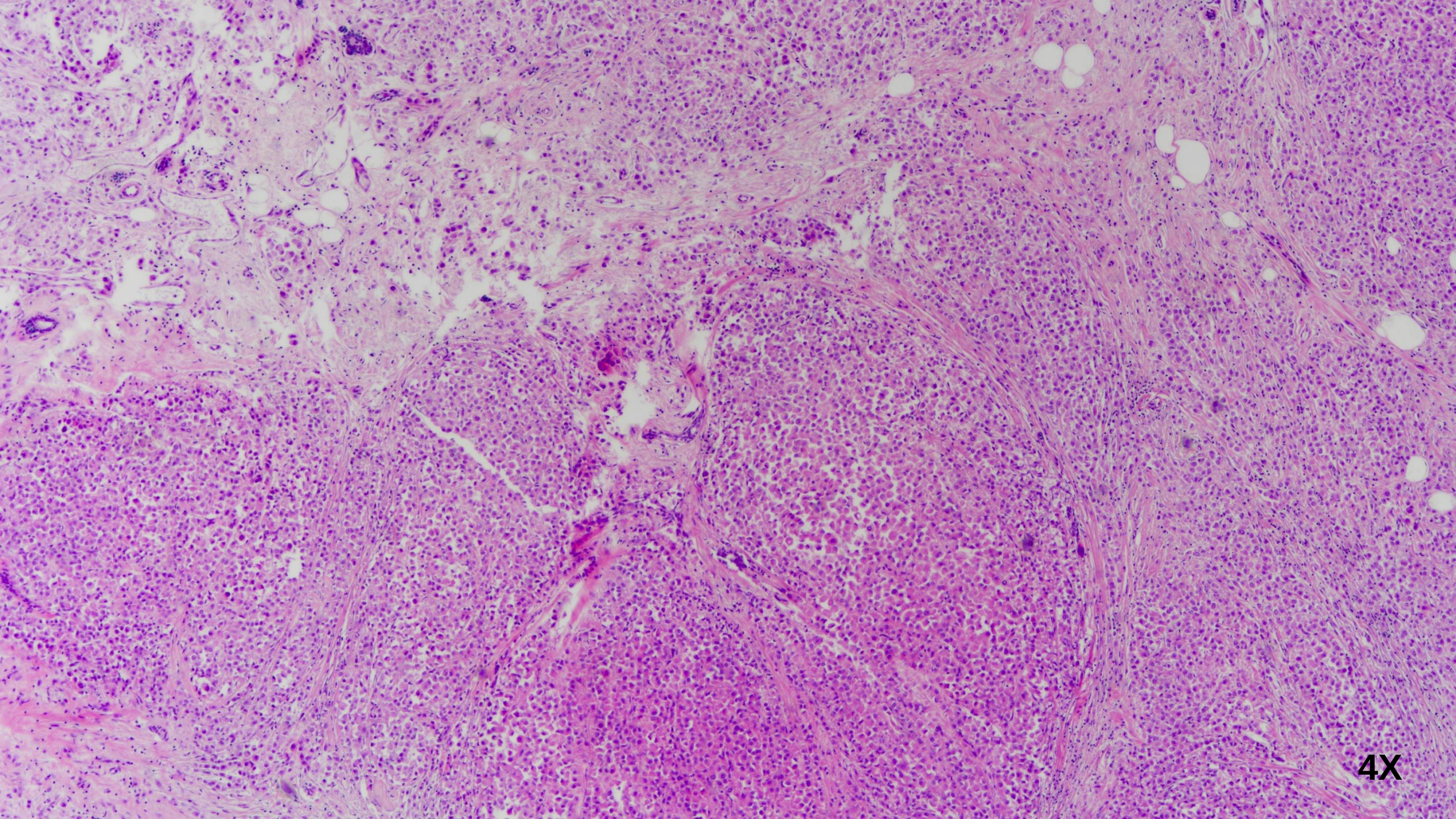
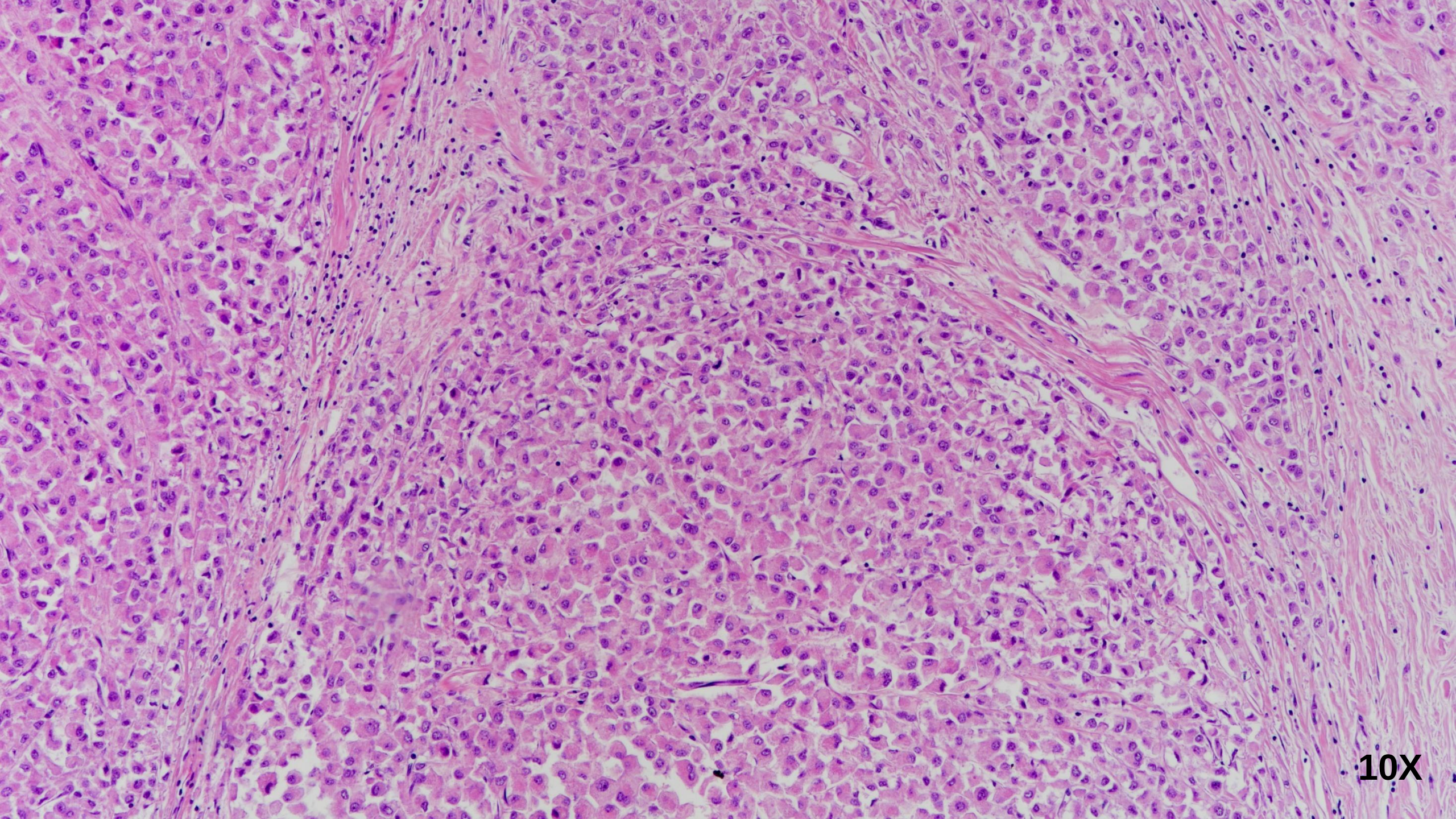
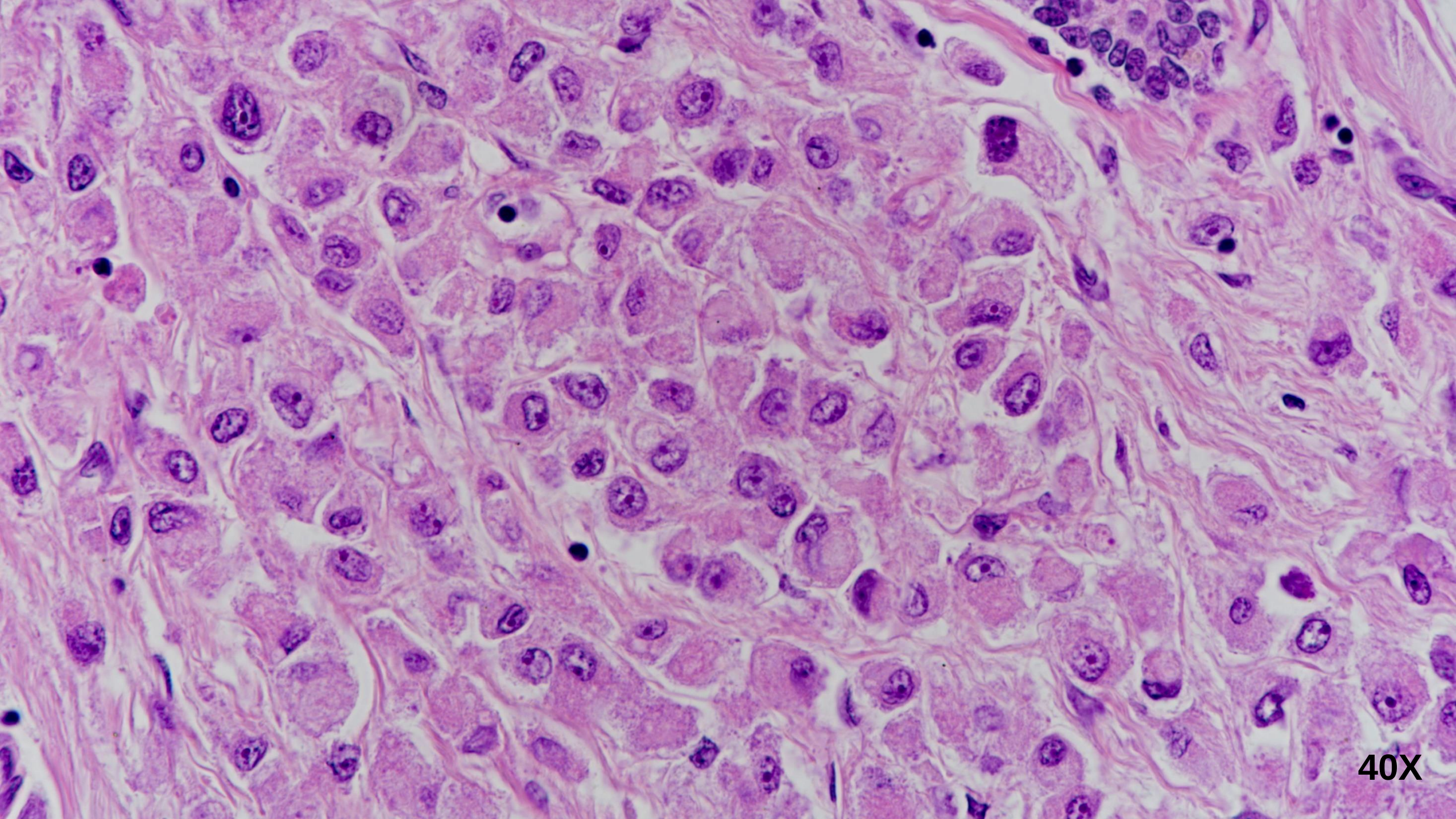
18T 2130-CO4

- 60 years old female
- Chief complaint: L7-8H breast mass x 2 months


4X


10X


40X

18T 2130-CO4

Immunohistochemical staining

- E-Cadherin: Negative
- Androgen Receptor (AR): Positive
- GCDFP-15: Positive

Diagnosis

Invasive lobular carcinoma, pleomorphic variant with apocrine differentiation

# Apocrine differentiation in breast cancer

- Characterized by large cells with abundant eosinophilic granular cytoplasm and enlarged nuclei with prominent nucleoli, resembling apocrine sweat glands
- Express  GCDFP-15 (an antigen also found in apocrine metaplasia)
- Characteristic steroid receptor profile: ER-negative, PR-negative, and AR-positive
  - AR is consistently expressed in carcinomas with apocrine differentiation
  - AR activation is associated with HER2 overexpression and/or *ERBB2* amplification in 30–60% of cases

# Pleomorphic ILC

- Retains the distinctive growth pattern of classic ILC but with marked cellular atypia and nuclear pleomorphism relative to classical ILC
- May have an increased mitotic rate
- Composed of signet ring cells
- May show apocrine or histiocytoid differentiation
  - 10/10 pILC were shown to have apocrine features based on both morphological and GCDFP15 expression
  - Another study with 34 cases pILC demonstrated GCDFP15 expression in 71% of their cases (Vs 33-50% in ILC)

| Feature | ILC | pILC |
|---|---|---|
| Single file/ targetoid pattern | 18/22 | 10/10 |
| Round oval nuclei | 22/22 | 0/10 |
| Pleomorphic nuclei | 0/22 | 5/10 |
| Size of cells | Small-medium | Medium-large |
| Shape of cells | Uniform | Variable |
| Foamy cytoplasm | 0/22 | 5/10 |
| Intracytoplasmic mucin | 2/22 | 8/10 |
| Intracytoplasmic lumina | 16/22 | 5/10 |
| Mucin crescents | 0/22 | 3/10 |
| GCDFP-15 | 0/22 | 10/10 |

Eusebi V et al 1992 Hum Pathol 23:655
Middleton L et al 2000 Am J Surg Pathol 24:1650

# Classical ILC: apocrine feature

- Classical ILC can unusually display HER2 overexpression with extracellular mucin production
- HER2+ cILC associated with histiocytoid morphologic features
  - some considered the feature an apocrine variant of lobular carcinoma/ pILC with apocrine metaplasia
  - cases included in the series showed small grade 1 or 2 nuclei and lack nuclear pleomorphism

**Table 3**
**Histomorphologic Characteristics of Classical Invasive Lobular Carcinoma With and Without HER2 Overexpression***

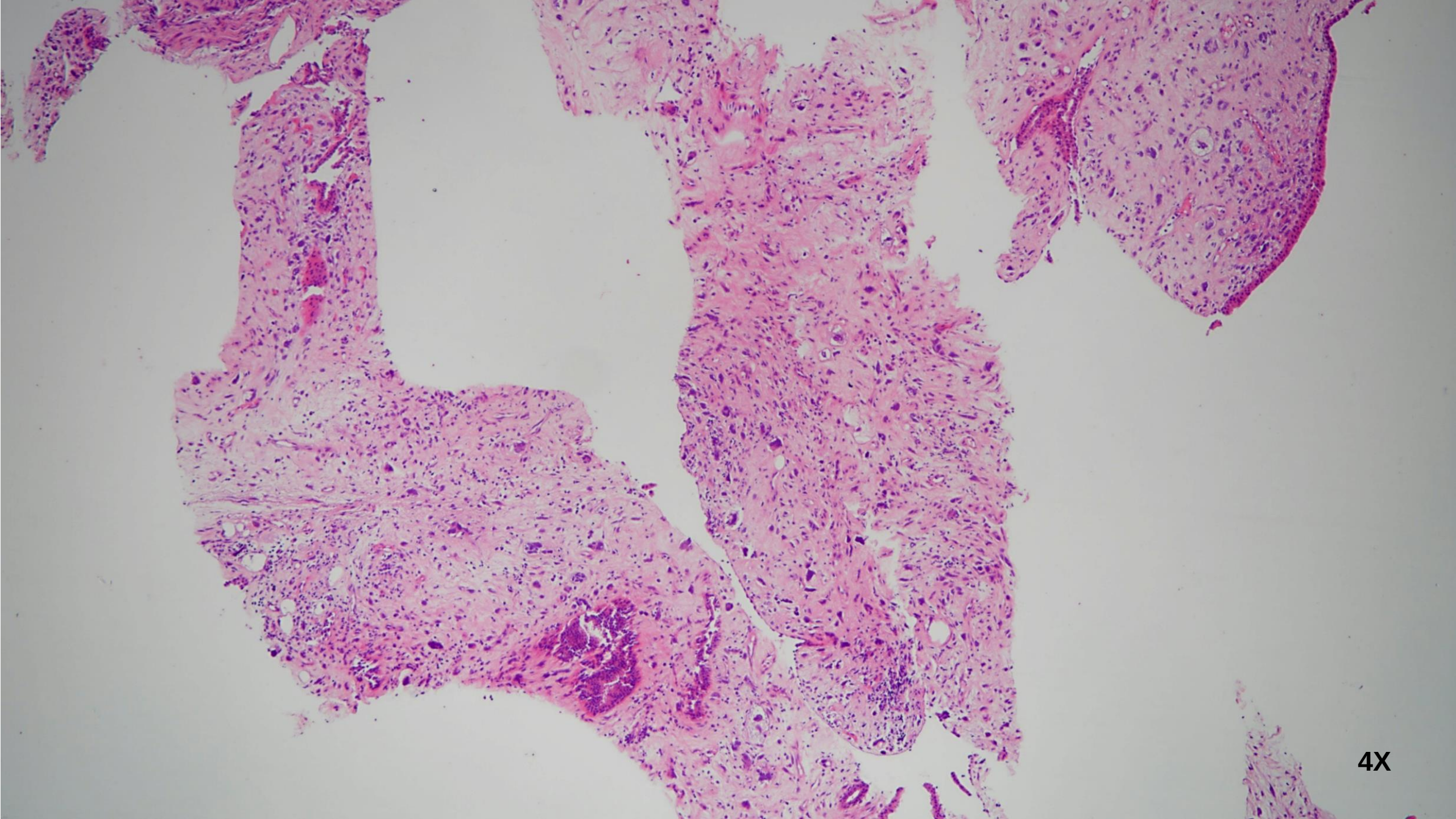
| | HER2+ (n = 12) | HER2– (n = 40) | *P* |
|---|---|---|---|
| Nuclear grade† | | | .026‡ |
| 1 | 1 (8) | 18 (45) | |
| 2 | 11 (92) | 22 (55) | |
| 3 | 0 (0) | 0 (0) | |
| Mitosis† | | | .013‡ |
| 1 | 10 (83) | 40 (100) | |
| 2 | 2 (17) | 0 (0) | |
| 3 | 0 (0) | 0 (0) | |
| Nottingham score† | | | .007‡ |
| 5 | 1 (8) | 18 (45) | |
| 6 | 9 (75) | 22 (55) | |
| 7 | 2 (17) | 0 (0) | |
| Average (range) Ki-67 index (%) | 33 (10-75) | 20 (1-50) | .07 |
| Special morphologic variant | | | |
| Histiocytoid | 4 (33) | 0 (0) | .001§ |
| Apocrine | 2 (16) | 1 (3) | .129 |
| Signet-ring | 4 (33) | 4 (10) | .071 |

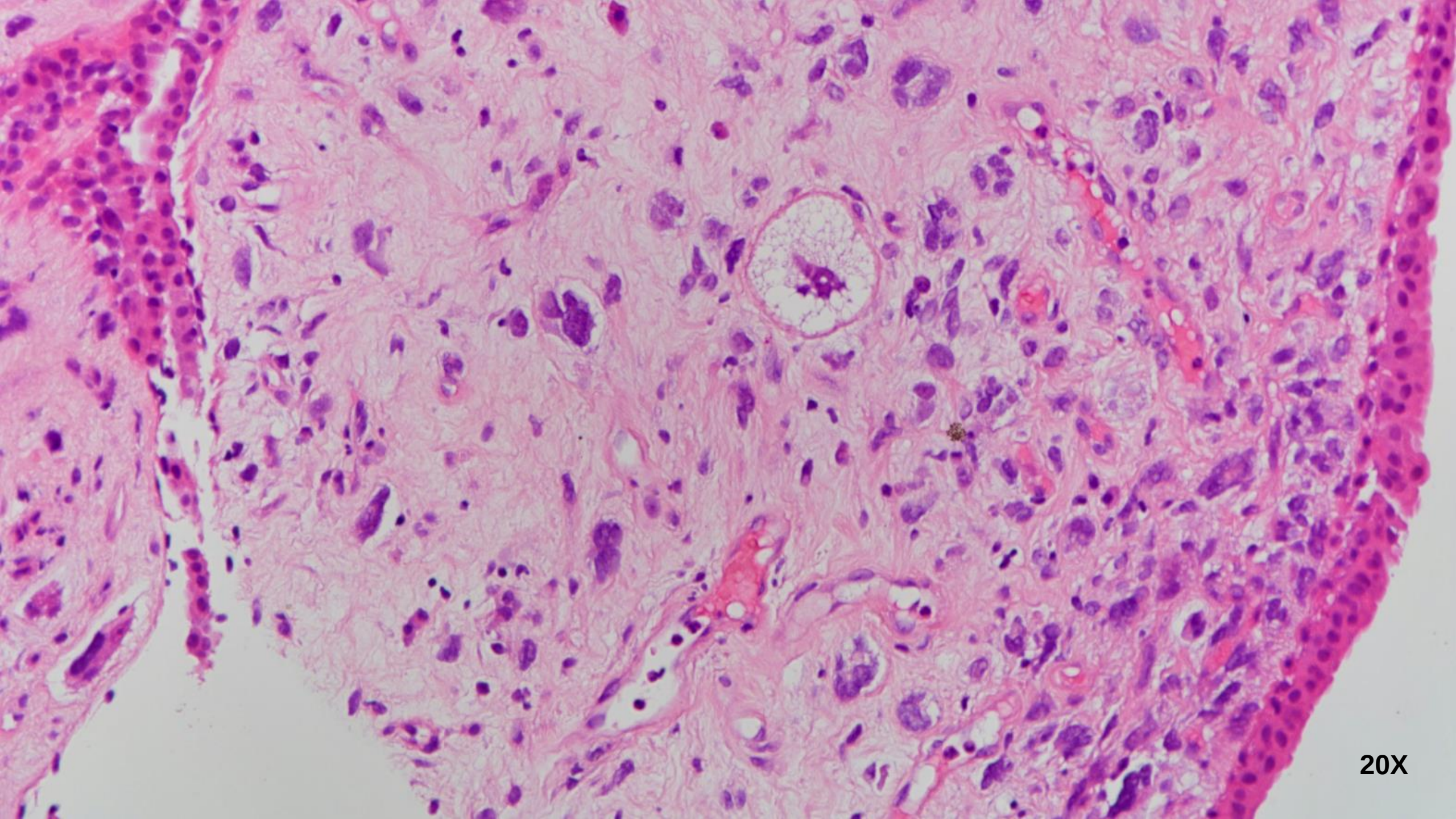
* Data are given as number (percentage) unless otherwise indicated.
† Graded according to the Elston and Ellis modification of the Nottingham grading system.
‡ Significant at the $P < .05$ level by the Wilcoxon 2-sample test.
§ Significant at the $P < .05$ level by the Fisher exact test.

Yu J et al 2011 Am J Clin Pathol 136:88

18US 1960

- 41 years old female
- Chief complaint: Right 12H breast mass (3cm)

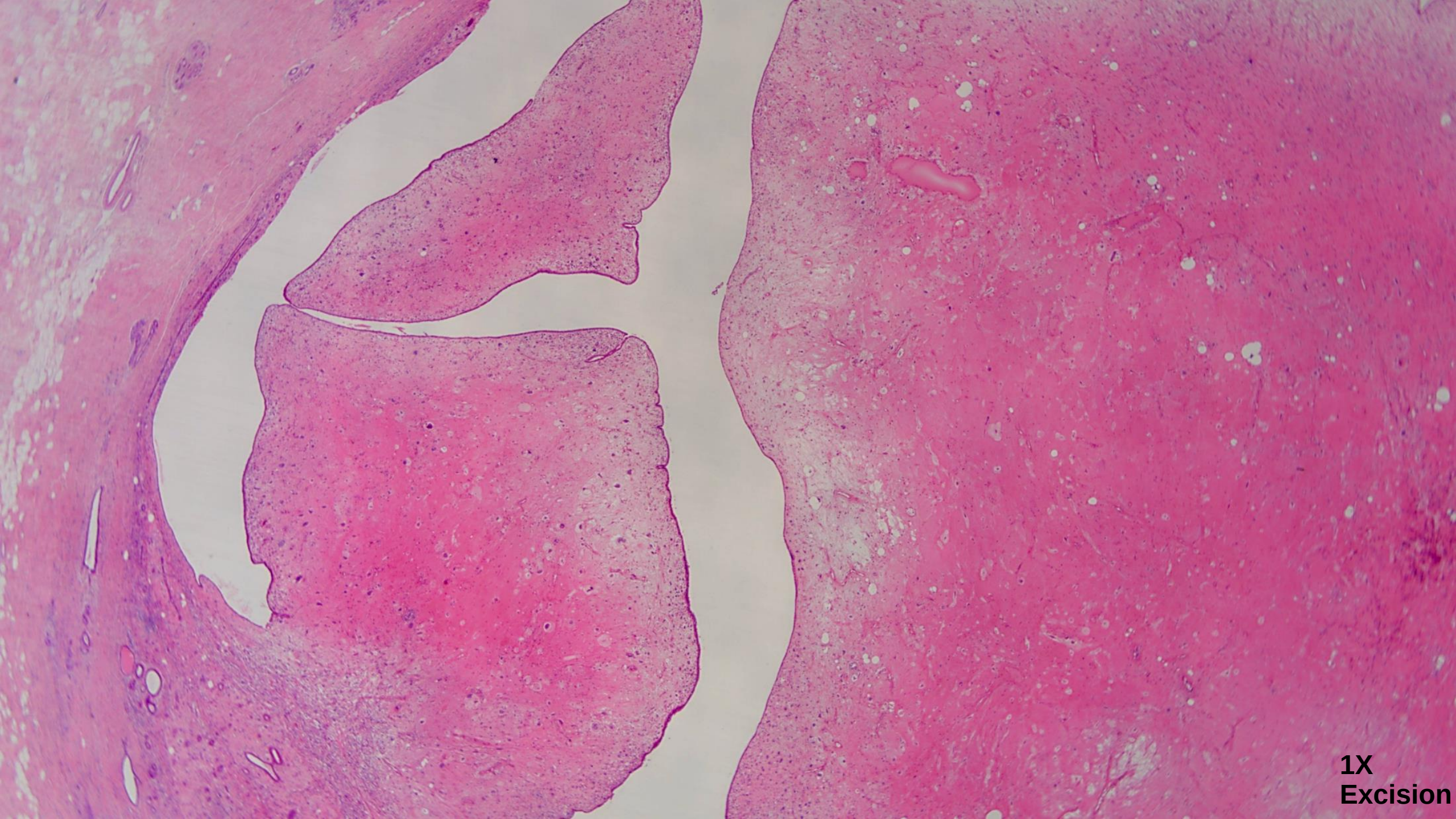

4X

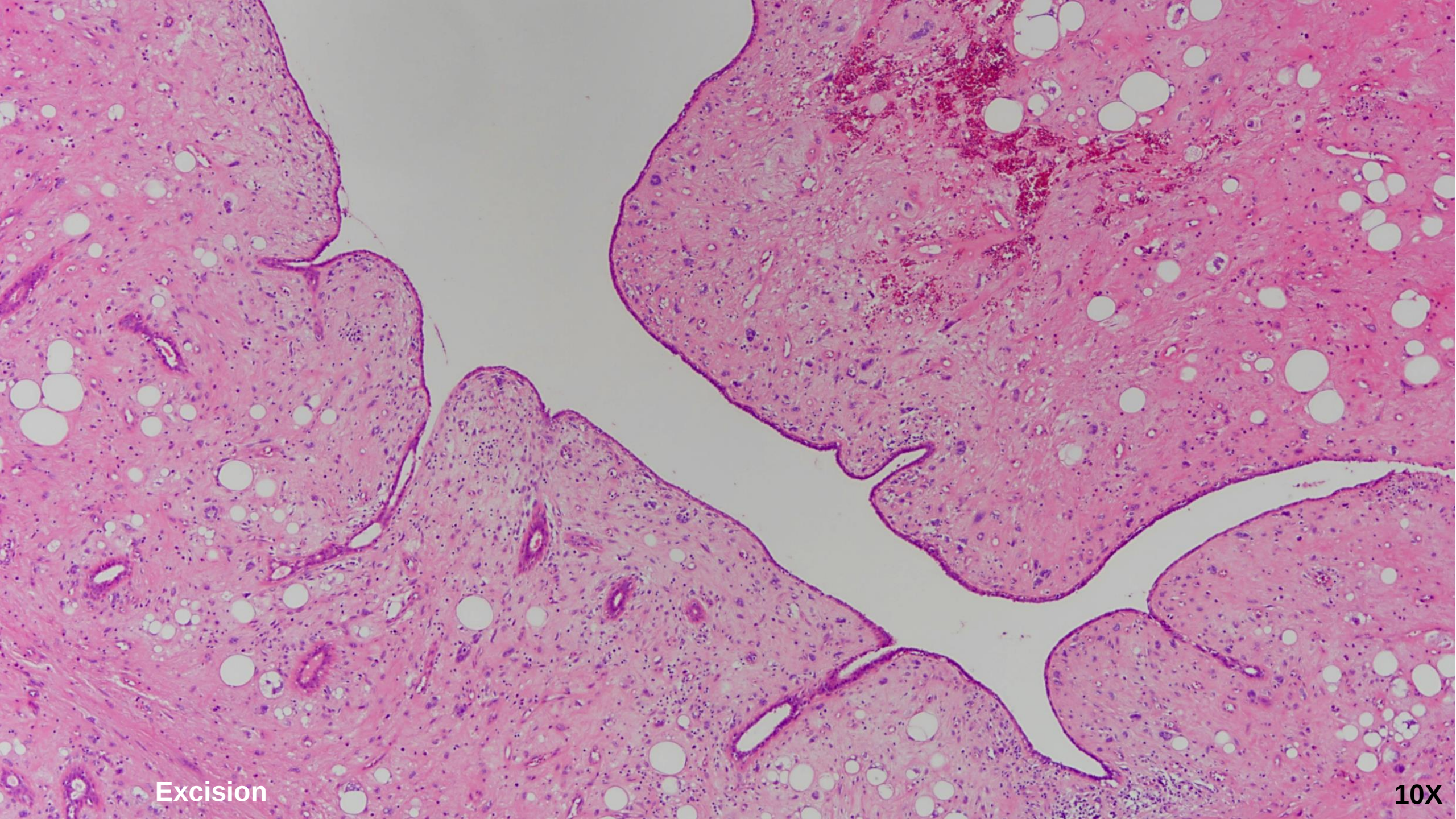

20X

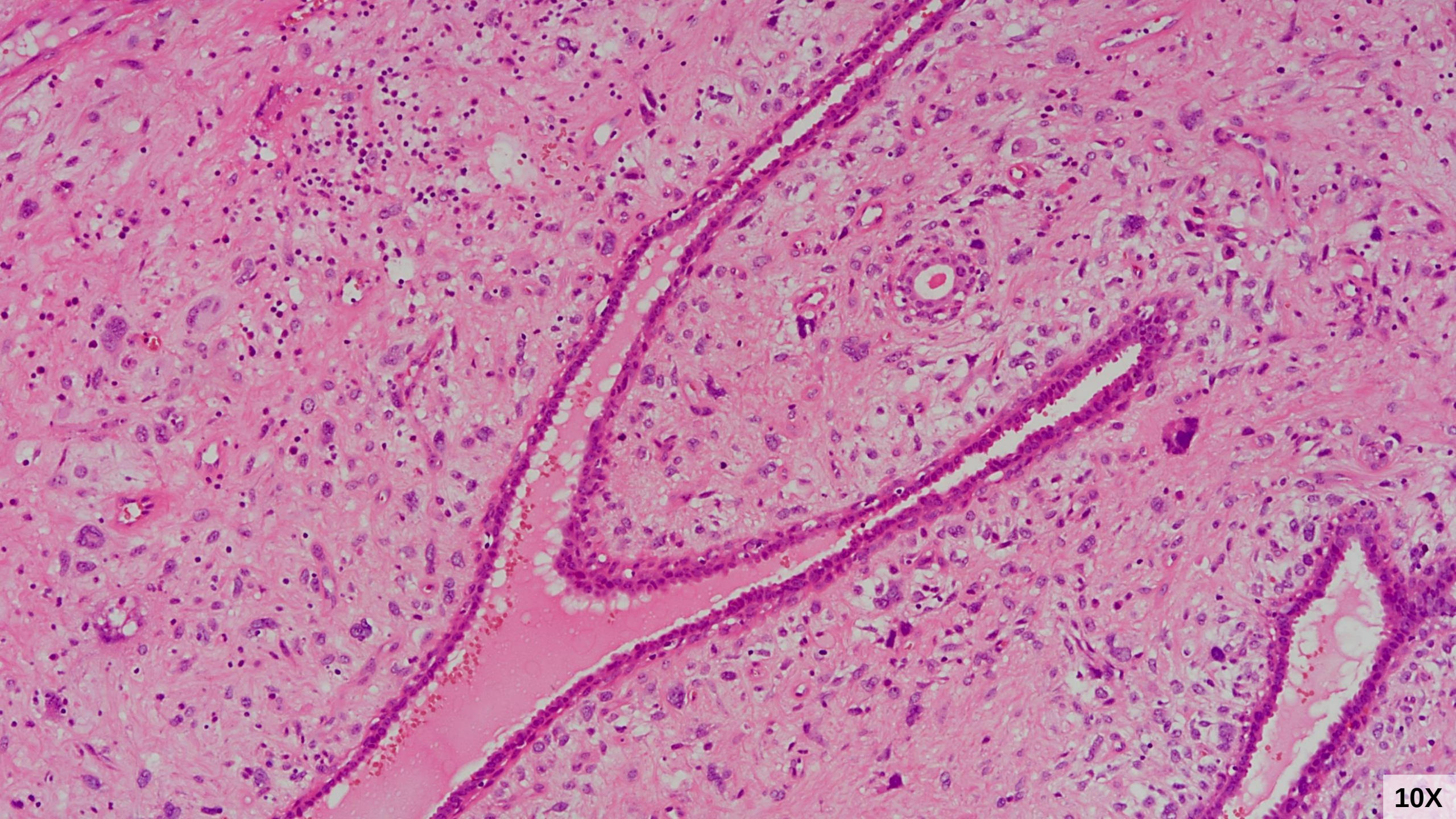
18US019604

Diagnosis (core biopsy)

- Fibroepithelial lesion with stromal giant cells


1X
Excision


Excision
10X

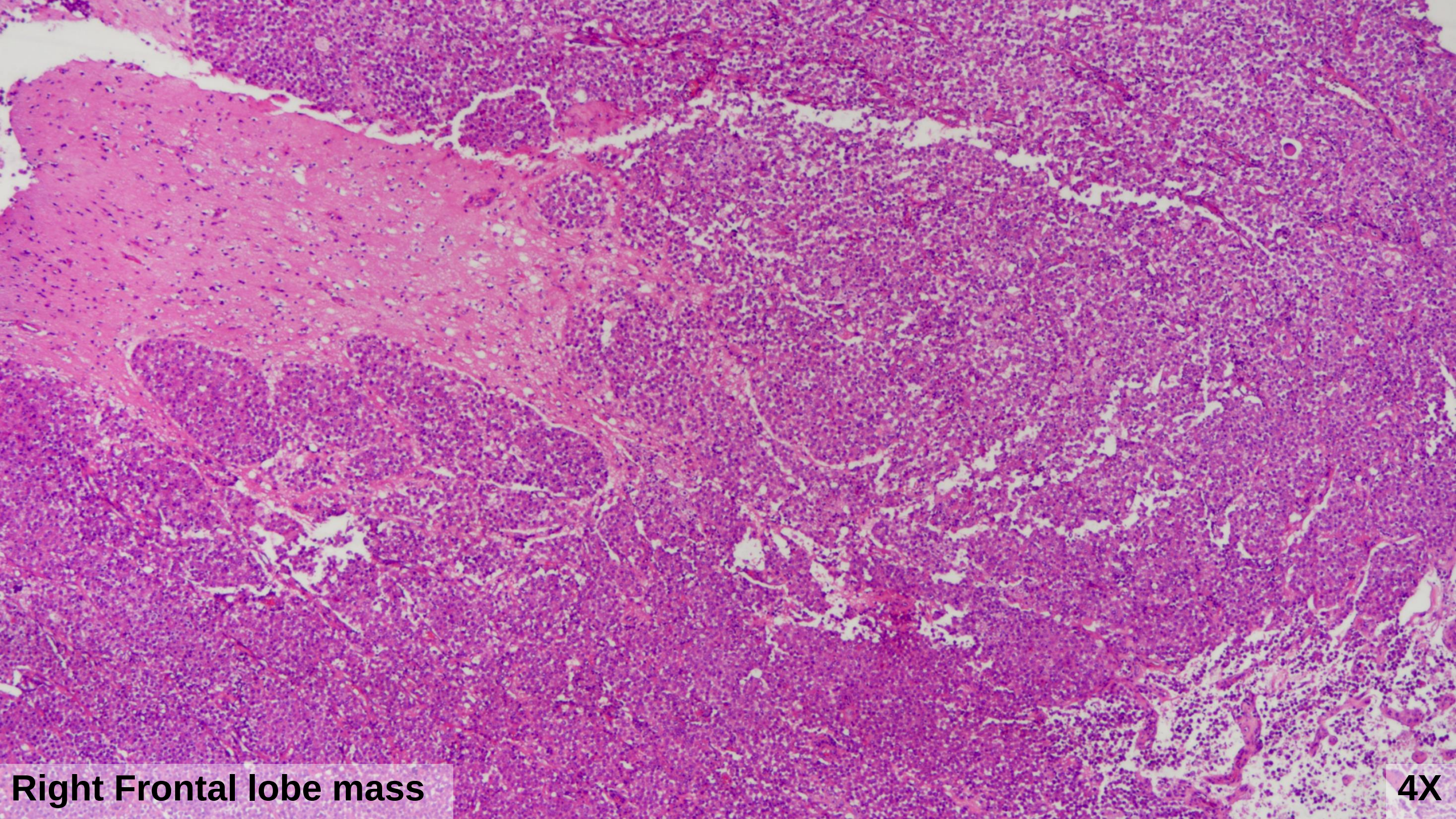

10X

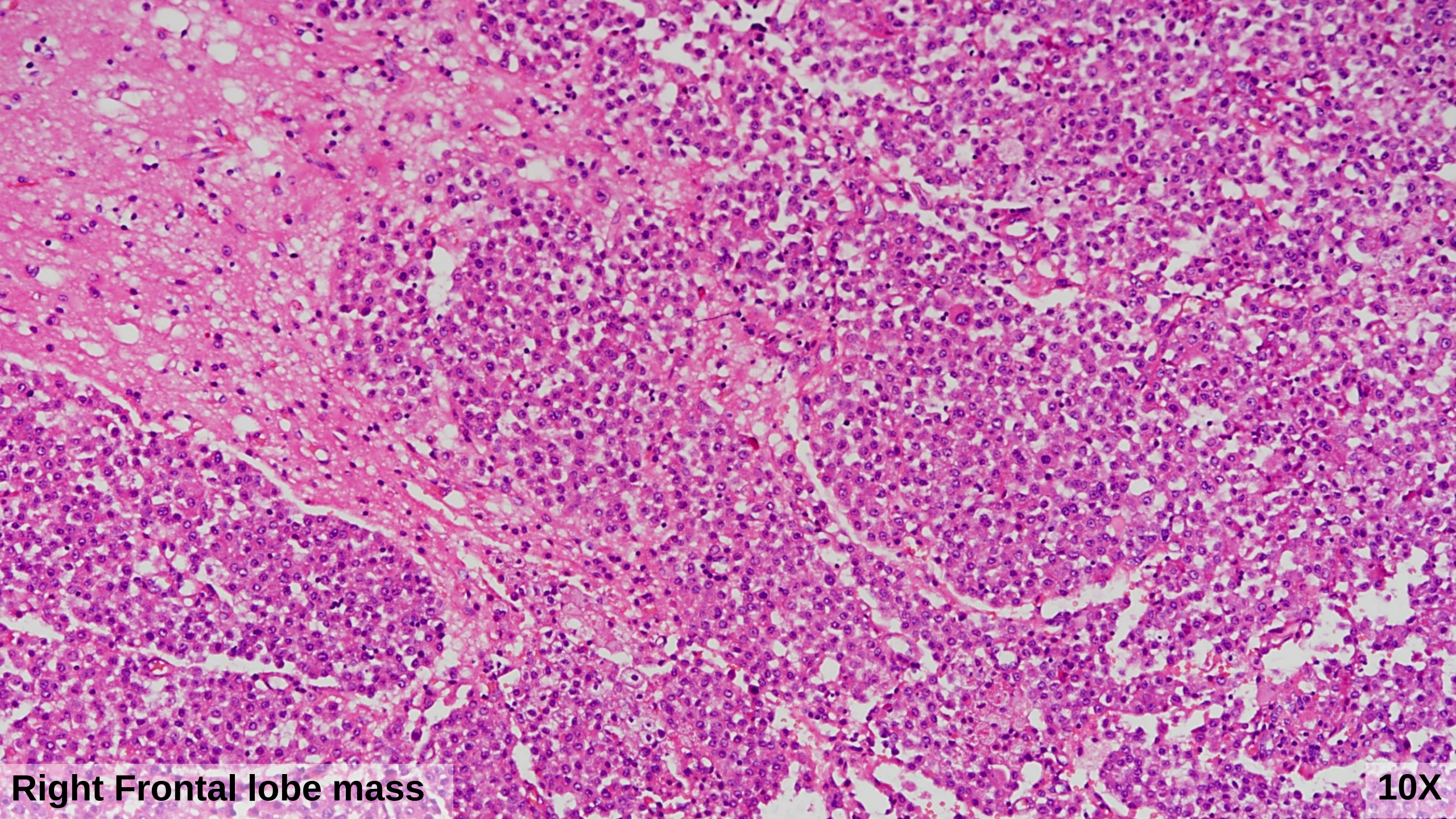
Diagnosis

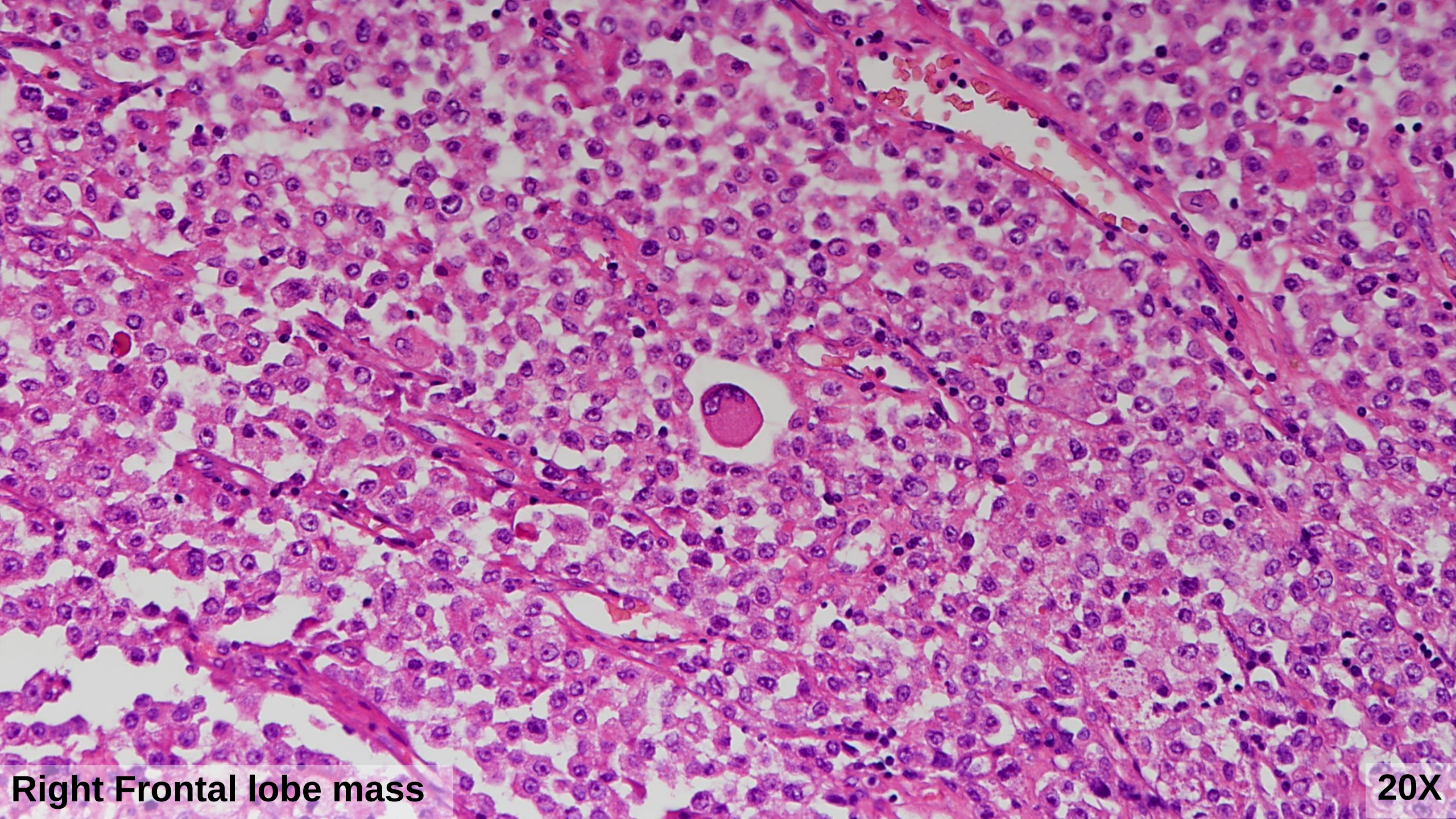
- Benign Phyllodes Tumor with bizarre giant cells

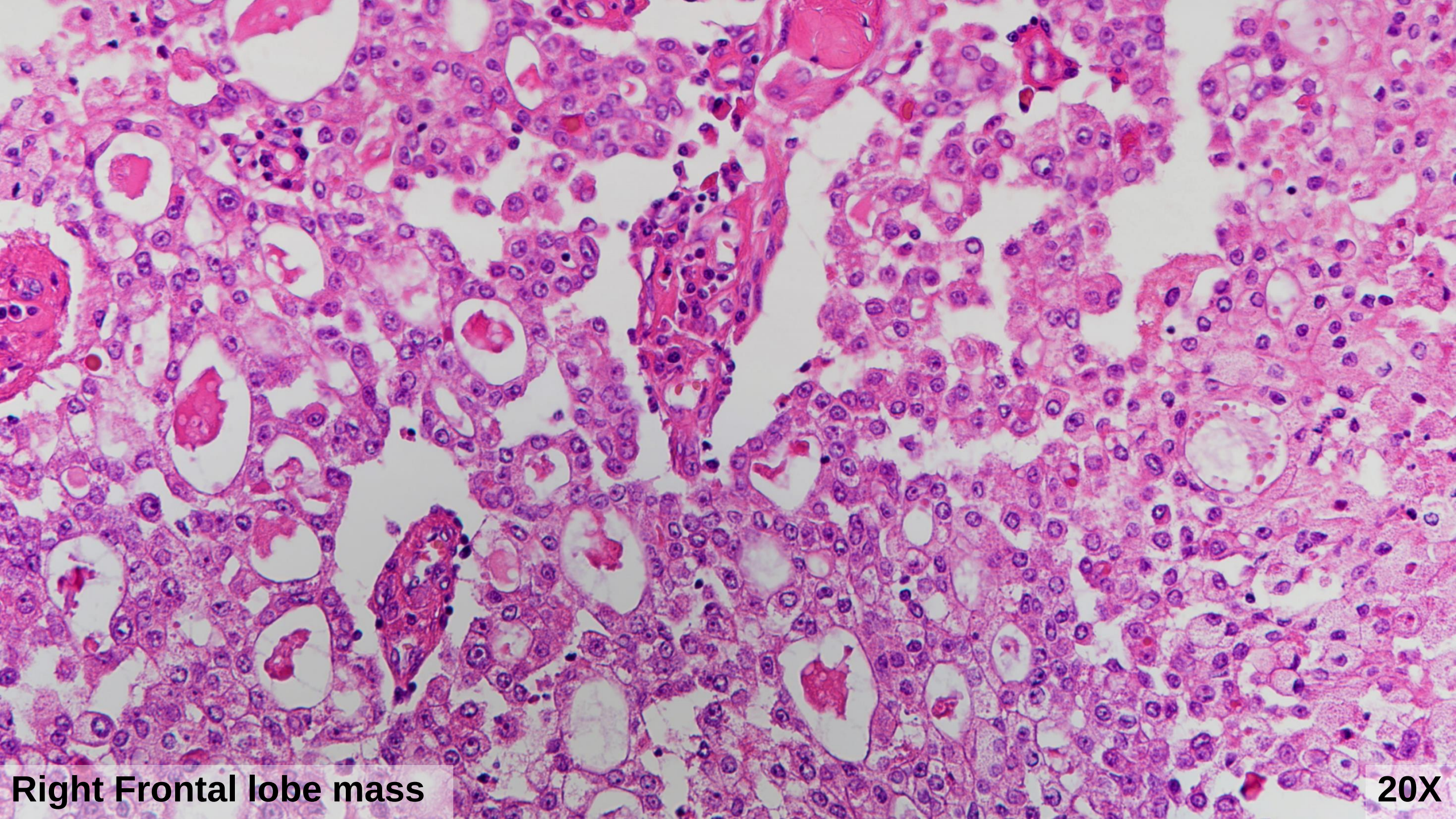
19S 12710-4

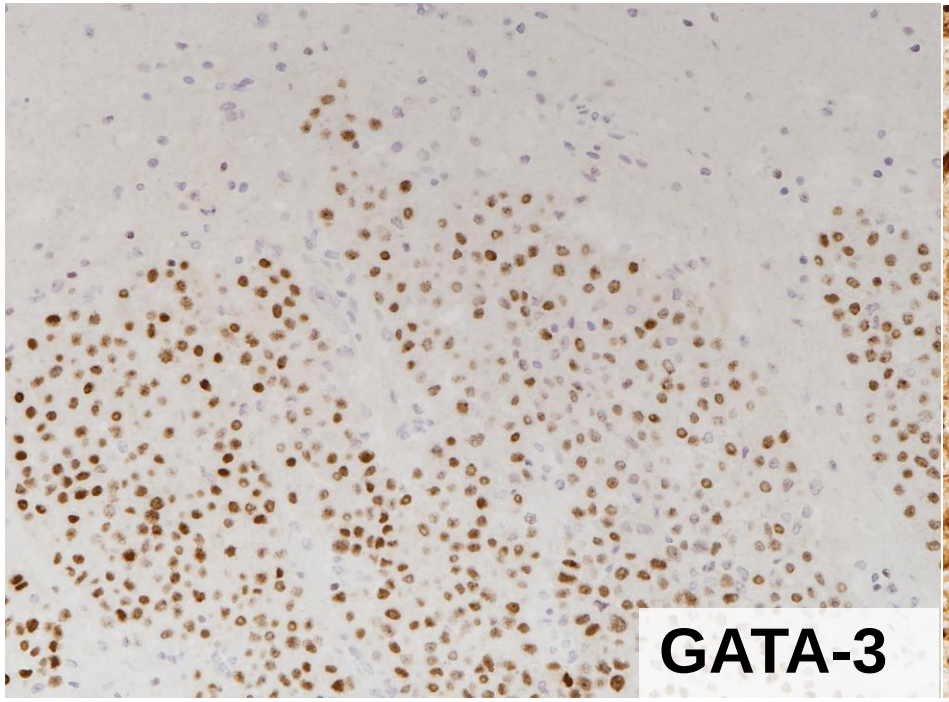
- 59 years old female
- Chief complaint: Unsteady gait and headache
- MRI brain: multiple cerebral and left cerebellar metastases with mass effect
- PET CT: Right breast nodule, 0.7 cm
- Breast US: Vague irregular lesion at R3H with indistinct border (7mm)- BI-RADS 4B
- Operation: Right frontal craniotomy for excision of brain metastasis

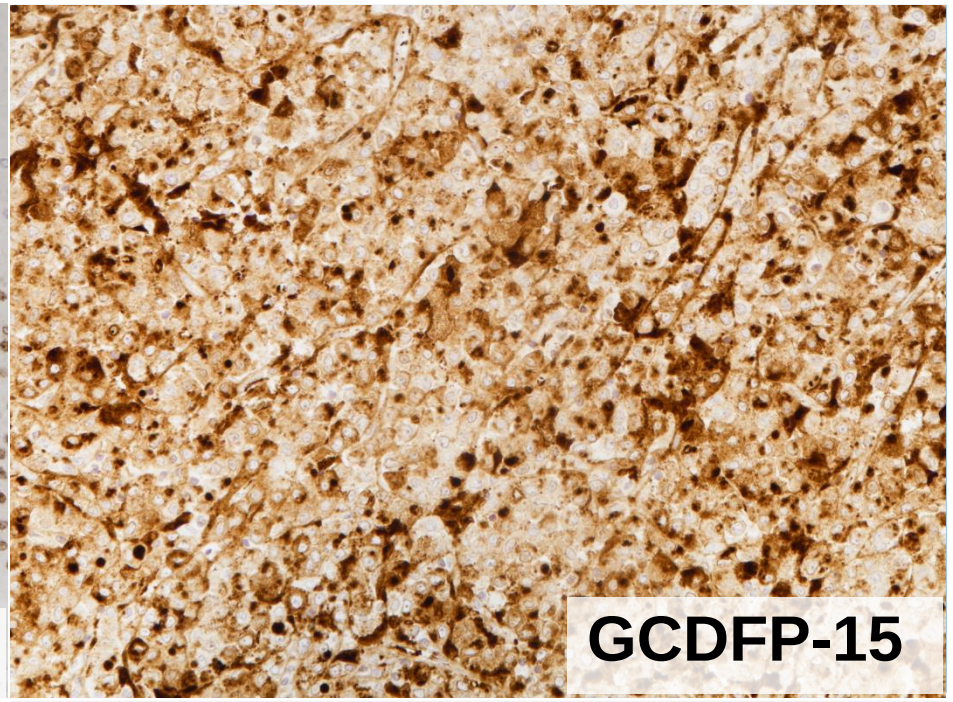

Right Frontal lobe mass
4X

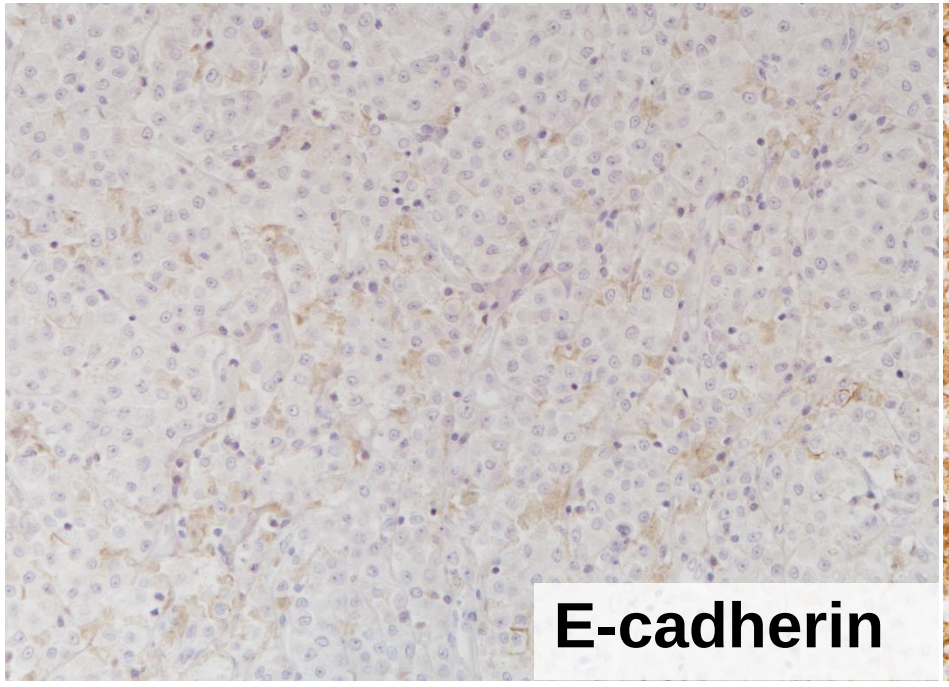

Right Frontal lobe mass
10X

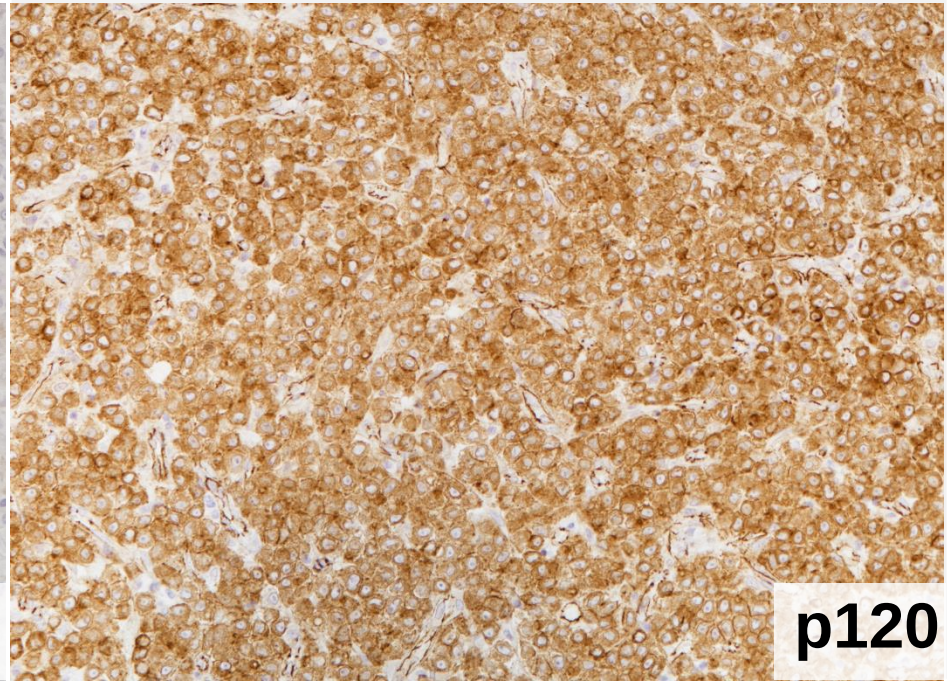

Right Frontal lobe mass
20X


Right Frontal lobe mass
20X

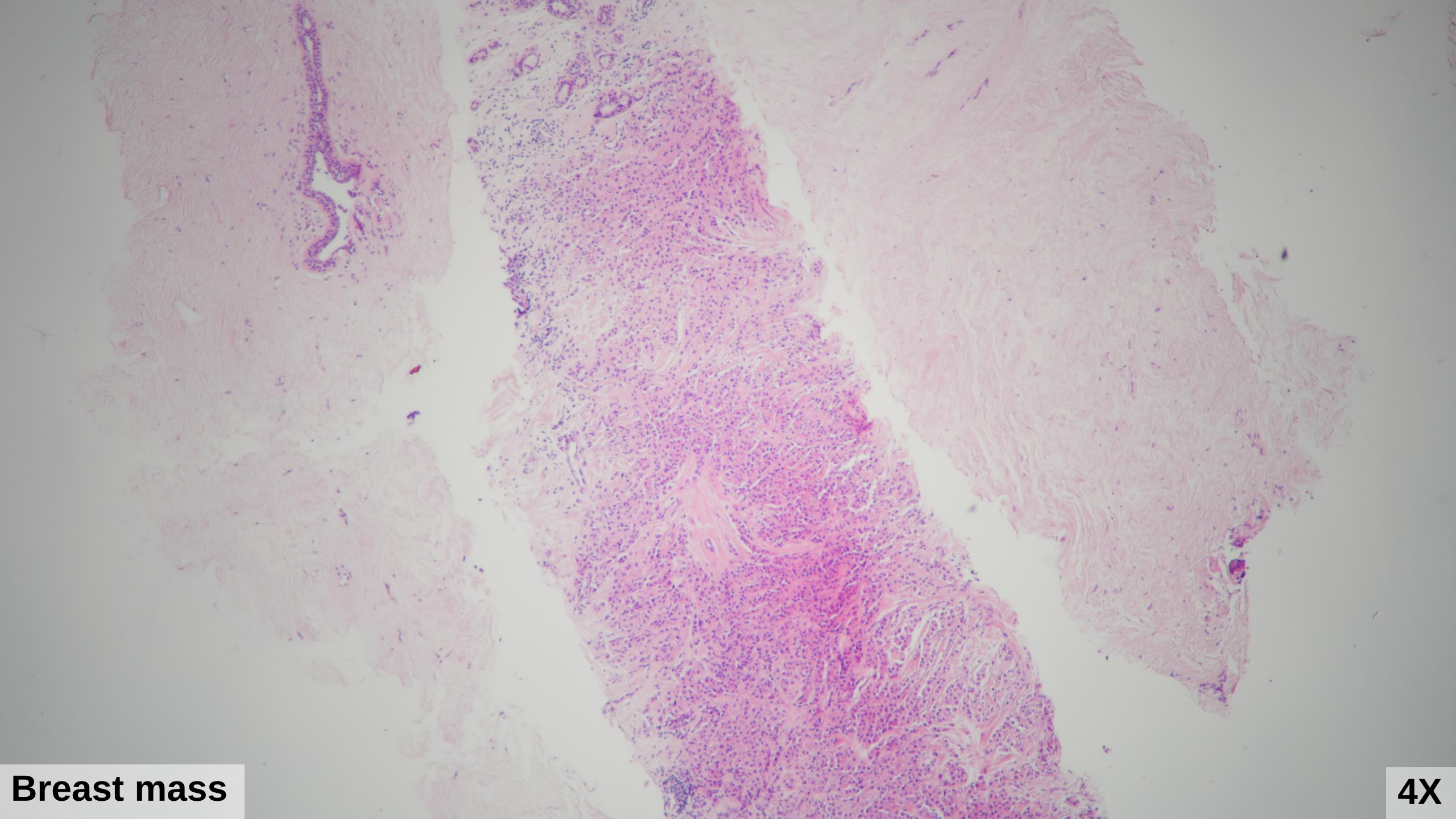

GATA-3

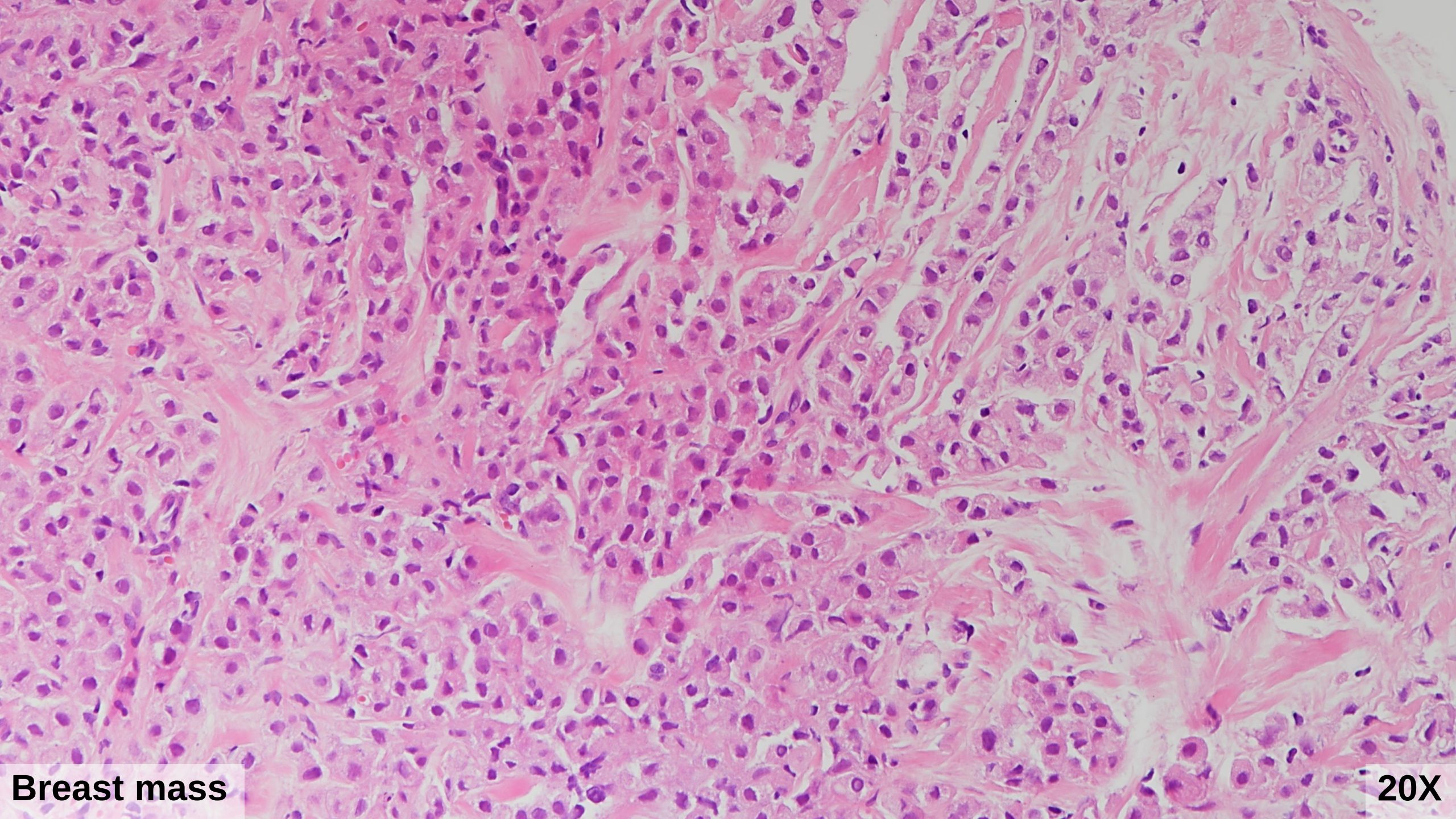

GCDFP-15


E-cadherin


p120

- Androgen receptor: Positive
- Estrogen receptor: Negative
- Progesterone receptor: Negative
- HER-2: Negative


Breast mass
4X

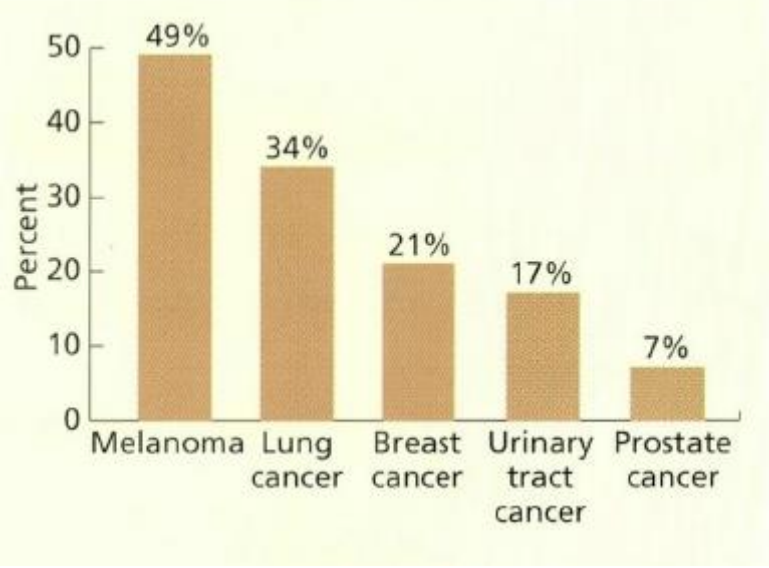

Breast mass
20X

- E-Cadherin: Negative
- p120: Positive (cytoplasmic staining)
- Androgen receptor: Positive
- GCDFP-15: Positive
- Estrogen receptor: Negative (<1%)
- Progesterone receptor: Negative (<1%)
- HER-2: Negative (1+)
- Ki67 index is about 10%

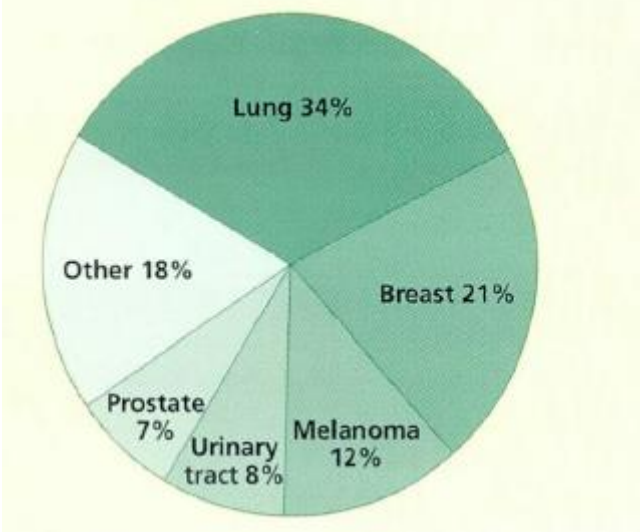
# Brain metastases

- Dissemination of cancer cells to brain via blood vessel
- Melanoma showed the highest frequency of brain metastases
- Most brain metastases are from primary lung cancers

Frequency of brain metastases in different malignancies




Distribution of primary sites for brain metastases




Au K et al 2017 Current Management of Brain metastases: Overview and Teaching
Chidel MA et al 2000 Cleveland Clinic J of Med 67:120

# Brain metastases at initial diagnosis

- Occasionally, neurologic and /or cognitive deficits are the first clinical sign of an intracranial tumor and some of these lesions turn out to represent distant seedings from extracranial primary tumors
- 1.7% of all primary tumor could present with synchronous brain metastases at initial diagnosis

# Brain metastases at initial diagnosis

**Table 1** Frequency of synchronous brain metastasis at diagnosis with primary cancer by selected cancer types, SEER 18, 2010–2013

| Site and histology | Total cases (2010–2013) | AAAIR per 100,000 and 95% CI (2010–2013) | Brain metastasis at diagnosis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | No (%) | | Yes (%) | | Missing or unknown (%) | |
| Esophagus | 15,739 | 4.2 (4.2–4.3) | 14,142 | 89.9 | 238 | 1.5 | 1359 | 8.6 |
| Colon/rectum | 147,592 | 40.3 (40.1–40.5) | 139,469 | 94.5 | 373 | 0.3 | 7750 | 5.3 |
| Lung/bronchus | 203,915 | 56.4 (56.1–56.6) | 164,479 | 80.7 | 22,032 | 10.8 | 17,404 | 8.5 |
| Small cell lung cancer | 23,280 | 6.3 (6.2–6.4) | 18,471 | 79.30 | 3518 | 15.1 | 1291 | 5.6 |
| Non-small cell lung cancer | 153,650 | 42.5 (42.3–42.8) | 128,930 | 83.90 | 16,483 | 10.7 | 8237 | 5.4 |
| Melanoma | 79,785 | 21.9 (21.8–22.1) | 75,714 | 94.9 | 980 | 1.2 | 3091 | 3.9 |
| Kidney/renal pelvis | 57,372 | 15.5 (15.4–15.6) | 54,429 | 94.9 | 814 | 1.4 | 2129 | 3.7 |
| Breast | 246,763 | 66.9 (66.6–67.2) | 239,256 | 97.0 | 1001 | 0.4 | 6506 | 2.6 |
| ER−, PR−, HER2− | 25,943 | 7.1 (7.0–7.2) | 25,415 | 98.0 | 178 | 0.7 | 350 | 1.3 |
| HER2+ | 32,929 | 8.9 (8.8–9.0) | 32,128 | 97.6 | 255 | 0.8 | 546 | 1.7 |
| ER+, PR+, HER− | 141,634 | 38.4 (38.2–38.6) | 139,814 | 98.7 | 266 | 0.2 | 1554 | 1.1 |

Kromer C et al 2017 J Neurooncol 134:55

# Brain metastases at initial diagnosis of primary BC

- The diagnosis of brain metastasis usually follows well after the initial diagnosis of breast cancer (occur a decade after primary diagnosis and successful treatment)
- Patients with brain metastases at initial diagnosis were likely diagnosed as a result of neurologic symptoms
- Autopsy studies showed that 5-35% of patients with breast cancer are found to have brain metastases which may not be clinically apparent
    - True incidence of brain metastases at initial diagnosis is likely to be underestimated

| Subtype | Patients, No. | | | Incidence Proportion of Brain Metastases, % | | Survival Among Patients With Brain Metastases, Median (IQR), mo |
|---|---|---|---|---|---|---|
| | With Breast Cancer | With Metastatic Disease | With Brain Metastases | Among Entire Cohort | Among Subset With Metastatic Disease | |
| $HR^+/HER2^-$ | 162 078 | 6607 | 361 | 0.22 | 5.46 | 14.0 (4.0-34.0) |
| $HR^+/HER2^+$ | 22 376 | 1704 | 136 | 0.61 | 7.98 | 21.0 (6.0-NR) |
| **$HR^-/HER2^+$** | **9719** | **926** | **106** | **1.09** | **11.45** | **10.0 (4.0-27.0)** |
| **Triple-negative** | **25 362** | **1522** | **173** | **0.68** | **11.37** | **6.0 (2.0-13.0)** |
| Unknown | 19 191 | 2042 | 192 | 1.00 | 9.40 | 6.0 (2.0-20.0) |
| All subtypes | 238 726 | 12 801 | 968 | 0.41 | 7.56 | 10.0 (3.0-30.0) |

Martin AM et al J 2017 JAMA Oncol 3:1069

# Site specific metastases among BC patients

- Younger patients, poorly differentiated tumors (high grade), HR negativity, >3 LN met have been associated with increased brain metastasis.
- The median OS for patient with brain met: 8.7 months (95% CI: 7.8-9.6)

| Site of relapse | Brain (%) | Bone (%) | Lung (%) | Liver (%) | Pleura (%) |
|---|---|---|---|---|---|
| Autopsy cases[a] | | | | | |
| Median | 21 | 71 | 71 | 62 | 50 |
| Range | 15–35 | 50–74 | 60–80 | 50–71 | 35–80 |
| All subtypes[b] | 12–17 | 48–62 | 23–32 | 15–27 | 7–31 |
| Luminal A | 8–15 | 65–67 | 6–7 | 12–29 | 15–28 |
| Luminal B | 11 | 58–71 | 24–30 | 4–32 | 11–35 |
| TNBC/basal | 25–27 | 17–39 | 40–43 | 13–21 | 3–29 |
| HER2-positive | 11–20 | 61–62 | 15–42 | 22–44 | 0–32 |

[a]Median value and range from seven different studies reported by [85, 86]
[b]Summarized data from the studies reported in [11, 12, 14]
*HER* human epidermal growth factor receptor, *TNBC* triple-negative breast cancer

Witzel I et al 2016 Breast Cancer Res 18:8

# Metastatic sites of ILC

| Sites | Histological type | | *P* value[b] |
|---|---|---|---|
| | ILC ($n=96$) *n* (%) | IDC ($n=2749$) *n* (%) | |
| Bone | 48 (50) | 1058 (38.5) | 0.02 |
| Liver | 17 (17.7) | 483 (17.6) | 0.97 |
| Lung | 9 (9.4) | 821 (29.9) | <0.001 |
| NALN | 6 (6.3) | 324 (11.8) | 0.1 |
| CNS | 5 (5.2) | 224 (8.2) | 0.3 |
| Others[a] | 33 (34.4) | 272 (9.9) | <0.001 |

NALN, non axillary lymph node; CNS, central nervous system; ILC, invasive lobular carcinomas; IDC, invasive ductal carcinomas.

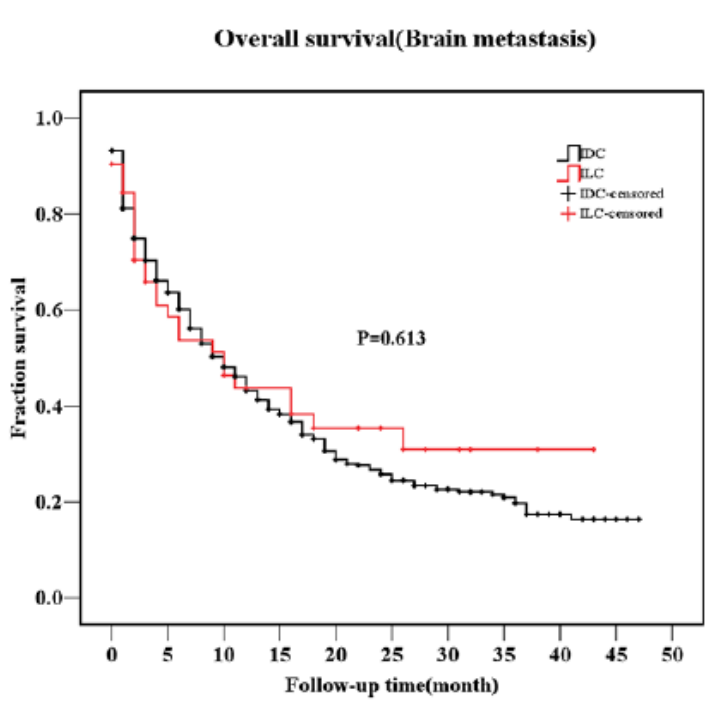
| Metastases ($n=247$) | | Subtype of ILC | | |
|---|---|---|---|---|
| Sites | *N* (%) | Classical | Pleomorphic | Others |
| Bone | 70 (28.3) | 62 | 5 | 3 |
| Liver | 38 (15.4) | 33 | 4 | 1 |
| Lung | 8 (3.2) | 8 | – | – |
| NALN | 12 (4.9) | 11 1 | – | |
| CNS | 9 (3.6) | 8 | 1 | – |
| Others | 110 (44.5) | 101 | 8 | 1 |
| Peritoneum | 36 (14.6) | 35 | 1 | – |
| Skin | 22 (8.9) | 19 | 2 | 1 |
| Pleura | 18 (7.3) | 14 | 4 | – |
| Ovary | 11 (4.5) | 10 | 1 | – |
| Meninges | 10 (4.0) | 10 | – | – |
| Stomach | 7 (2.8) | 7 | – | – |
| Uncommon[a] | 6 (2.4) | 6 | – | – |

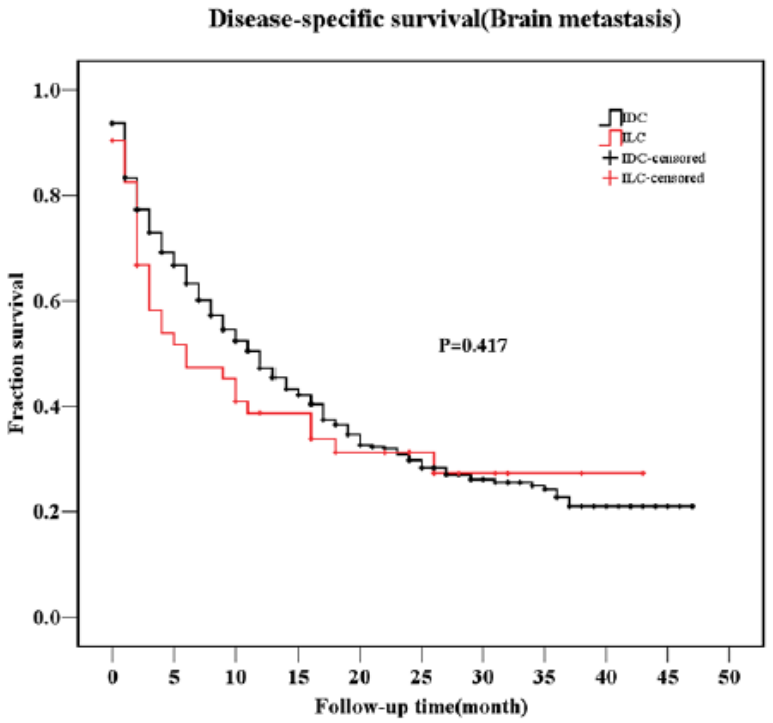
- ILC and IDC demonstrated different pattern of metastasis
  - ILC with higher rate in bone and various other organs
  - ILC was more likely to have multiple metastatic sites
- 15% of metastatic ILC belongs to pILC
- Pattern of metastatic site in ILC did not relate to subtypes

Ferlicot S et al 2003 EJC 40:336

# ILC Vs IDC with brain metastasis

- ILC and IDC from SEER (1990-2013)
- ILC and IDC showed similar outcome in cases with brain metastasis
  - But ILC with liver / lung met showed poor DFS

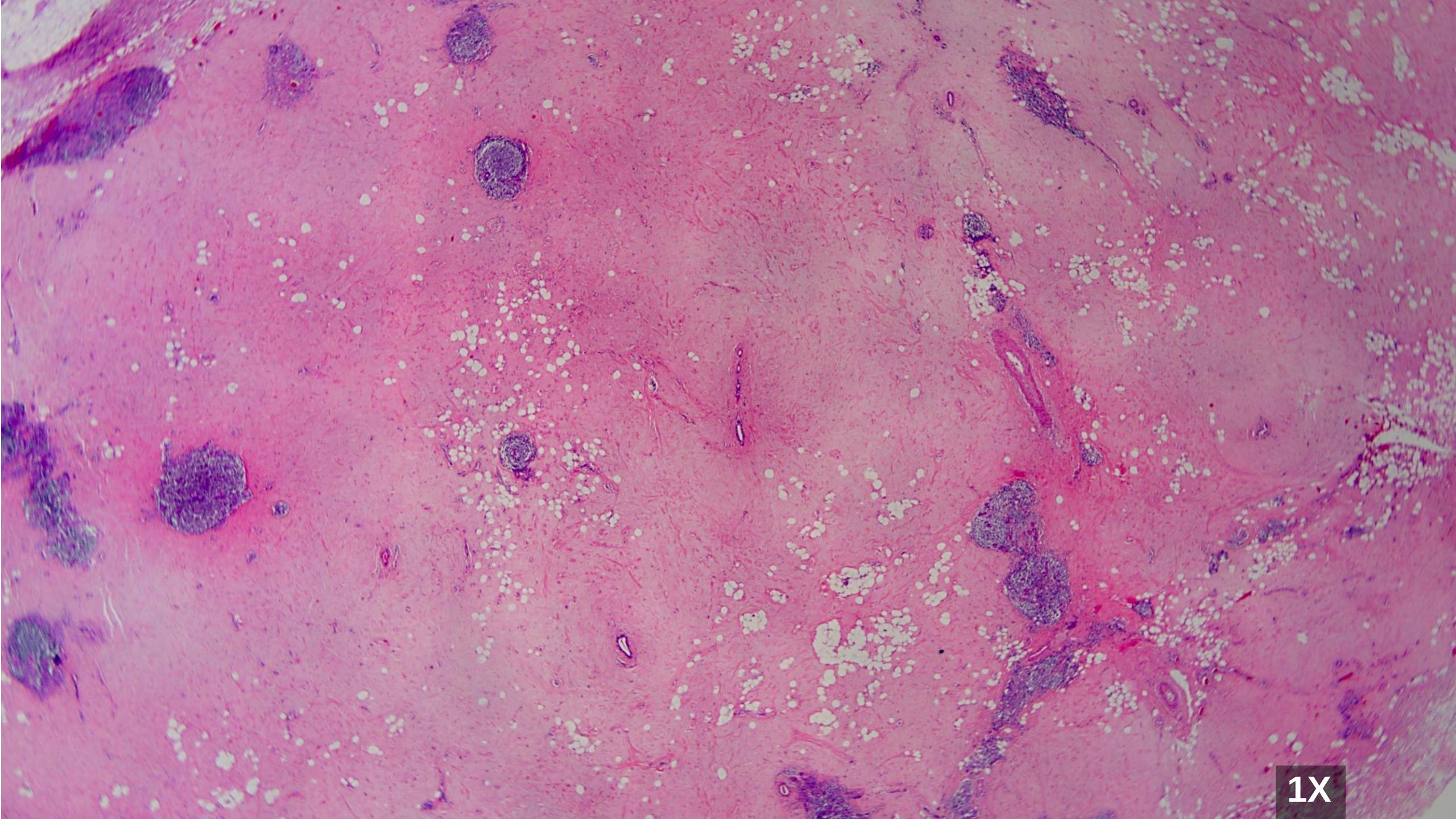


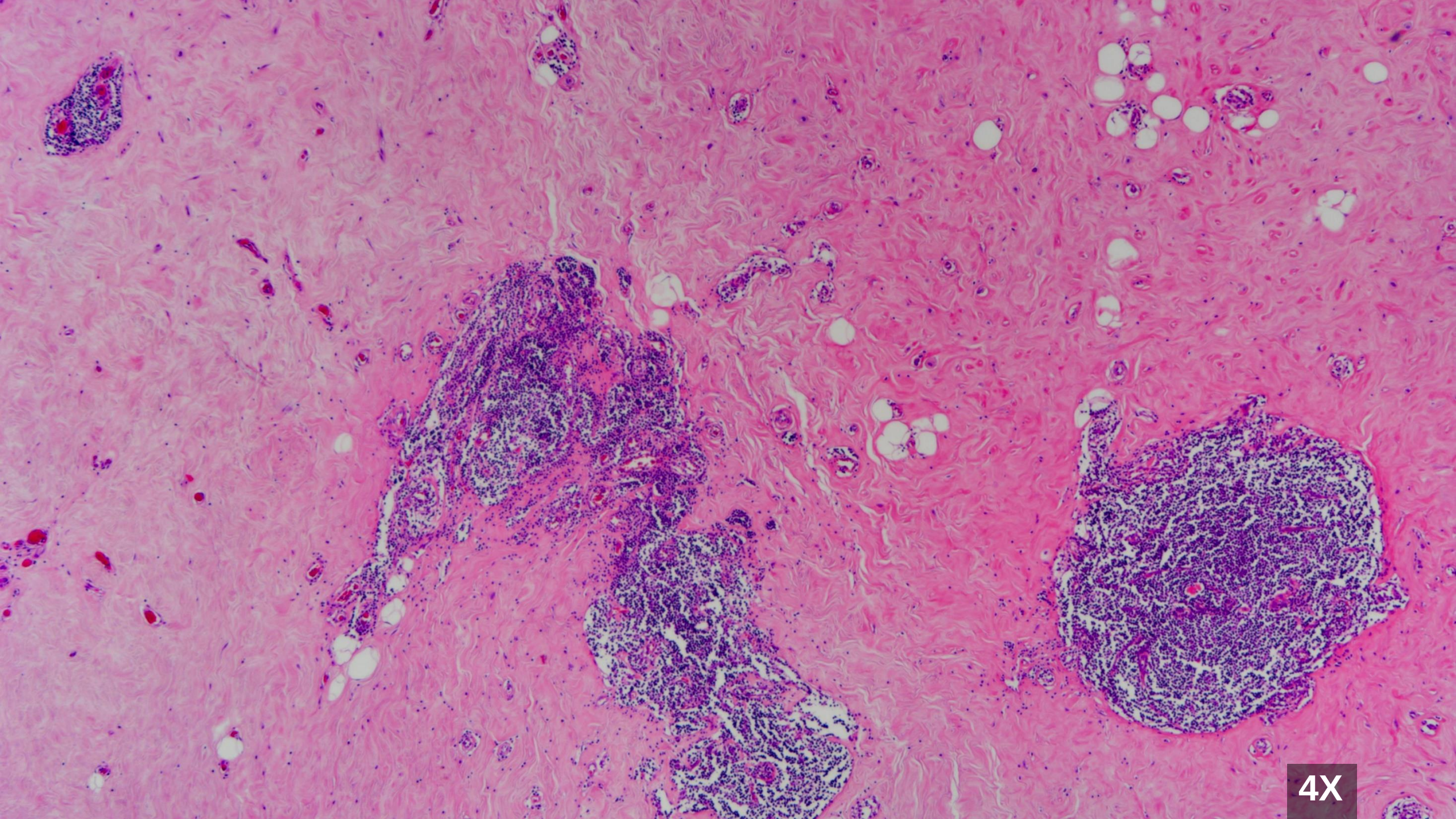



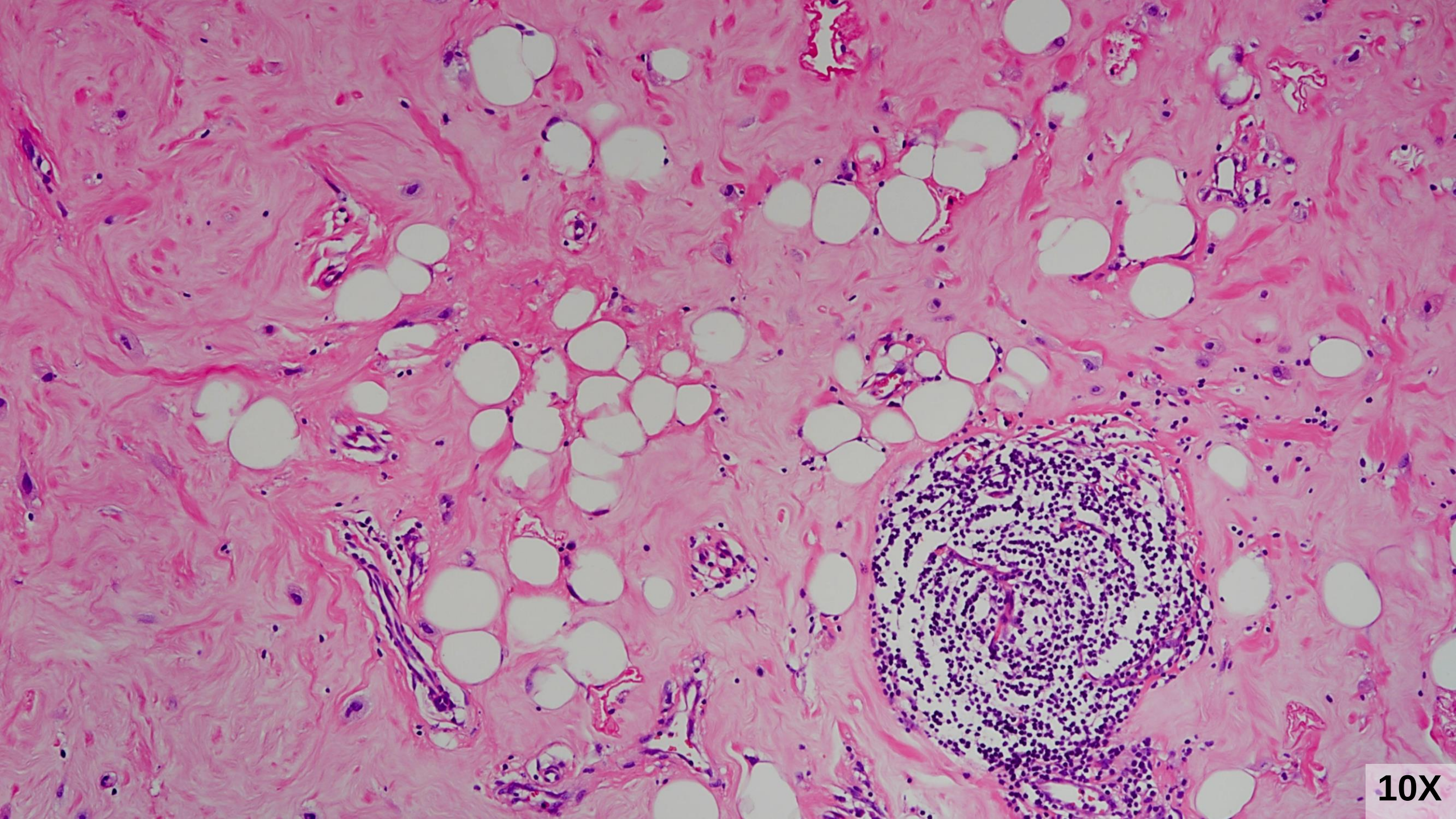

Chen Z et al 2017 PLoS ONE 12:e0182397

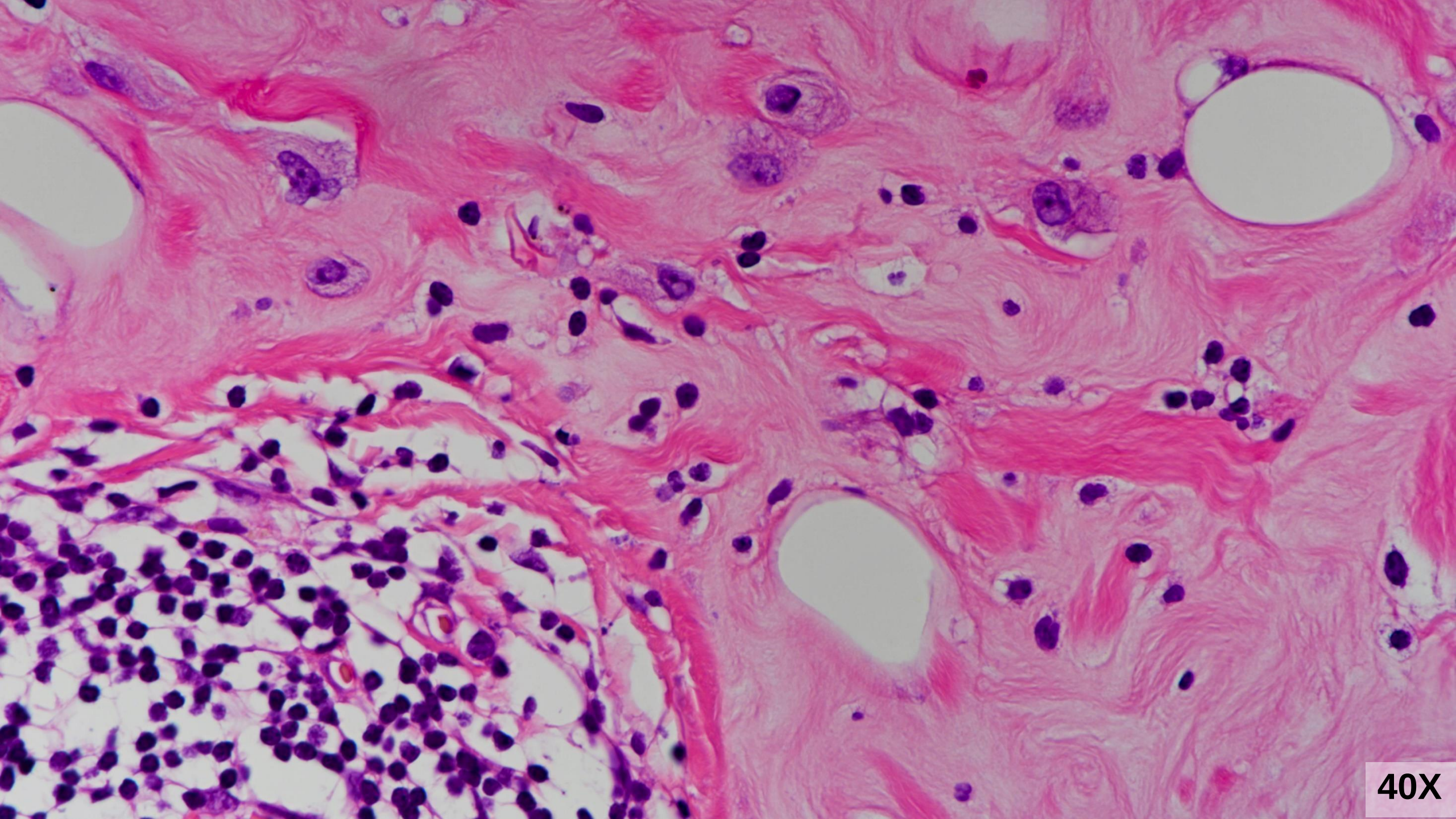
19US 6830-1

- 65 years old female
- Chief complaint: R12-1H breast mass
- History of Diabetes Mellitus x 30 years


1X


4X


10X


40X

19US 6830-1

- Diabetic mastopathy

# Diabetic Mastopathy

- Also known as “ lymphocytic mastopathy” or sclerosing lymphocytic lobulitis”
- Uncommon mass forming lesion seen in patient with insulin dependent type 1 diabetes mellitus, particularly to those with long standing disease with microvascular complications
- The characteristic histologic findings can also be seen in patients with type 2 diabetes mellitus, autoimmune diseases such as Hashimoto’s thyroiditis, and even those with no history of diabetes or autoimmune disease
- Most often occurs in premenopausal women

- Typical presentation is a palpable unilateral mass
  - In some instances, multiple masses or ill-defined nodules are clinically detectable.
- Radiological features may be suspicious for malignancy
  - Mammography may reveal an ill-defined mass, distortion, or dense glandular breast tissue
  - US may show an irregular hypoechoic mass with posterior shadowing
  - MRI shows nonspecific enhancement

# Diabetic Mastopathy

- Characteristic features:
  - lymphocytic lobulitis and ductitis
  - lymphocytic perivasculitis
  - stromal fibrosis with epithelioid fibroblasts

# Diabetic Mastopathy

- Lymphocyte infiltrates can be fairly dense, surround ducts, lobules, and small vessels, and may sometimes be associated with plasma cells
- Mostly mature B-lymphocytes with a small population of T cells
  - Germinal centers are not typically seen here
- Involved lobules may be atrophic or unremarkable
- Dense stroma showed keloidal appearance
- Intra-stromal epithelioid fibroblasts appear as plump cells with eosinophilic cytoplasm
- The distribution of fibroblasts within the stroma can be heterogeneous, and show a whorled or nodular growth pattern
- Nuclei are oval to round with vesicular nuclei
  - Neither significant nuclear atypia nor mitotic figures are seen

# Diabetic Mastopathy: differential diagnosis

- Differential diagnosis in CNB depends on the components presented in the limited sample
- Dense keloidal fibrosis is the predominant finding
  - fibrocystic change
    - However, it is unlikely to for diabetic mastopathy without coexisting perilobular or perivascular lymphocytic infiltrates, unless the sample is quite limited
  - pleomorphic lobular carcinomas that exhibit “histiocytoid” and/or apocrine features
    - a broad-spectrum cytokeratin stain can be performed to rule out carcinoma
  - granular cell tumors with cells of abundant pink granular cytoplasm and bland nuclear features.
    - These tumors stain positive for S100 and CD68
  - multinucleated stromal giant cells
    - occur as an incidental microscopic findings (vs diabetic mastopathy is a mass-forming proliferation) and have multiple hyperchromatic nuclei and scant, versus abundant, cytoplasm
- Lymphocytic ductitis, lobulitis, and perivasculitis are shown
  - lymphoma in the breast
    - tends to diffusely infiltrate the stroma, a pattern of inflammation distinct from that seen in diabetic mastopathy
    - immunostaining and molecular analysis will reveal a clonal proliferation of lymphocytes in lymphoma, but not in diabetic mastopathy

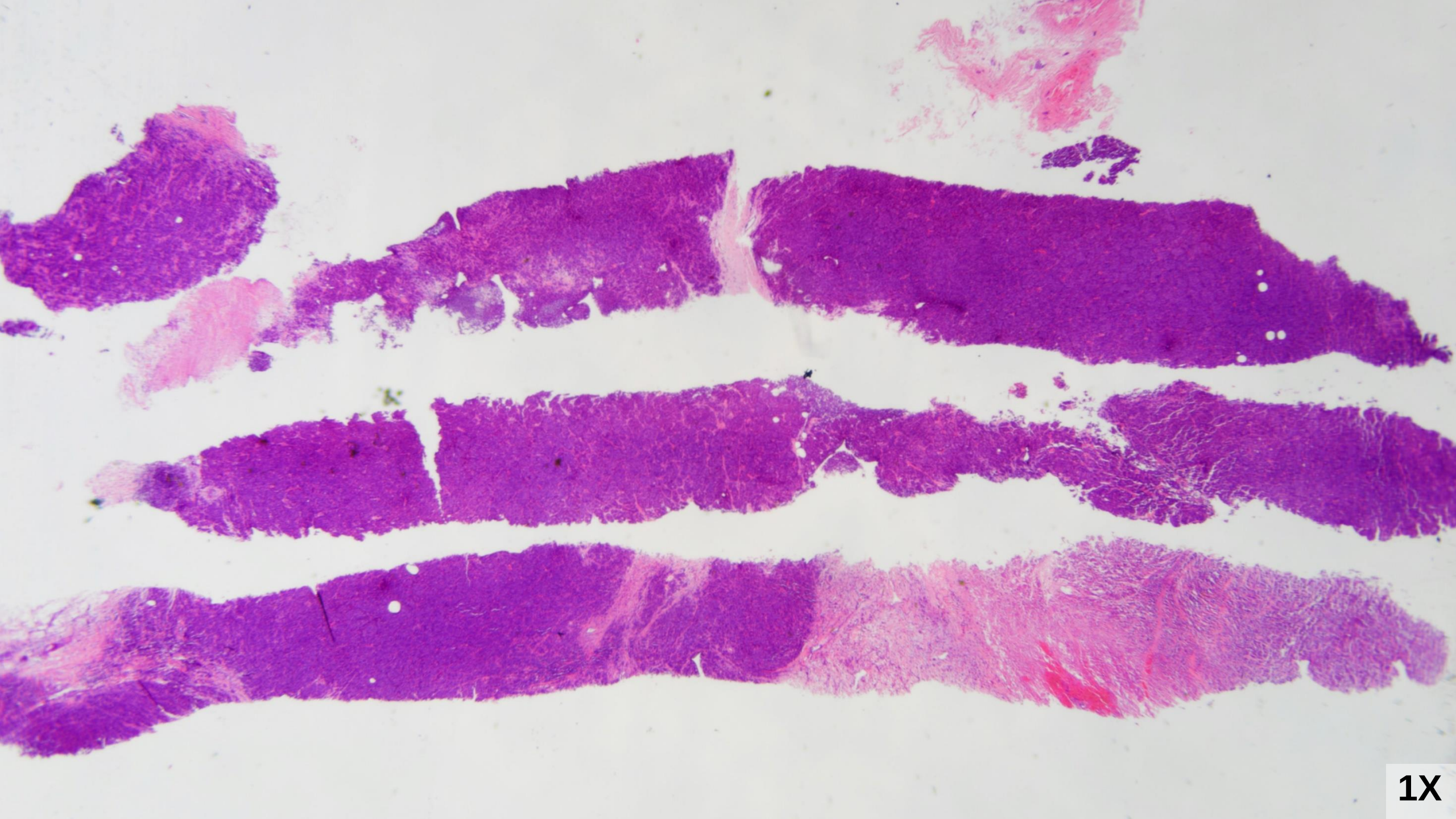
# Diabetic mastopathy management

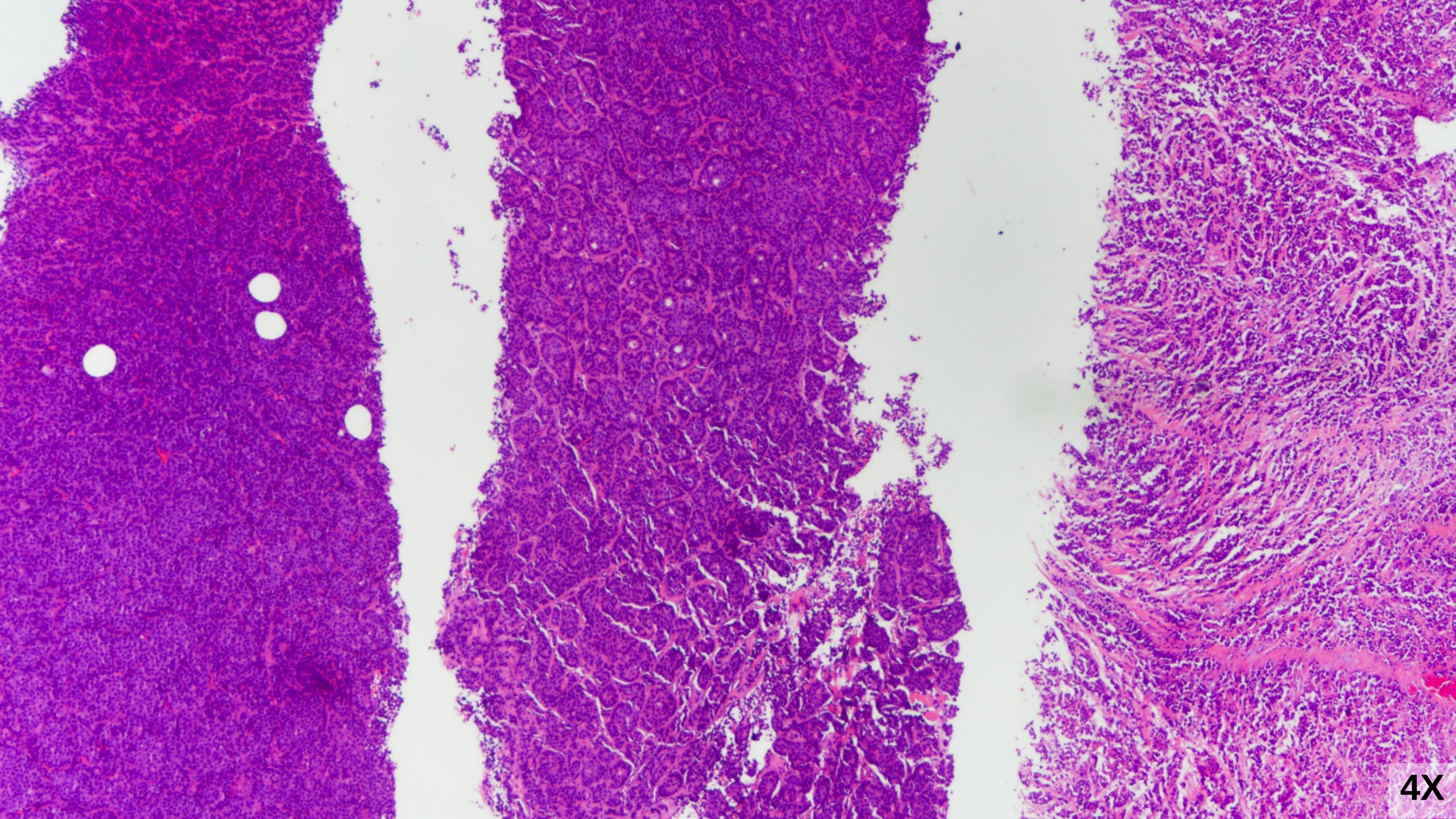
- As a benign condition, patients can be managed with routine mammographic surveillance
- In one study, 15% of patients recurred (ipsilateral /bilateral) after excision
- Patients are not at increased risk for subsequent development of breast cancer and lymphoma

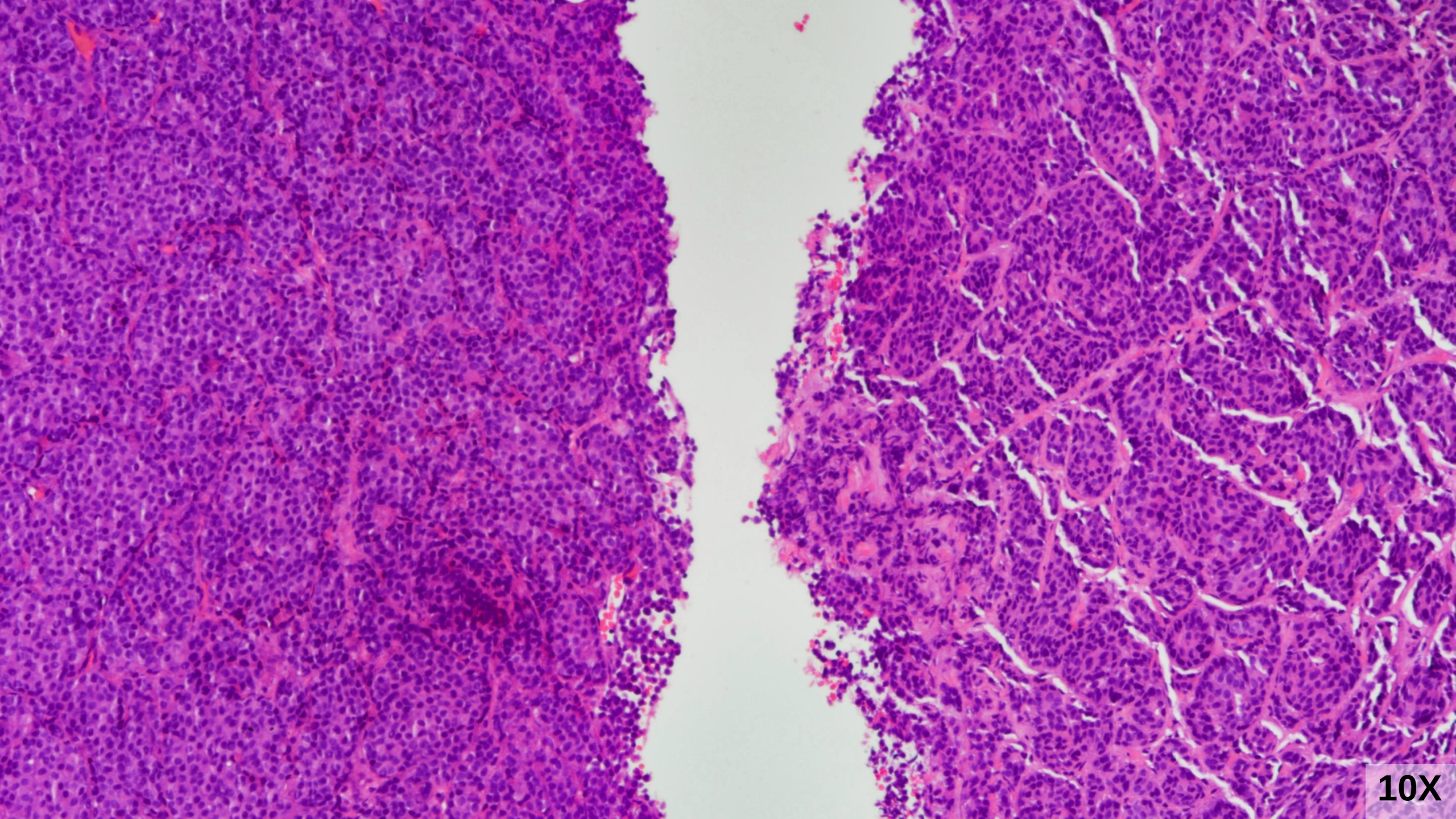
Alfonso T et al 2015 JPTM 48:279

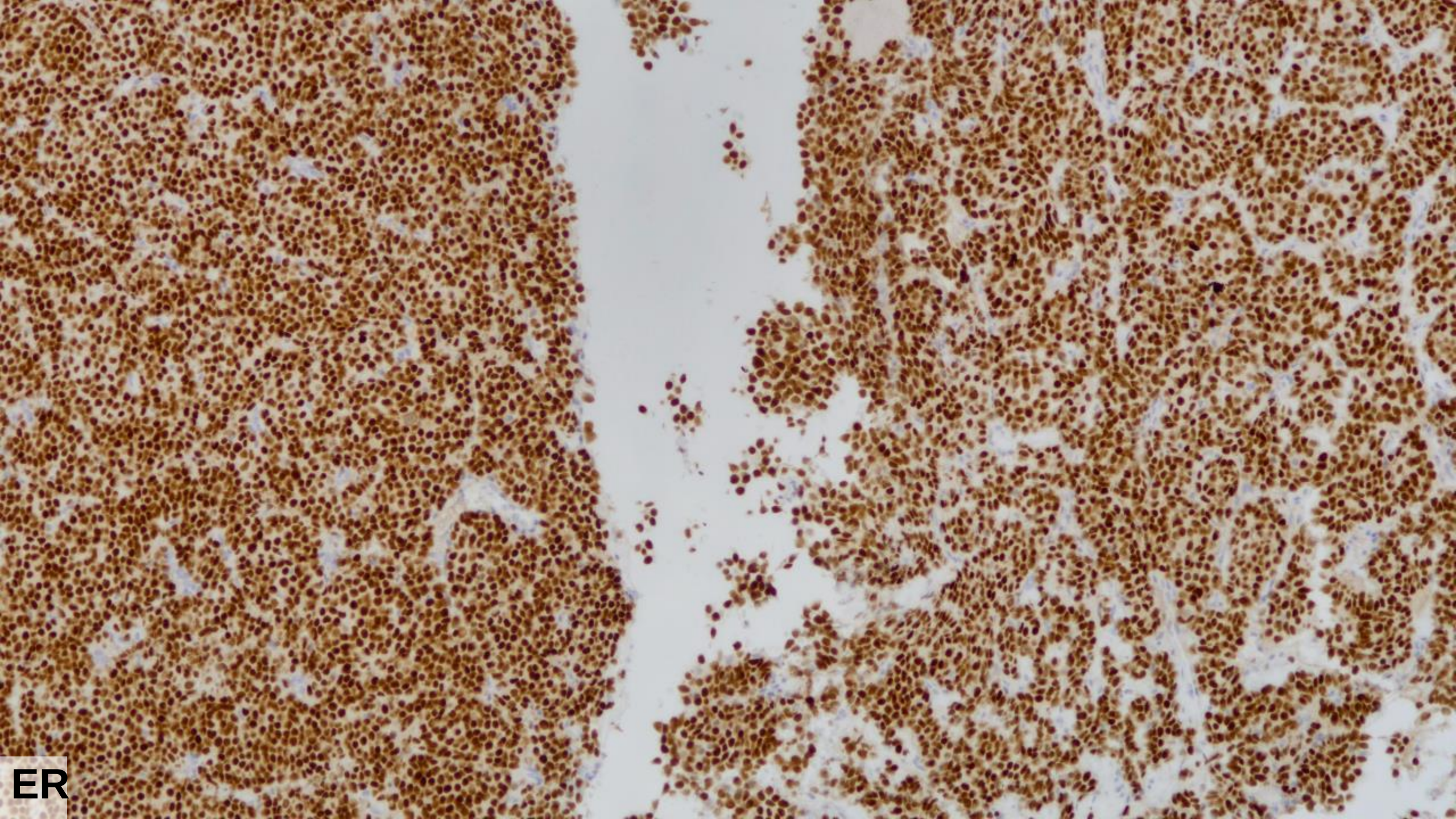
16S 3609

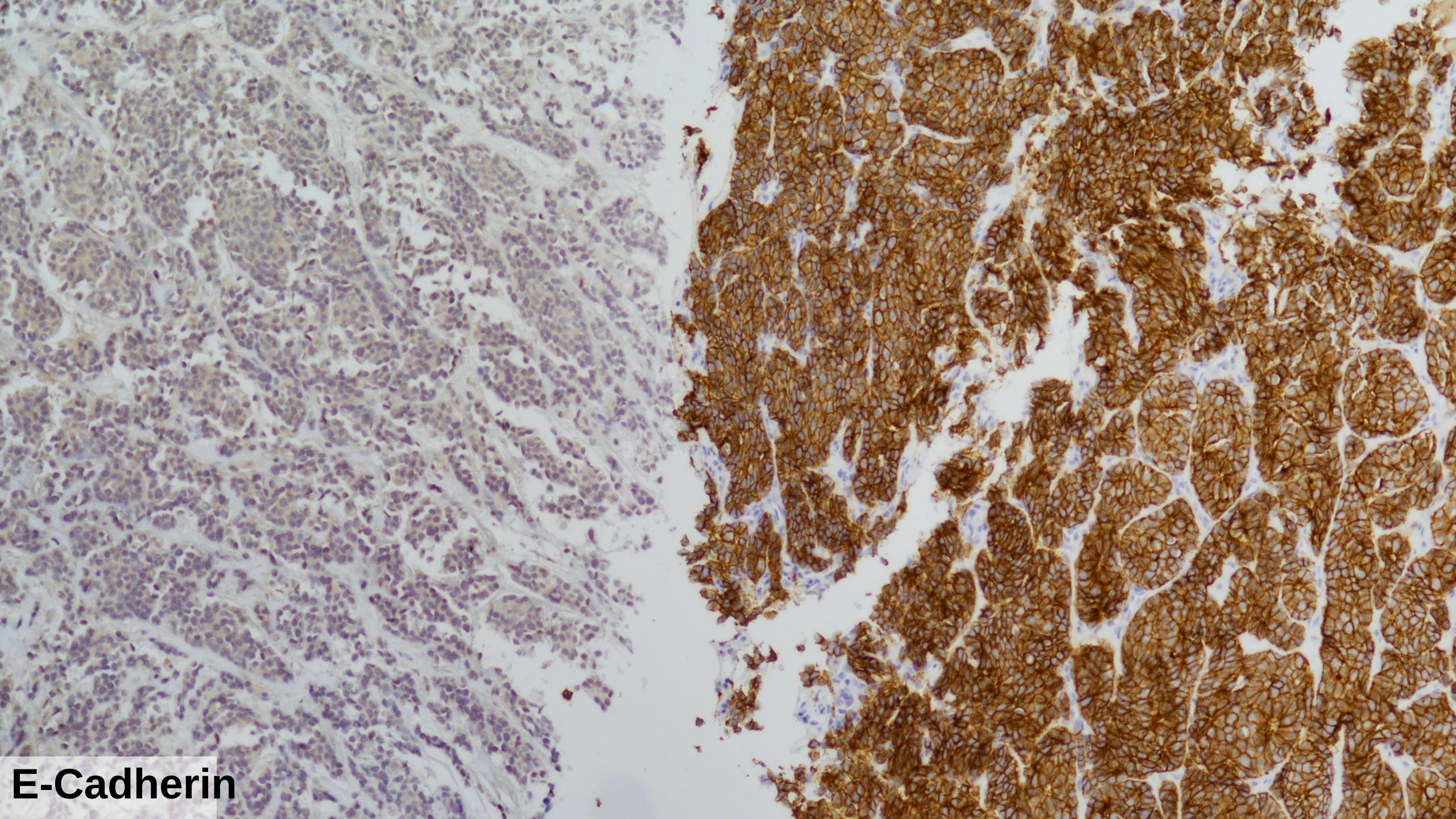
- 46 years old female
- Chief complaint: R9H breast mass
- History of breast conservation therapy over RUOQ
- Mammogram: two medium density masses with circumscribed margins (2cm each) in RUOQ neat the BCT scar (BI-RADS 5)
- US: two well-defined hypoechoic masses with increased vascularity (2cm & 1.8cm)

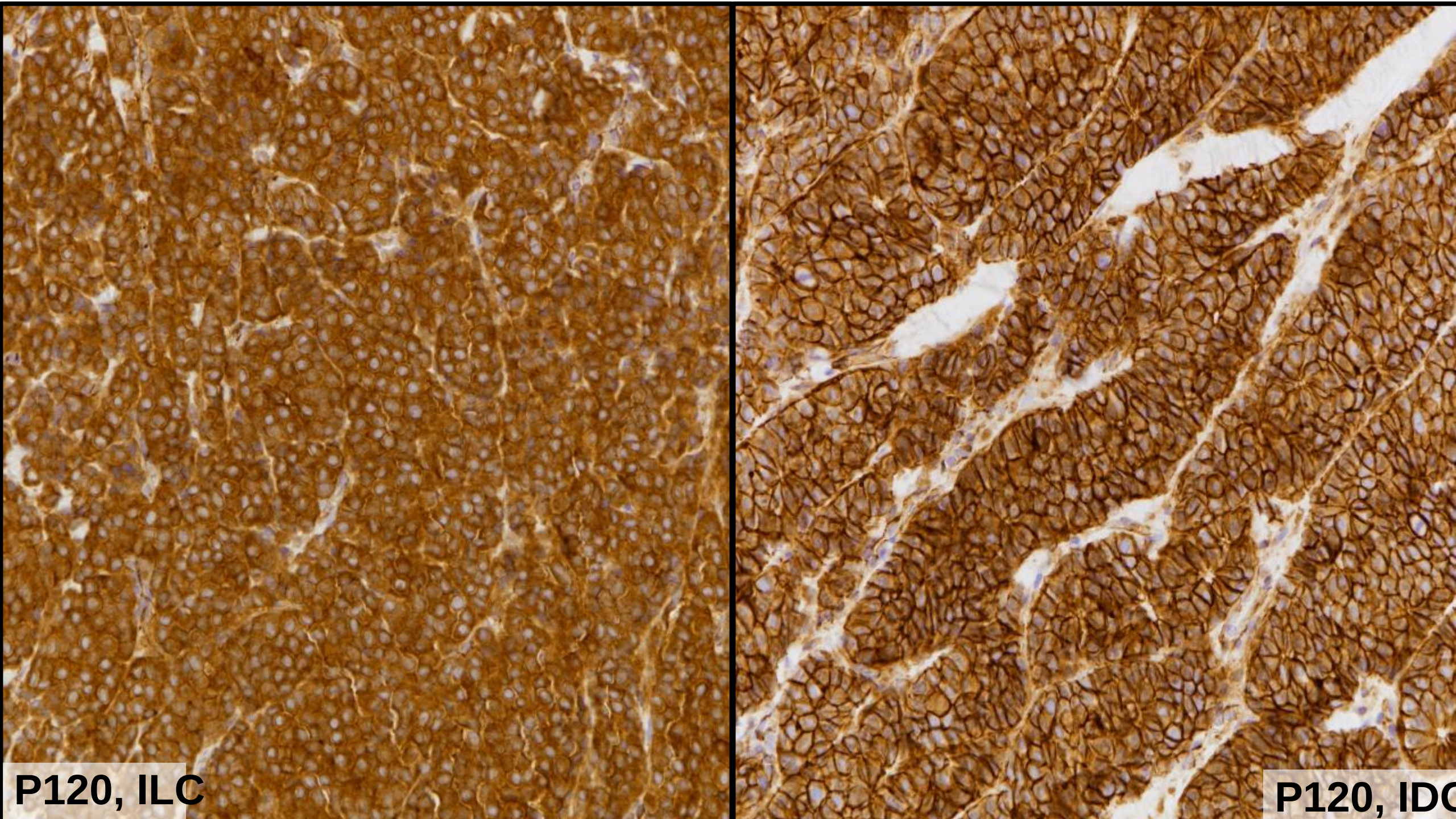

1X

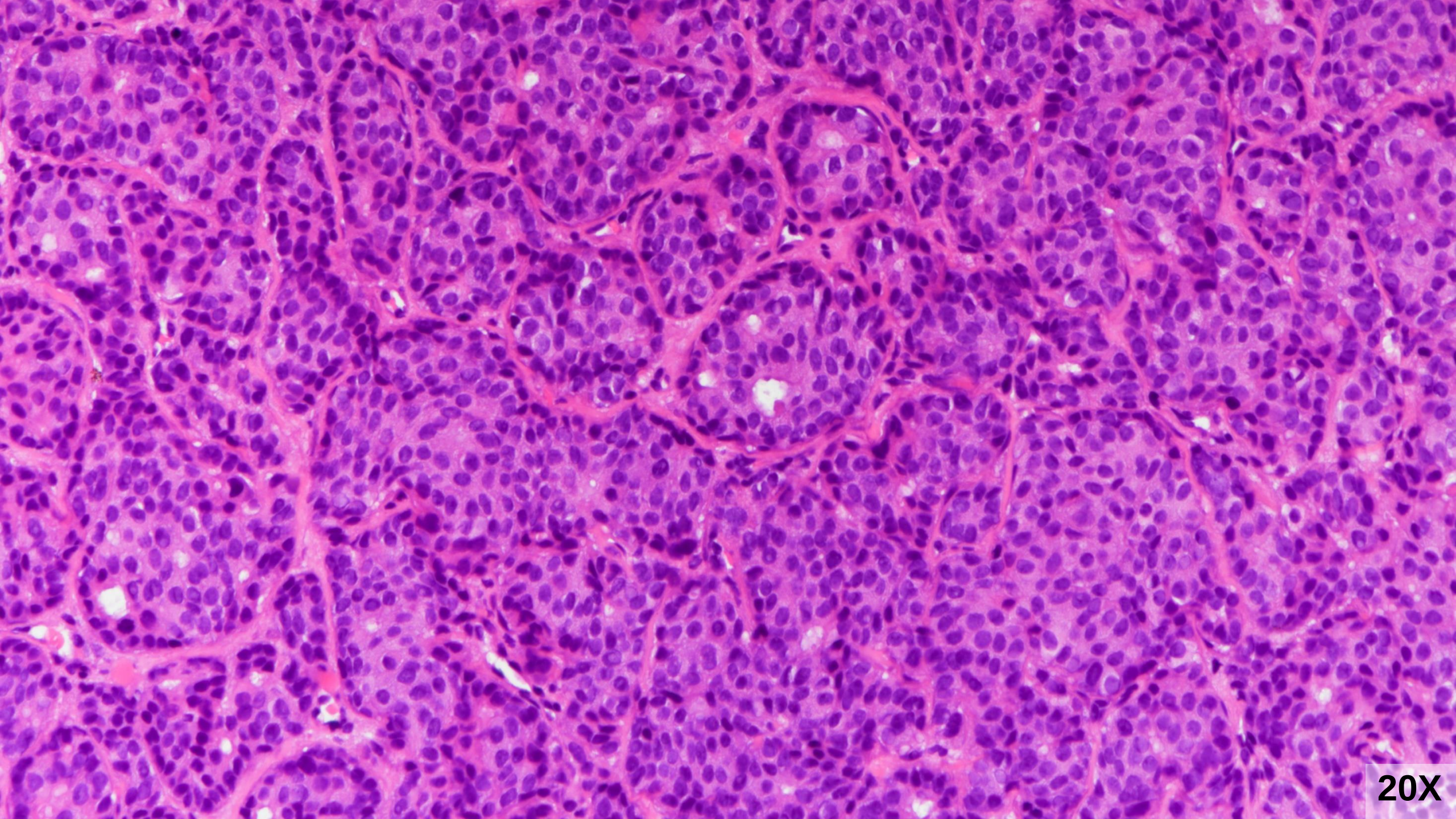

4X

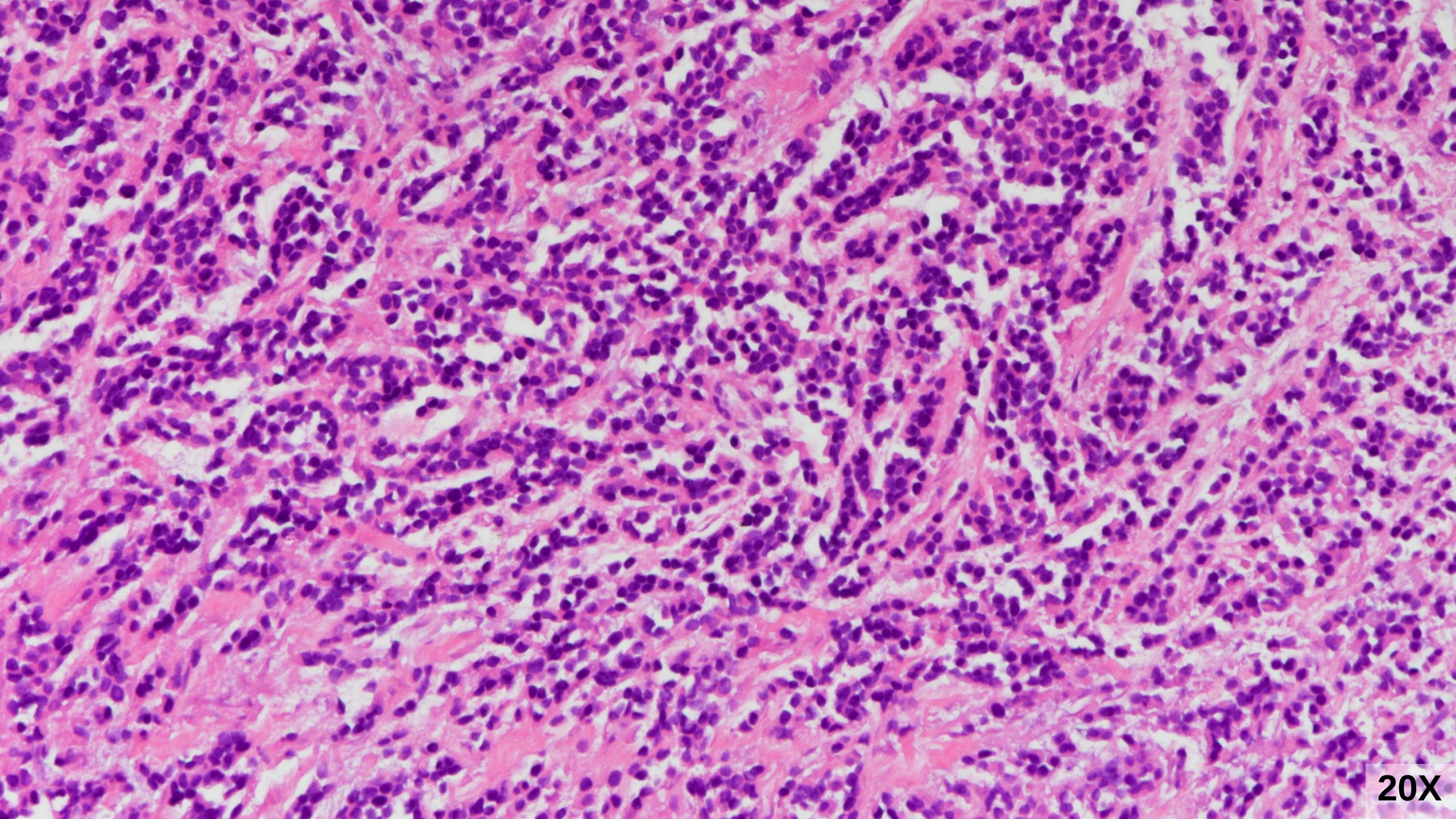

10X

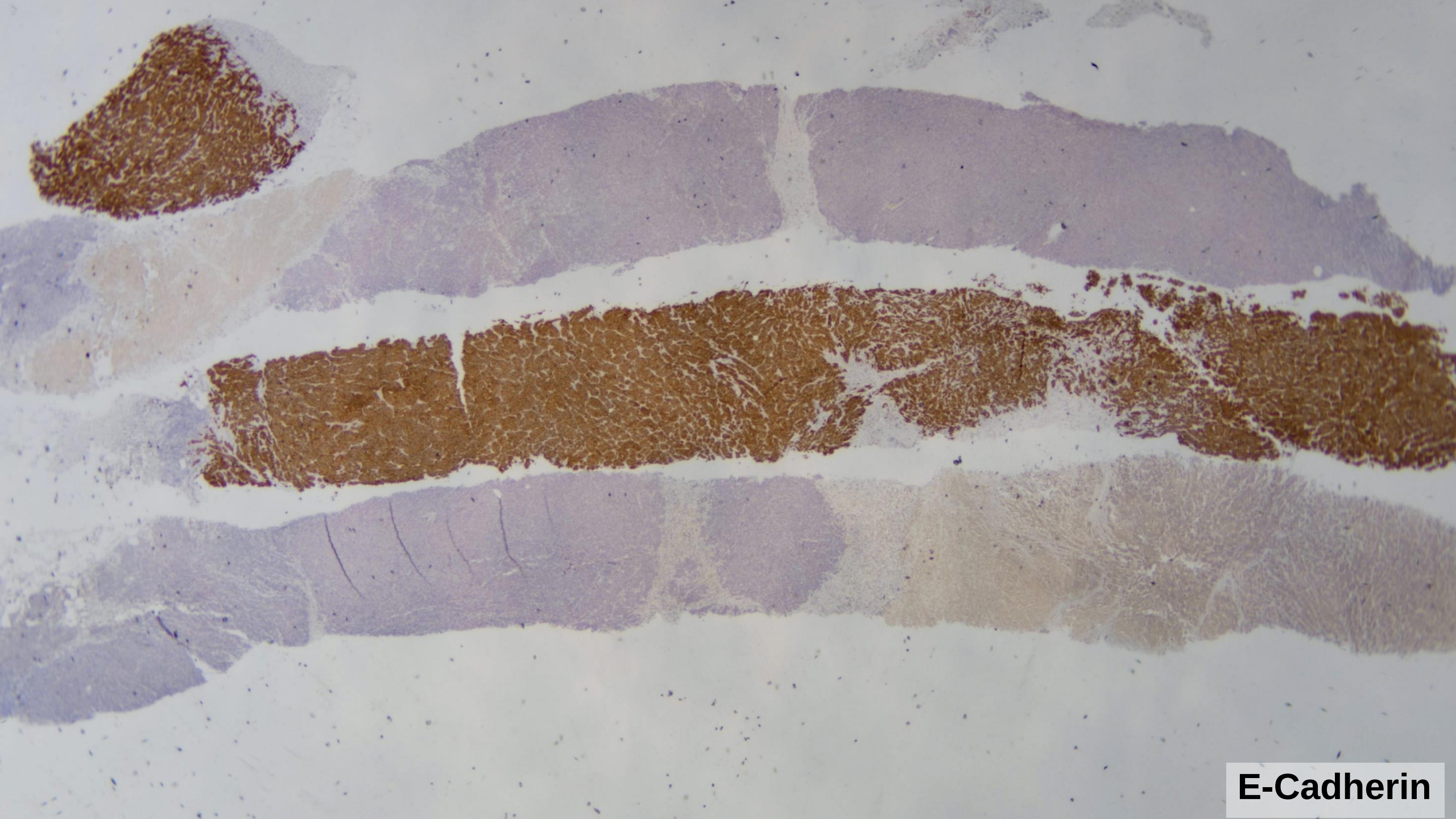

ER


E-Cadherin


P120, ILC
P120, IDC


20X


20X

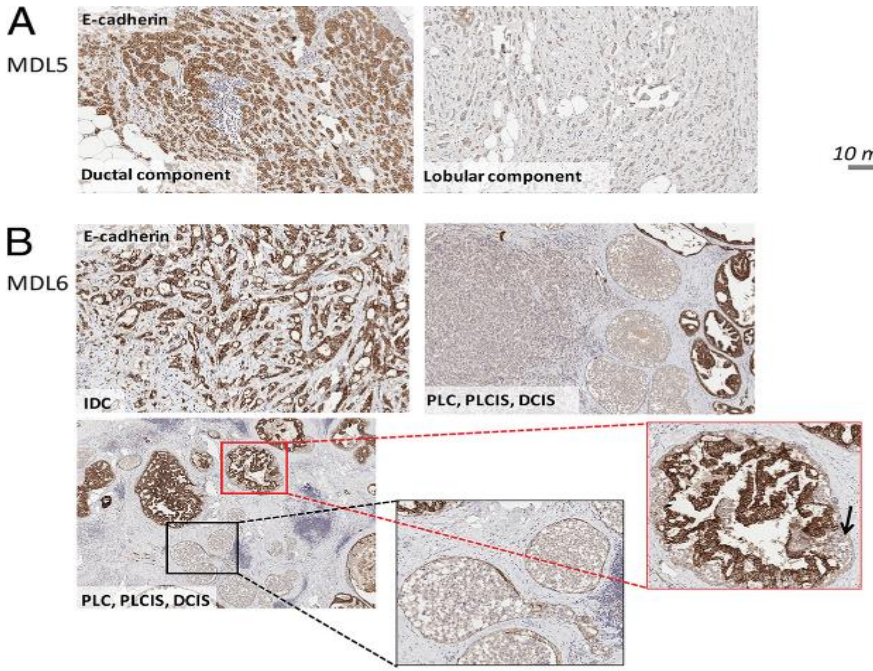

E-Cadherin

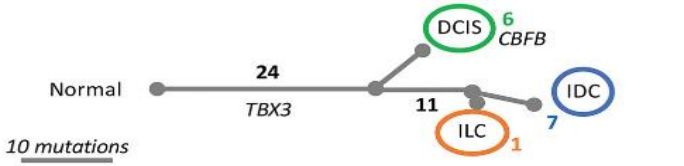
- Estrogen receptor: Positive (2-3+, 80%)
- Progesterone receptor: Positive (2-3+, 90%)
- HER2: Negative (score 0)
- Ki67 index is about 30%

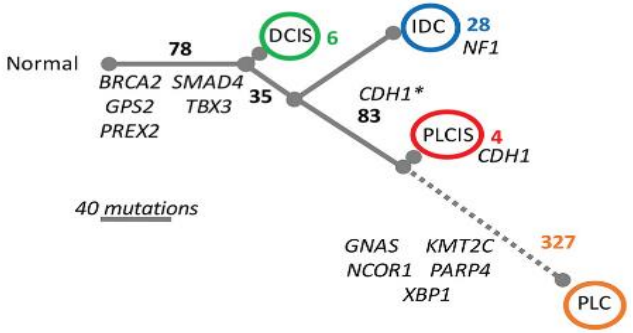
- Diagnosis: Mixed infiltrating duct and lobular carcinoma

# Intra-tumor genotypic-phenotypic correlation

- Mixed ductal-lobular carcinoma
  - Morphologic distinct components within an individual case were clonally related supporting a common ancestor
  - Clonal divergence occur during tumor evolution
  - Lobular like phenotype can arise via a modified ductal pathway in some cases



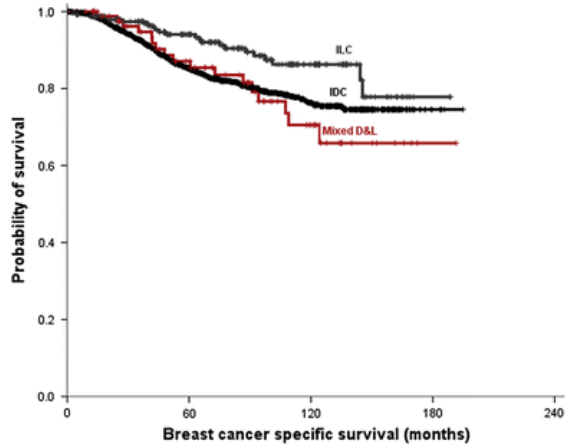




Patani N et al 2011 J Clin Pathol 64:822

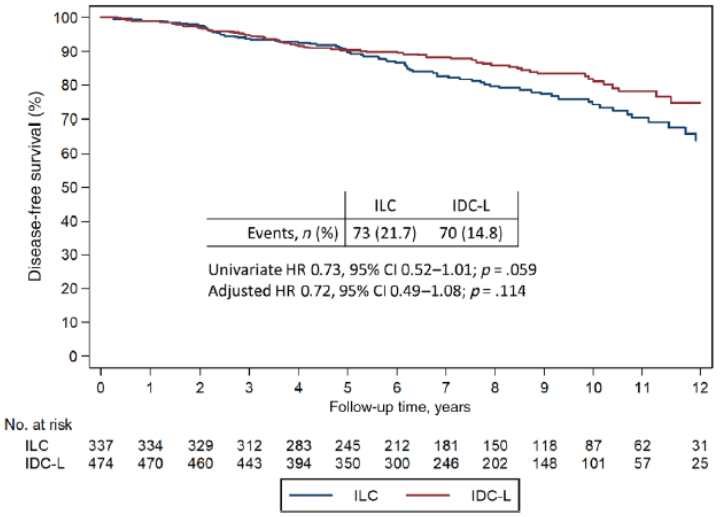
# Prognosis : mixed ductal-lobular breast cancer

- Mixed IDC-L showed association with lower grade, ER positivity, lower metastatic rate compared to IDC, but higher grade, more LN met, vascular invasion and local relapse compared to ILC
- The prognostic value was not consistently reported
  - In one study, mixed IDC-L showed worse survival than ILC. However, no apparent differences were observed after adjustment with grade.
  - Another study showed mixed IDC-L have a better prognosis than ILC, particularly among post-menopausal women. Histological grade is an important prognostic factor in IDC-L, but not ILC.
- Poorer prognostic features of a component type may determine the outcome and the good prognostic characteristics of the other may have no effect?

Metzger-Filho O et al 2019 Oncologist 24:e441

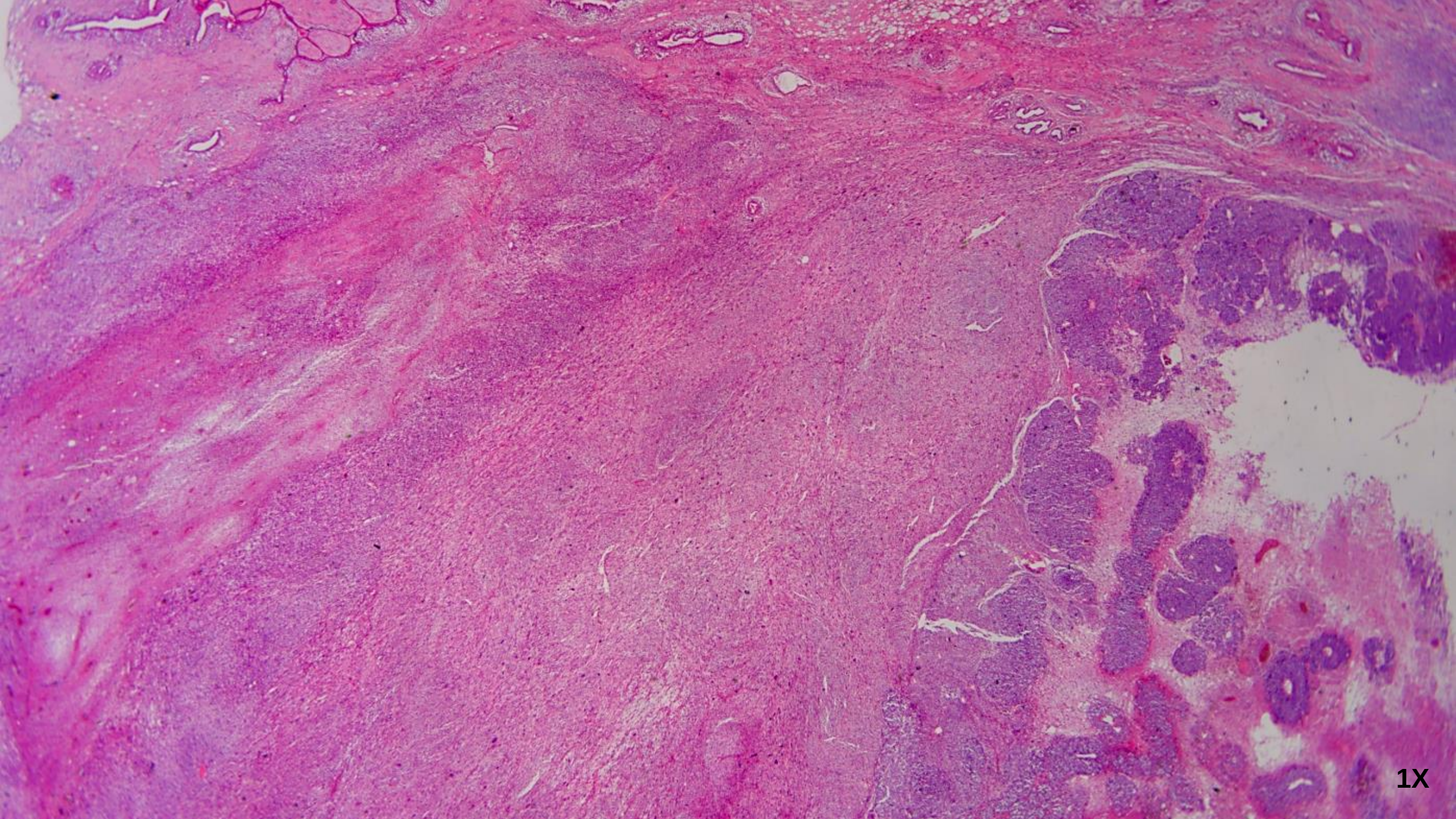


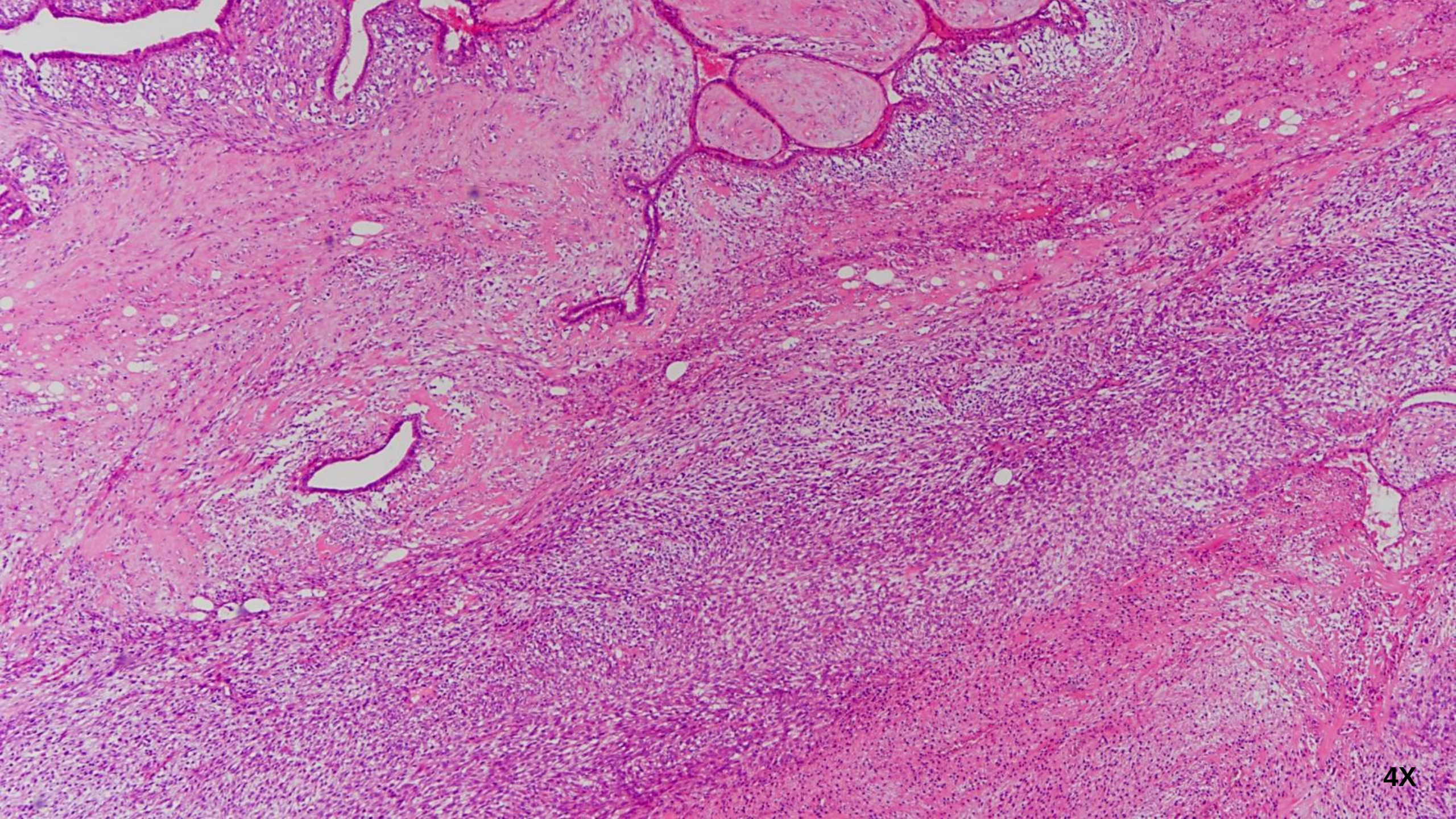

Rakha EA et al 2009 Breast Cancer Res Treat 114:243

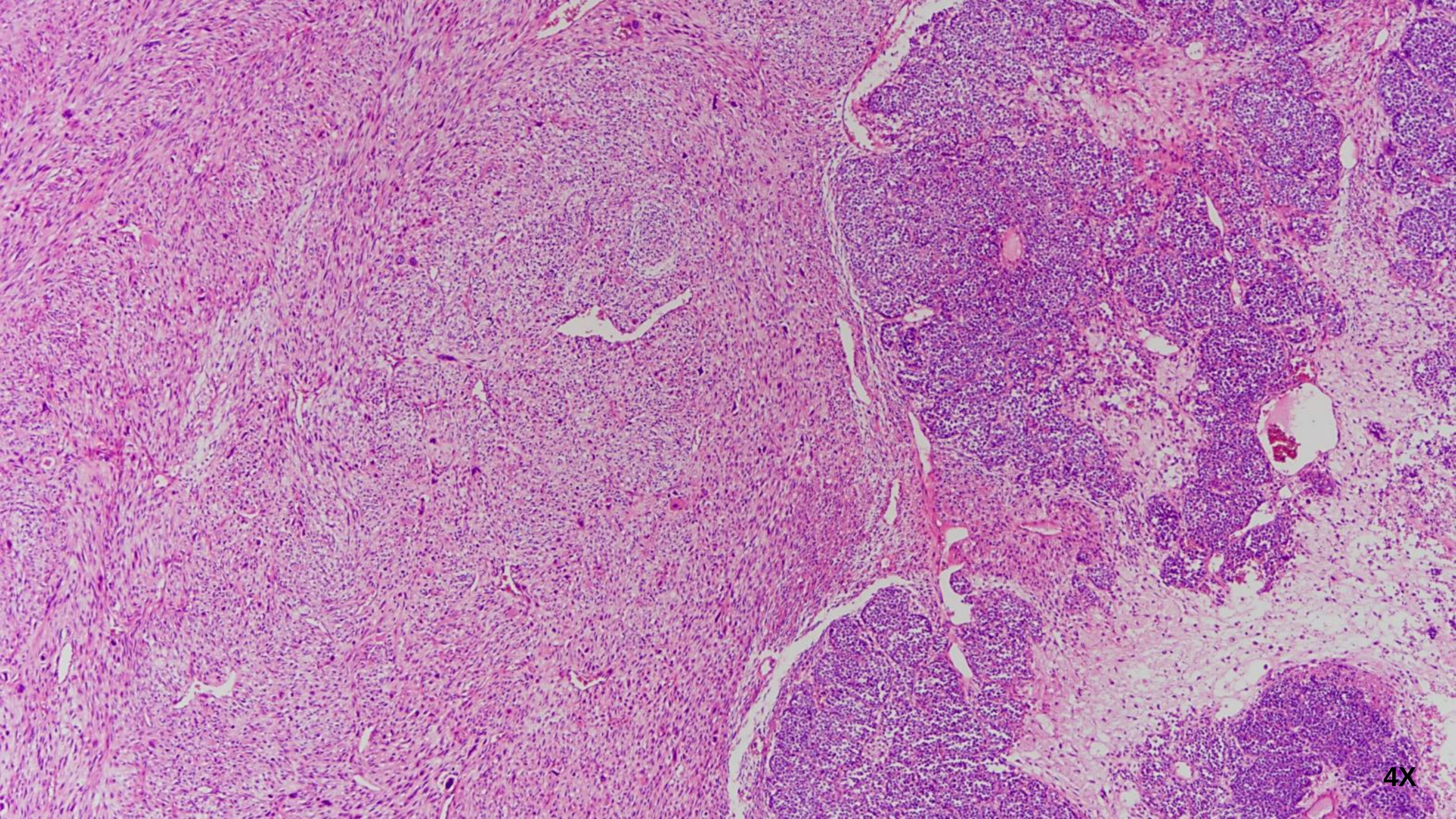


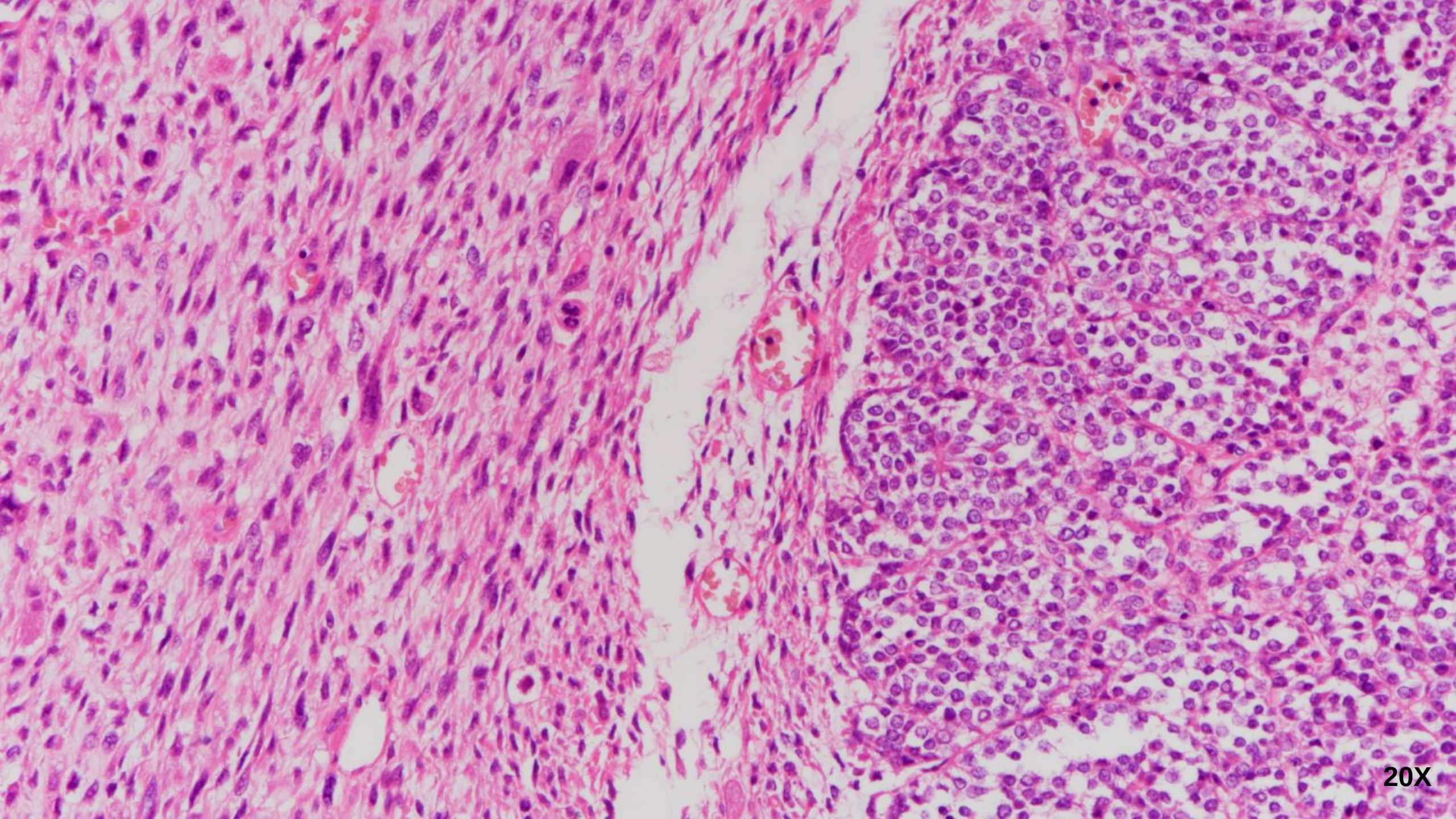
19US  67573

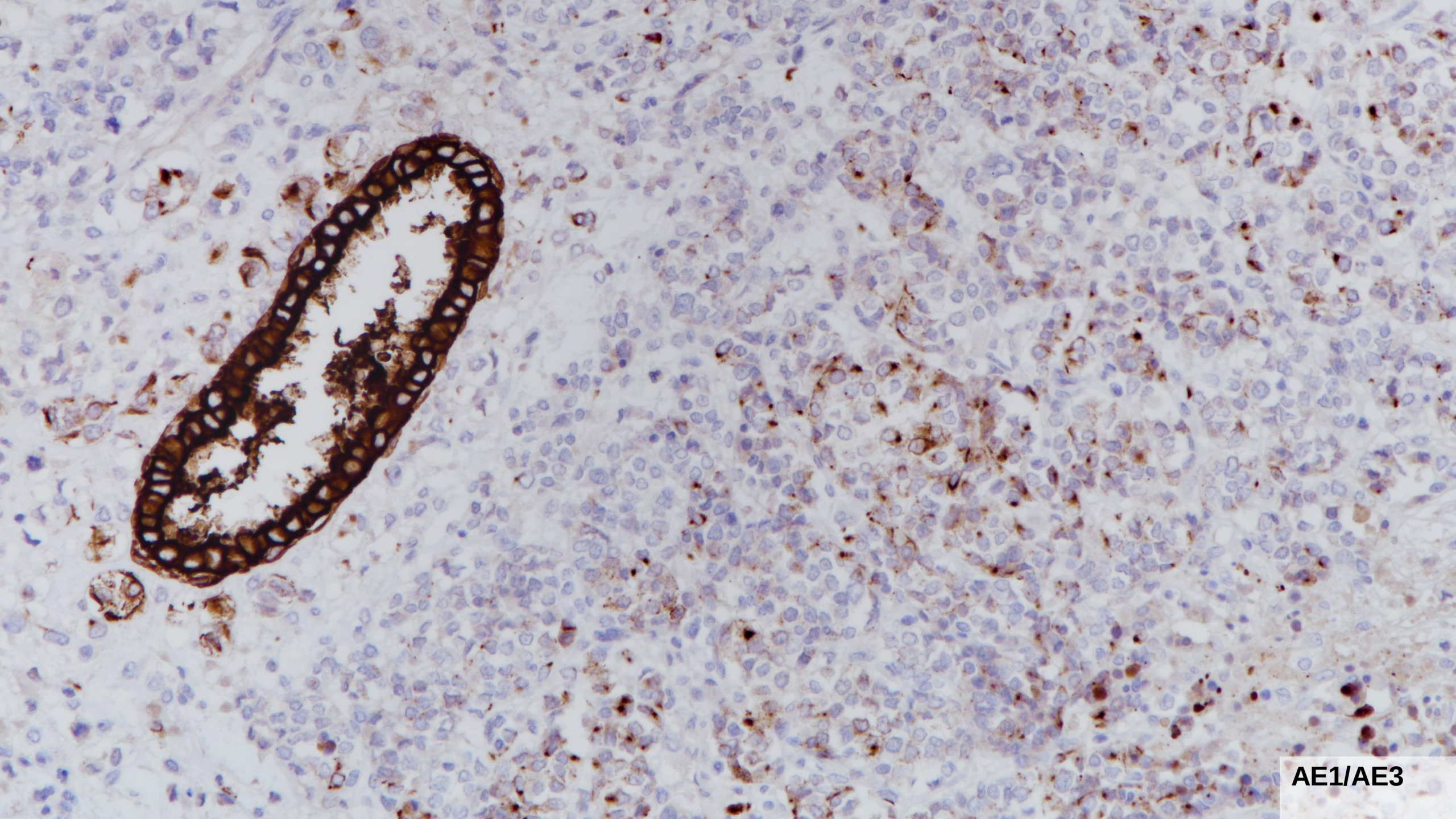
- 50 years old female
- Chief complaint: Rapidly enlarging LUOQ breast mass x 2 months
- PE: 7 cm left breast mass

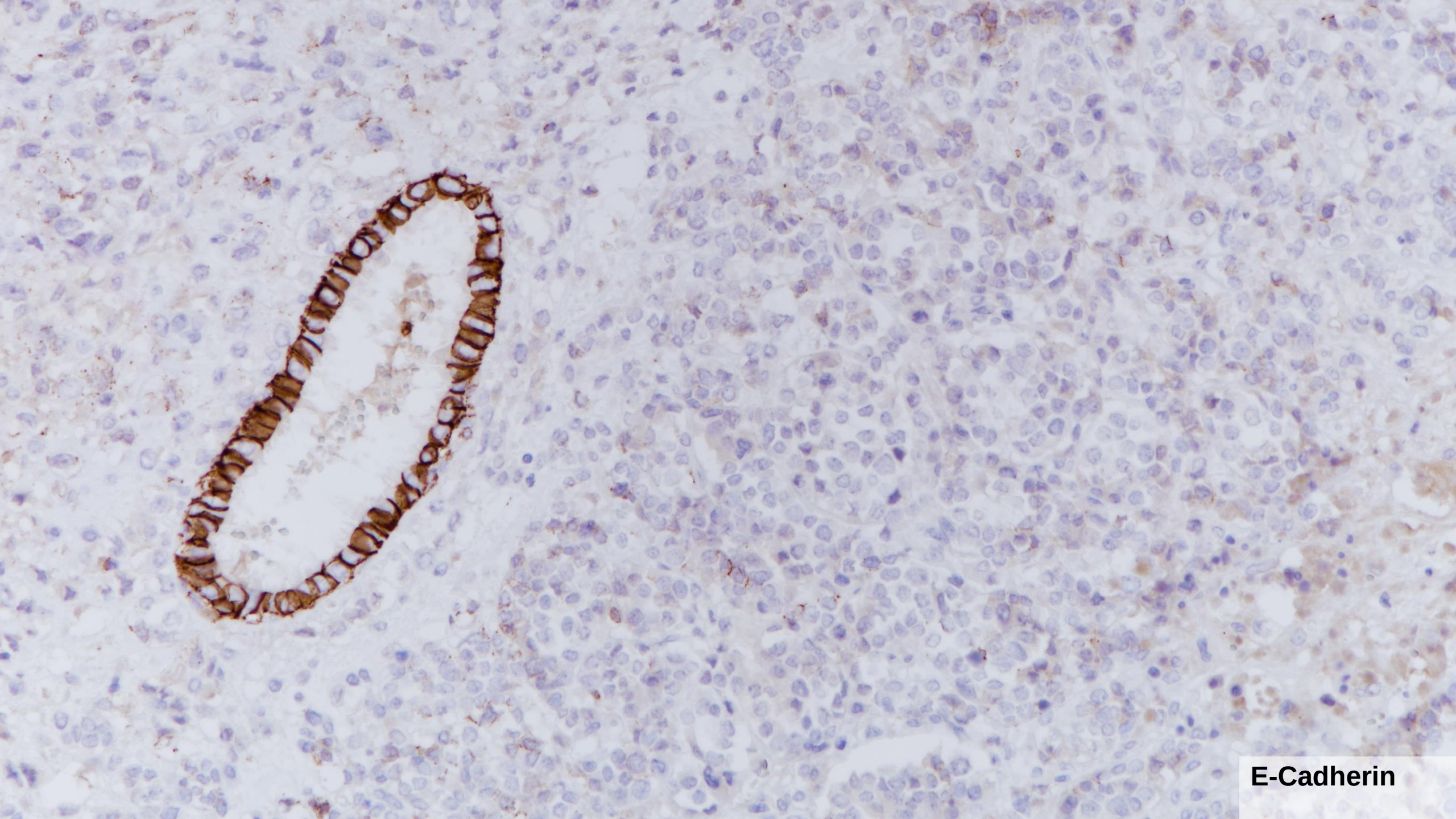

1X

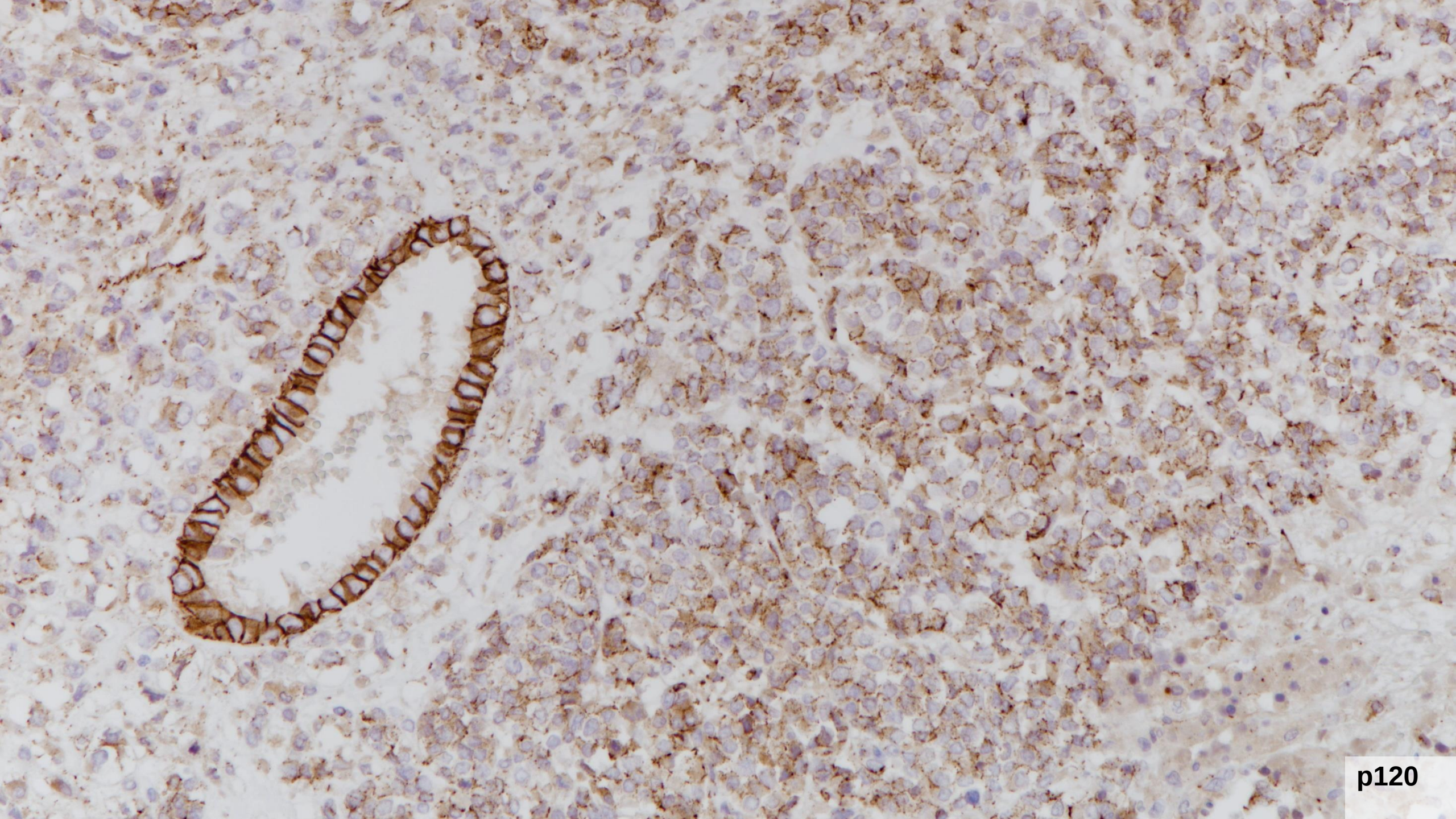

4X

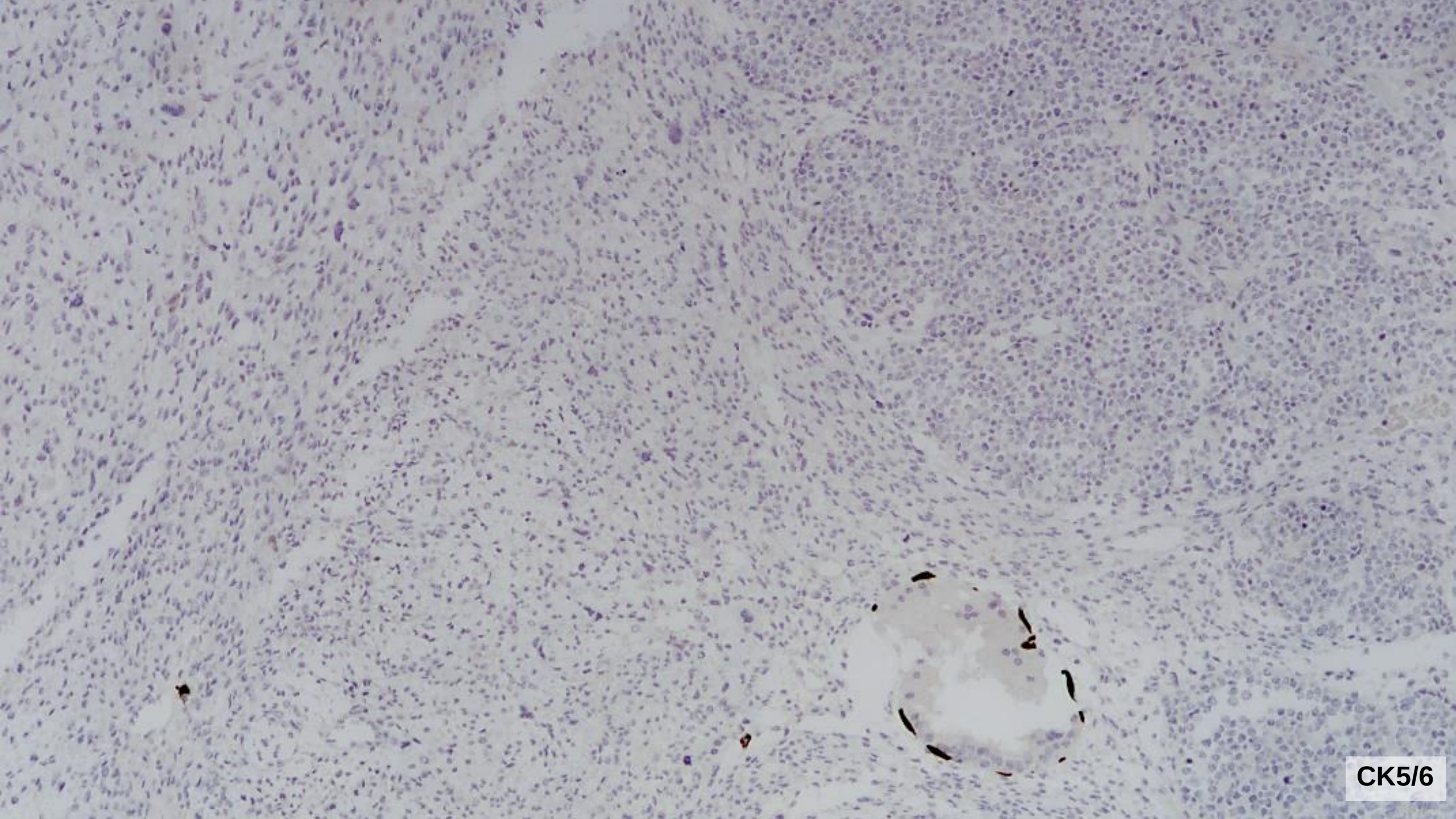

4X


20X


AE1/AE3


E-Cadherin


p120


CK5/6

Diagnosis

- Malignant phyllodes tumor with invasive lobular carcinoma