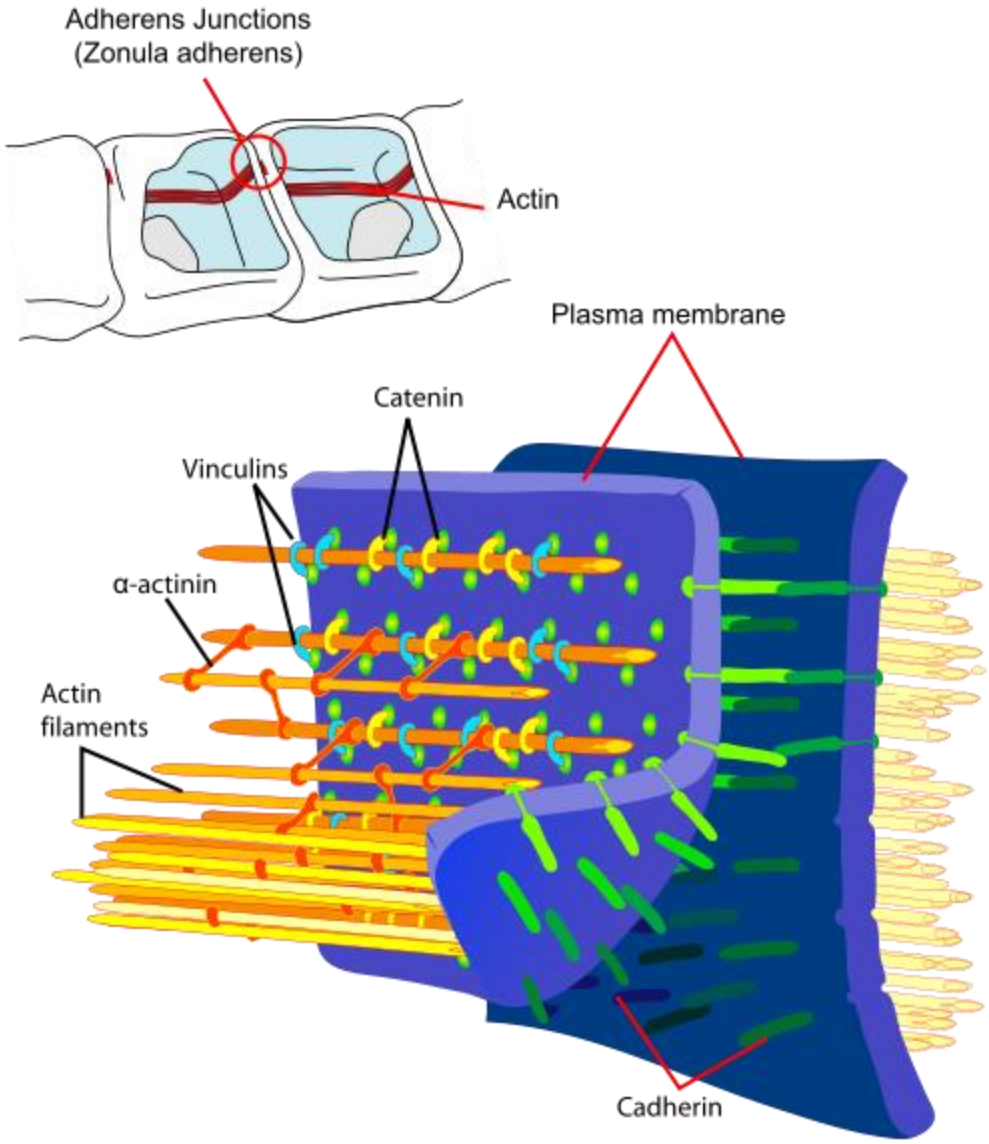
- Ddx: metaplastic carcinoma, phyllodes tumor, primary/secondary sarcoma
- Pitfall: weak expression of p63, p40 and keratins can be seen in malignant phyllodes tumors!
- Include CD34 (for PT) and GATA3 in w/u, especially in core biopsy specimens

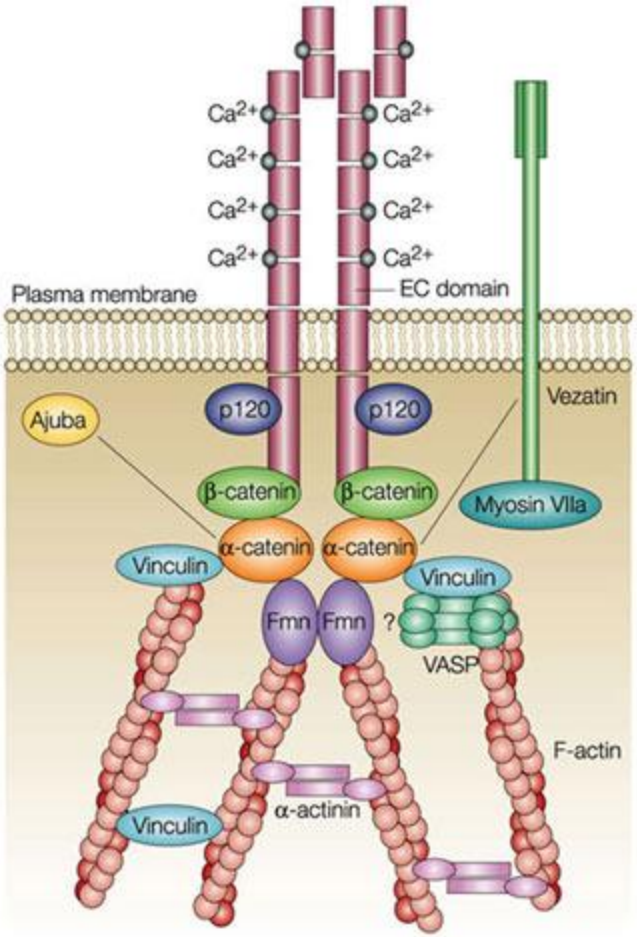
2. E-cadherin IHC: uses and pitfalls

- Commonly used to help distinguish:
  - LCIS from DCIS
  - Invasive lobular carcinoma from invasive ductal carcinoma
- Most lobular lesions have genomic and/or epigenetic alterations in the gene encoding e-cadherin, *CDH1*, resulting in biallelic silencing and loss of expression of the e-cadherin protein, therefore loss of intercellular cohesion

E-cadherin biology

- E-cadherin gene, *CDH1*, located on 16q
- Encodes a Ca2+-dependent transmembrane protein involved in intercellular adhesion and maintenance of cell polarity
- Cell-cell adhesion function resides in the extracellular domain
- E-cadherin is linked to the actin cytoskeleton via α-, β-, ɣ- and p120 catenins


Adherens Junctions
(Zonula adherens)
Actin
Plasma membrane
Catenin
Vinculins
α-actinin
Actin
filaments
Cadherin



Nature Reviews | Molecular Cell Biology

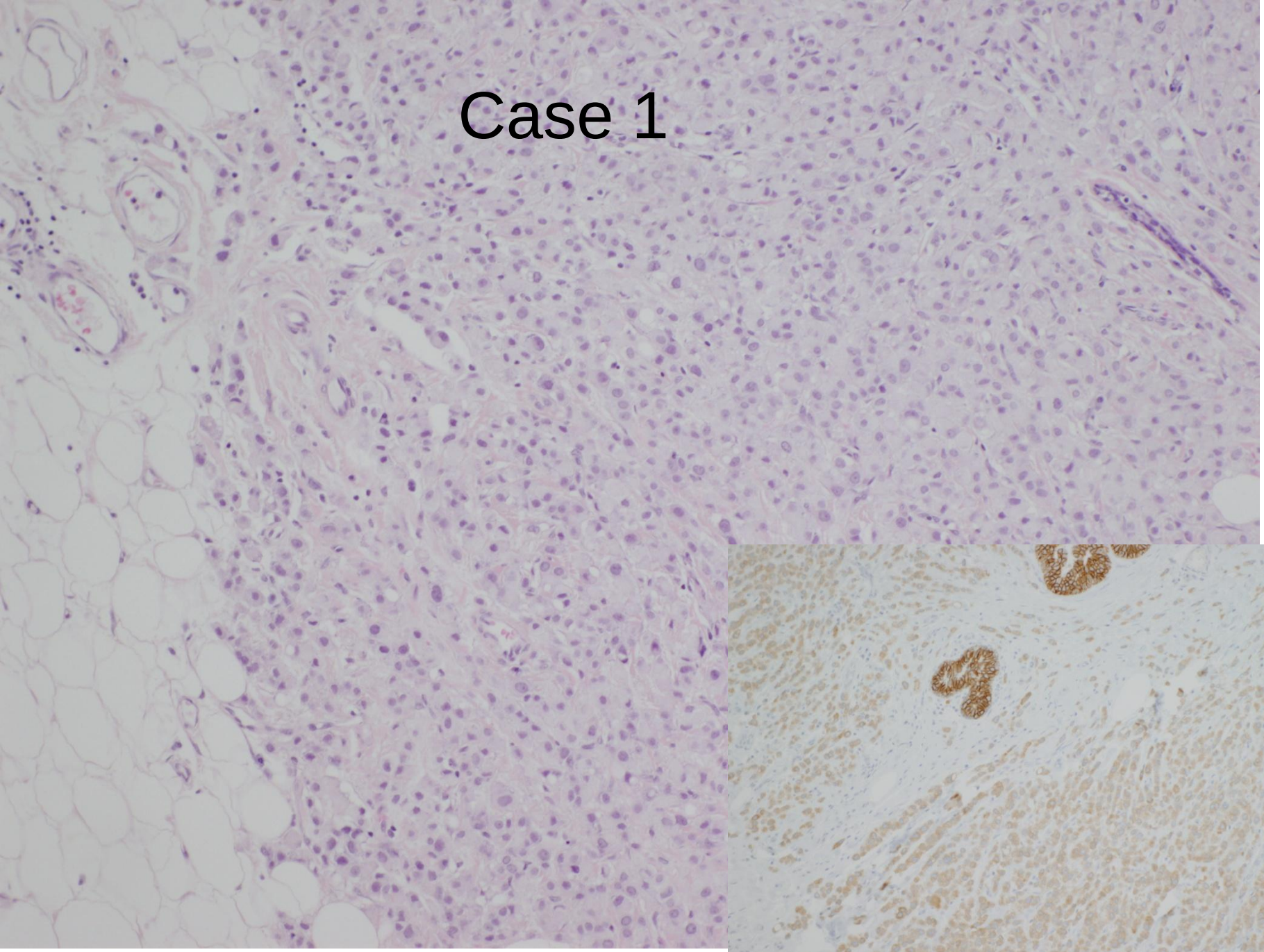
E-cadherin

- Lobular lesions: disruption of cadherin-catenin complex and loss of membrane expression of e-cadherin and catenins
- Accumulation of p120 catenin in the cytoplasm
- Most common molecular alteration in lobular lesions is LOH at 16q; other molecular aberrations can occur (deletions, transcriptional repression)

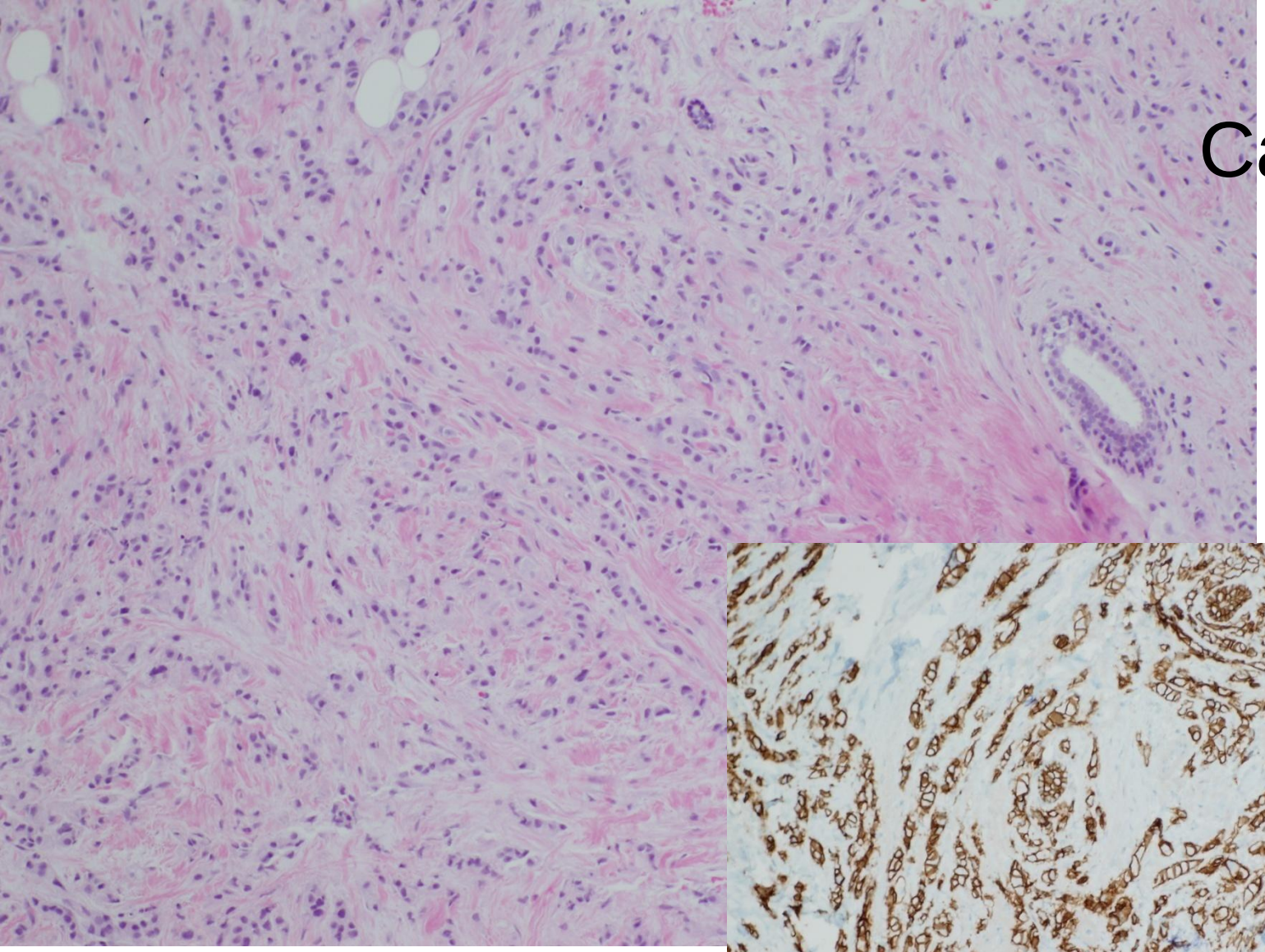
E-cadherin IHC

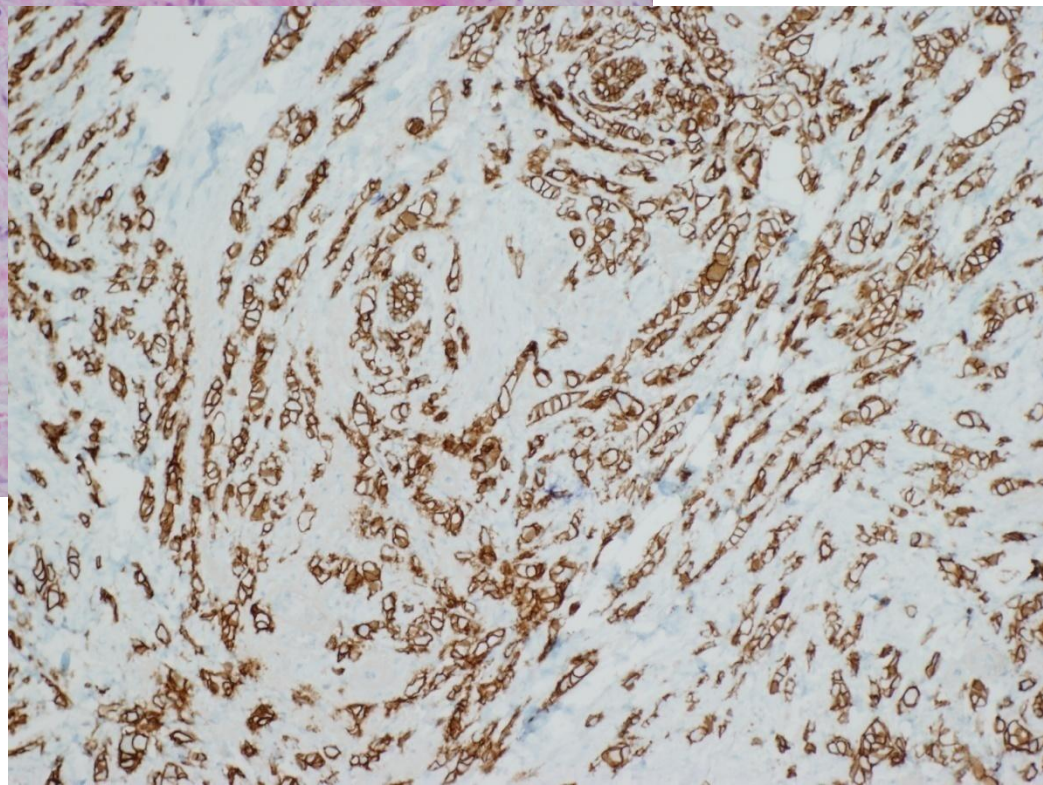
- Lobular lesions typically exhibit loss of membranous expression of e-cadherin
- Ductal lesions typically retain it
- This is not always the case:
  - Related to the type of molecular inactivation of e-cadherin
  - Invasive lobular can have membranous expression (~15%)
  - ILC may have partial/fragmented membrane staining or perinuclear cytoplasmic staining
  - Invasive ductal carcinomas can have aberrant/loss of expression of e-cadherin (~7%), usually high grade

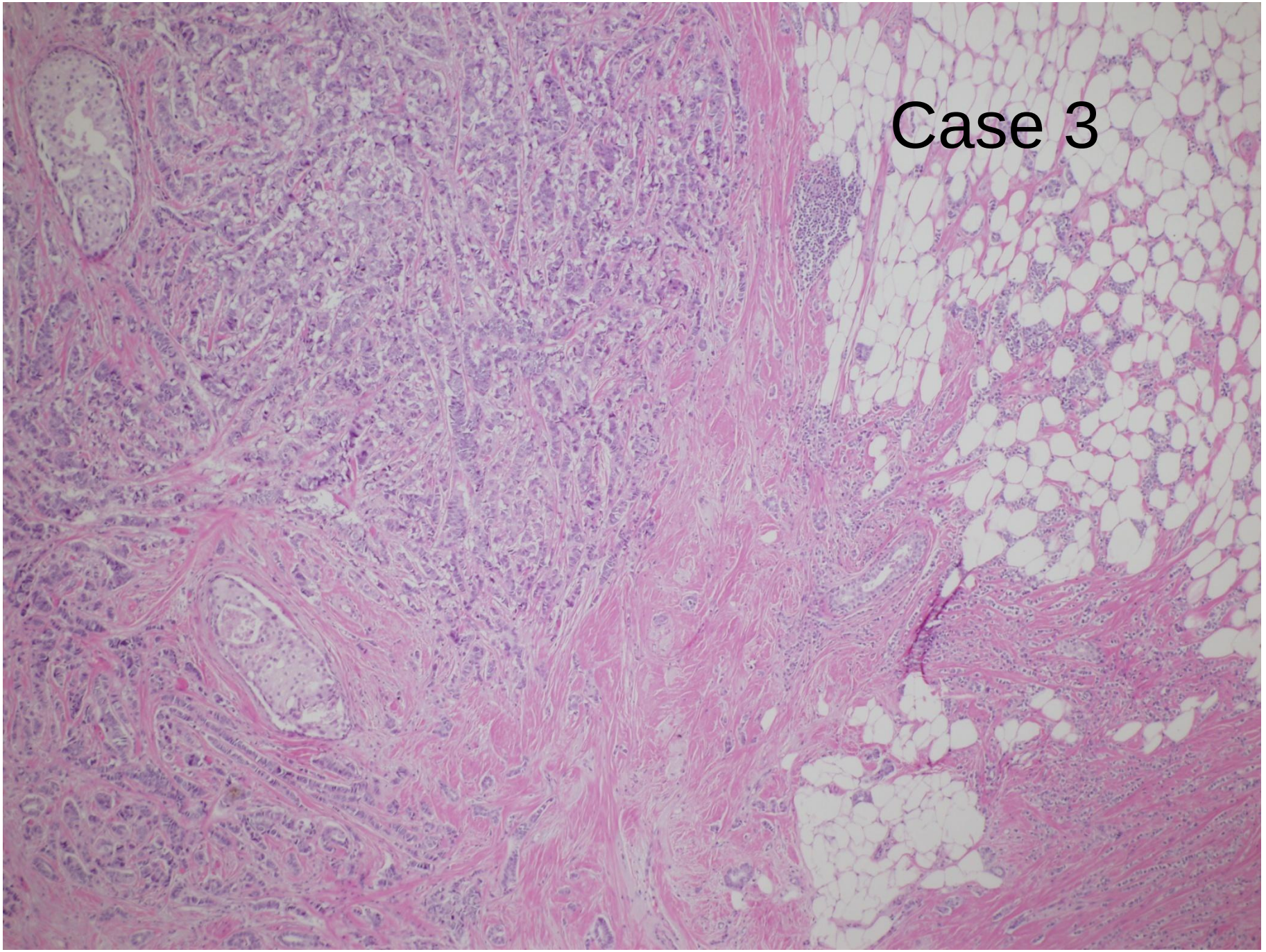
Case 1

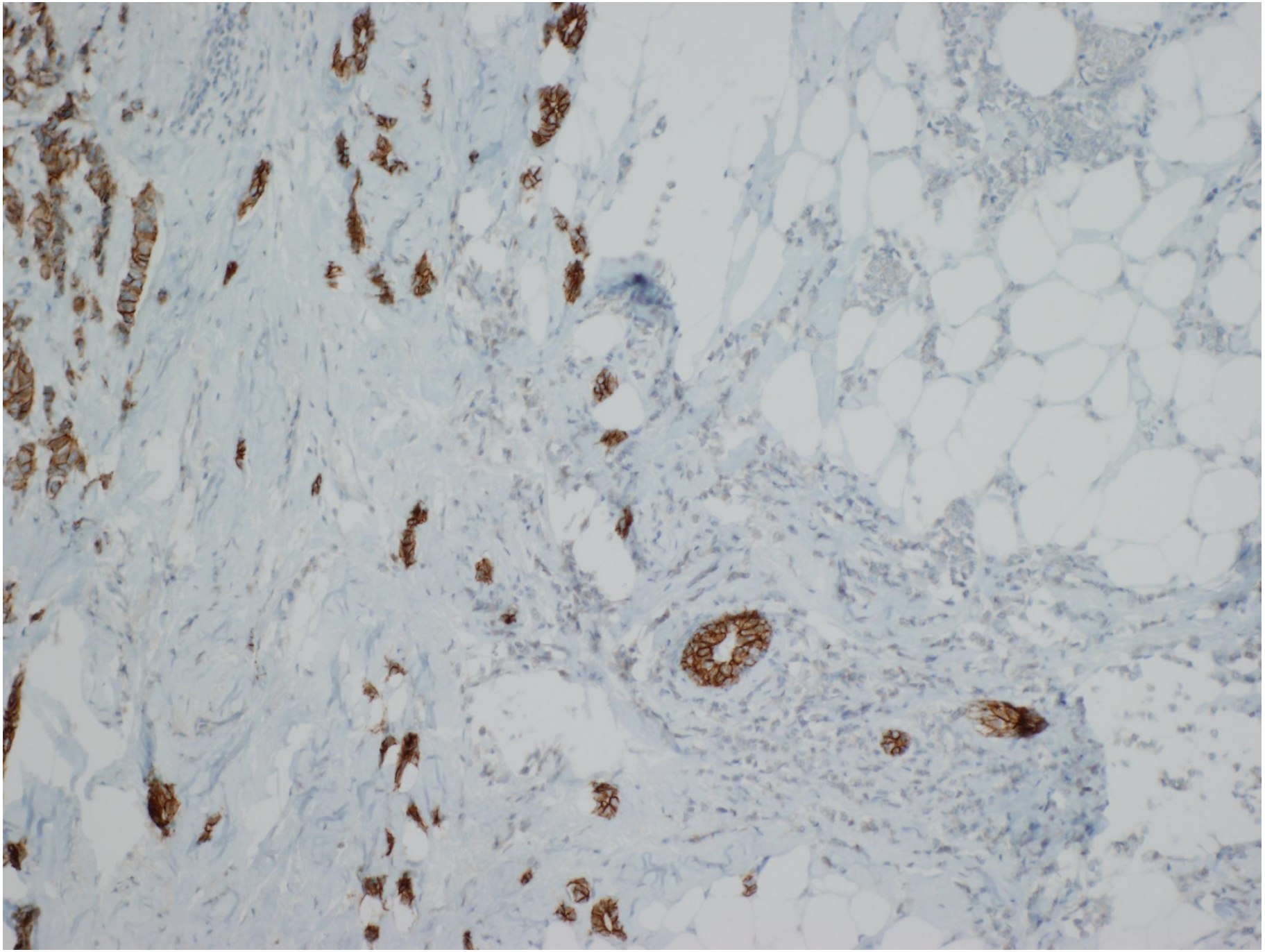


Case 2





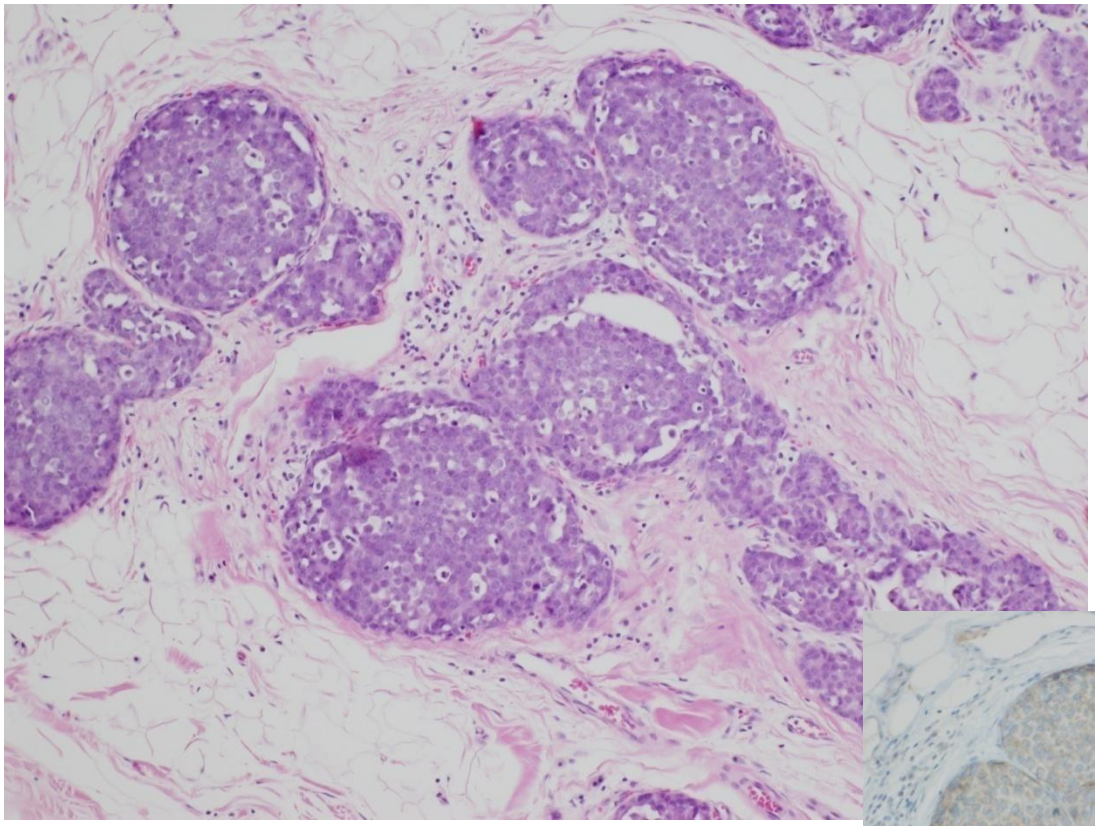

Case 3

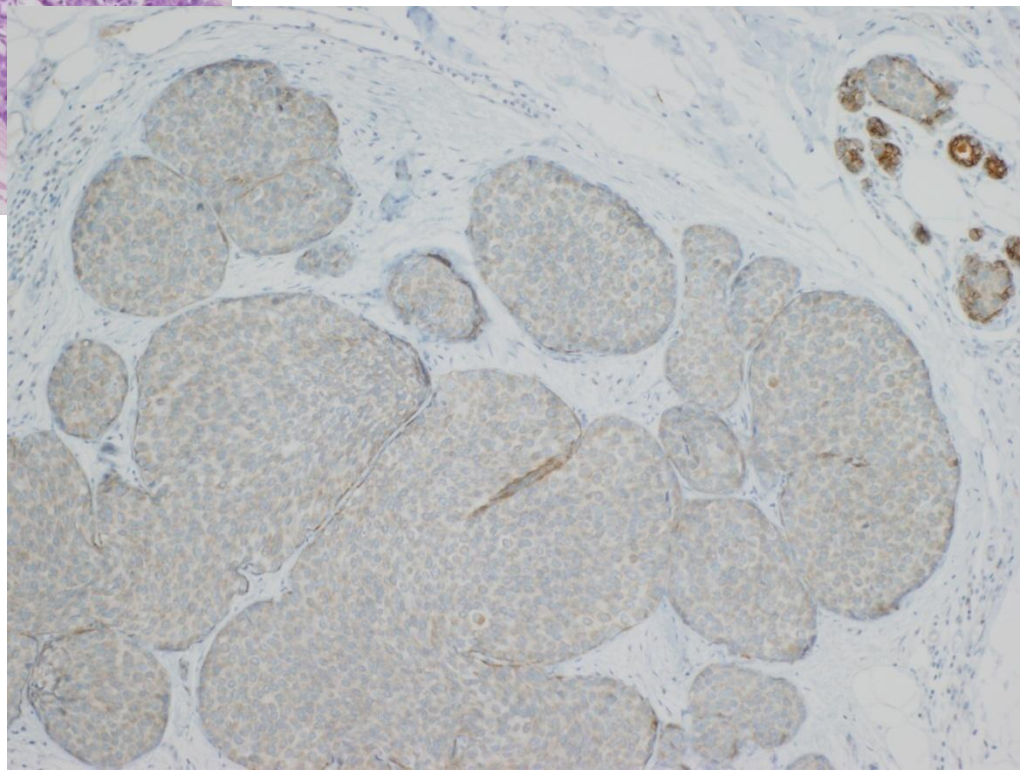


E-cadherin IHC

- In situ lesions:
- Aberrant expression of E-cadherin in LCIS cells
  - Partial/fragmented membrane staining or perinuclear cytoplasmic staining
  - Staining of admixed luminal cells
  - Consider a mixed LCIS/DCIS lesion

Case 4





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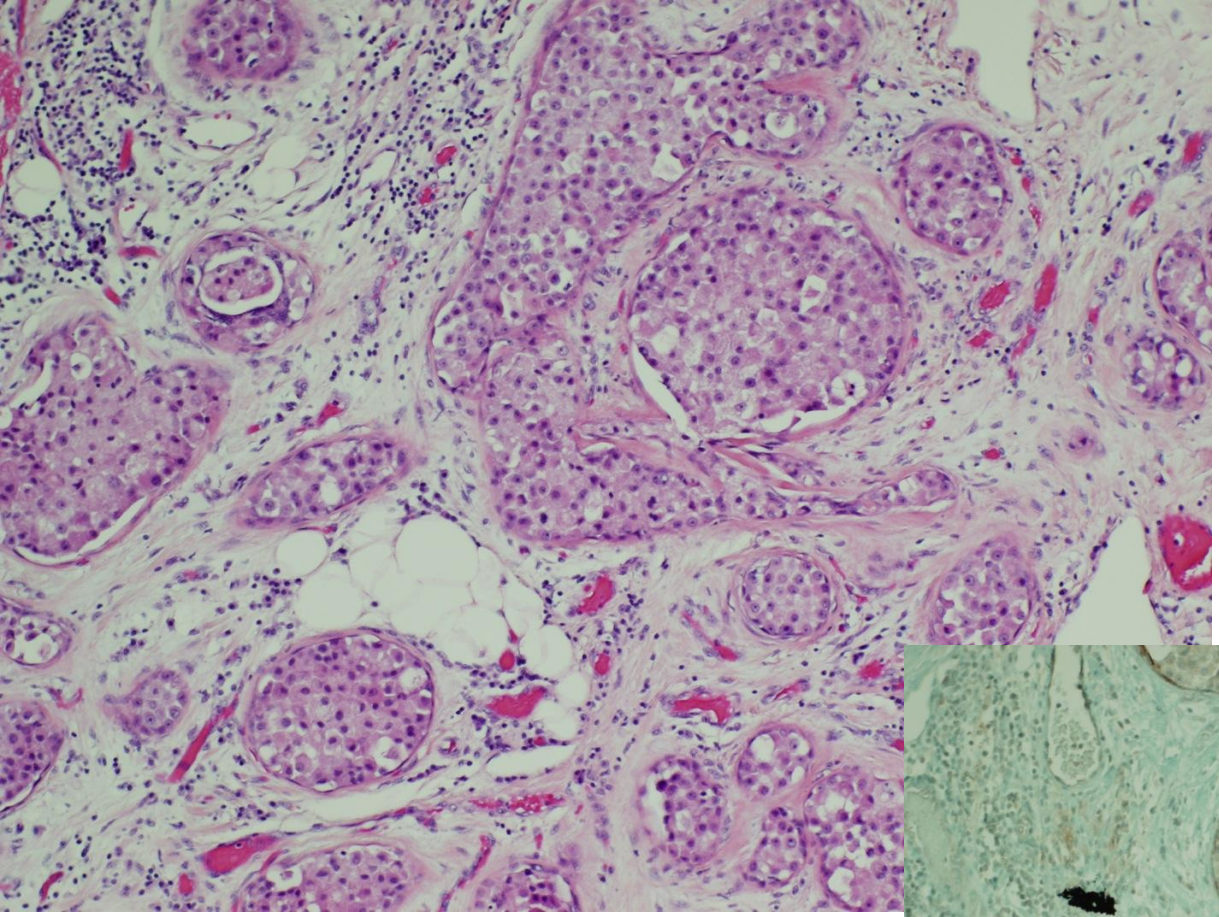

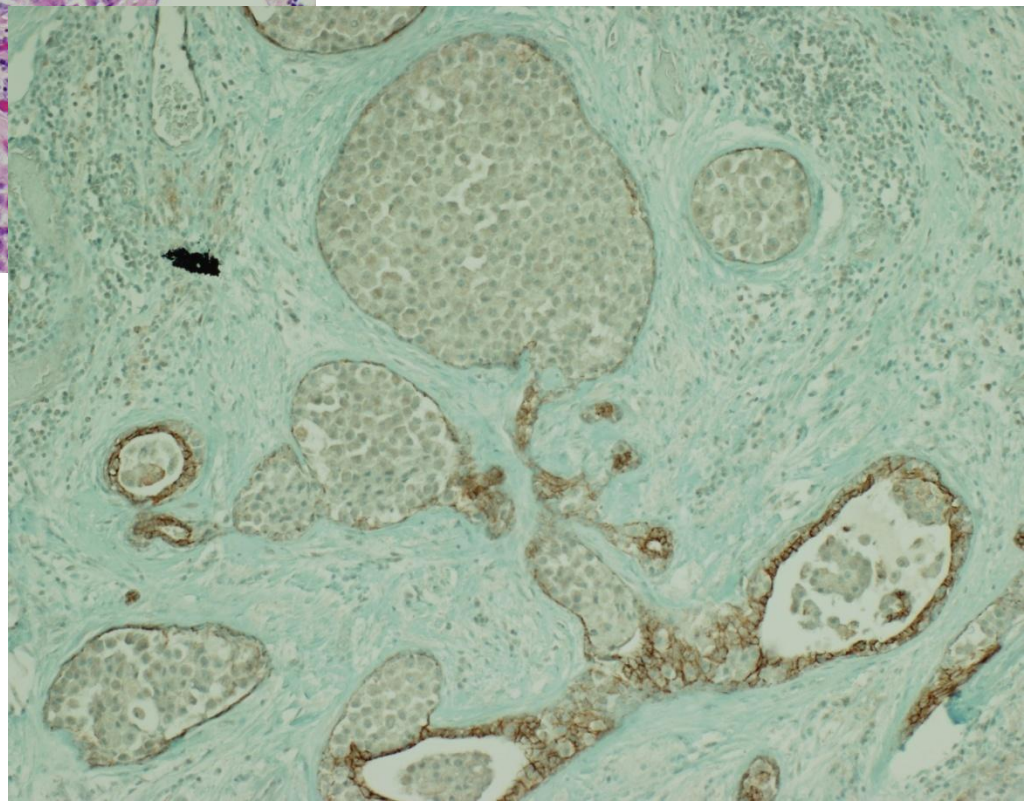

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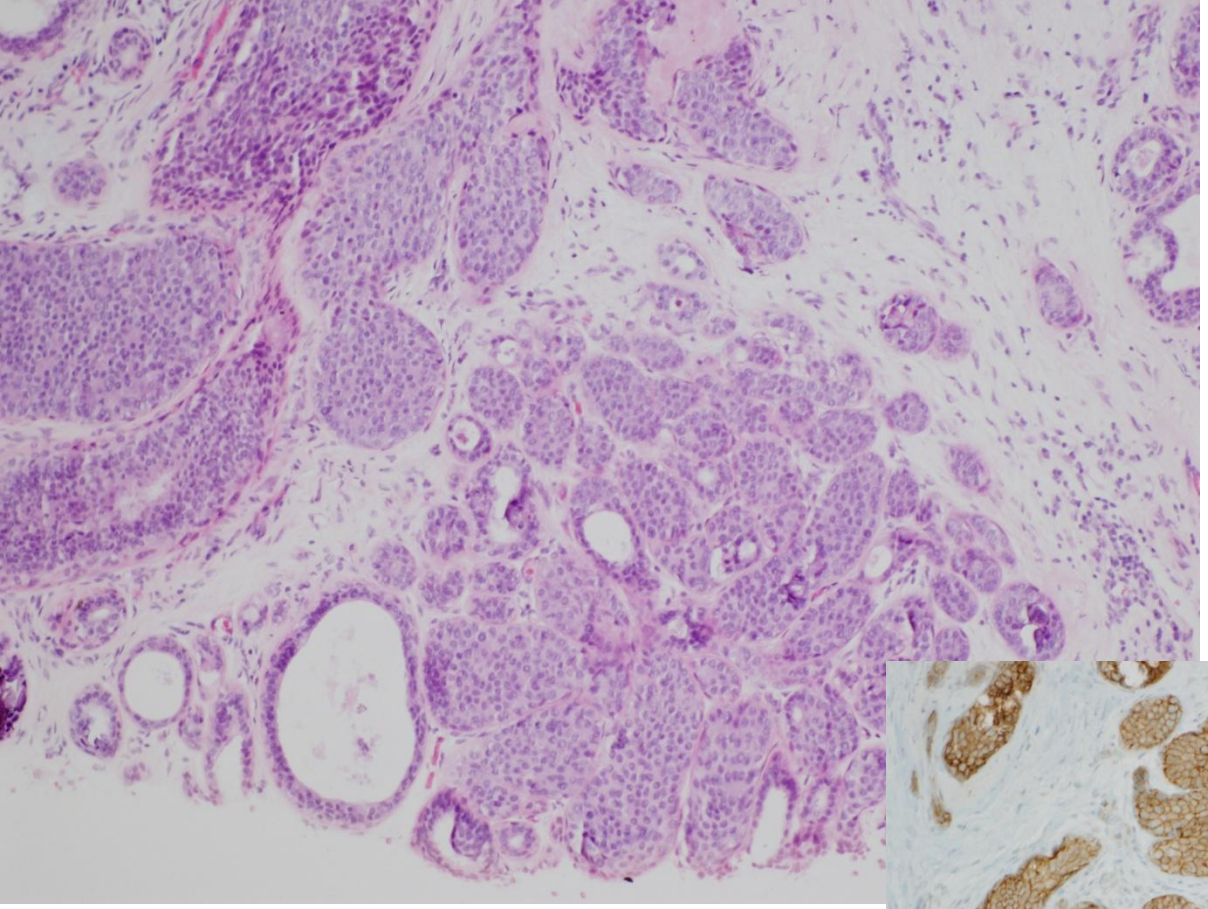
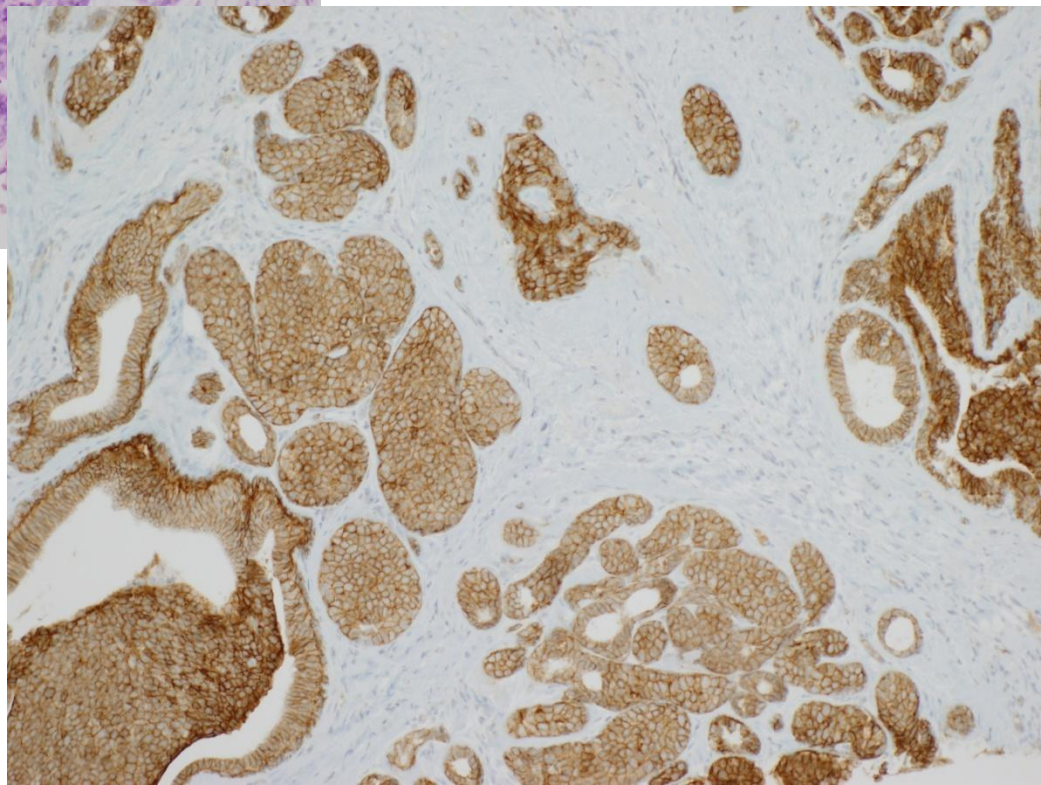
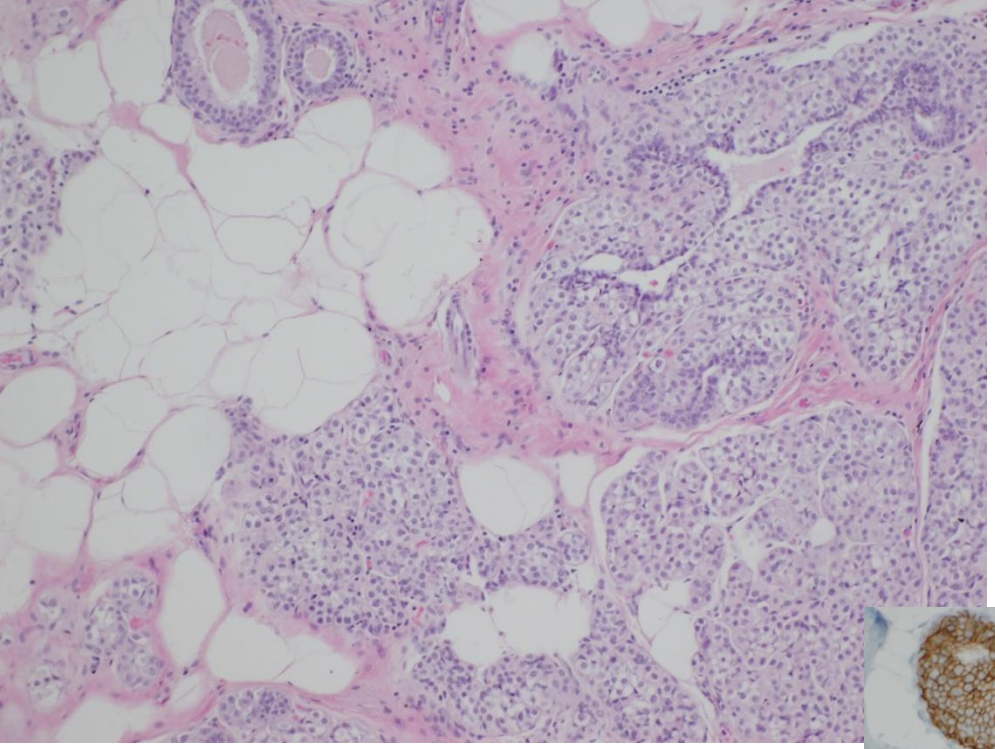
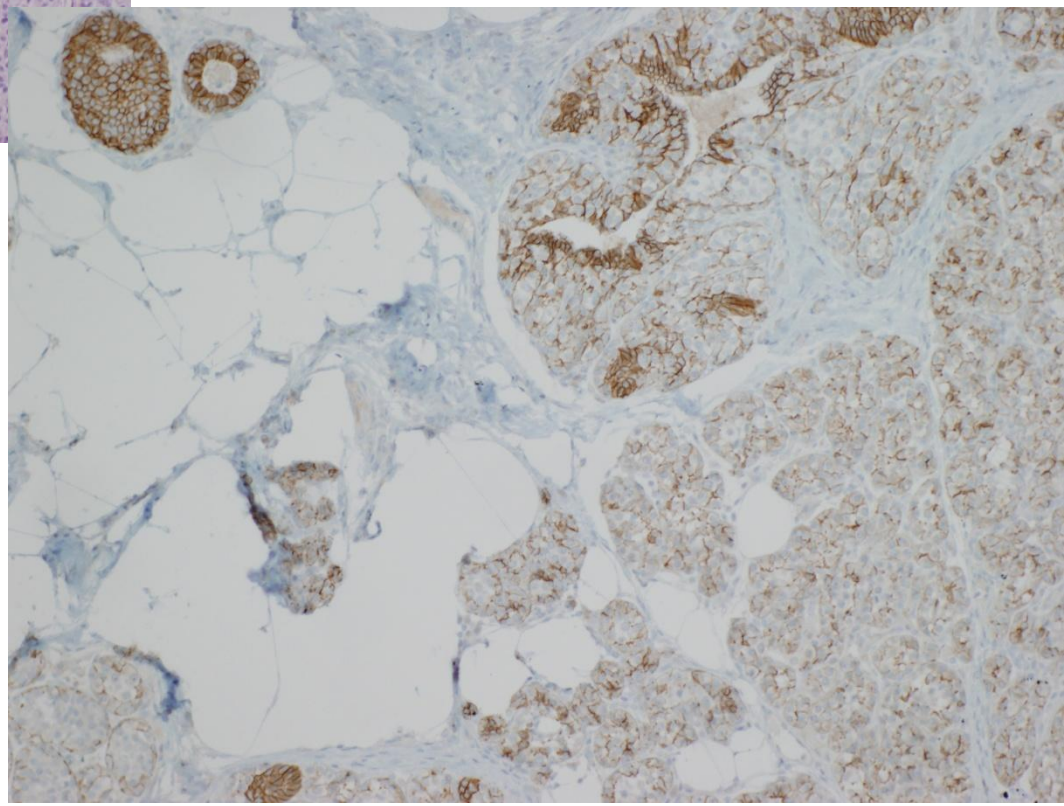


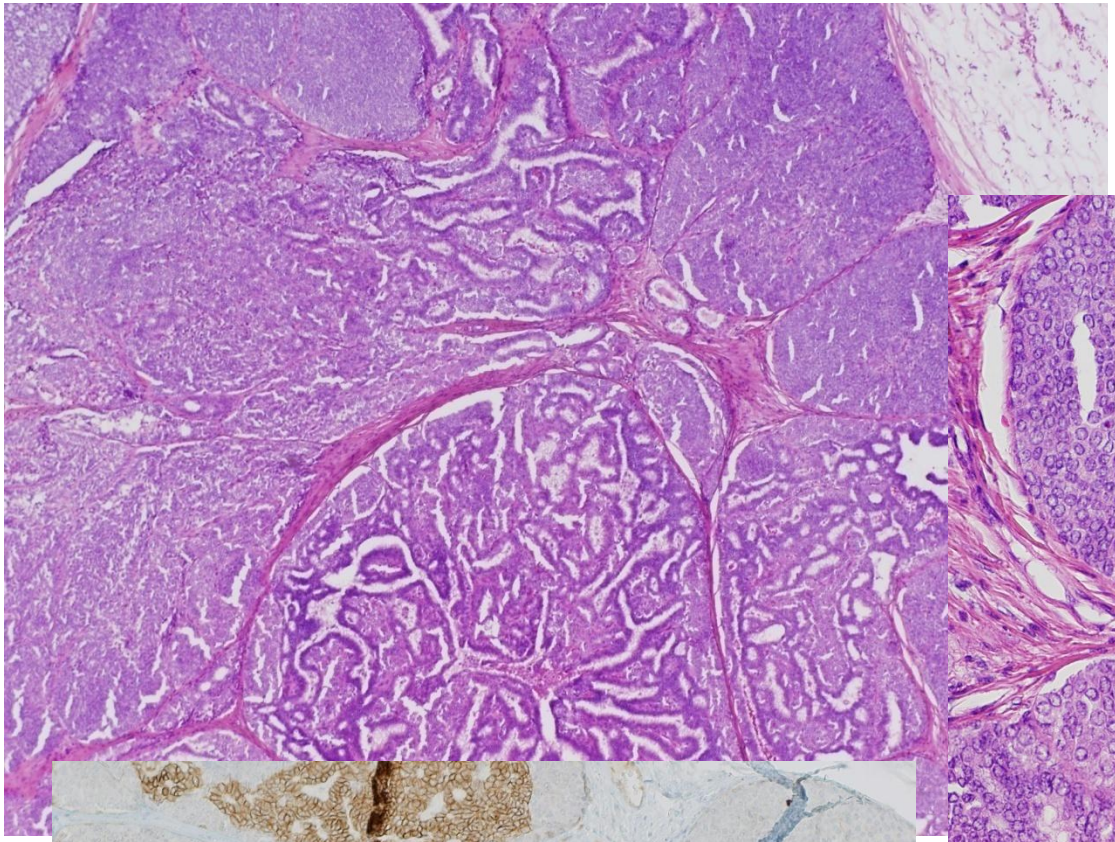


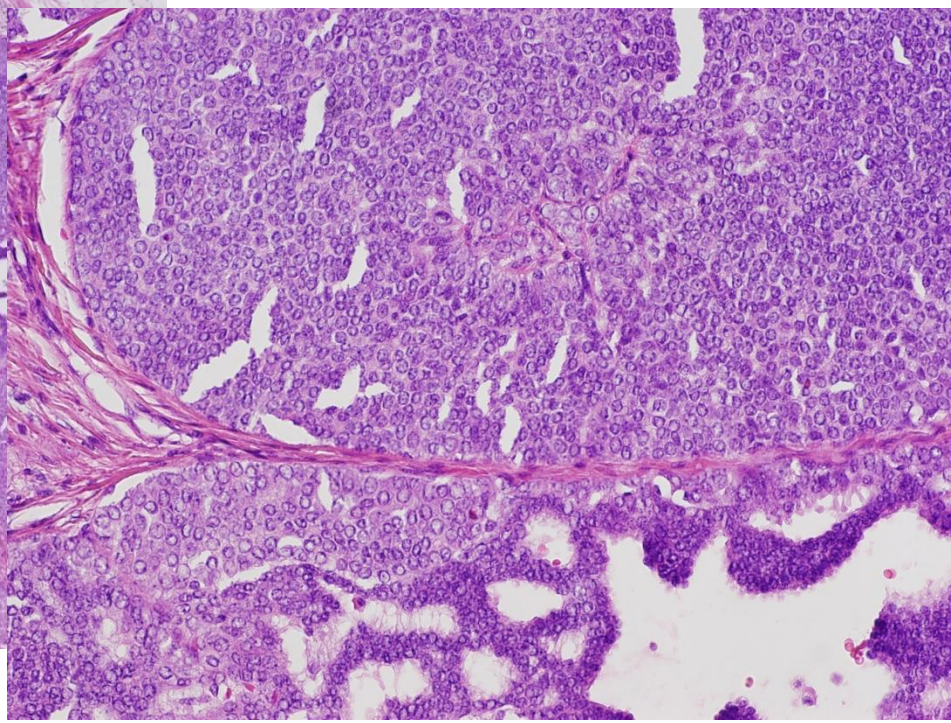
Case 7

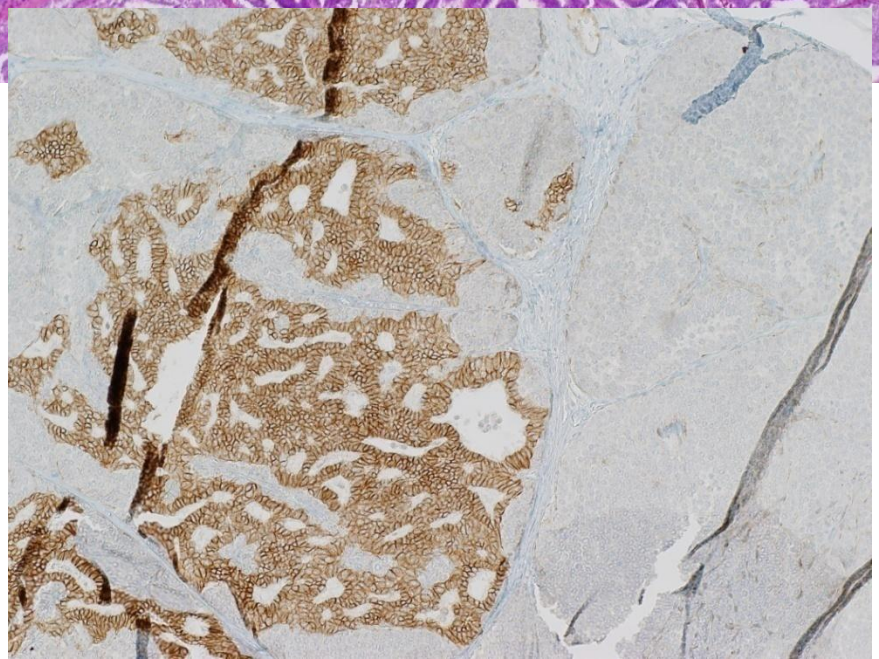




Case 8







Use of e-cadherin IHC

- Not necessary in unambiguous straight-forward cases; rely on morphology of ILC
- Another marker may be helpful: p120 catenin, β-catenin

	Normal epithelium	LCIS and ILC	DCIS and IDC
E-cadherin	Membrane staining	Aberrant membrane staining	Membrane staining
p120 catenin	Membrane staining	Cytoplasmic	Membrane staining
B-catenin	Membrane staining	Absence of membrane staining	Membrane staining

Use of e-cadherin IHC

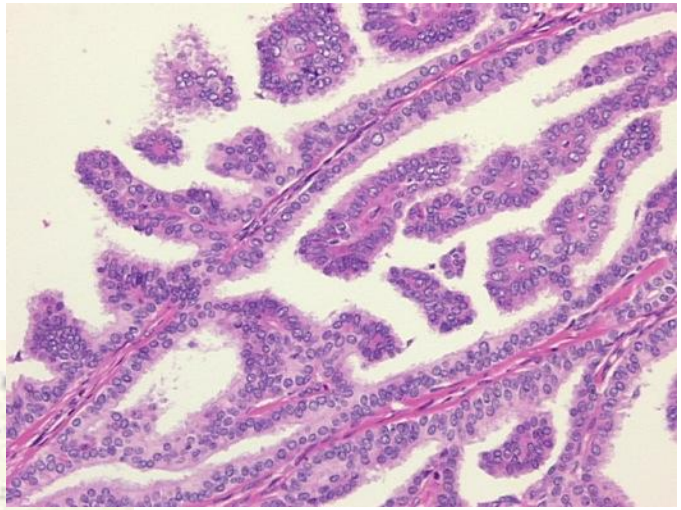
- When is it more important:
  - Core biopsy diagnosis of ILC may prompt pre-op MRI
  - Diagnosis of LCIS in CB may prompt excision
  - LCIS vs DCIS e.g. margin assessment

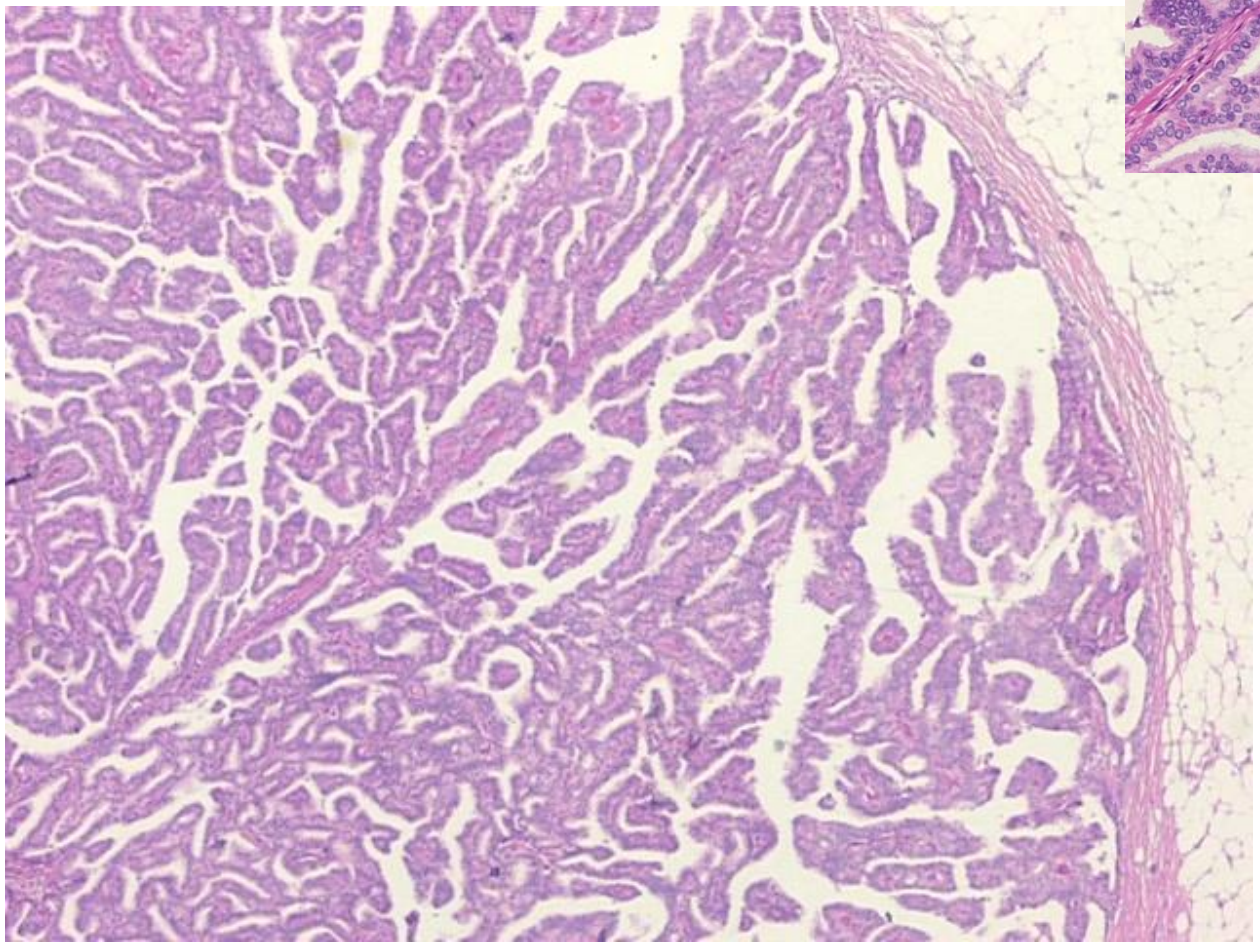
3. Breast neoplasms with limited metastatic potential

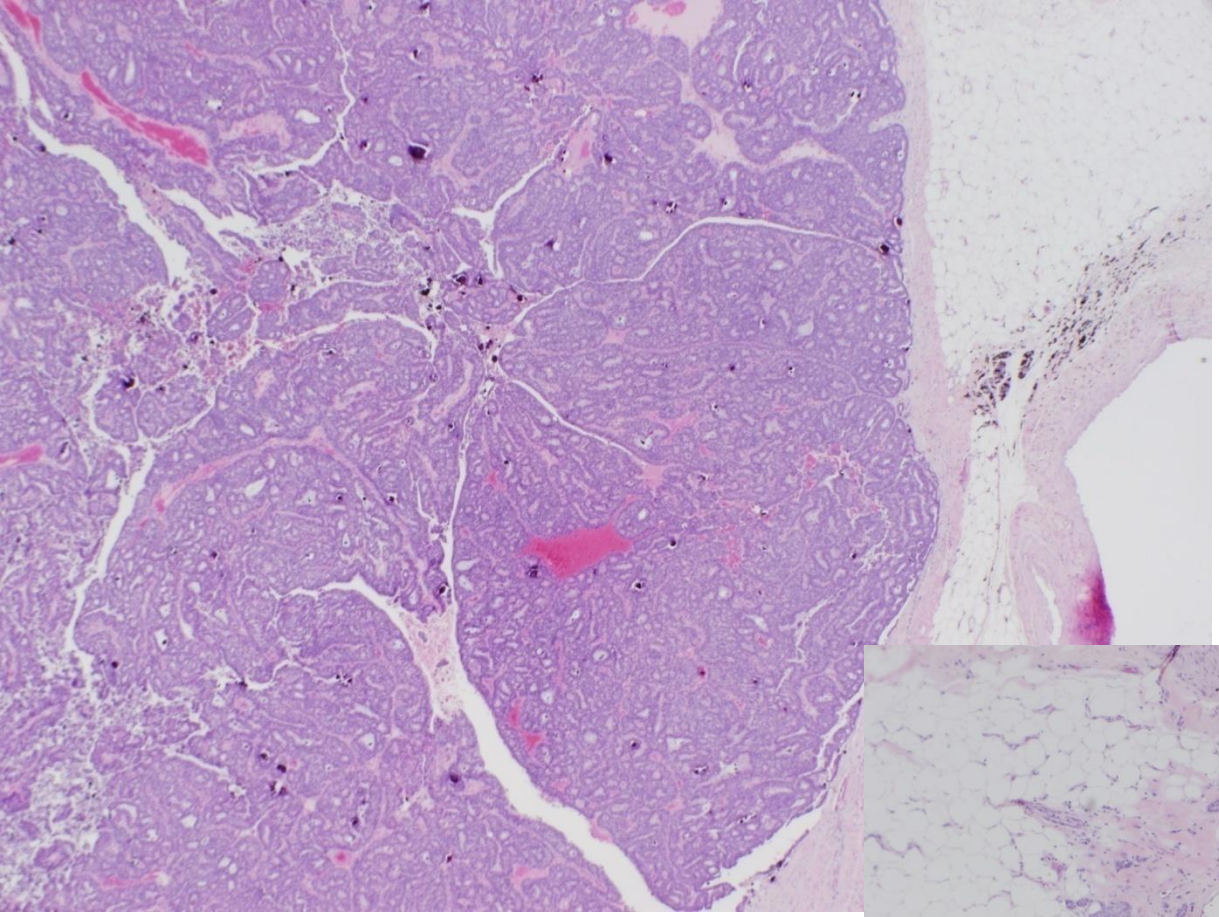
- **Encapsulated papillary carcinoma (EPC)**
- **Solid papillary carcinoma (SPC)**
- Low grade adenosquamous carcinoma
- Low grade fibromatosis-like metaplastic carcinoma
- Borderline phyllodes tumor
- Atypical adenomyoepithelioma

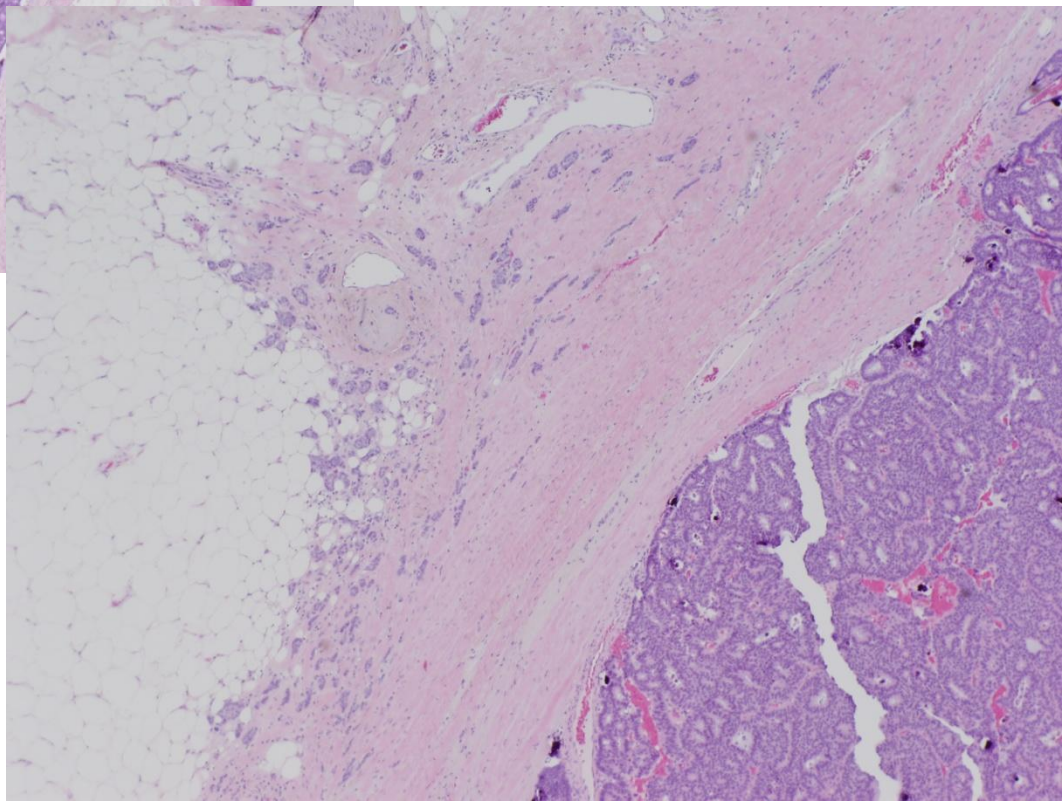
Encapsulated papillary carcinoma

- Architecture
- Low-intermediate grade nuclear atypia
- ER positive; HER2 negative
- >80% completely lack a myoepithelial component
- Current consensus: EPC should be managed and staged as Tis (DCIS) disease
- Look for conventional invasive component outside of the fibrous capsule; sample well
  - pT stage based on focus of conventional invasive tumor









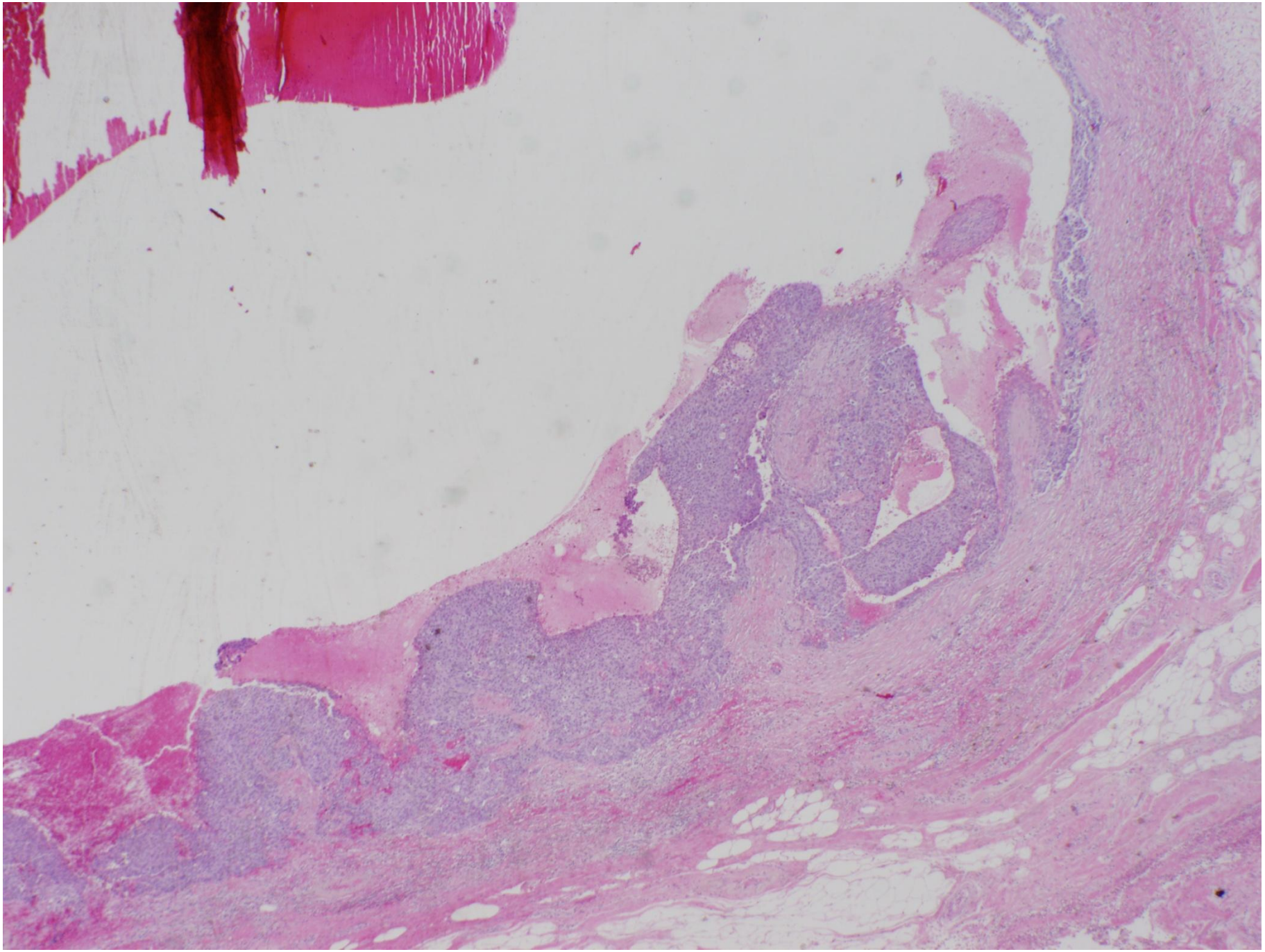
Encapsulated papillary carcinoma

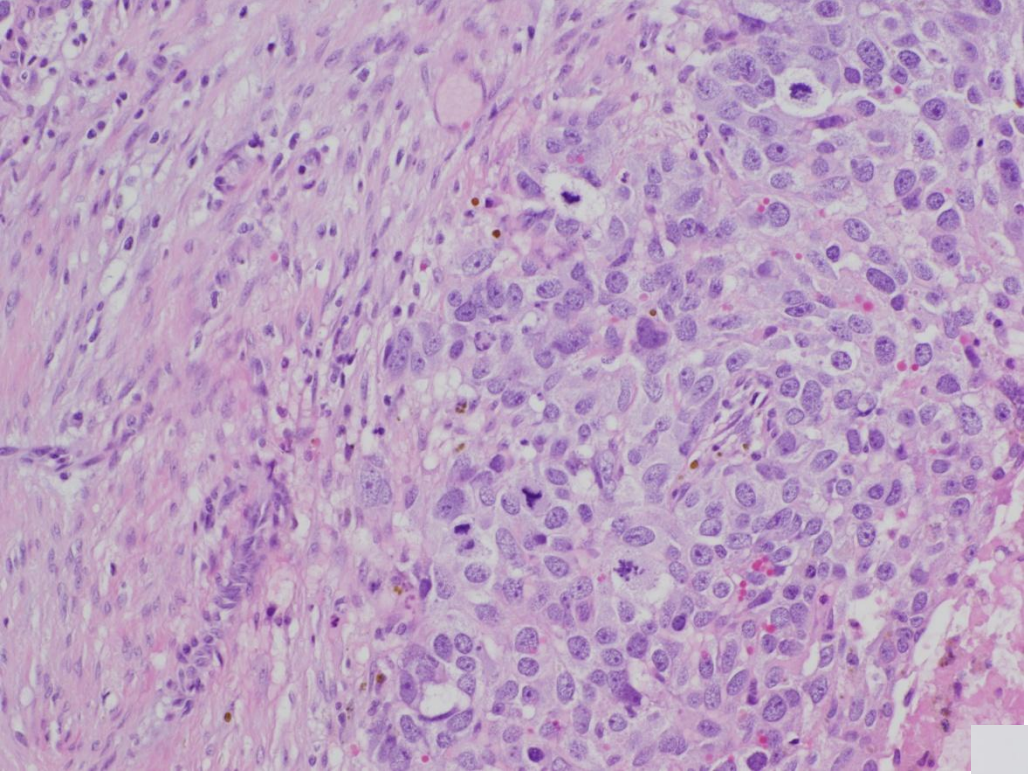
- Tend to occur in older women
- Usually have indolent clinical course
  - LVI 3%
  - Nodal mets 3% (microscopic)
  - Chest wall recurrence 7%
    - Recurrence is associated with aggressive behaviour

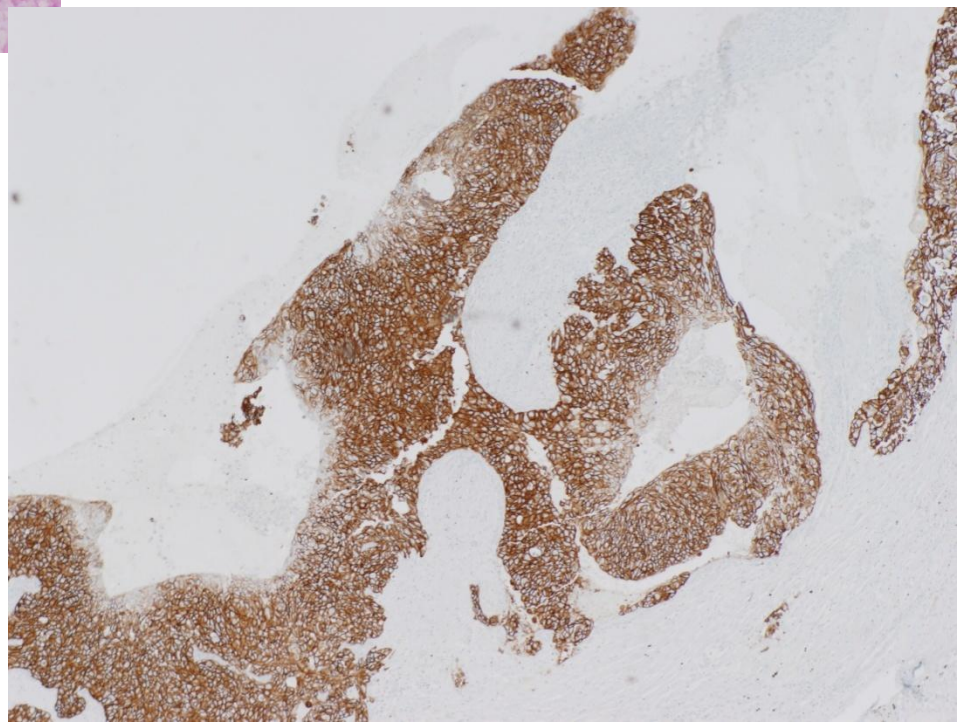
Rahka EA et al. Encapsulated papillary carcinoma of the breast: an invasive tumor with excellent prognosis. *Am J Surg Pathol*. 2011;35:1093-1103.

High grade EPC-like carcinoma

- Rare
- Often ‘triple negative’
- High mitotic rate +/- necrosis
- Should be managed as invasive carcinoma
- Report as ‘invasive high-grade carcinoma with EPC-like features’



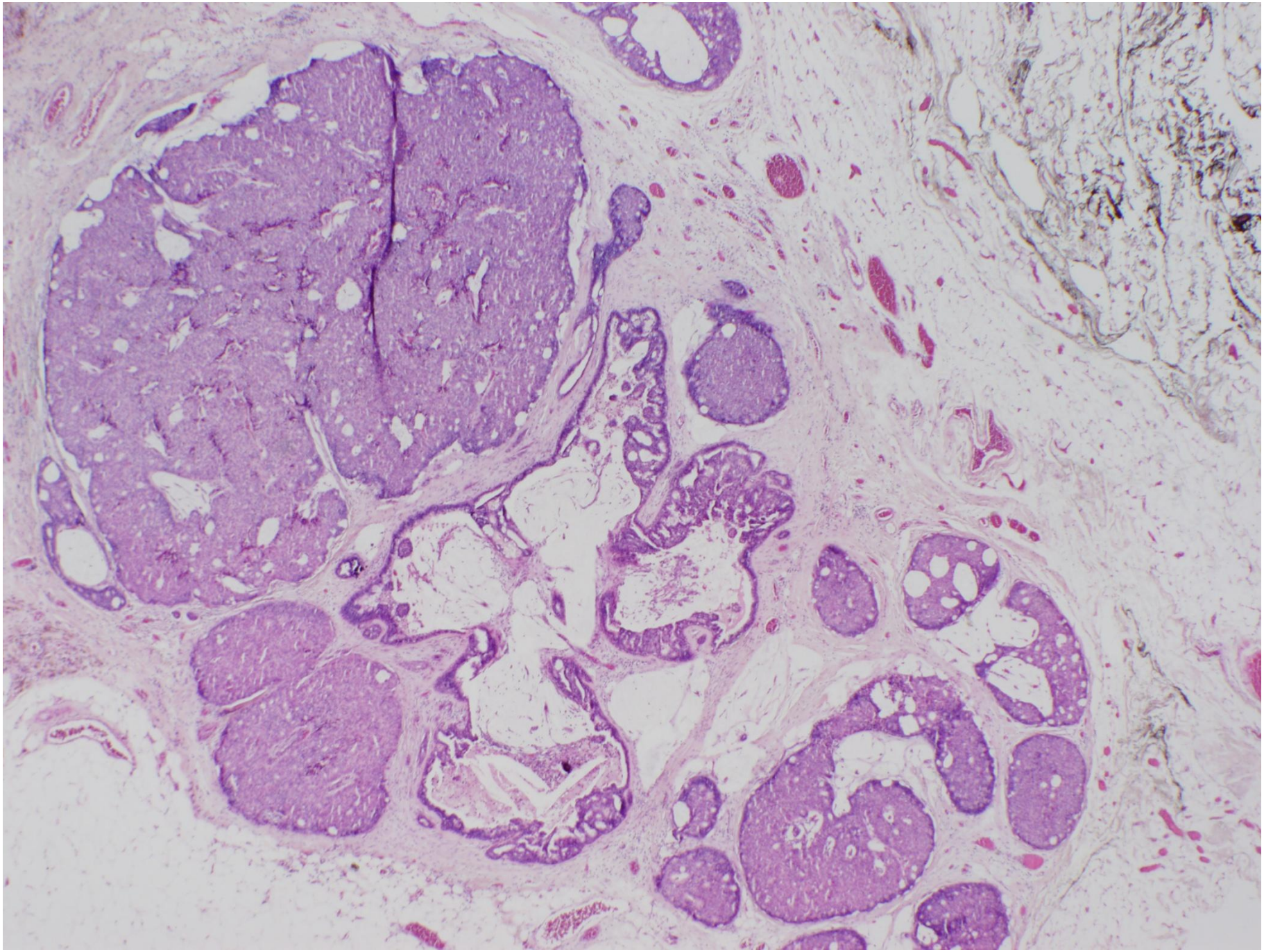


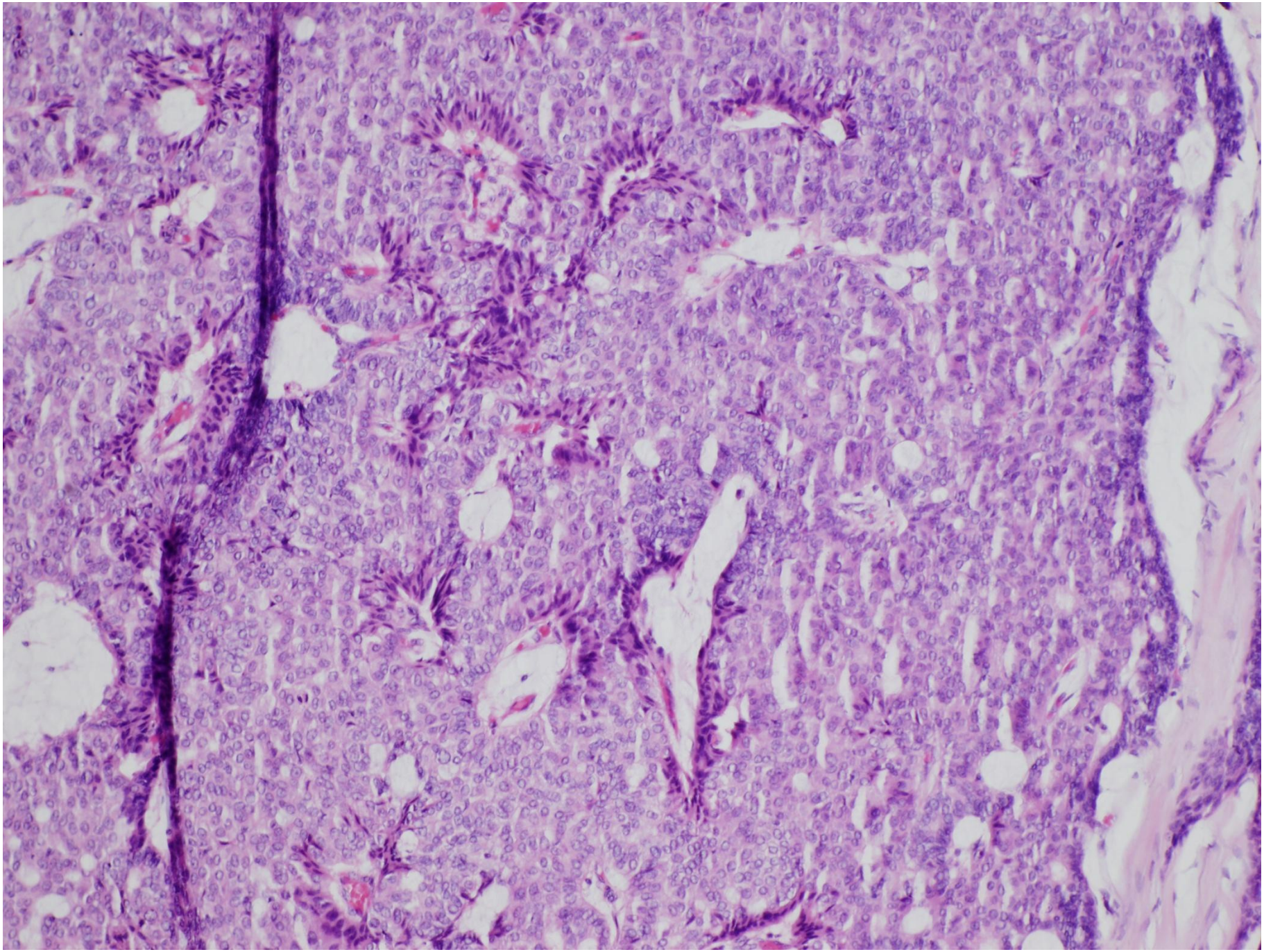


HER2

Solid papillary carcinoma

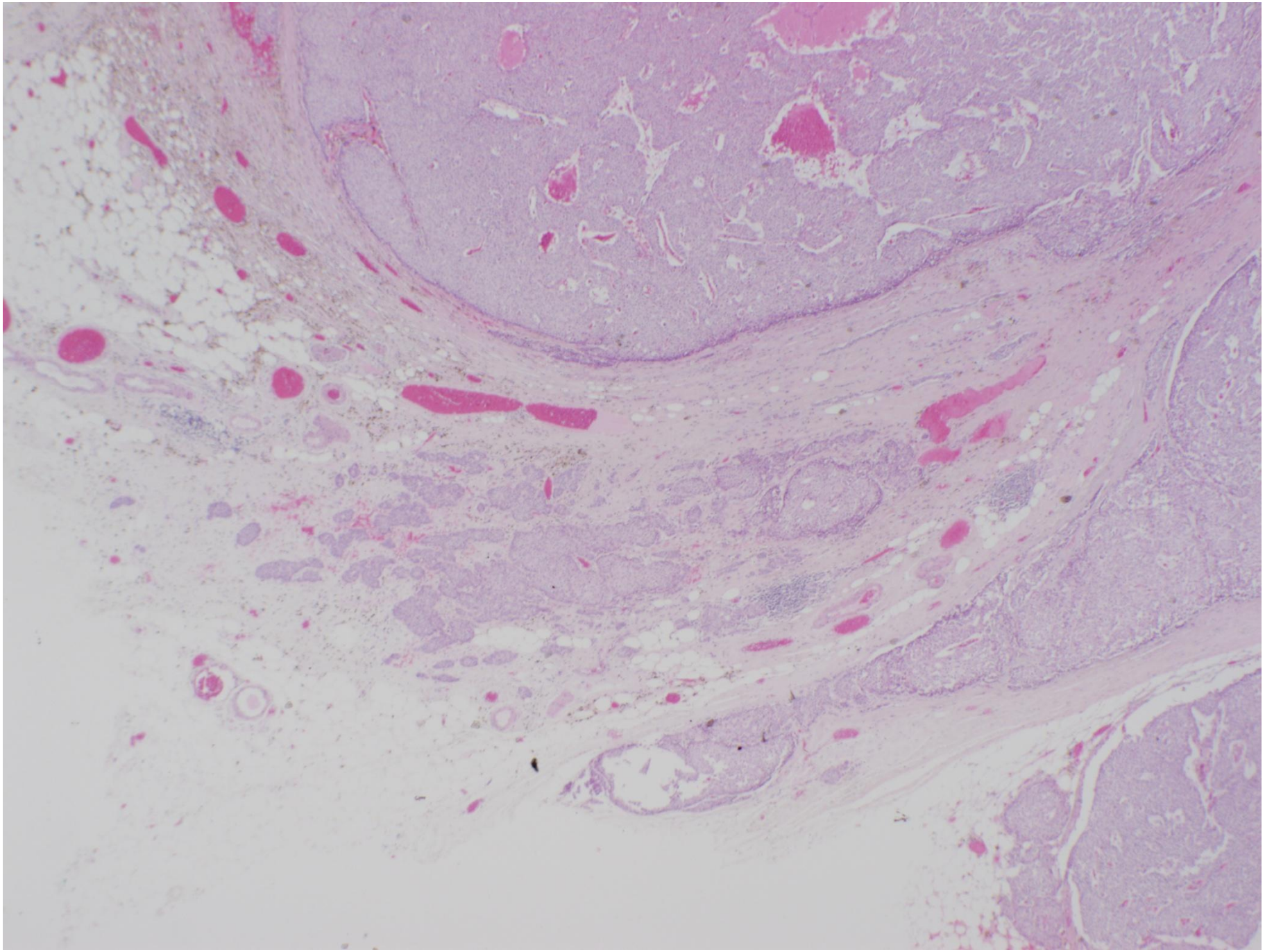
- Architecture
- Neuroendocrine cytology
- May not see a myoepithelial layer around all tumour nests





Solid papillary carcinoma

- Identification of frank invasion can be problematic
  - Look for ragged irregular margins and complex architecture with complete lack of myoepithelial cells
  - When in doubt, classify as pTis
- Managed/staged as Tis (DCIS) unless associated with conventional invasion



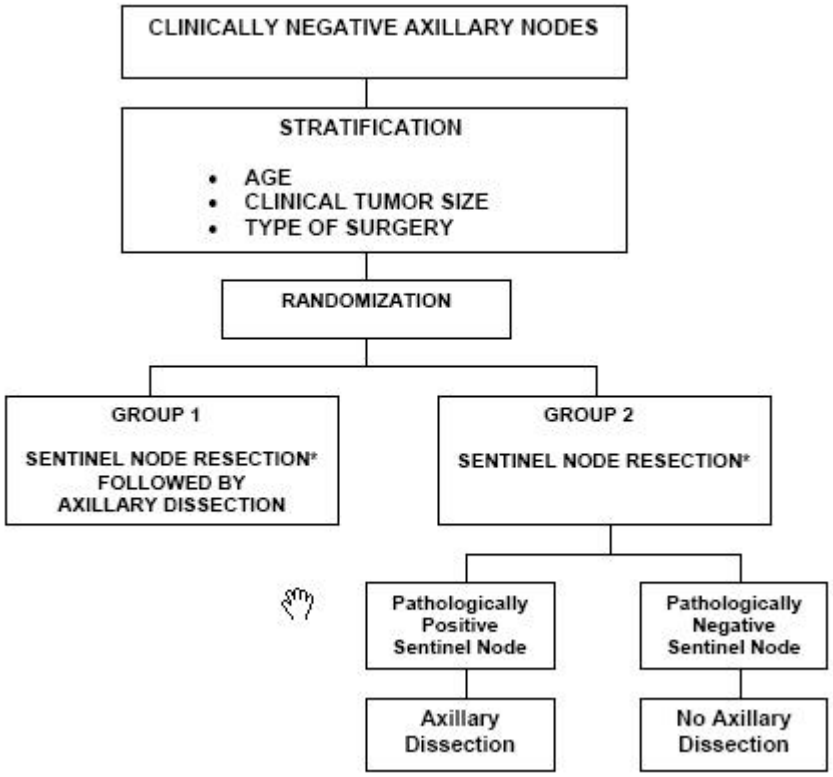
4. Sentinel lymph nodes in breast cancer

- Gross specimen handling
- Reporting/staging
- Changes to the clinical management of nodal disease

National Surgical Adjuvant Breast and Bowel Project B-32 trial

- Randomized prospective clinical trial
  - Demonstrated that in patients with T1/T2 cN0 tumors and negative SLNs, staging by SLN biopsy is equivalent to ALND

NSABP B-32 trial



NSABP B-32 trial

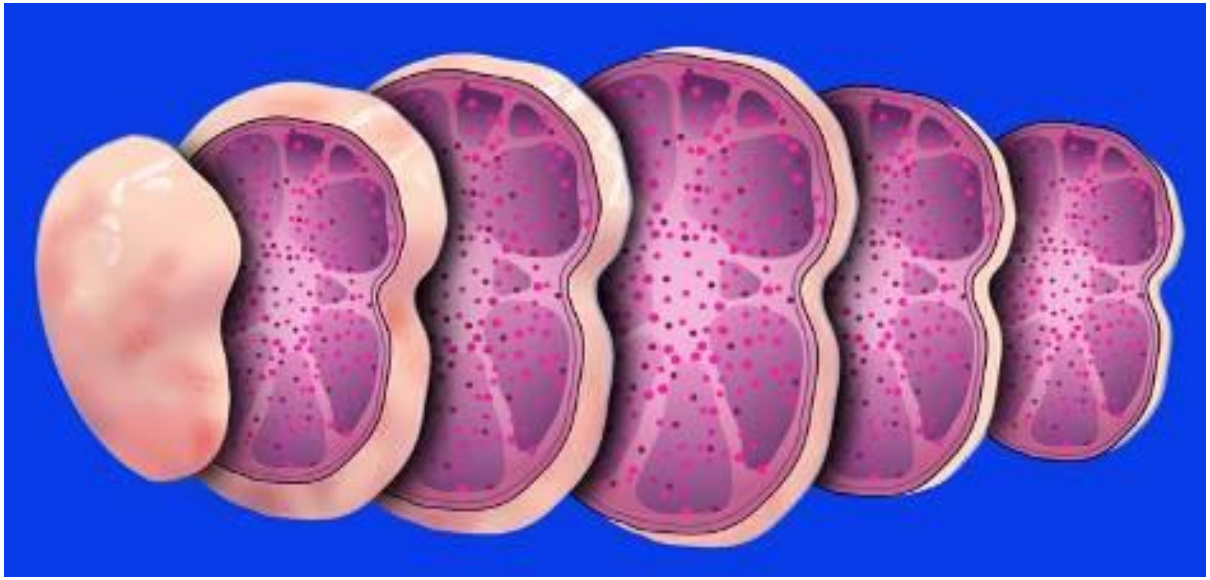
- Mean study time 95.6 mo (~8 yrs)
  - Axillary recurrence 0.4% SLN vs 0.7% for SLN-ALND for SLN+ disease
  - Fewer side effects without ALND
  - SLN predicts burden of axillary disease in 90-99% of patients

Sentinel lymph nodes - basic recommendations

- **Thin gross sections: 2mm**
- **Embed and examine each slice; only one H&E section required**
- If levels used, evenly space sections through block (0.5mm or 0.2 mm intervals)
- IHC not required, but can be helpful especially for lobular carcinoma

Gross Examination

- Rationale: by sectioning node at 2mm intervals, there is a high probability of identifying macrometastases (>2mm)



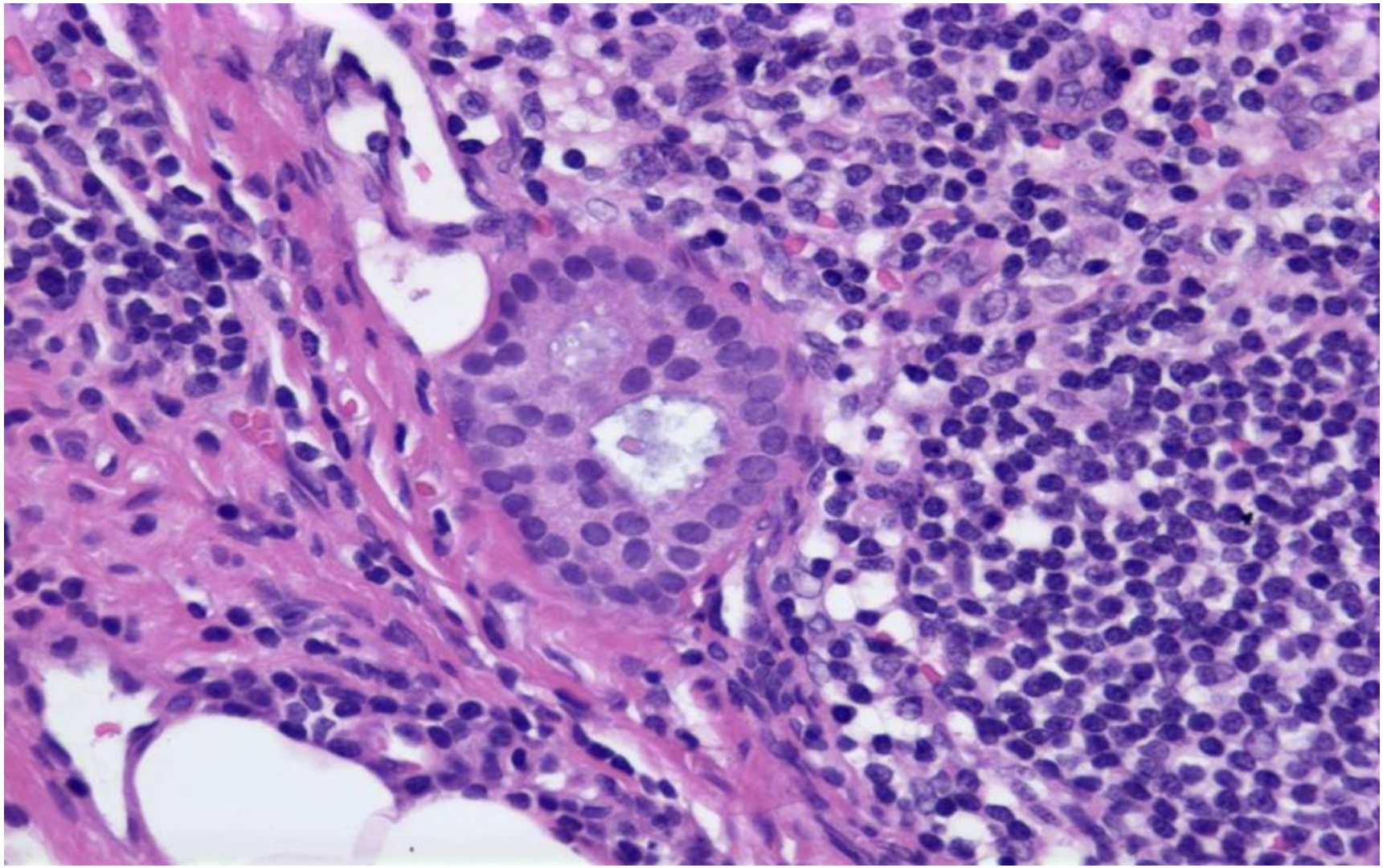
pN staging, 7th ed. AJCC

- Isolated tumor cells ≤0.2 mm (< 200 cells) considered pN0(i+)
  - considered node negative

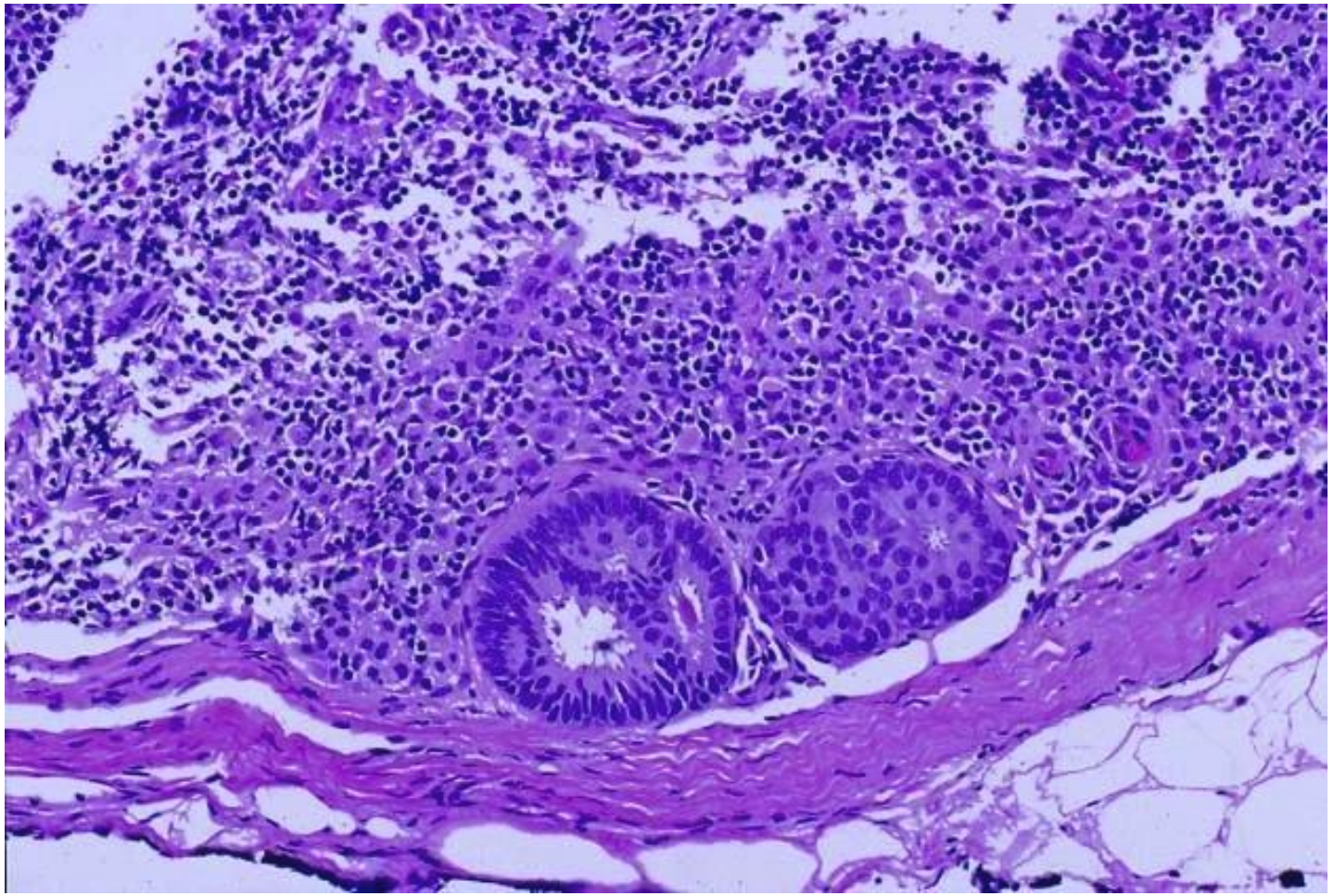
- Micromets >**0.2mm** - ≤2mm (and /or >200 cells) are pN1(mi)

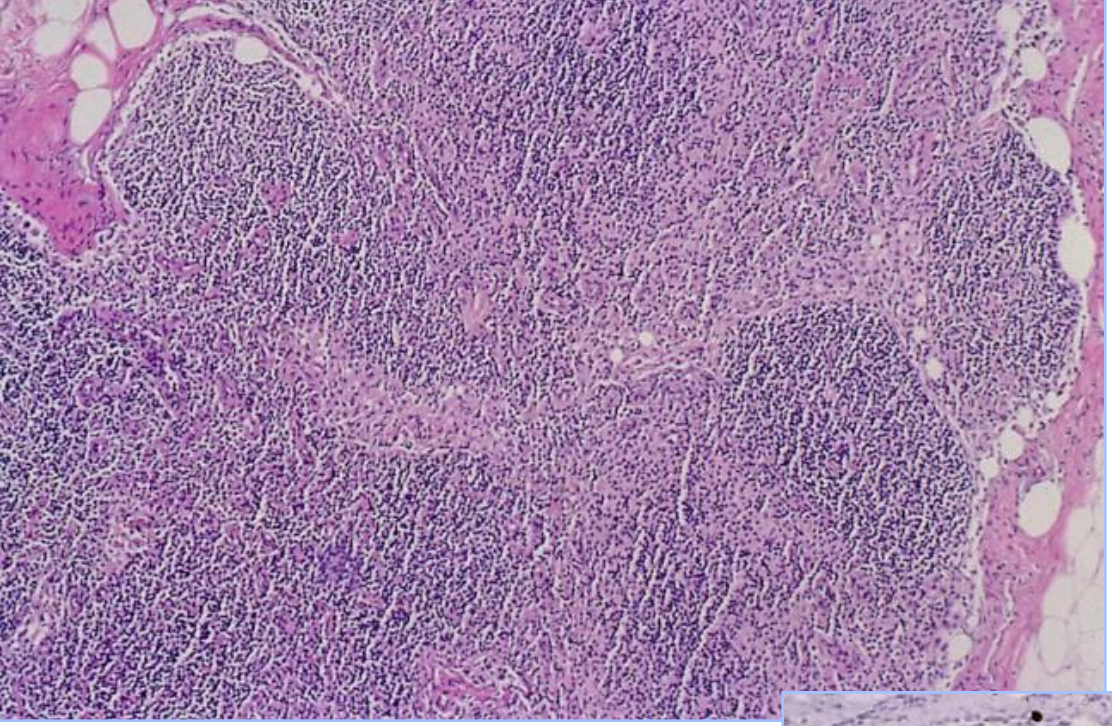
- Macromets >2mm are pN1

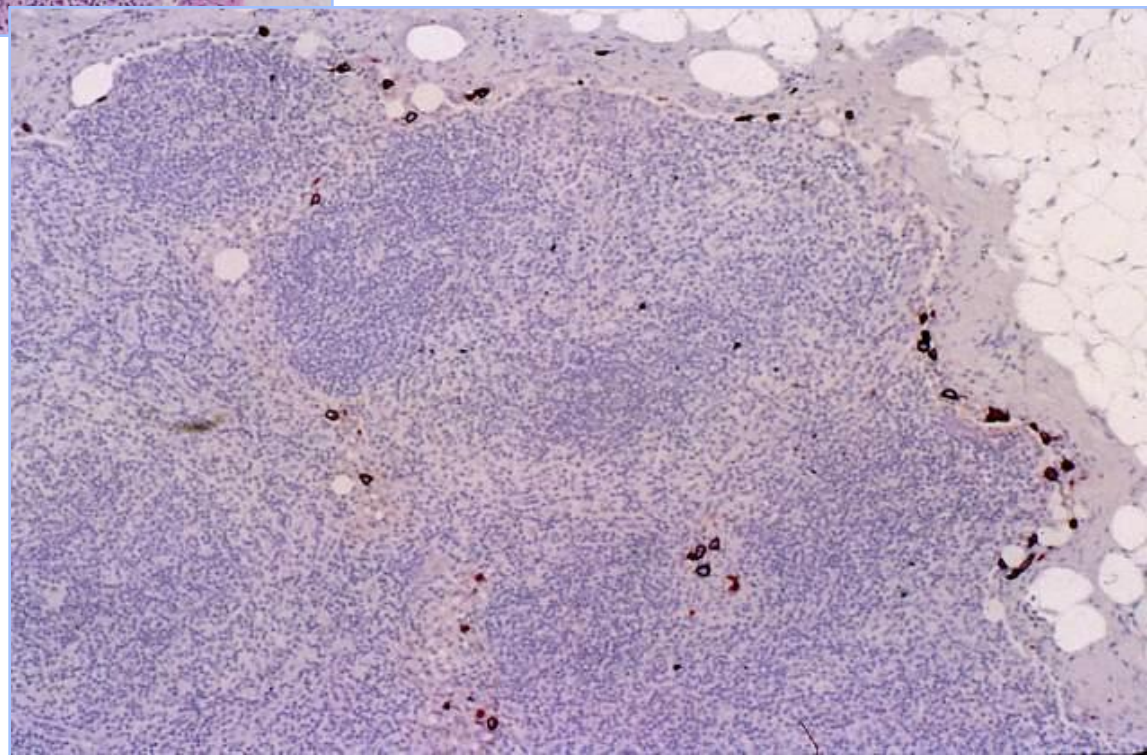
pN0(i+)



pN1mi







Nodal disease: breast carcinoma

- Clinical trial data has changed clinical practice
- Trend to avoid axillary dissection due to morbidities
- Limited non-palpable SLN mets may be treated with axillary radiotherapy and chemotherapy instead of axillary dissection

- Palpable nodal disease: axillary dissection

American College of Surgeons Oncology Group Z0011 trial

- Among patients with T1/T2 tumors and limited SLN metastatic disease (1-2 positive nodes) treated with BCS and tangential whole breast irradiation, the use of SLNBx alone compared with ALND did not result in inferior survival

ASOSOG Z0011 trial

- Axillary recurrence <1% at 6.3 years median f/u (0.9% in SLN group vs 0.5% in ALND group)
- Local recurrence at 5 years did not differ between the 2 groups (1.6% in SLN group vs 3.1% in the ALND group)
- No difference in DFS or OS

EORTC AMAROS trial

- Radiotherapy or surgery after a positive SLN bx
  - T1/T2 (<3 cm), clinically node negative
  - Both provide excellent comparable regional control
  - Less lymphedema with RT

EORTC AMAROS trial

- Axillary recurrence at 6.1 years median

f/u (1.03% in SLN group vs 0.54% in ALND group)

MA.20

- Examined the incremental benefit of adding nodal RT to ALND
- Standard breast RT vs breast RT plus regional nodal fields (including supraclav, infraclav, ipsilateral internal mammary chain)
- Inclusion:
  - SLN positive
  - High risk node negative, tumors >2cm, < 10 axillary node removed + 1 other high risk feature (gr 3, ER neg, +LVI)

MA.20

- Improved 5 yr DFS (89.7% for nodal and whole breast RT vs 84% for whole breast RT alone)
- No difference in overall survival
- More adverse outcomes in the nodal RT arm (side effects of RT)

Limitations of the trial data: Z0011 & AMAROS

- Underpowered for adverse events
- Favoured accrual of low-risk T1, ER positive cases
- Z0011 did not meet accrual goal, closed early

Limitations of the trial data: MA.20

- More patients with > 2 positive nodes and extracapsular extension
- Only 10% were node negative
- Higher risk patient population/heterogeneous group

Approach to the axilla in early stage breast cancer

- T1/T2, clinically node negative
  - BCS with:
    - SLN negative including ITC positive: breast irradiation
    - 1-3 SLN positive: breast and axillary irradiation
    - >3 SLN positive or unexpected bulky nodal disease: breast and axillary irradiation, and axillary LN dissection
  - Mastectomy with:
    - SLN negative including ITC positive: no further Rx
    - 1-3 SLN positive: consideration of axillary irradiation
    - >3 SLN positive or unexpected bulky nodal disease: axillary irradiation and axillary LN dissection

Lack of data…

- Microscopic extracapsular extension
- Use/timing of SLN biopsy in patients receiving neoadjuvant Rx
  - may be suitable for patients with cN0 disease prior to chemo

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