Memorial Sloan Kettering Cancer Center

29th Annual Seminar in Pathology

Pittsburgh, PA. April 27, 2023 to April 29, 2023

# The Spectrum of Triple Negative Breast Cancer

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*Director, Breast Pathology Fellowship*
*Memorial Sloan Kettering Cancer Center*

# Disclosure

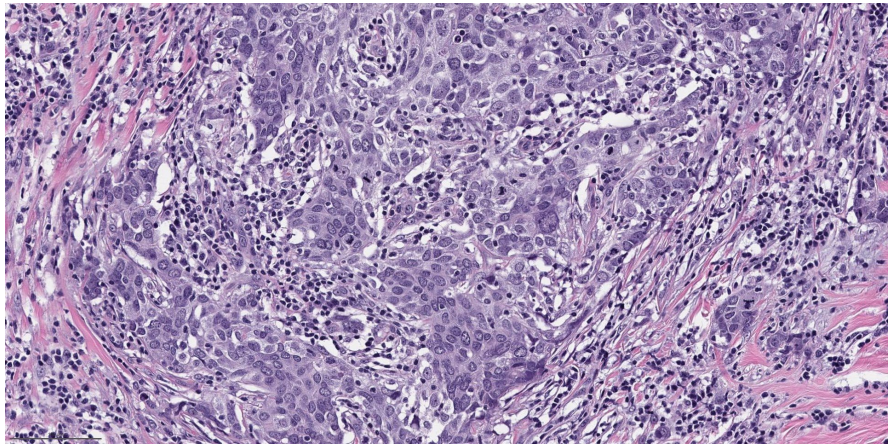
- Advisory faculty, AstraZeneca

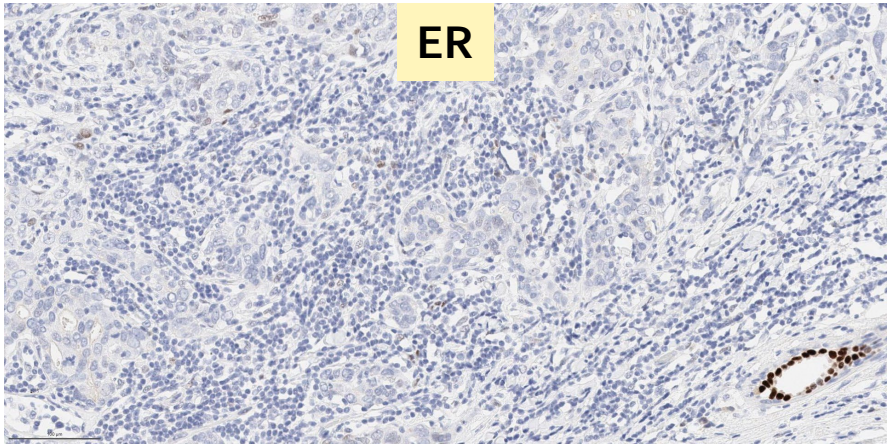
# Outline

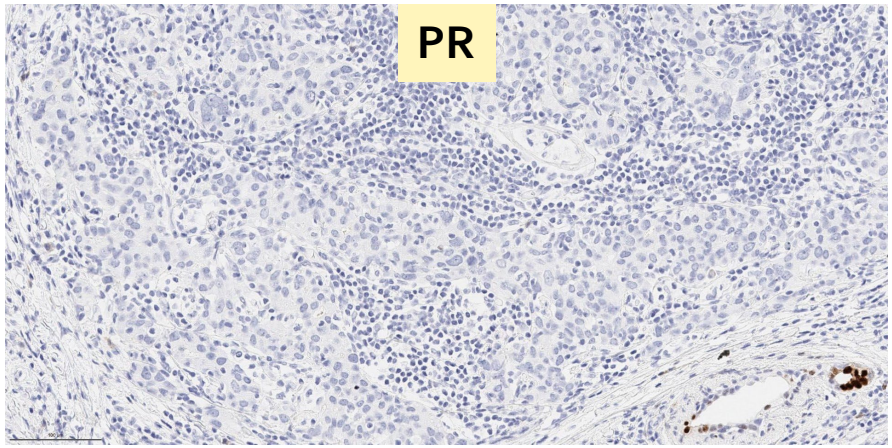
- Special histologic subtypes of triple negative breast cancer
  - Histologic features
  - Differential diagnosis
  - Molecular pathology
  - Treatment and outcome

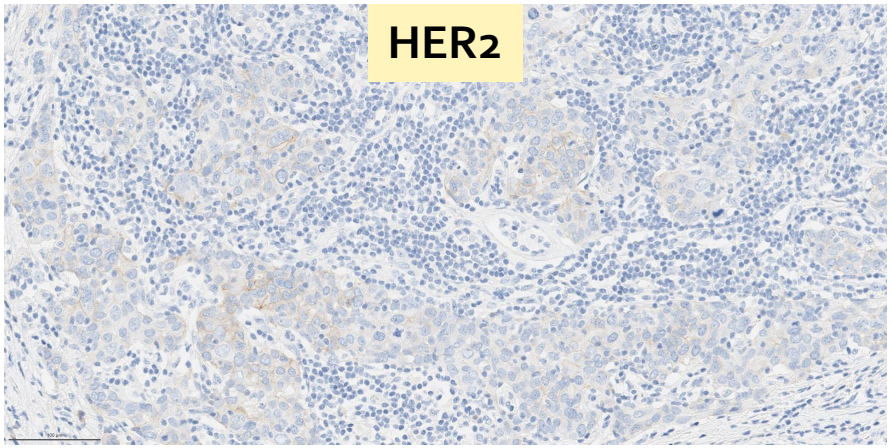
# Triple negative breast cancer (TNBC)

- A heterogeneous group of breast cancers defined by the lack of expression of ER, PR, and HER2



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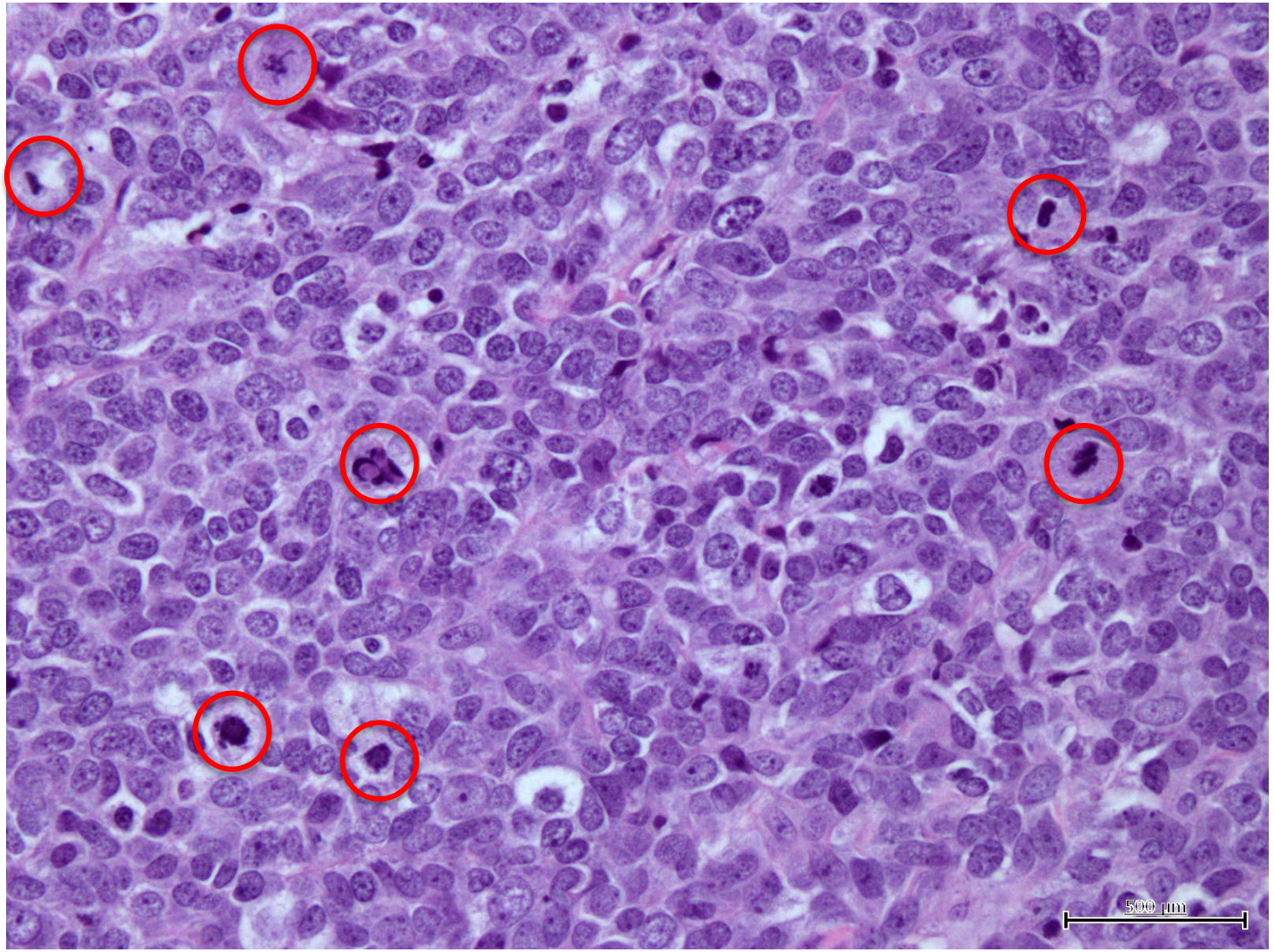
# Invasive carcinoma NST: high grade, high mitotic rate

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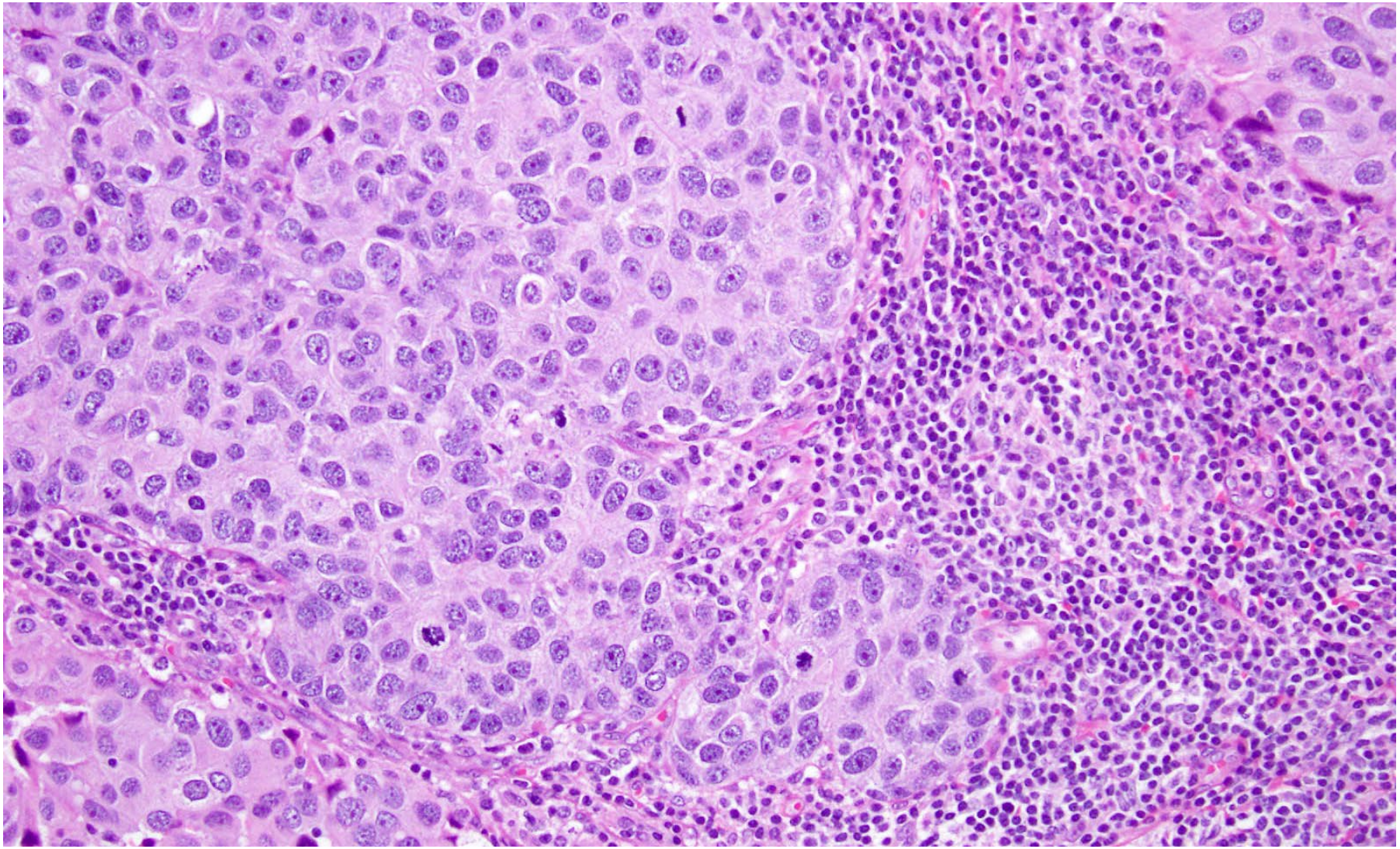
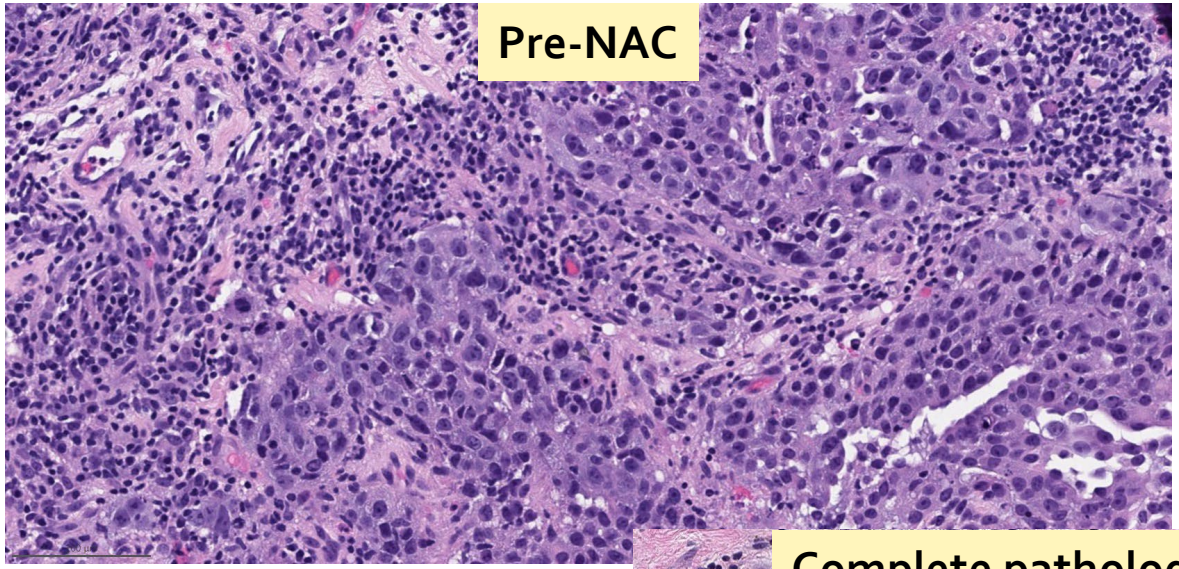
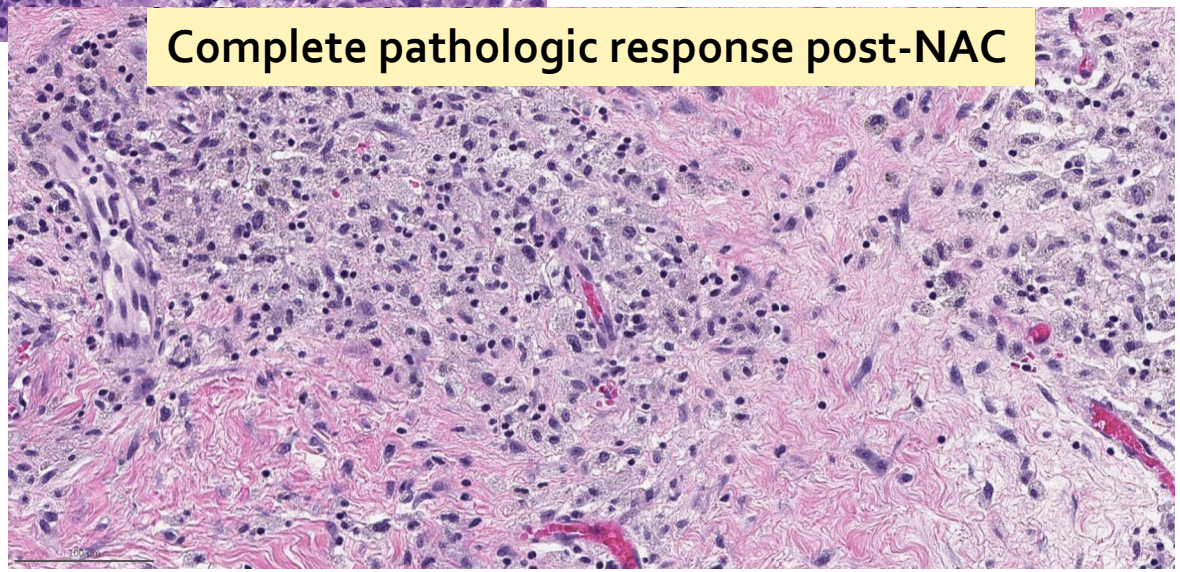
# Extensive TILs: more frequently seen in TNBC



# Increased TILs predicts response to neoadjuvant chemotherapy

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# TILs quantification: % of stromal TILs

reviews

*Annals of Oncology* 26: 259–271, 2015
doi:10.1093/annonc/mdu450
Published online 11 September 2014

## The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014

R. Salgado[1,2,†], C. Denkert[3,†], S. Demaria[4,†], N. Sirtaine[5], F. Klauschen[3], G. Pruneri[6], S. Wienert[3], G. Van den Eynden[7], F. L. Baehner[8,9], F. Penault-Llorca[10], E. A. Perez[11], E. A. Thompson[12], W. F. Symmans[13], A. L. Richardson[14,15], J. Brock[15,16], C. Criscitiello[17], H. Bailey[8], M. Ignatiadis[18], G. Floris[19], J. Sparano[20], Z. Kos[21], T. Nielsen[22], D. L. Rimm[23], K. H. Allison[24], J. S. Reis-Filho[25], S. Loibl[26], C. Sotiriou[18], G. Viale[27], S. Badve[28], S. Adams[4,†], K. Willard-Gallo[29,†] & S. Loi[30*,†]

- ***We do not report TILs percentage in routine clinical practice***

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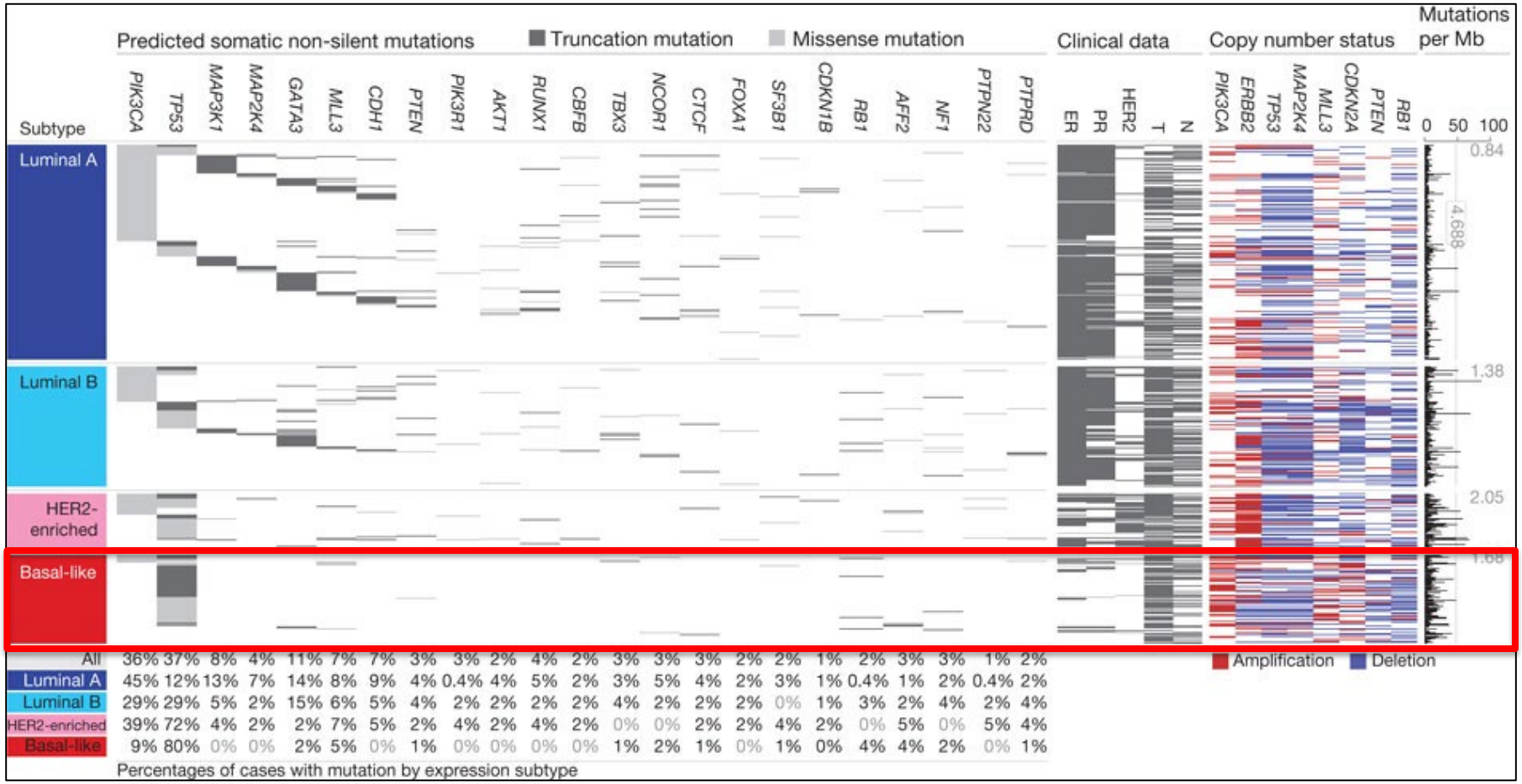
# Significantly mutated genes by breast cancer subtypes

- TNBC: high frequency of *TP53* mutations (80%). *PIK3CA* (~9%)




Cancer Genome Atlas Network. *Nature*. 2012; 490:61-70

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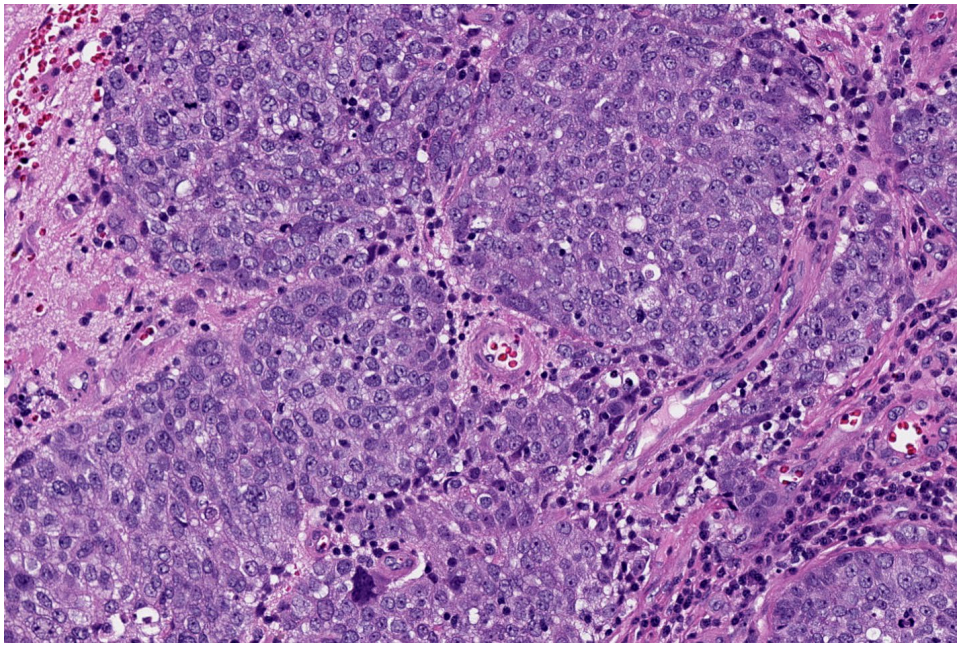
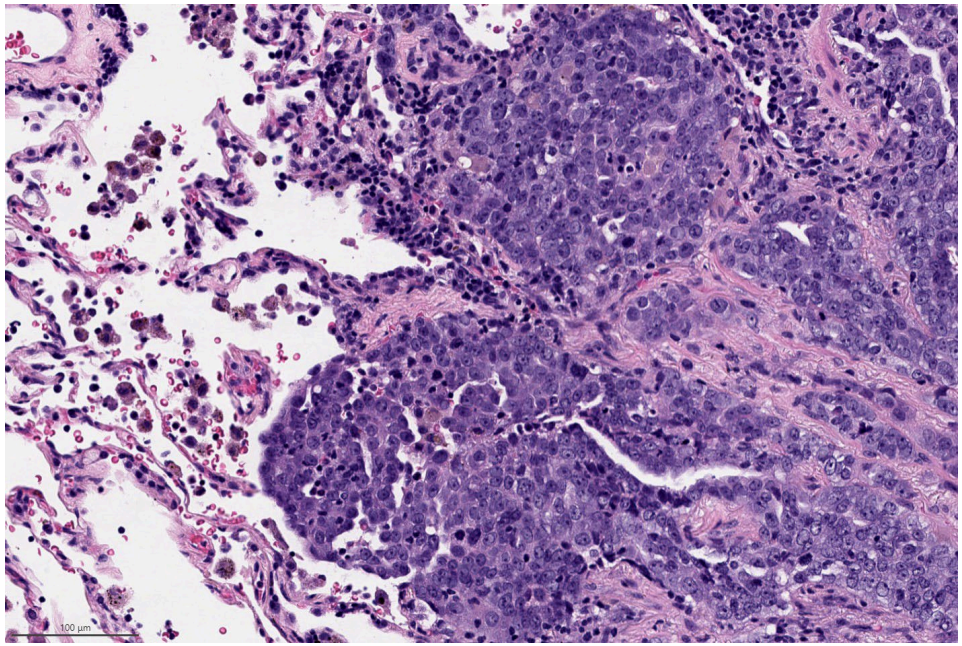
# Higher rate of distant metastases

Brain metastasis



Lung metastasis

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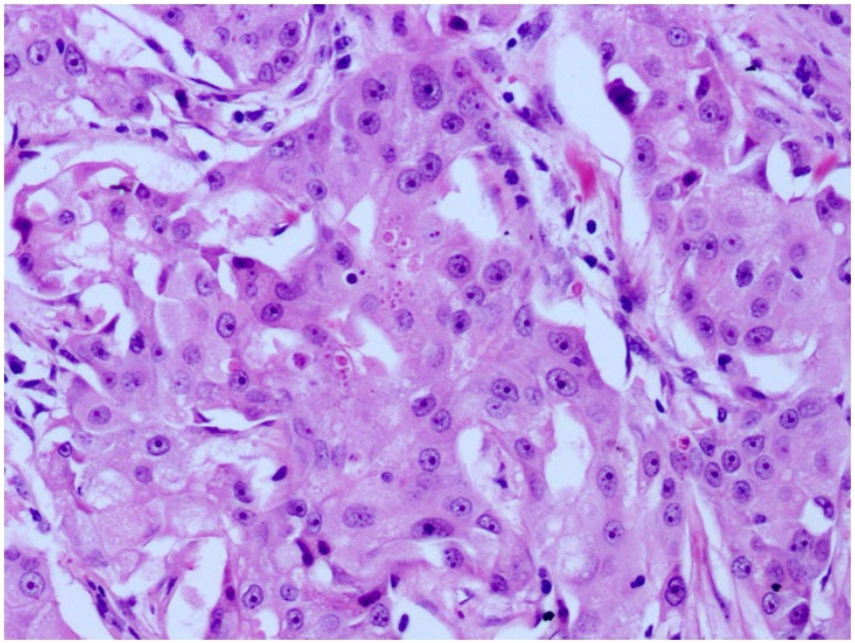
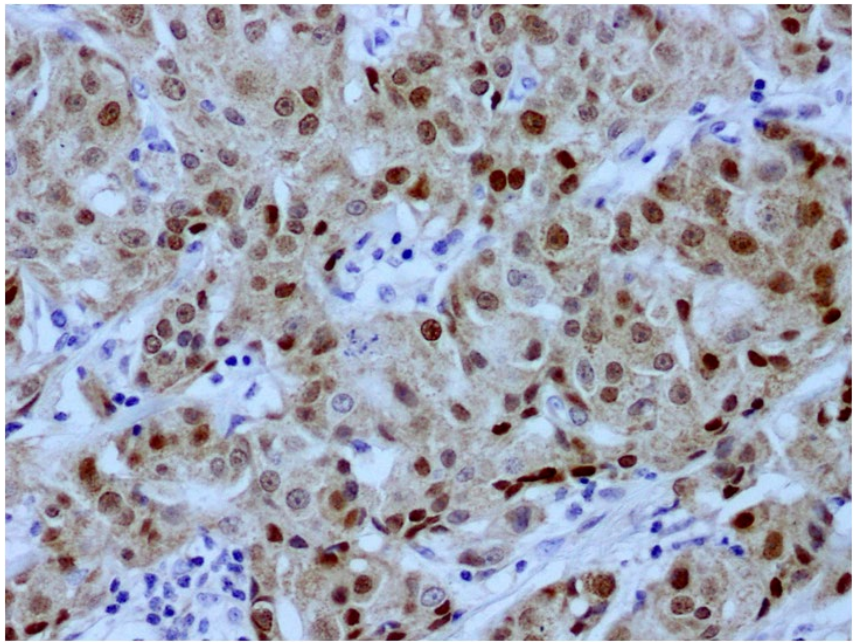
# Androgen receptor (AR)

**H&E: with apocrine features**



**AR**



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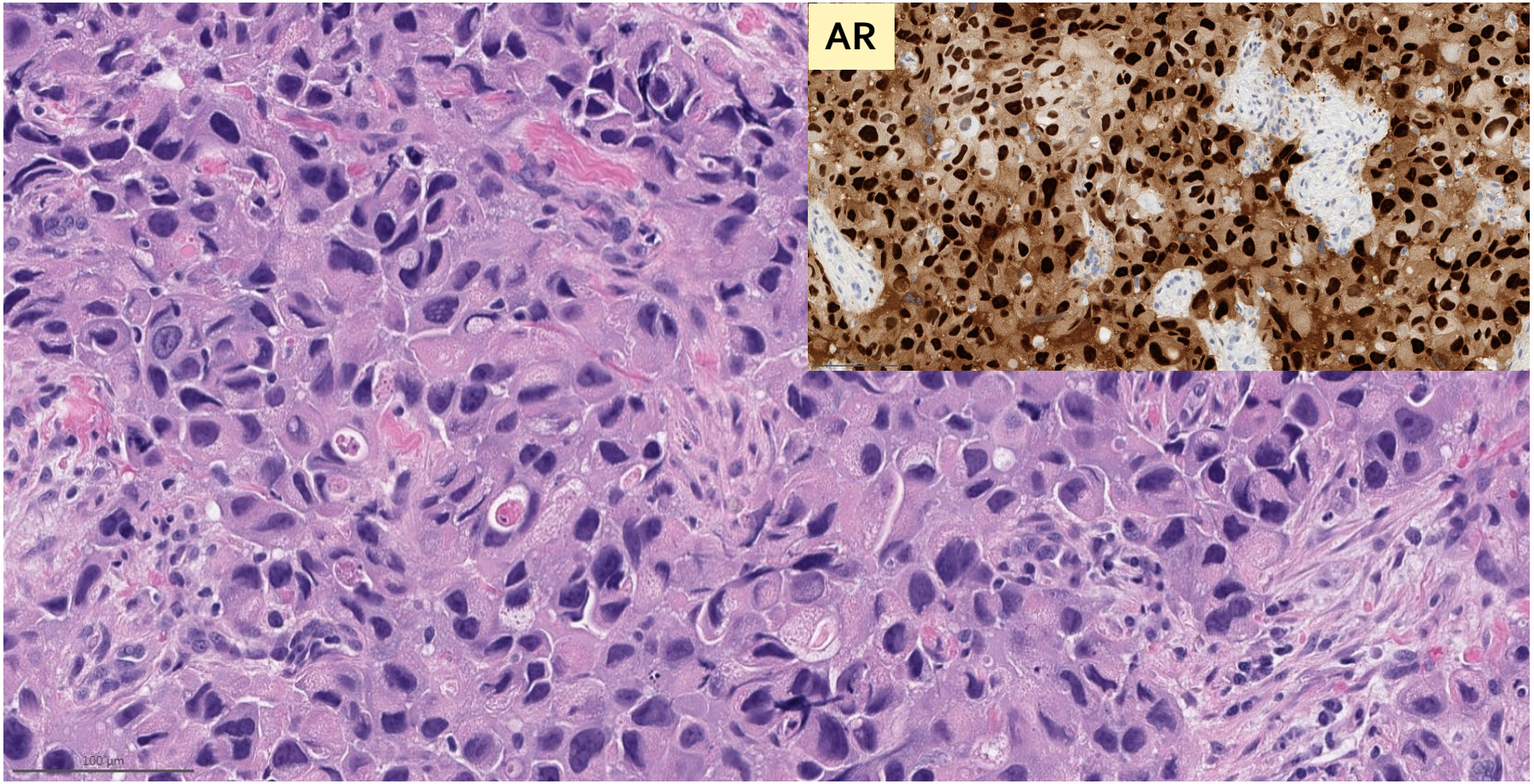


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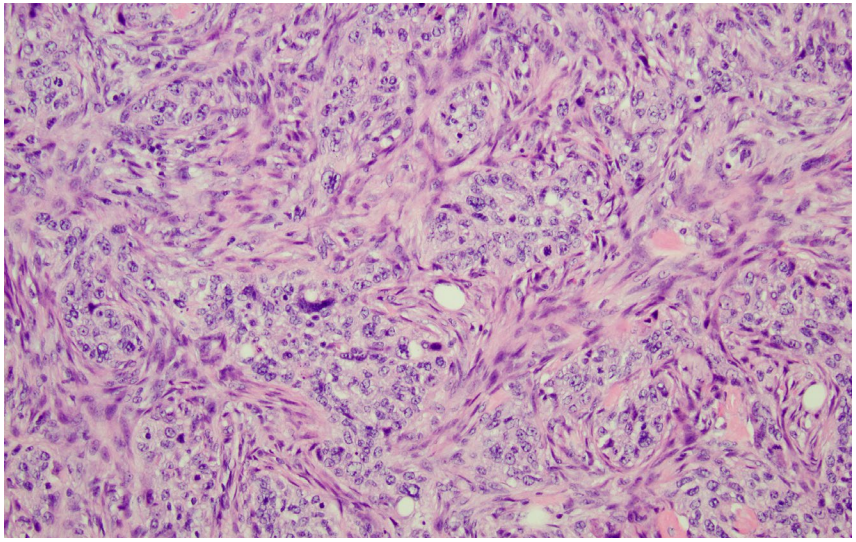
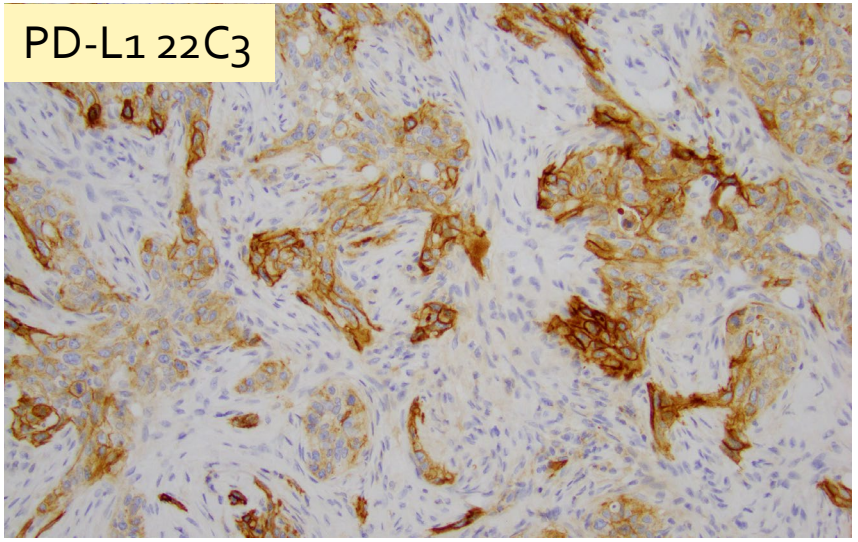
# PD-L1

- Pembrolizumab for patients with PD-L1 positive (CPS >=10) locally advanced or metastatic TNBC





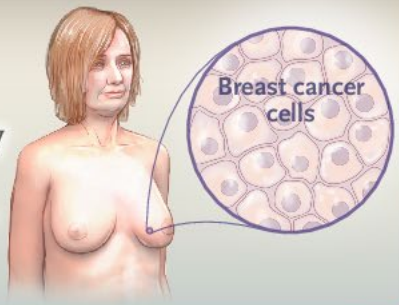
# Neoadjuvant treatment with pembrolizumab

The NEW ENGLAND JOURNAL of MEDICINE

## Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

**1174 Patients** with previously untreated triple-negative breast cancer




| | Neoadjuvant Pembrolizumab + chemotherapy, followed by surgery and adjuvant pembrolizumab (N=784) | Neoadjuvant Placebo + chemotherapy, followed by surgery and adjuvant placebo (N=390) |
|---|---|---|
| Pathological complete response at time of surgery | 64.8% | 51.2% |
| | Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001 | |
| Event-free survival | 91.3% (95% CI, 88.8–93.3) | 85.3% (95% CI, 80.3–89.1) |
| | HR for an event or death, 0.63; 95% CI, 0.43–0.93 | |
| Grade ≥3 adverse events | 76.8% | 72.2% |

P. Schmid et al. 10.1056/NEJMoa1910549



Schmid P. et al. *N Engl J Med*. 2020; 382:810-821

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# Special histologic subtypes

- Metaplastic carcinoma
- Adenoid cystic carcinoma
- Secretory carcinoma
- Tall cell carcinoma with reverse polarity

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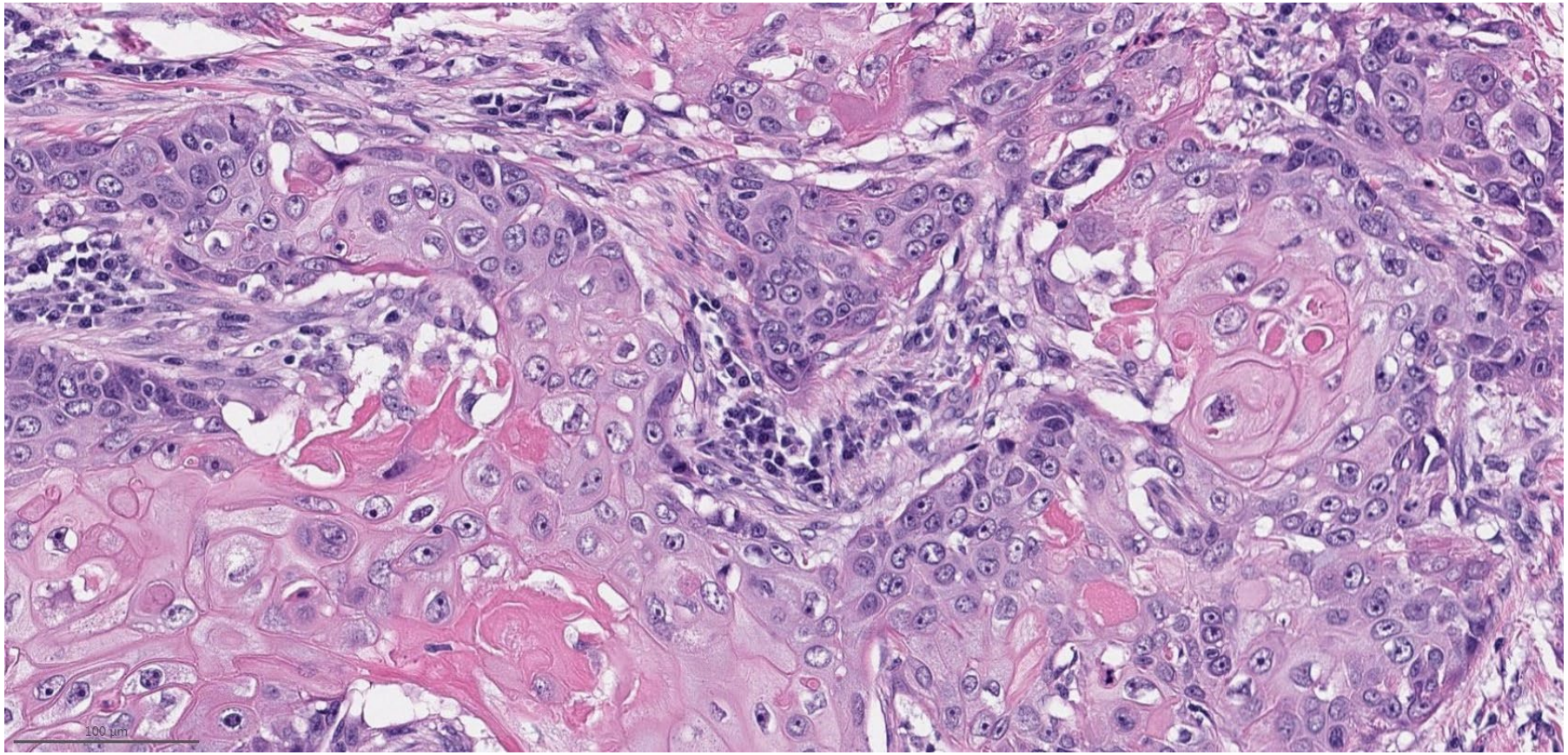
# Metaplastic carcinoma

# Metaplastic breast carcinoma

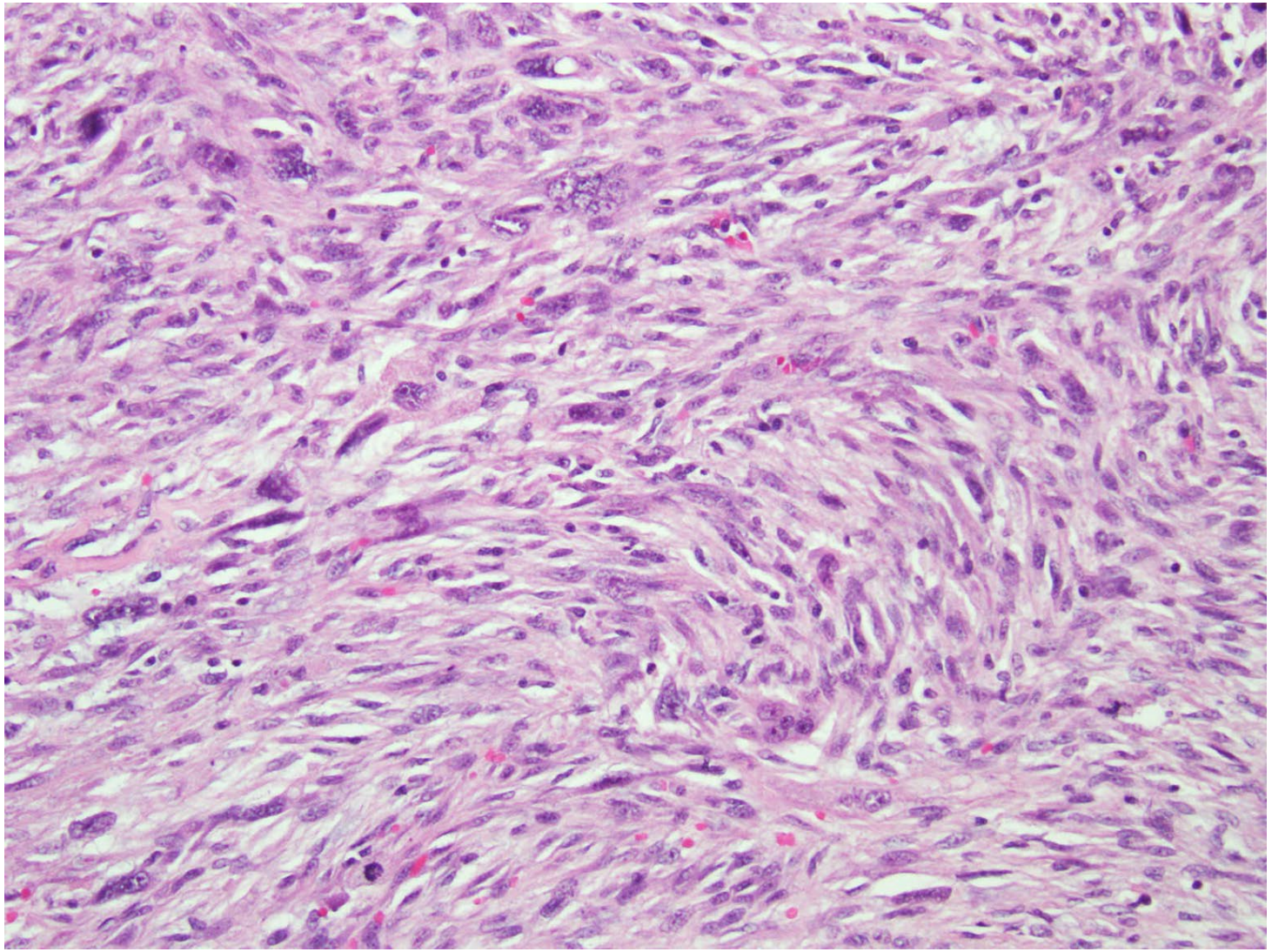
- A heterogeneous group of invasive carcinoma
  - Squamous cell carcinoma
  - Spindle cell carcinoma
  - Carcinoma with mesenchymal differentiation
    - Chondroid  or osseous: matrix producing carcinoma
  - Low-grade variants
    - Low grade adenosquamous carcinoma
    - Fibromatosis like metaplastic carcinoma

# Metaplastic squamous cell carcinoma

- Differential diagnosis: squamous cell carcinoma of skin or other sites

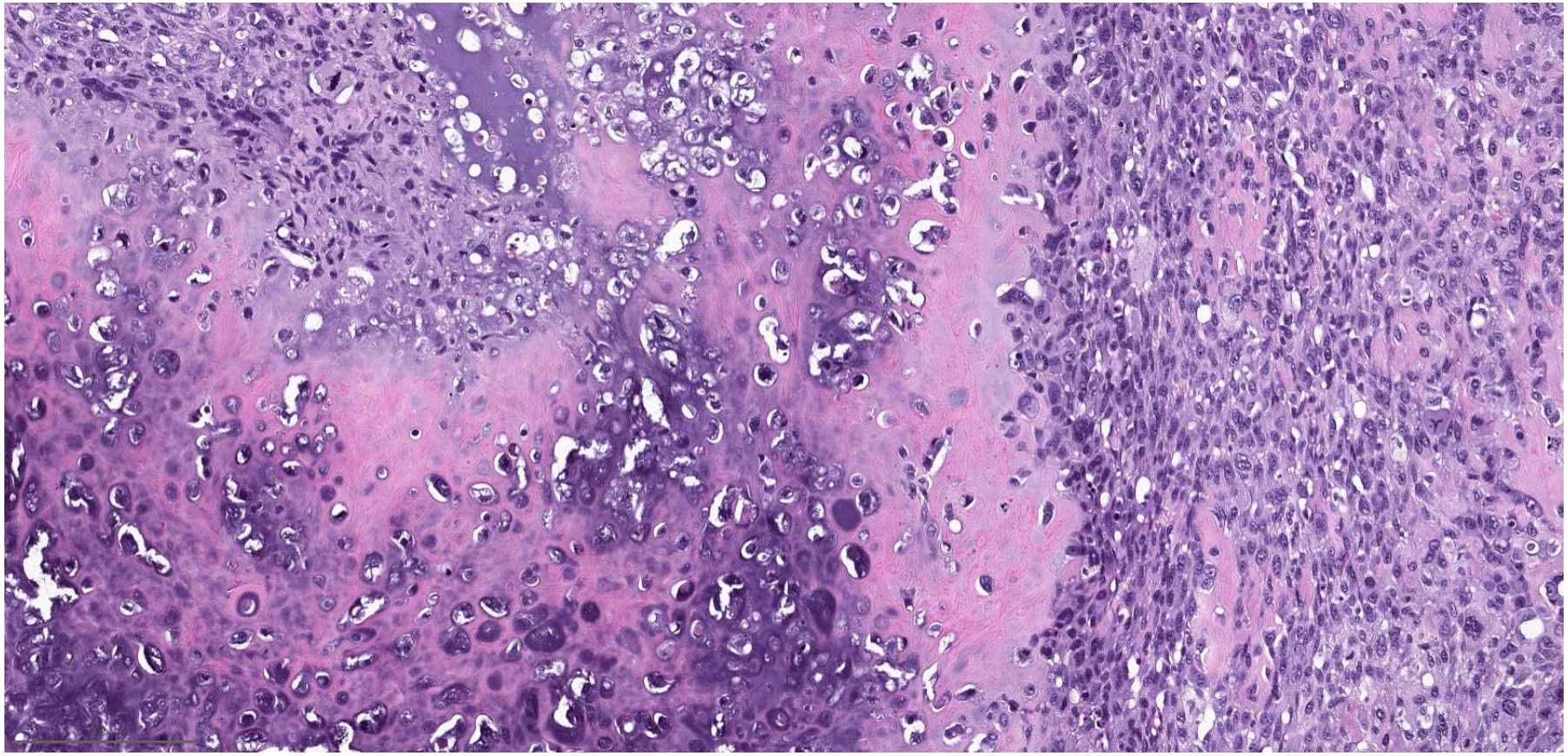


# Metaplastic spindle cell carcinoma



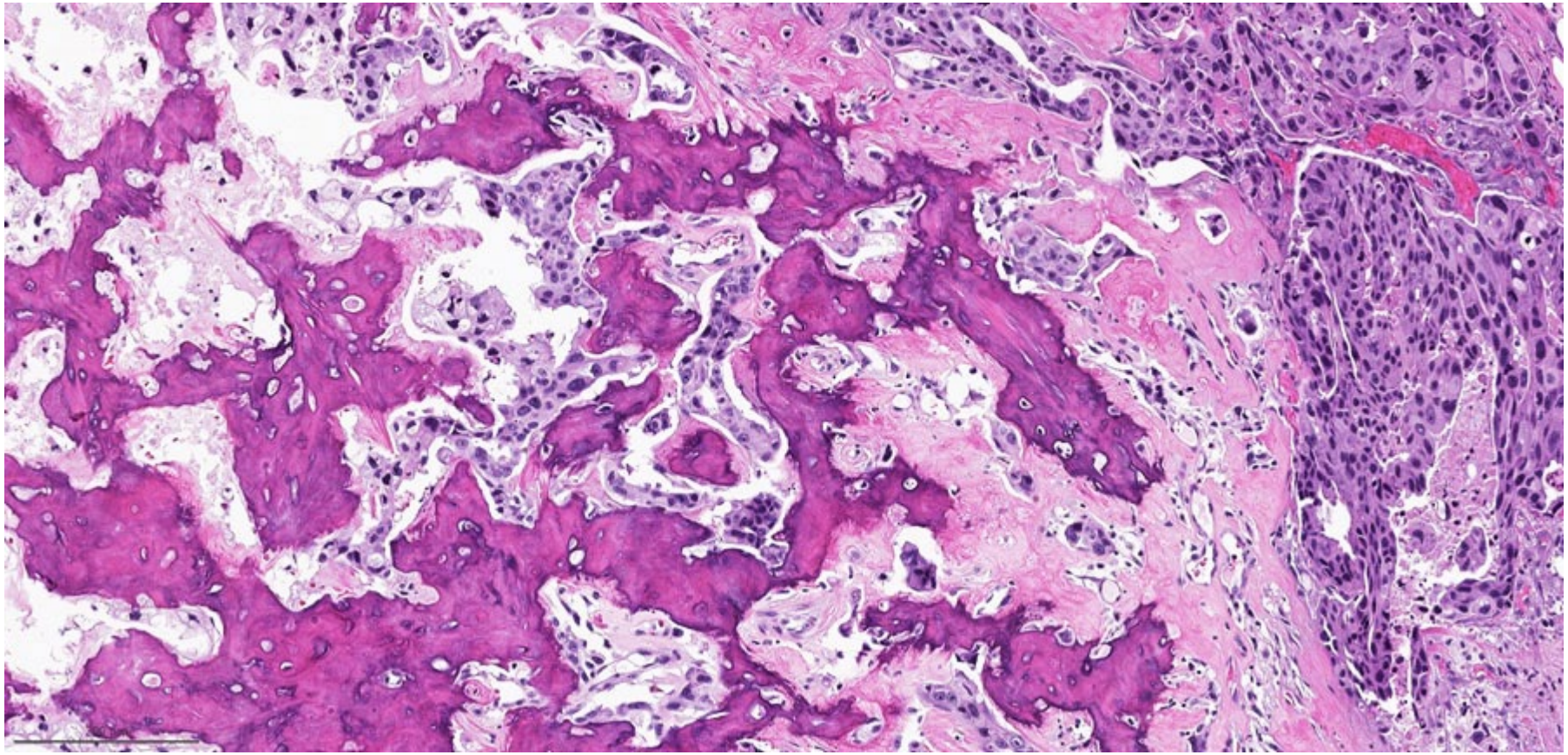
# Carcinoma with mesenchymal differentiation

- Metaplastic carcinoma with chondroid differentiation

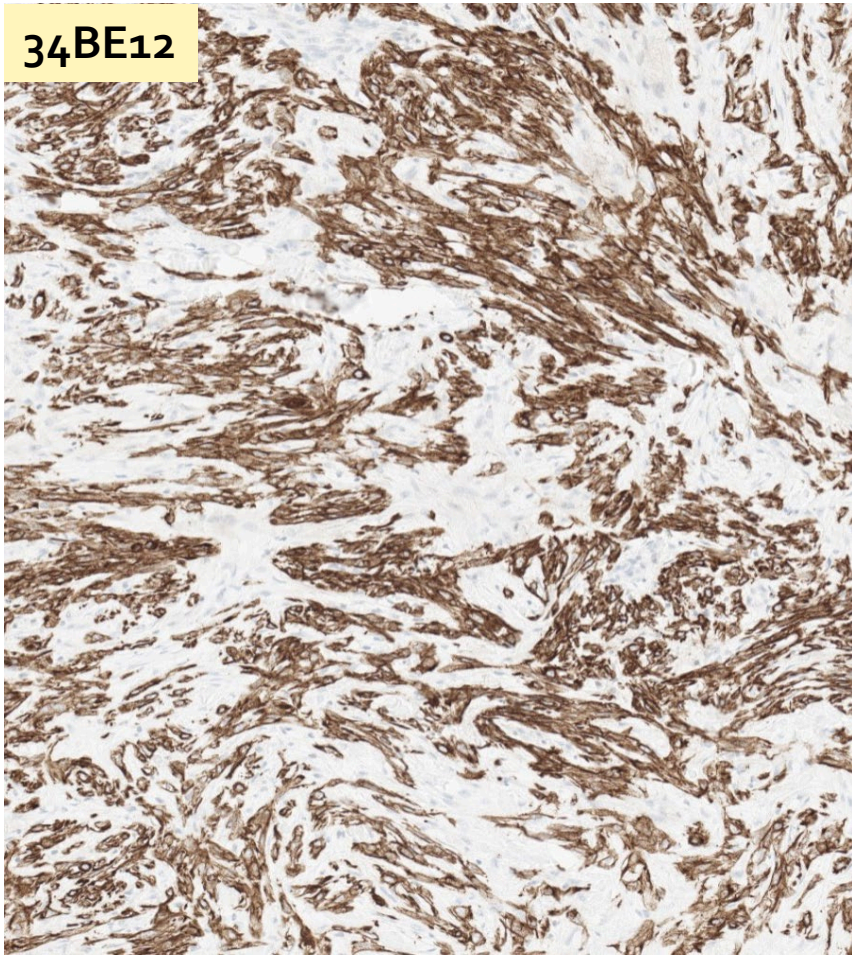


# Carcinoma with mesenchymal differentiation

- Metaplastic carcinoma with osseous differentiation

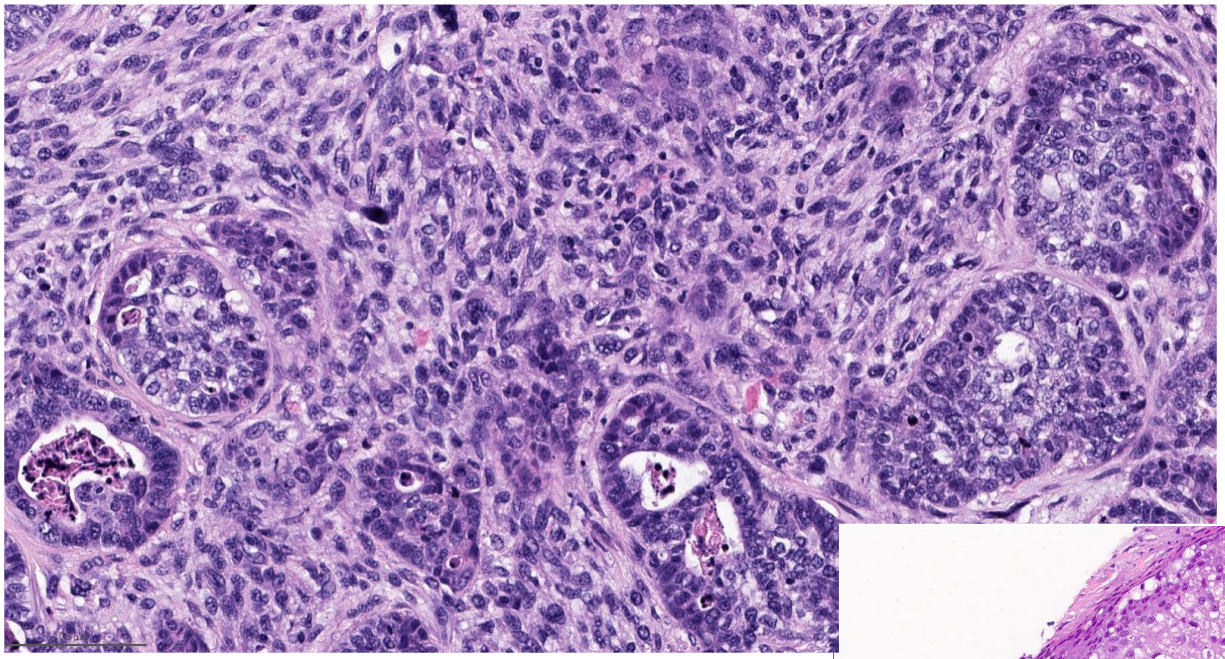


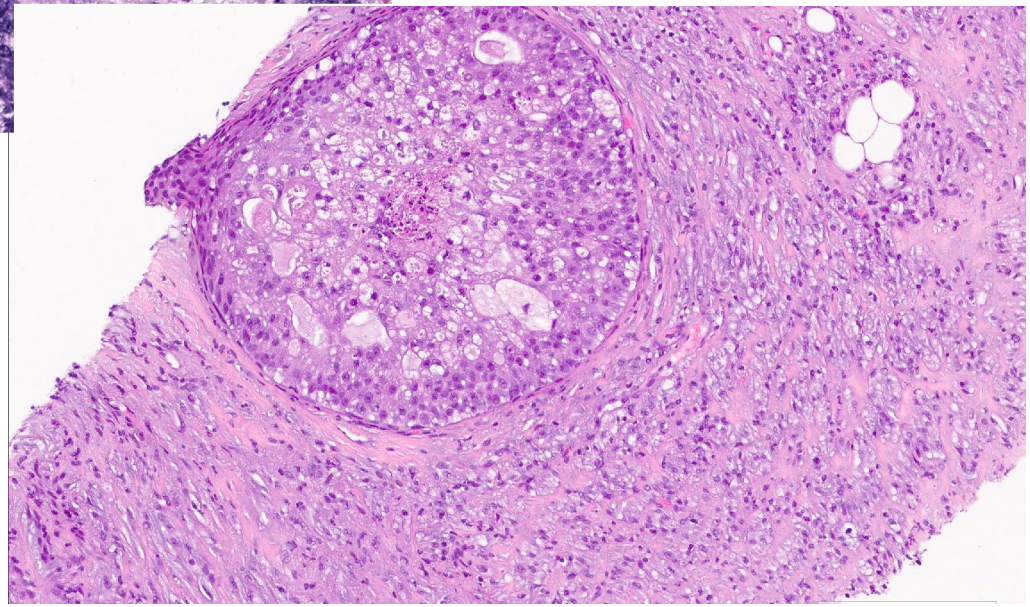
# Diagnosis: evidence of epithelial differentiation



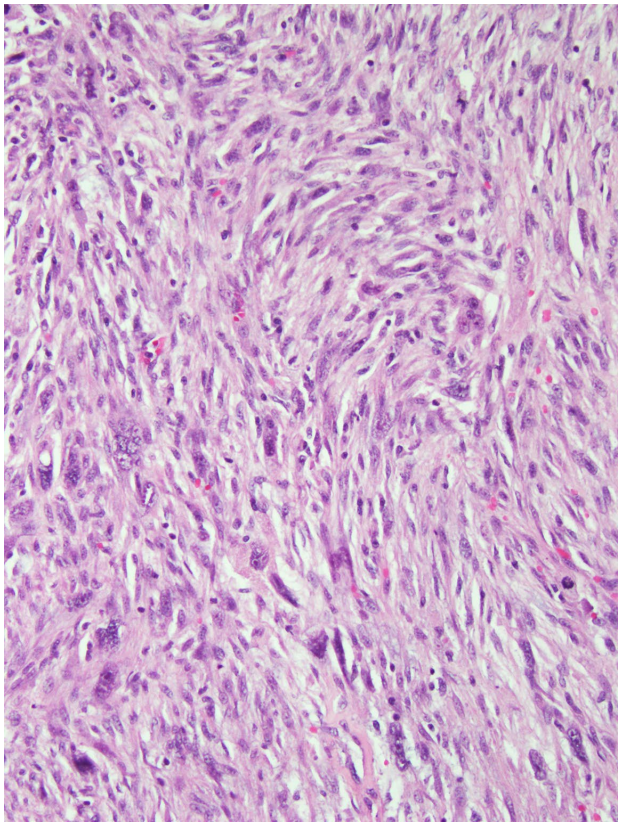

- Immunohistochemistry
- A panel of cytokeratins, especially high molecular weight cytokearatins
  - 34BE12
  - CK5/6
  - CK14
  - MNF116
  - AE1:AE3
  - CK7
- p63

# Diagnosis by association with DCIS or invasive carcinoma NST

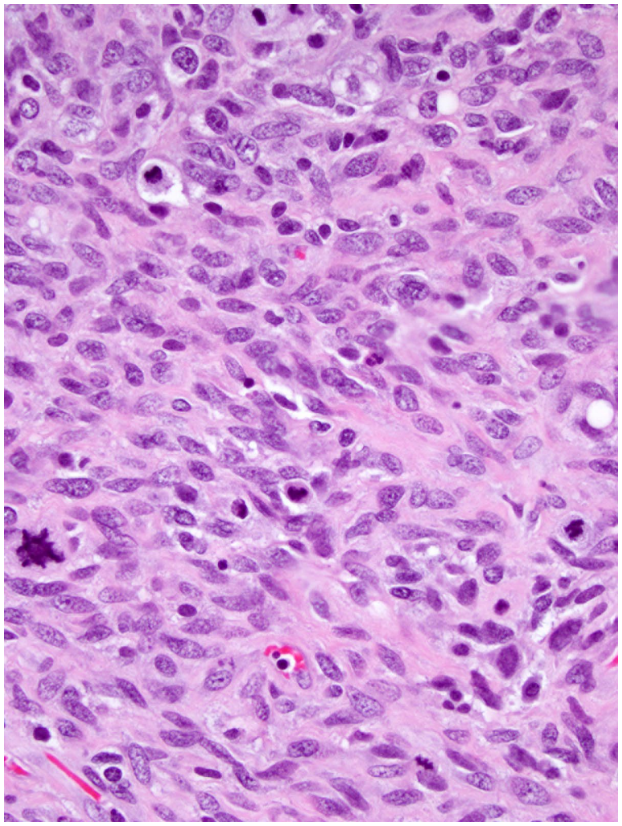




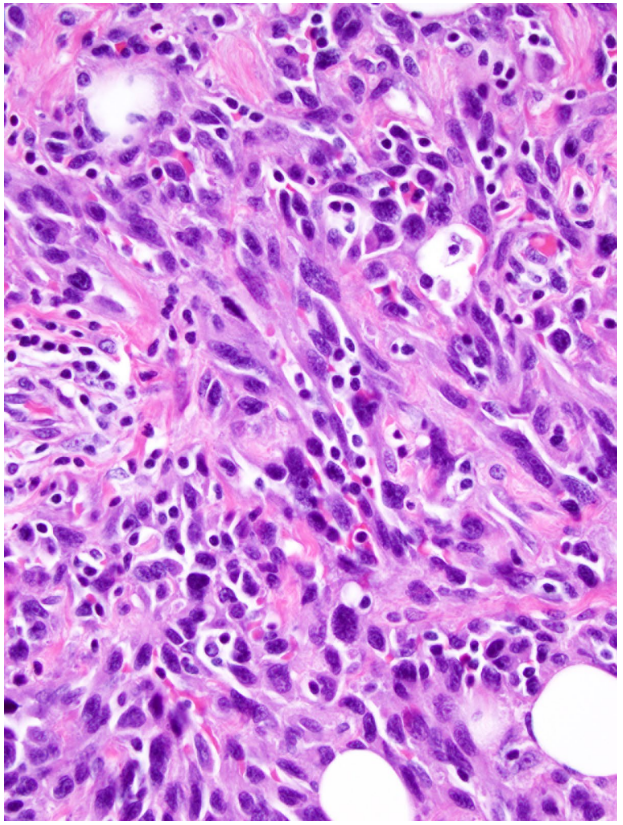
# Differential diagnosis of spindle cell carcinoma



Spindle cell carcinoma



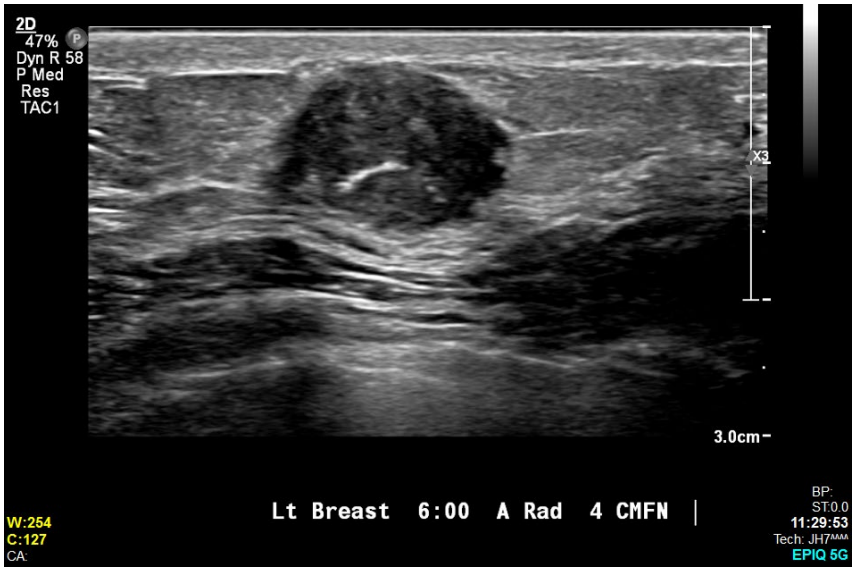
Malignant phyllodes tumor with sarcomatous overgrowth

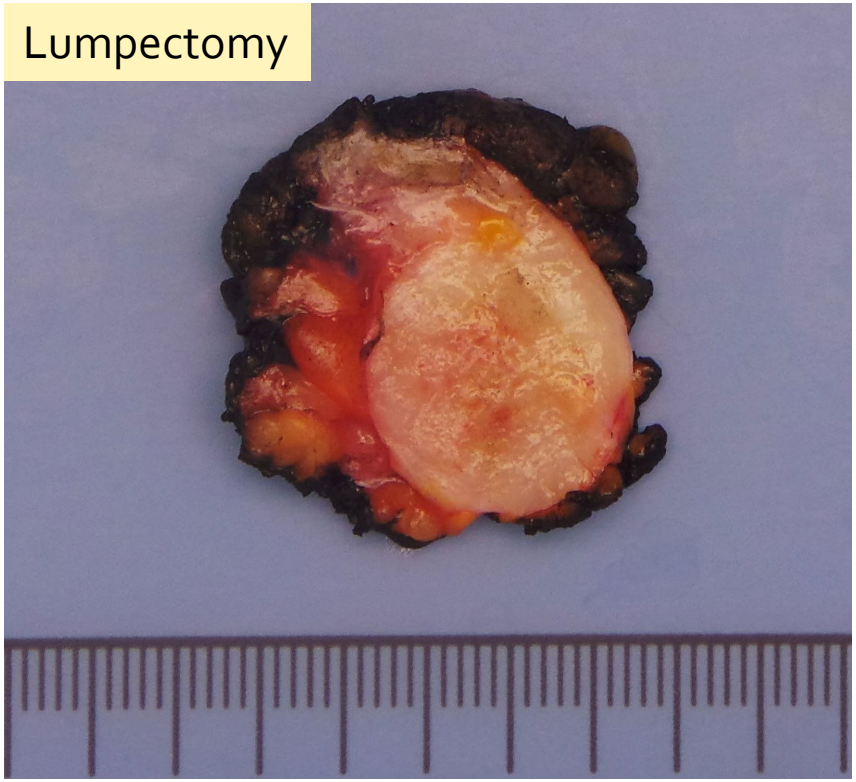


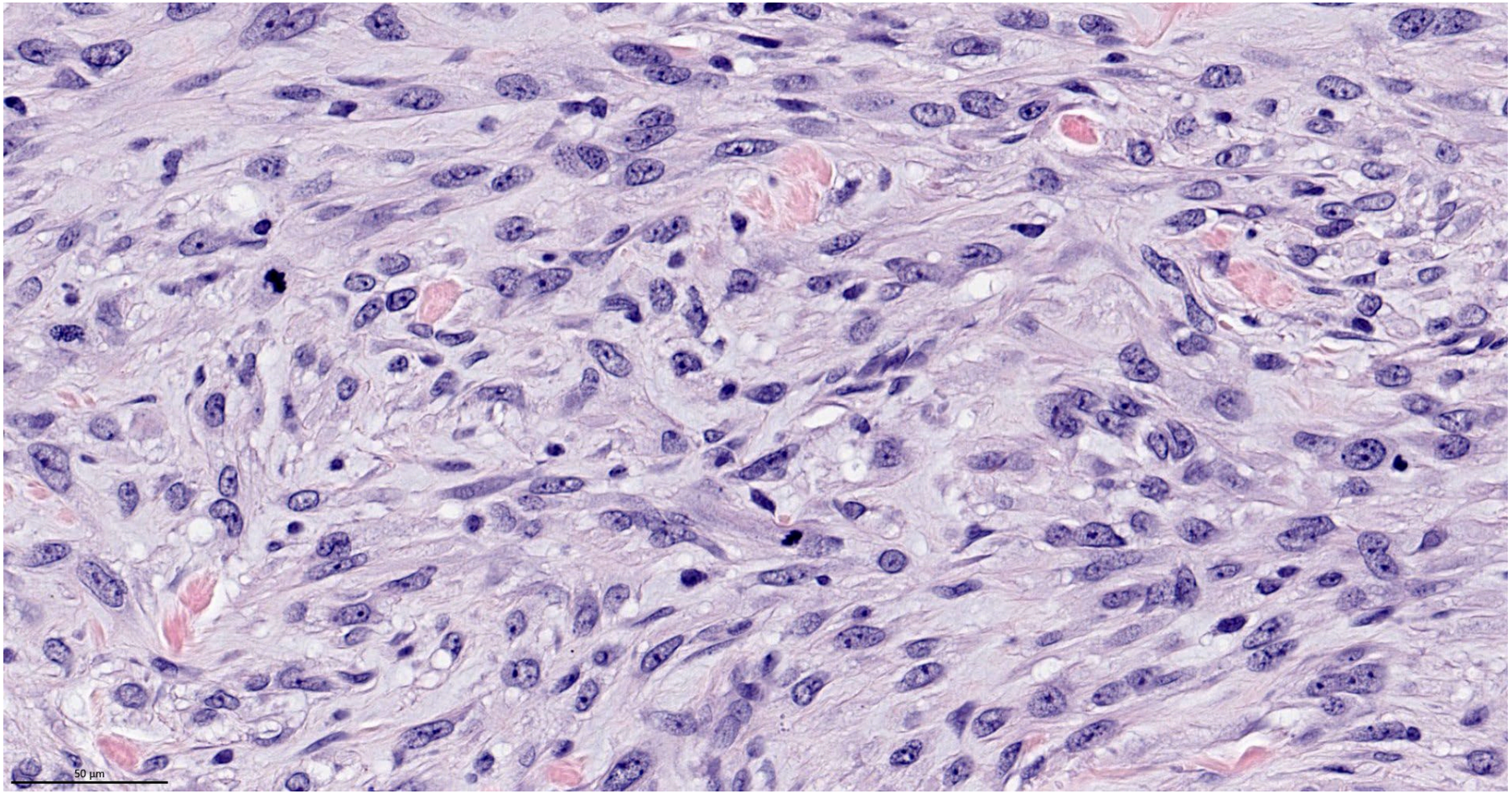
Sarcoma

# Case example

- 55-year-old woman, screening detected left breast mass



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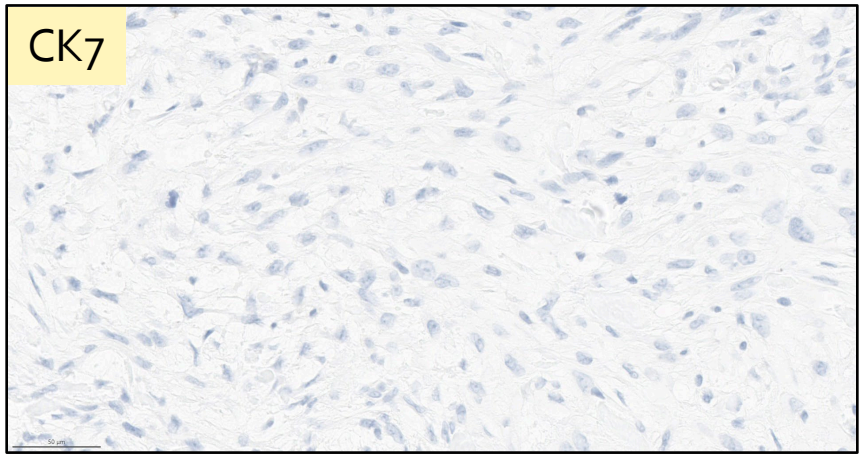
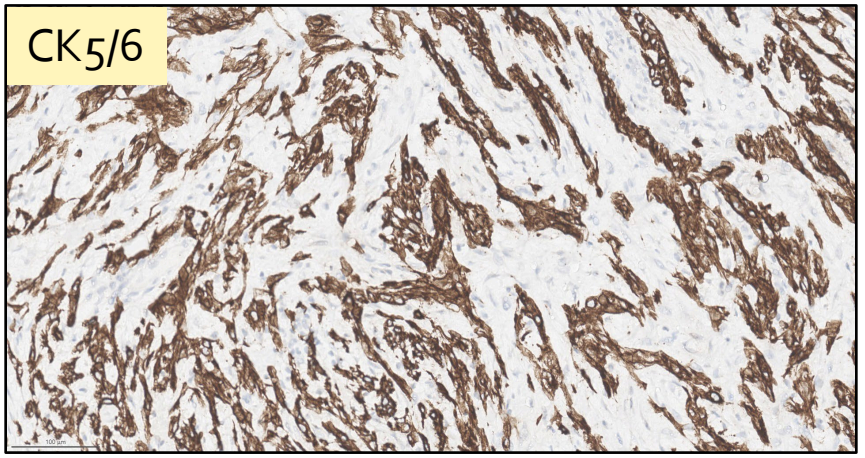
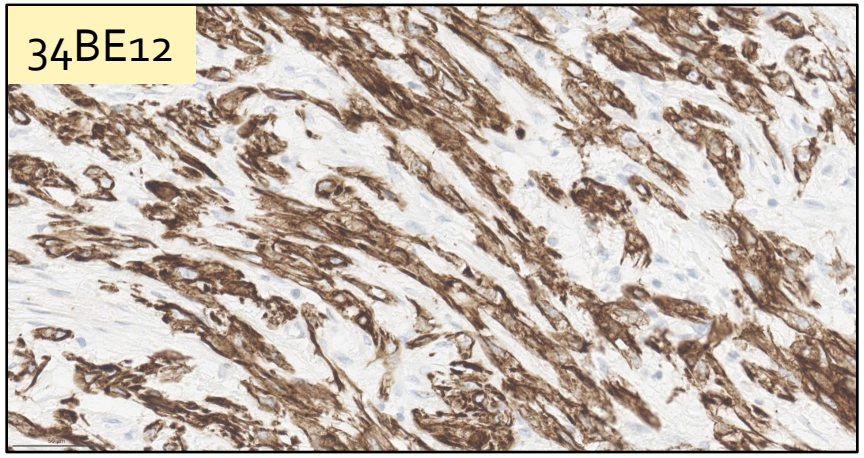
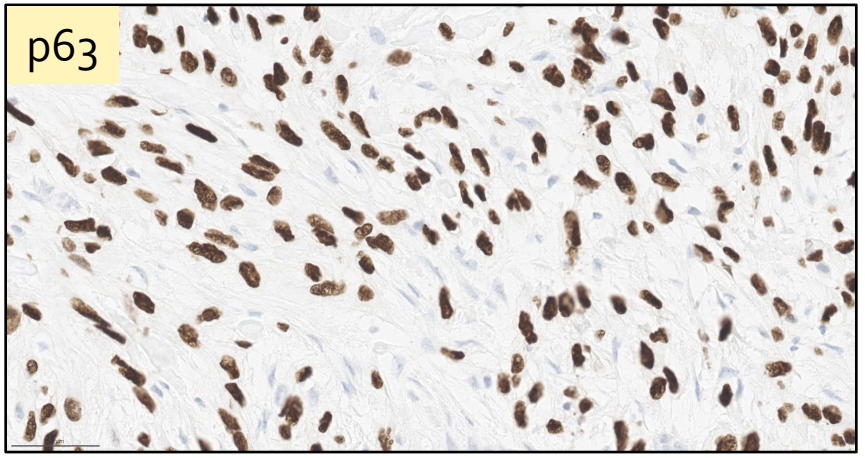
# Metaplastic spindle cell carcinoma

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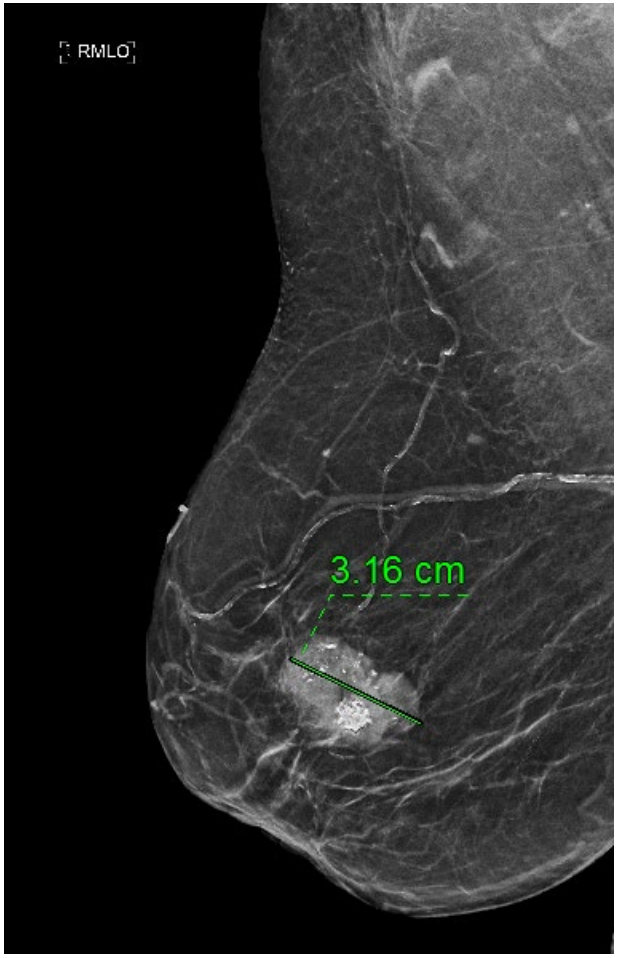
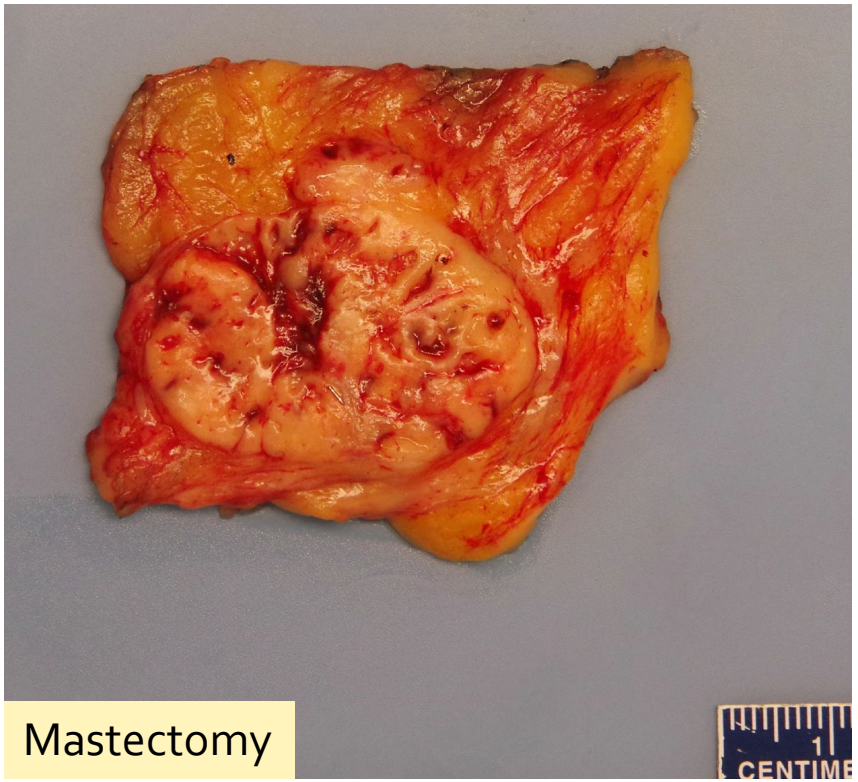
# Case example

- 85-year-old woman, with palpable right breast mass

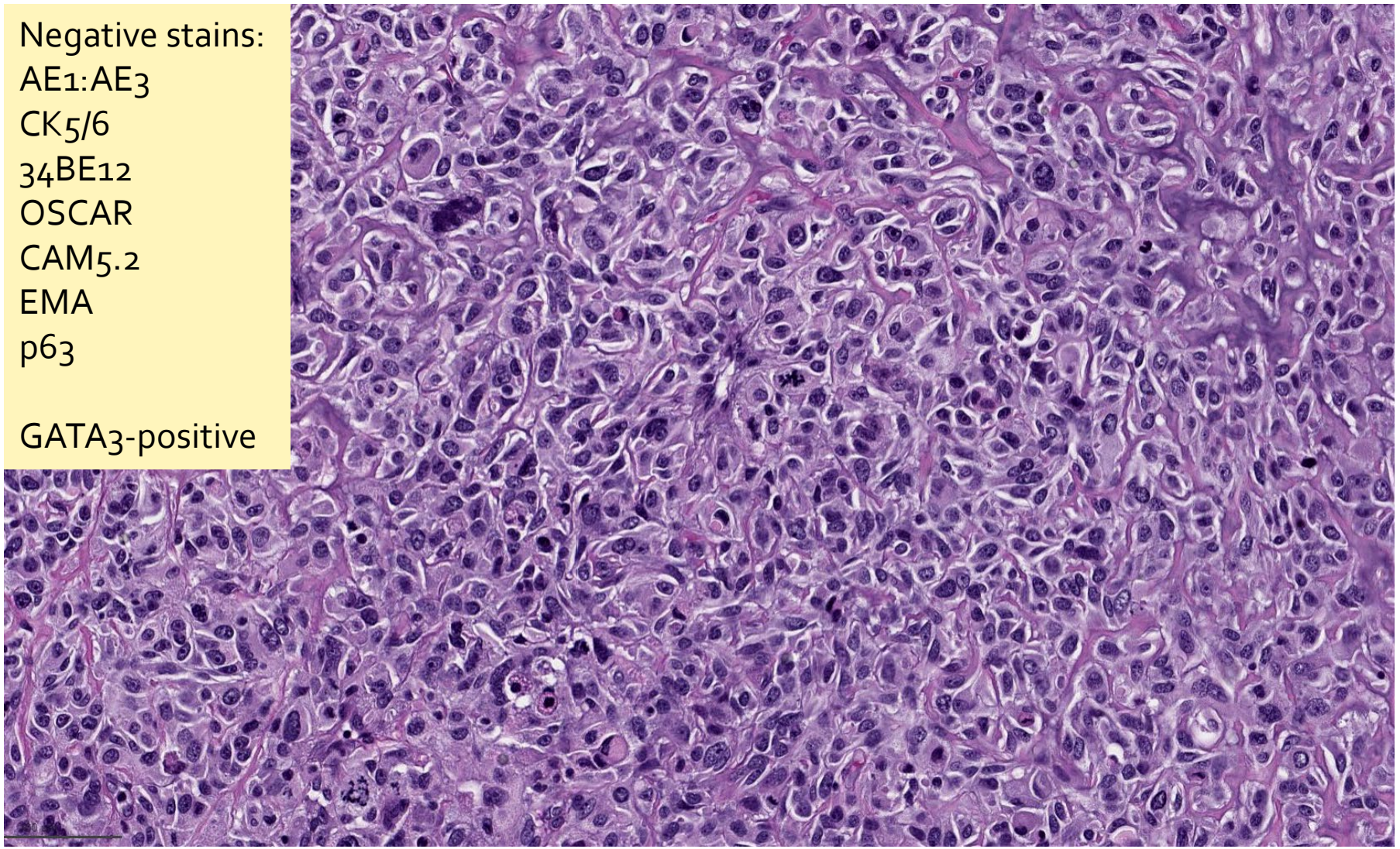


Mastectomy

Negative stains:
AE1:AE3
CK5/6
34BE12
OSCAR
CAM5.2
EMA
p63

GATA3-positive



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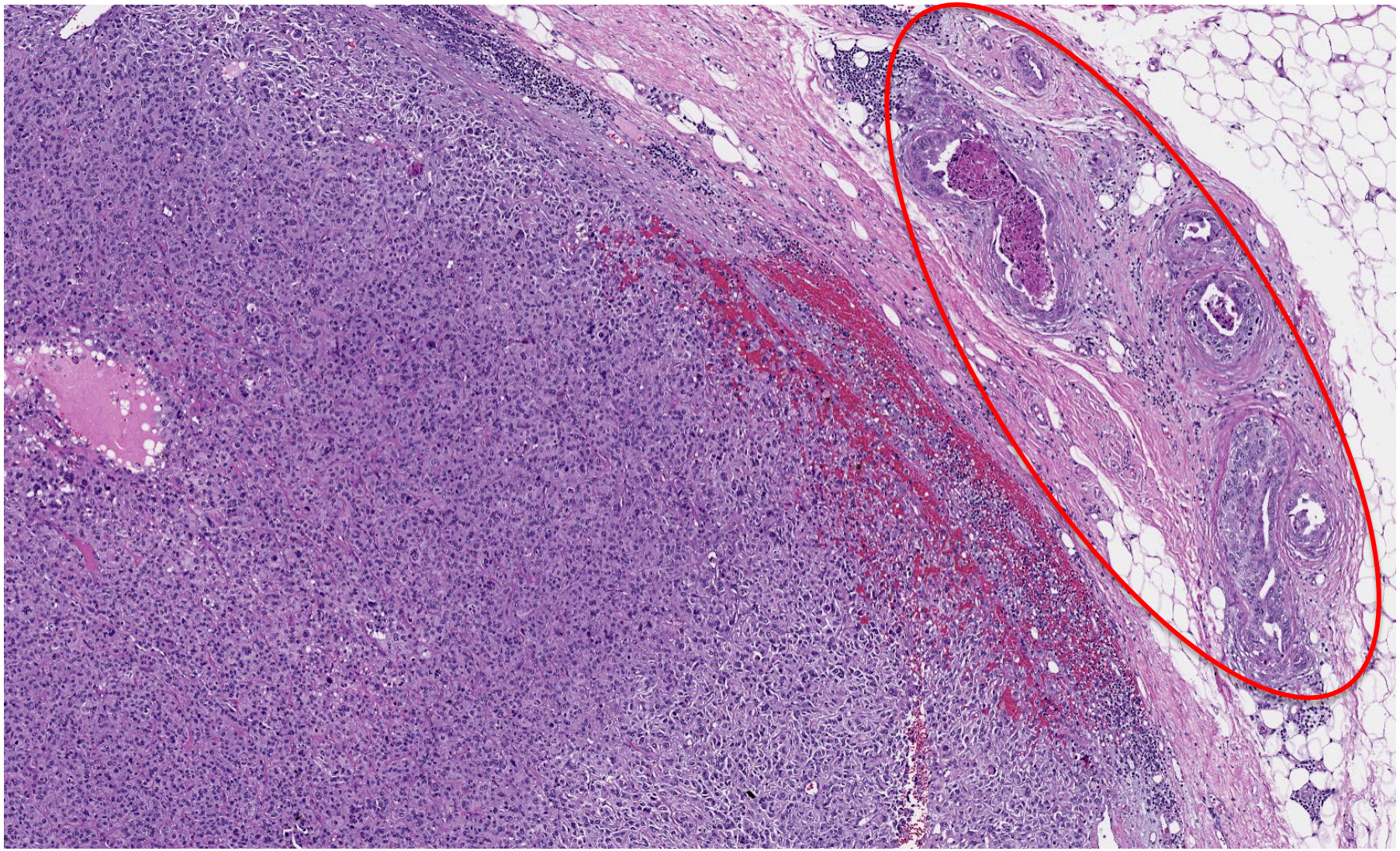

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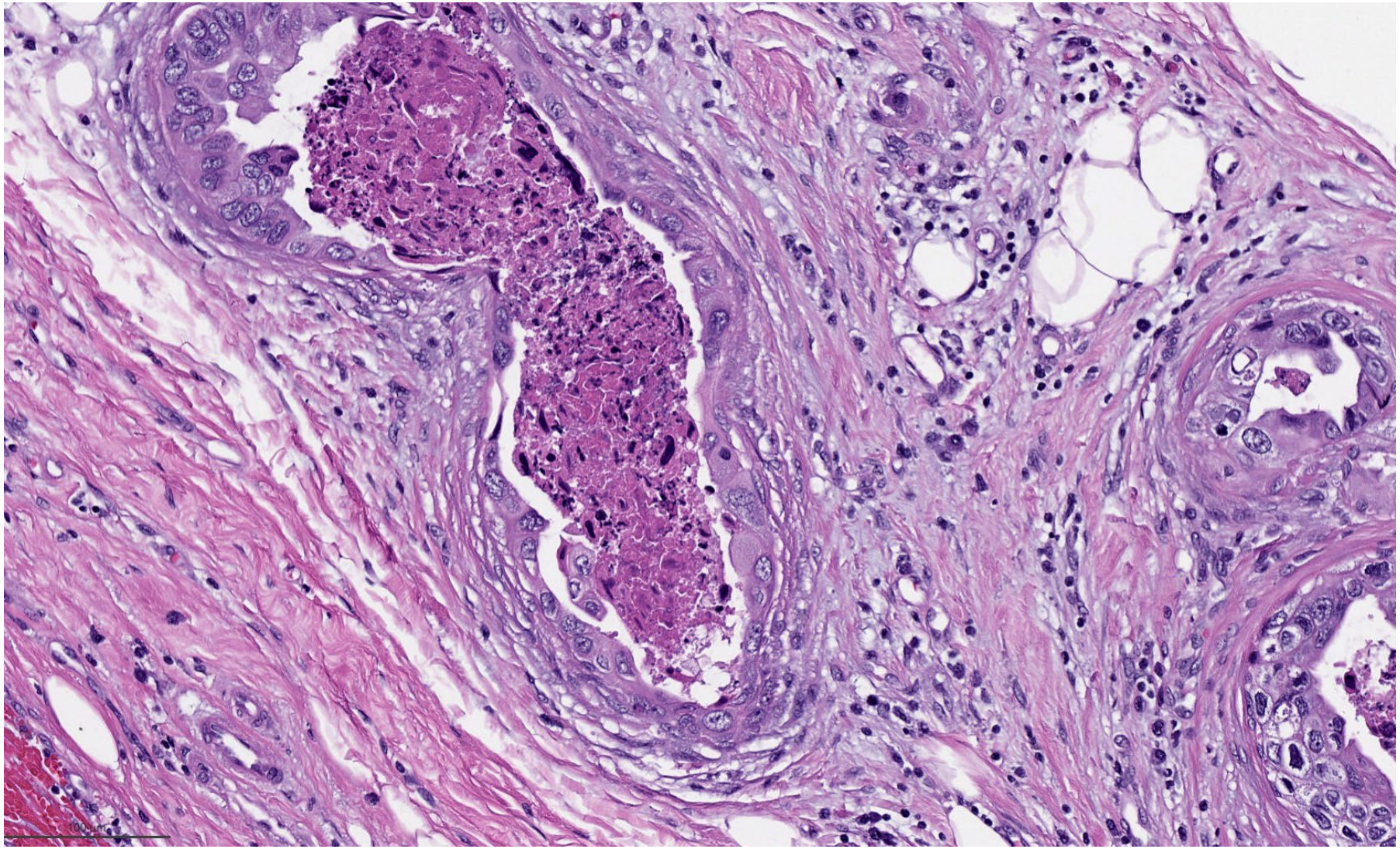
# Association with DCIS >> Metaplastic carcinoma



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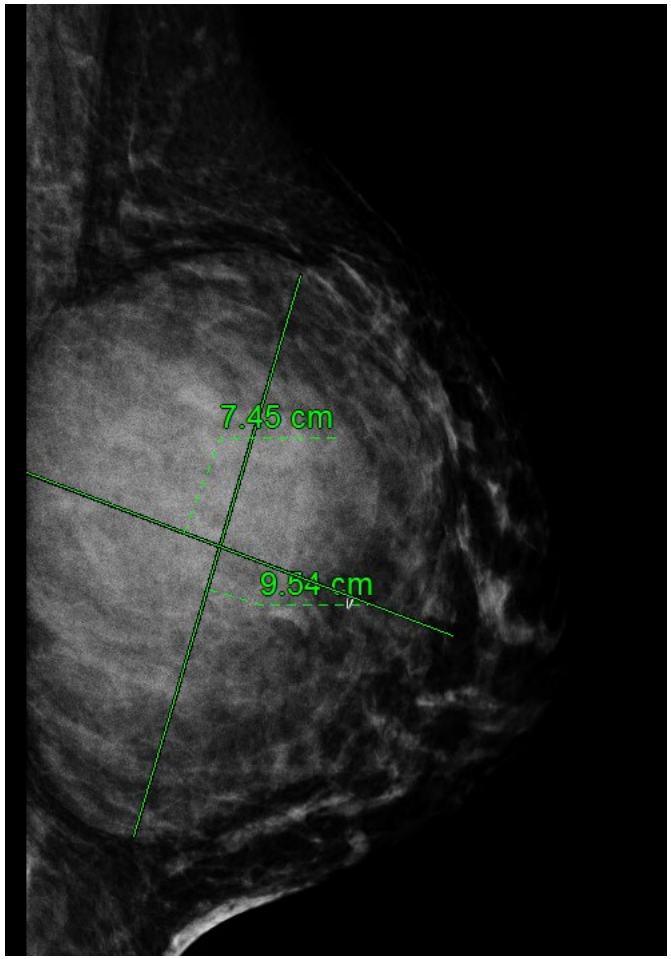
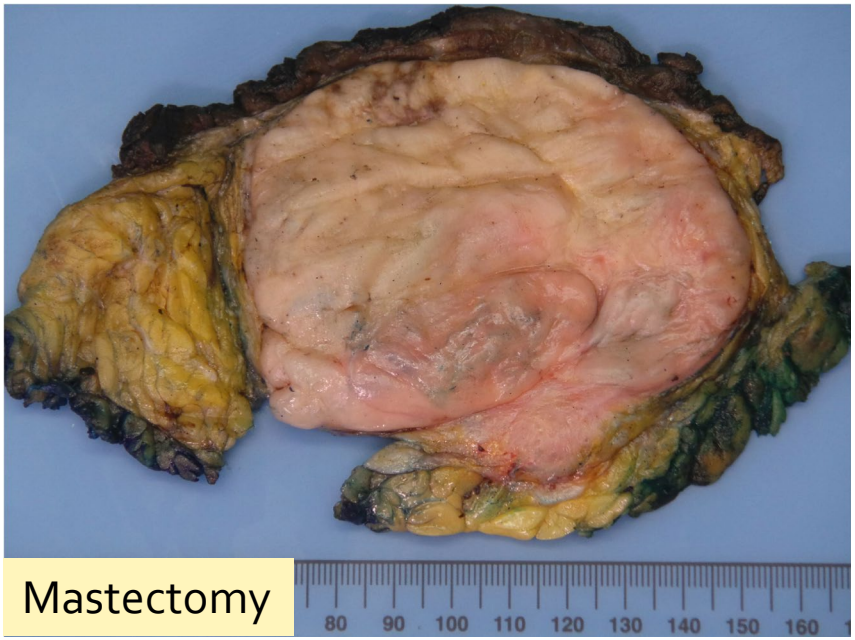
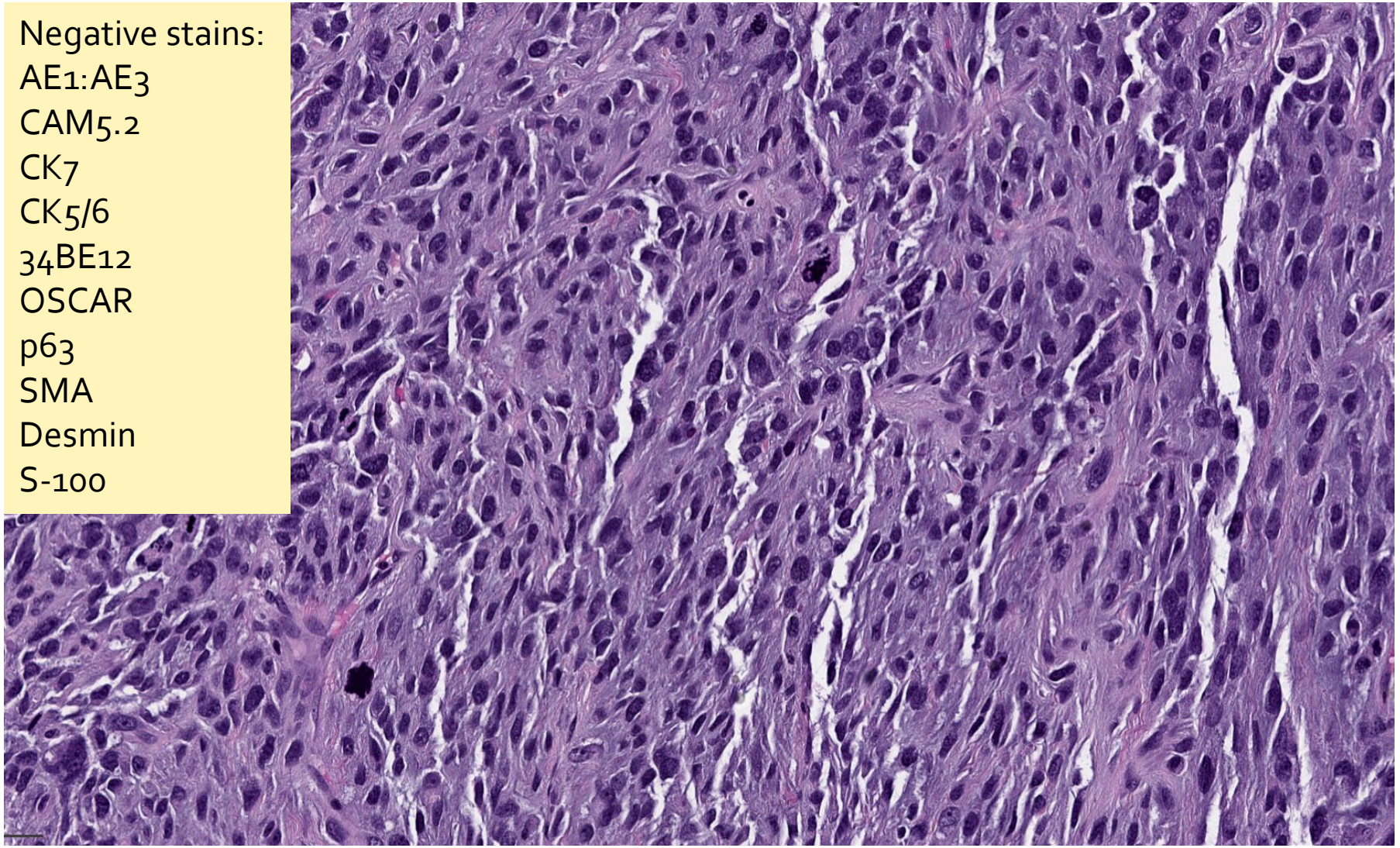
# Case example

- 49-year-old woman with palpable left breast mass



Negative stains:
AE1:AE3
CAM5.2
CK7
CK5/6
34BE12
OSCAR
p63
SMA
Desmin
S-100



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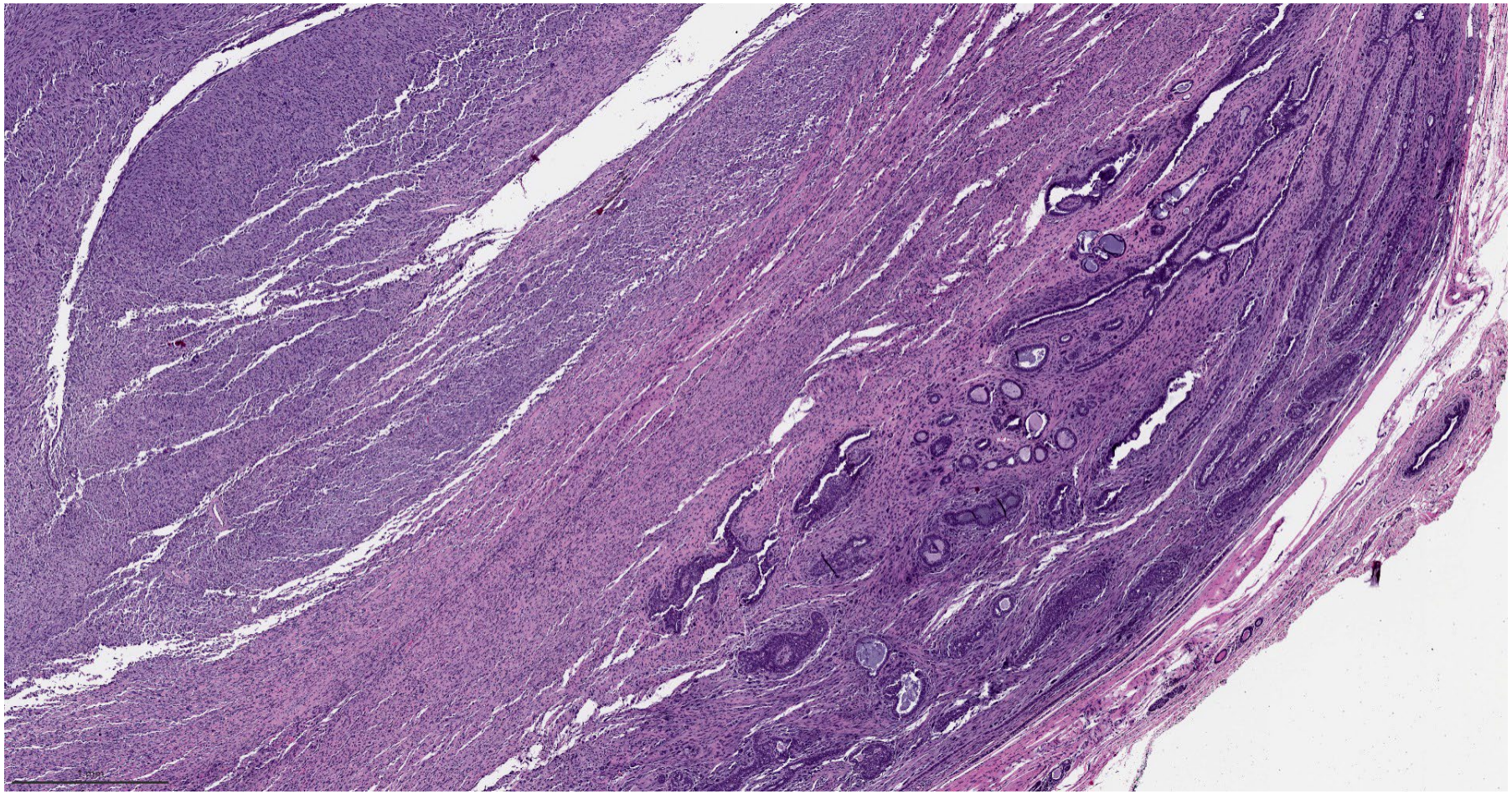
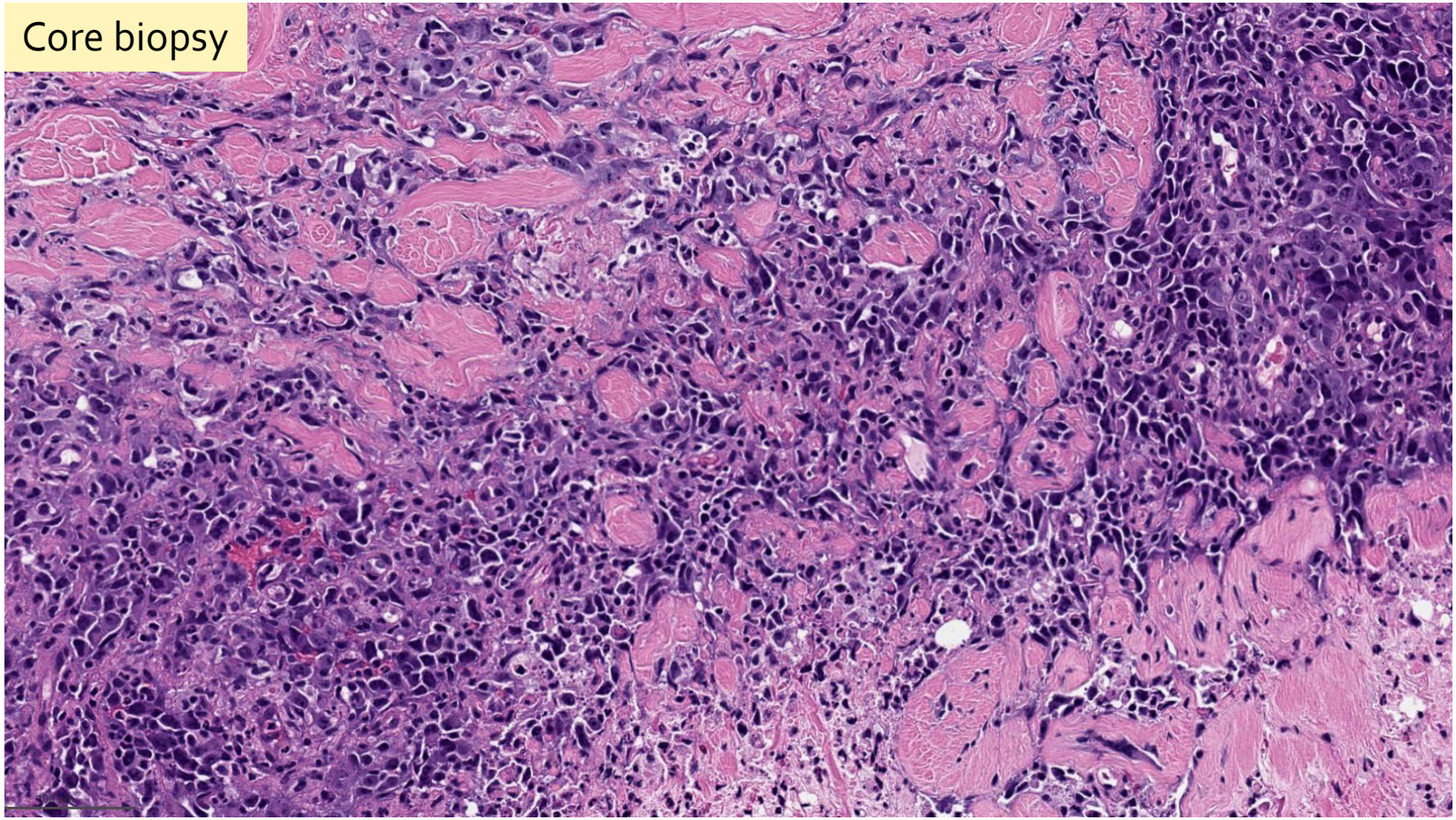
# Malignant phyllodes tumor

- Biphasic fibroepithelial growth pattern



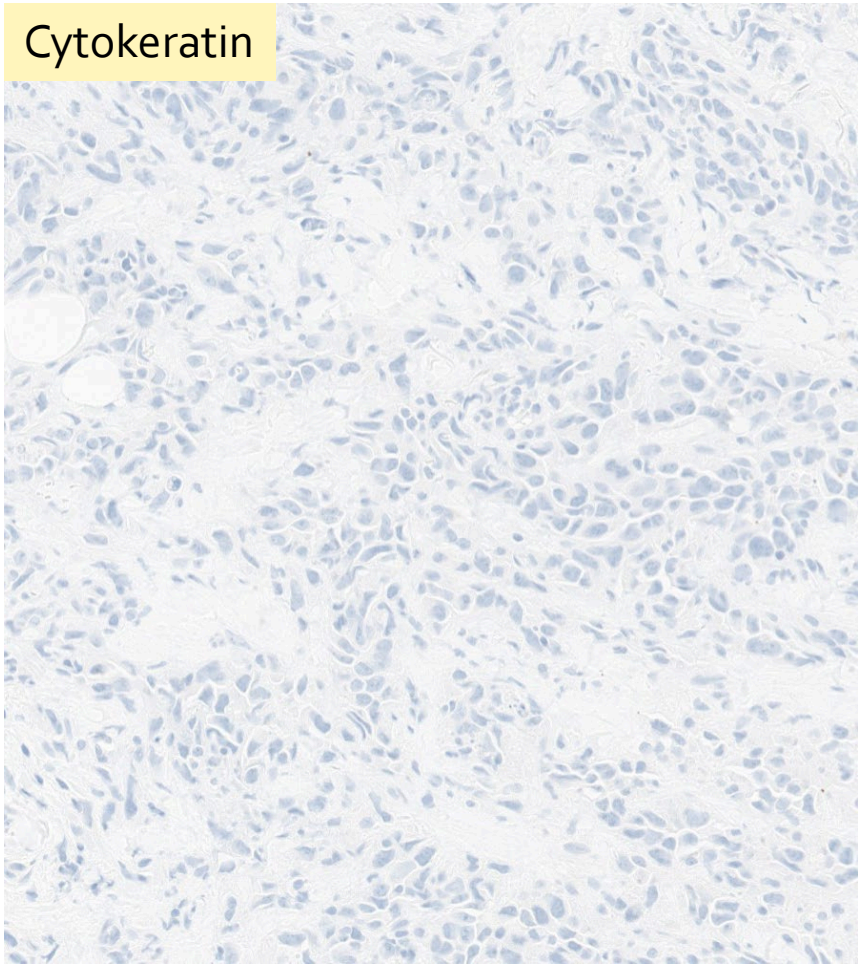
# Case example

- 58 yo woman h/o of triple negative breast carcinoma 12 years ago, pT2N1, treated with BCS, chemo, RT, presented with ipsilateral breast mass

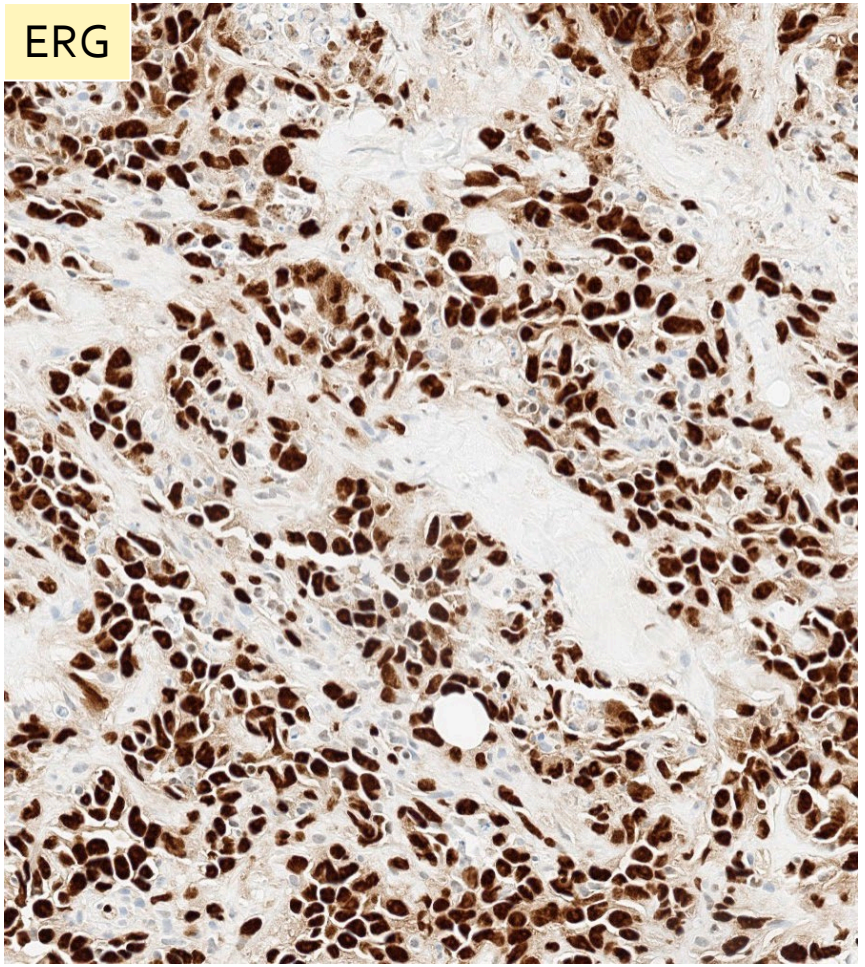


# Radiation associated angiosarcoma

Cytokeratin



ERG



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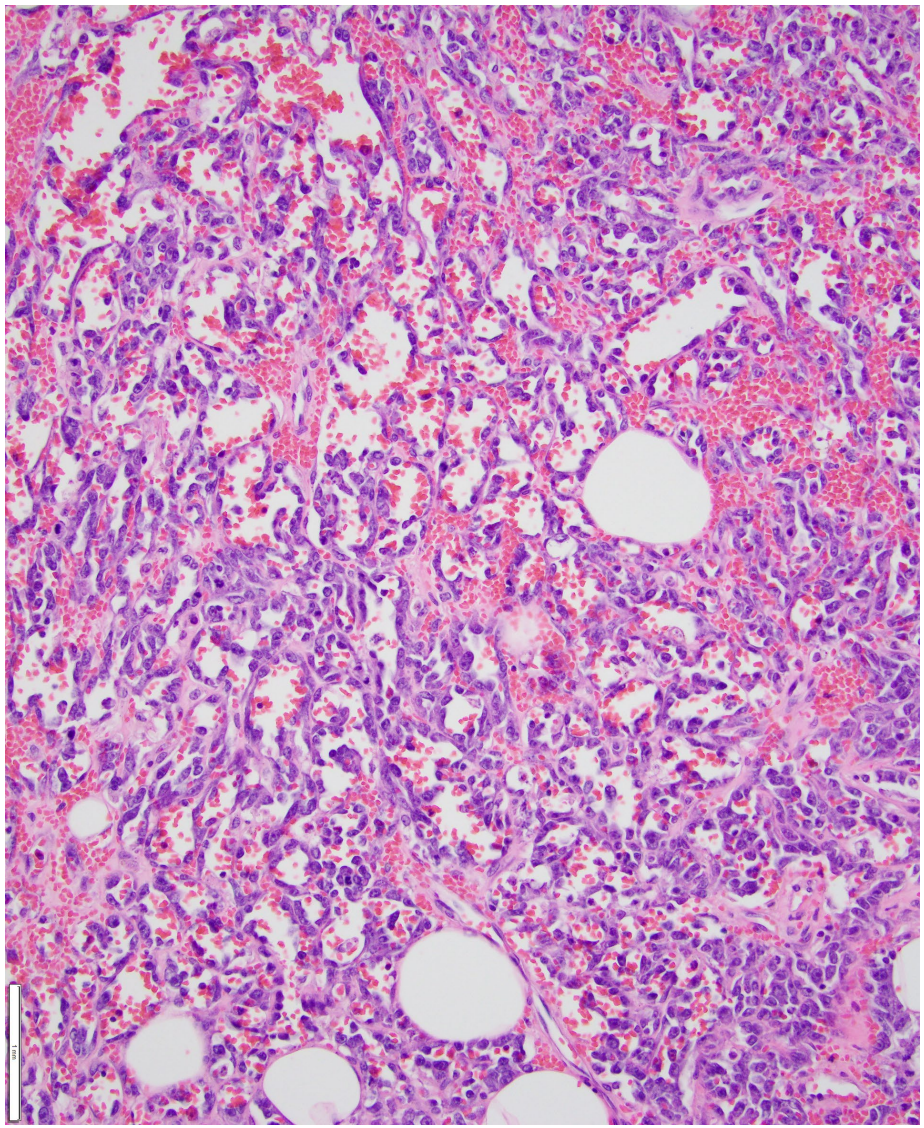
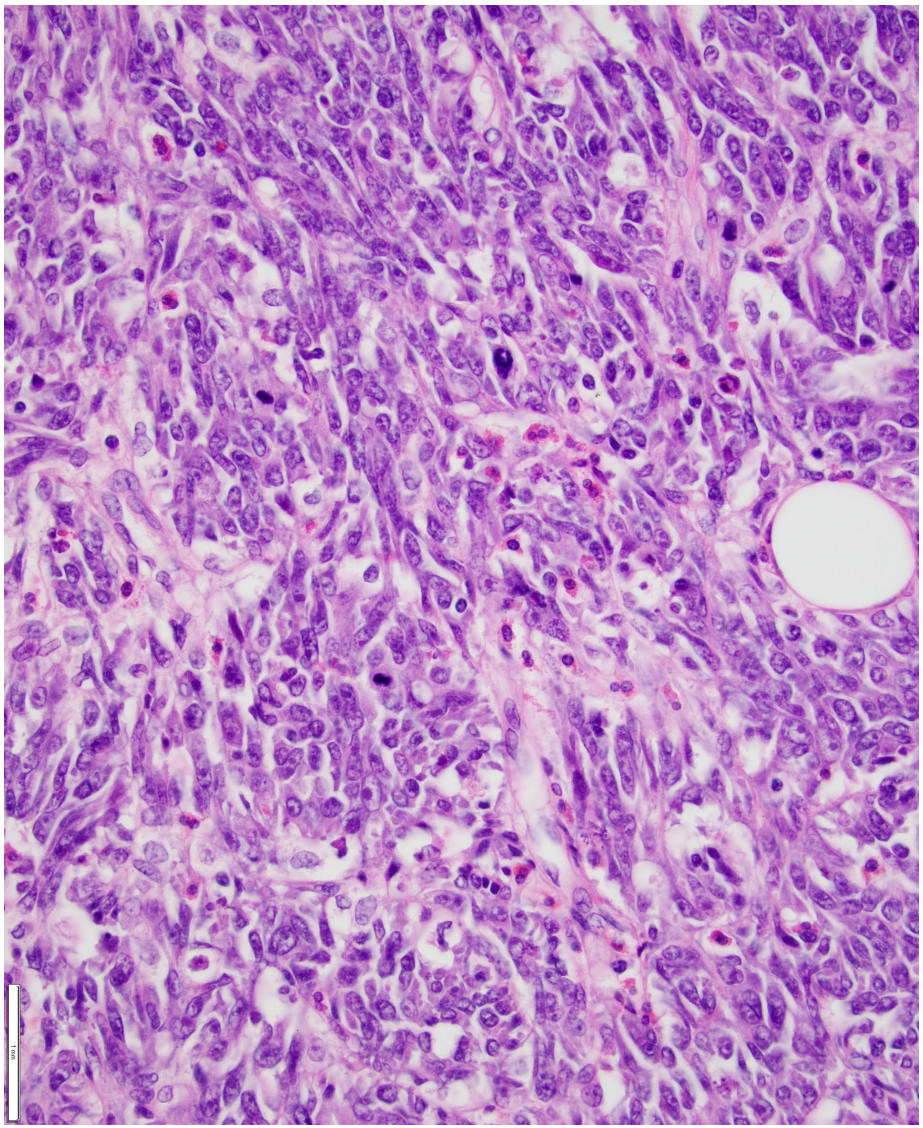
# Radiation associated angiosarcoma: mastectomy





Anastomosing vascular channels, extravasation of blood
High grade spindle cells, solid growth pattern

# Genomic alterations in metaplastic carcinoma

- The most frequent somatic mutations in metaplastic carcinoma
  - *TP53* and *PIK3CA*
- Compared with triple-negative IDC-NSTs
  - *TP53 mutations: similar* frequencies (69% vs. 81%, $P = 0.2174$)
  - *PIK3CA mutations*: more frequent in metaplastic carcinoma (29% vs. 7%, $P = 0.0064$)

Ng CK et al. *Clin Cancer Res*. 2017; 23: 3859-3870

npj | Breast Cancer

www.nature.com/npjbcancer

ARTICLE OPEN

Check for updates

# Poor response to neoadjuvant chemotherapy in metaplastic breast carcinoma

Willard Wong[1], Edi Brogi[1], Jorge S. Reis-Filho[1], George Plitas[2], Mark Robson[3], Larry Norton[3], Monica Morrow[2] and Hannah Y. Wen[1]✉

- 44 metaplastic breast cancer patients treated with NAC
- Only one patient had a pathologic complete response (pCR)
  - pCR rate 2%
- 49% showed no clinical response or clinicoradiological progression while on therapy

Wong W et al *npj Breast Cancer* 2021; 7 (1): 96

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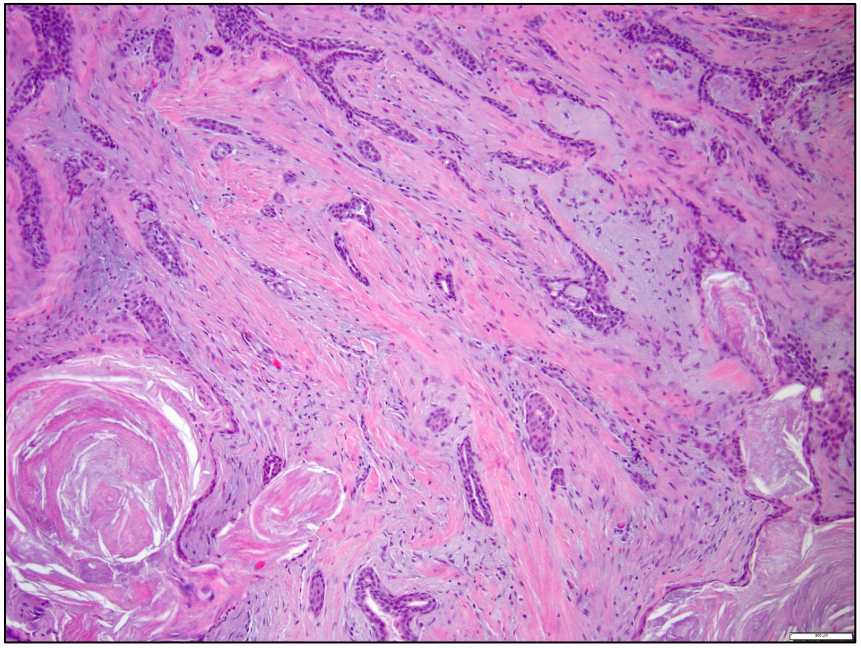
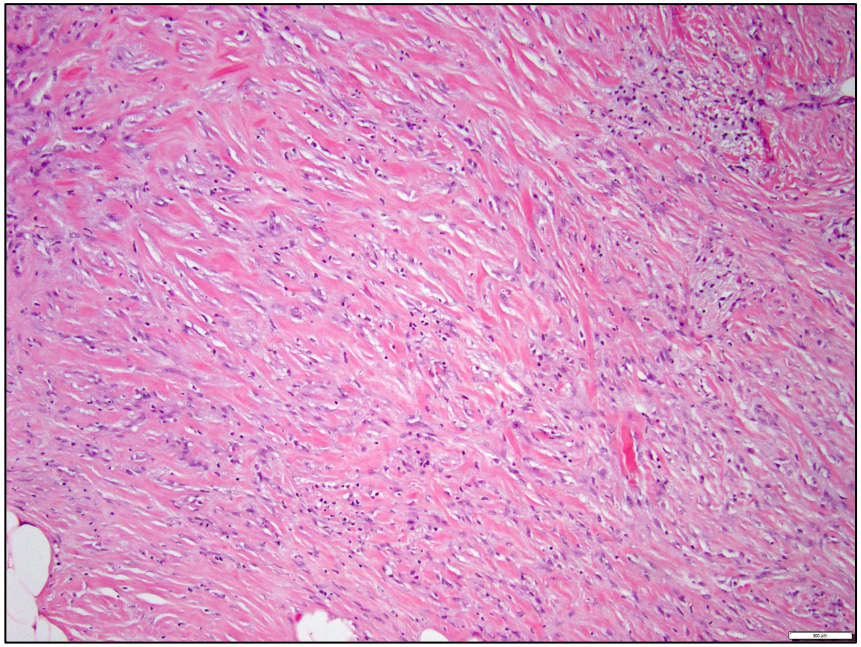
# Low grade variants of metaplastic carcinoma

**Low-grade adenosquamous carcinoma**

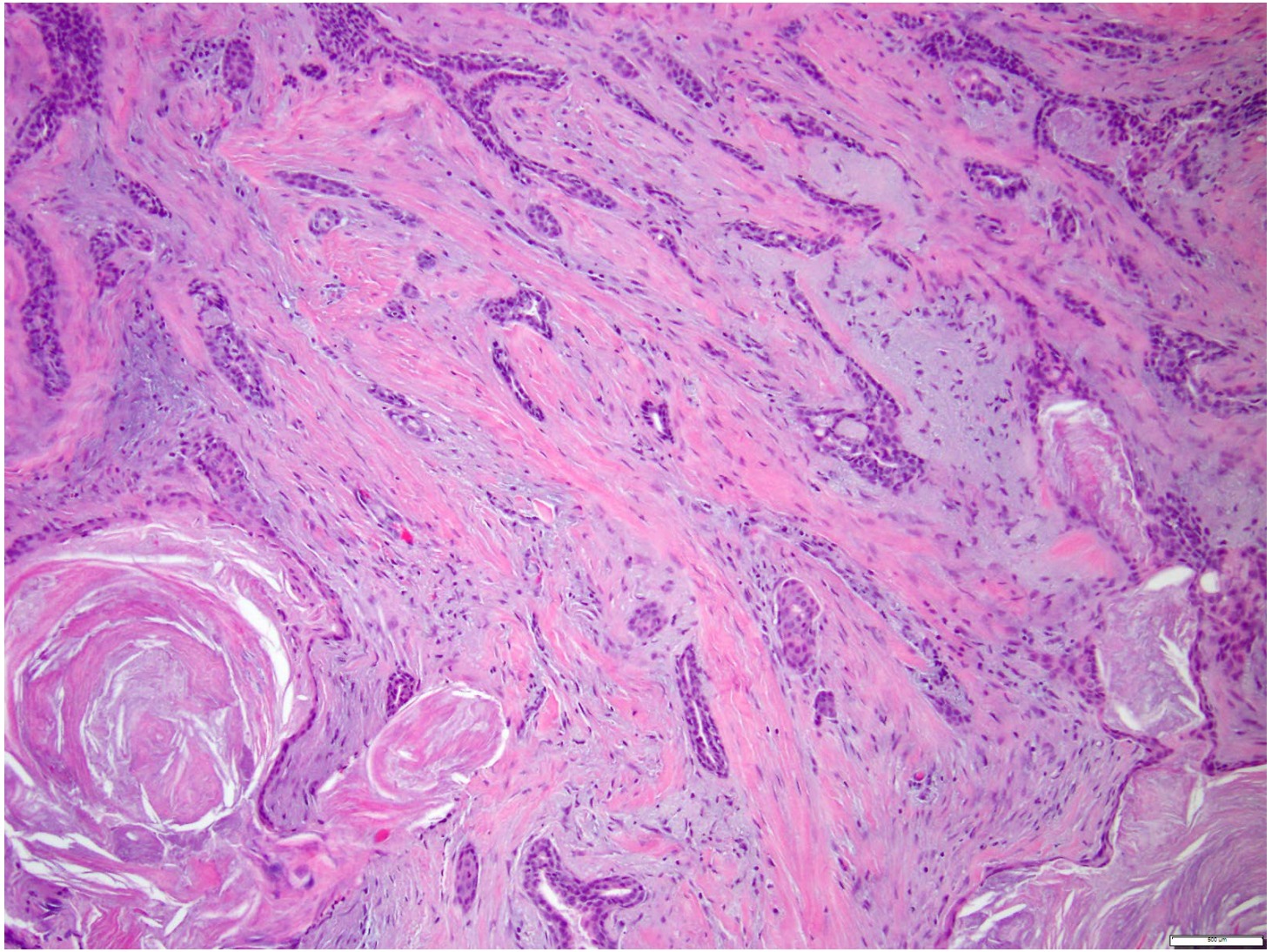


**Fibromatosis-like metaplastic carcinoma**



- Associated with indolent clinical course
- Capable of local recurrence. The incidence of distant metastasis is low

# Low-grade adenosquamous carcinoma (LGASC)



Small compressed glandular proliferation, infiltrative pattern, desmoplastic stroma

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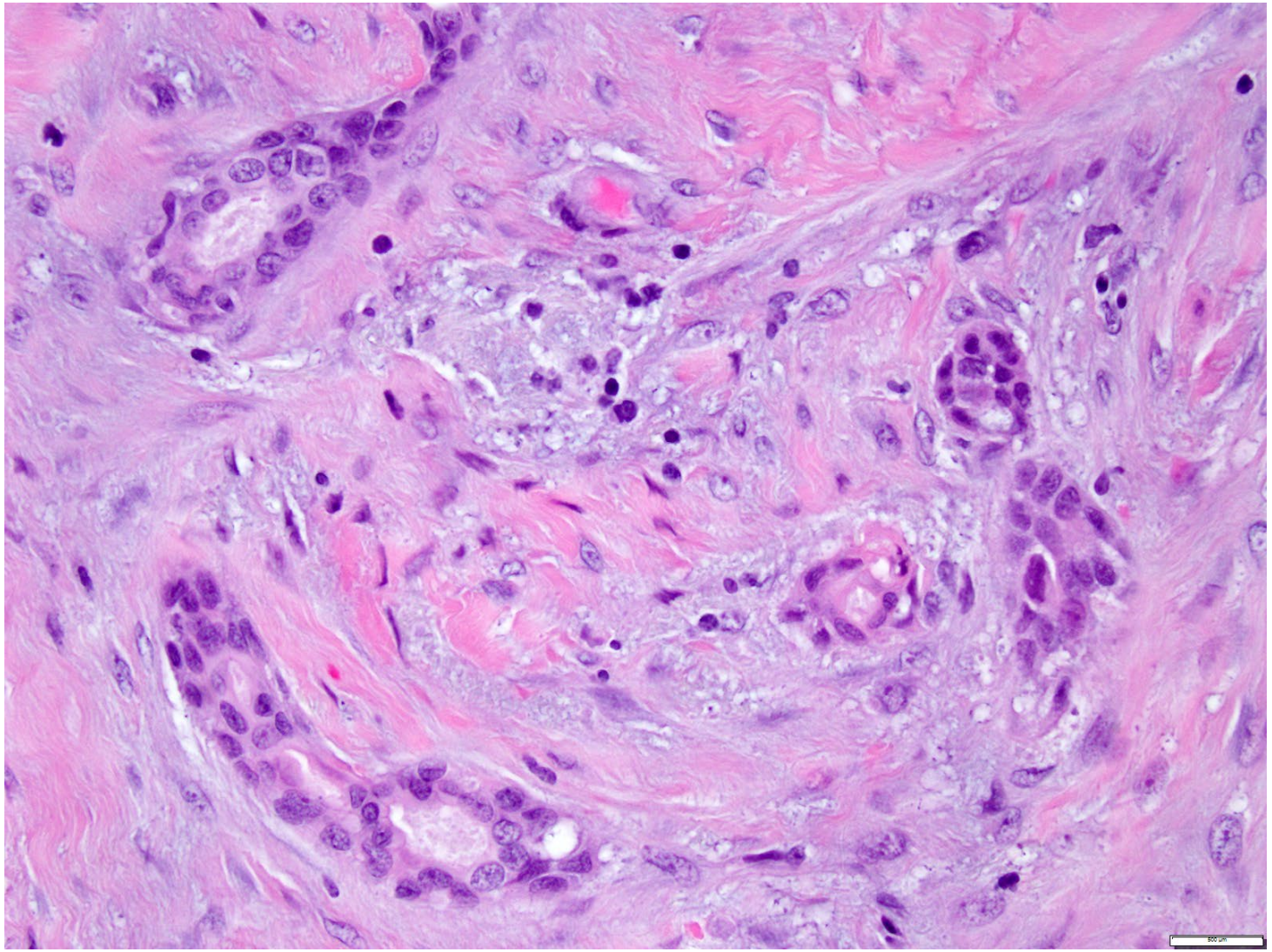
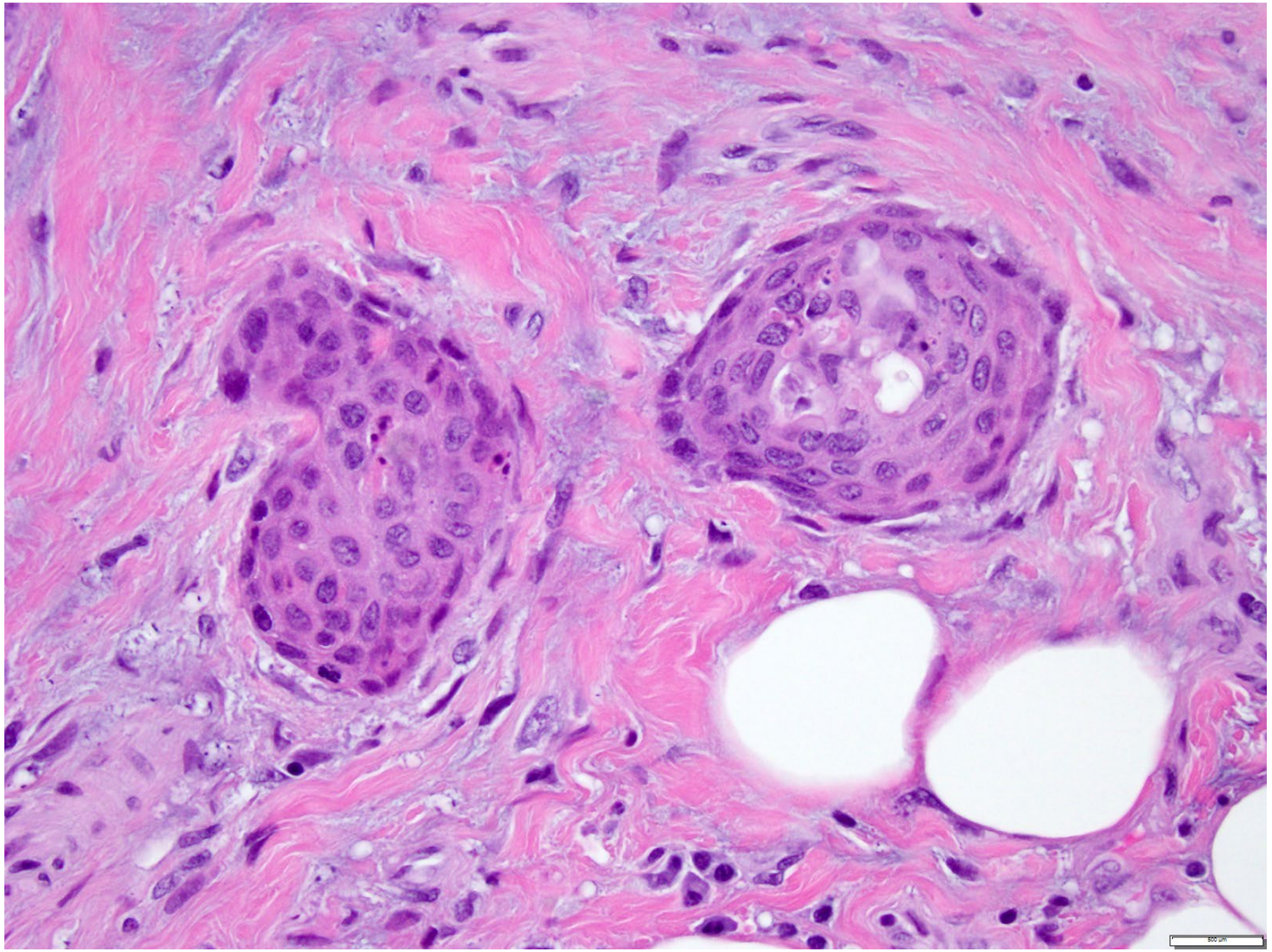
# Low-grade adenosquamous carcinoma (LGASC)



Low grade morphology, mimicking benign glands

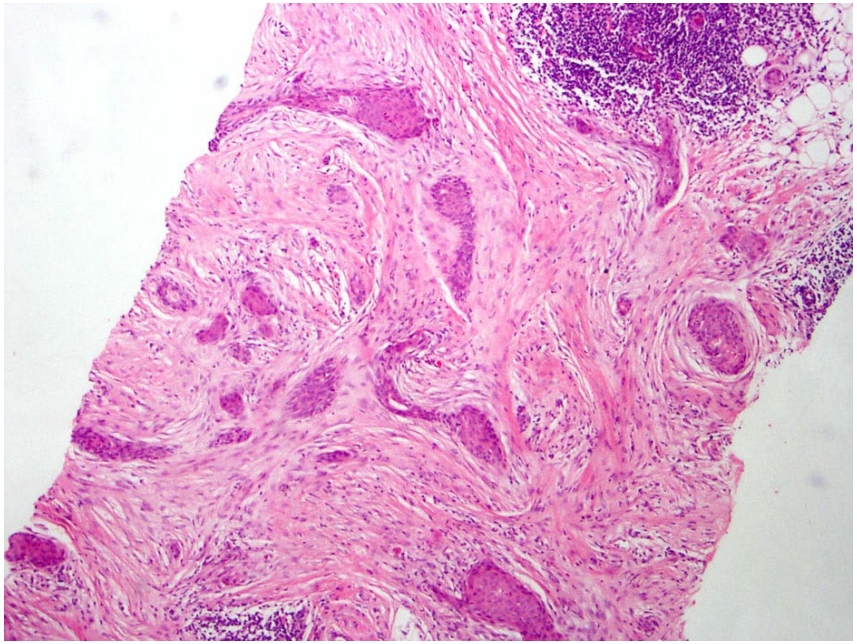
# Low-grade adenosquamous carcinoma (LGASC)

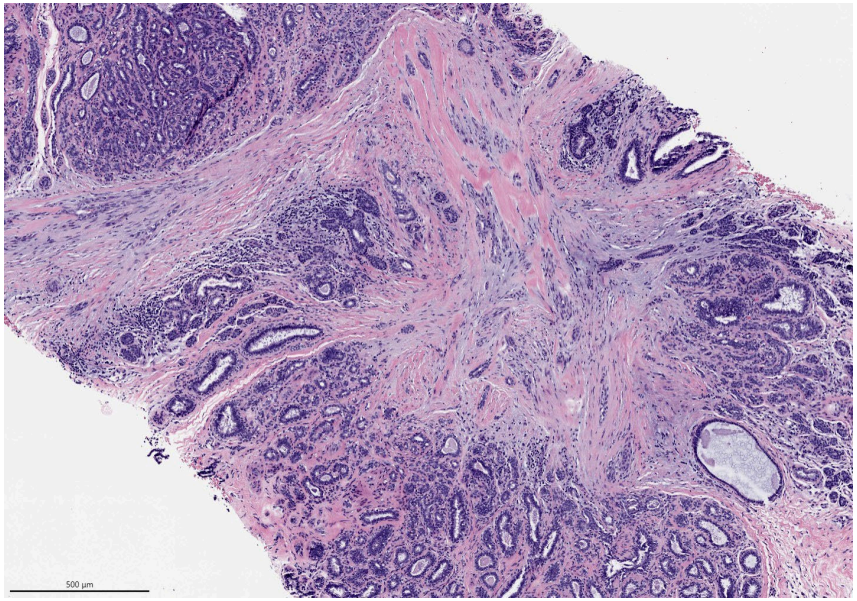


Variable degrees of squamous differentiation

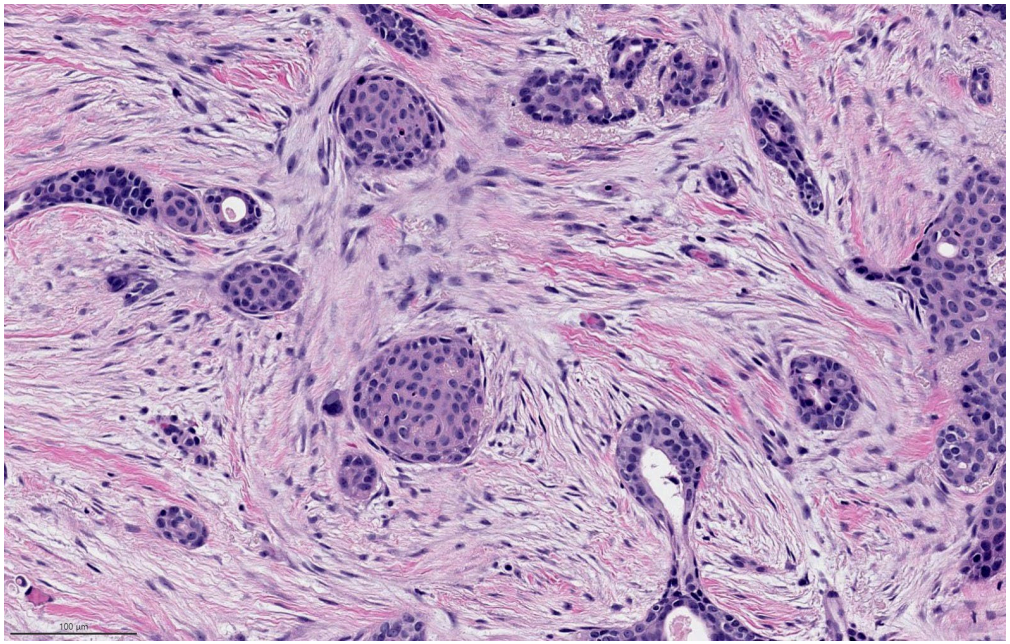
# Differential diagnosis: benign sclerosing lesion

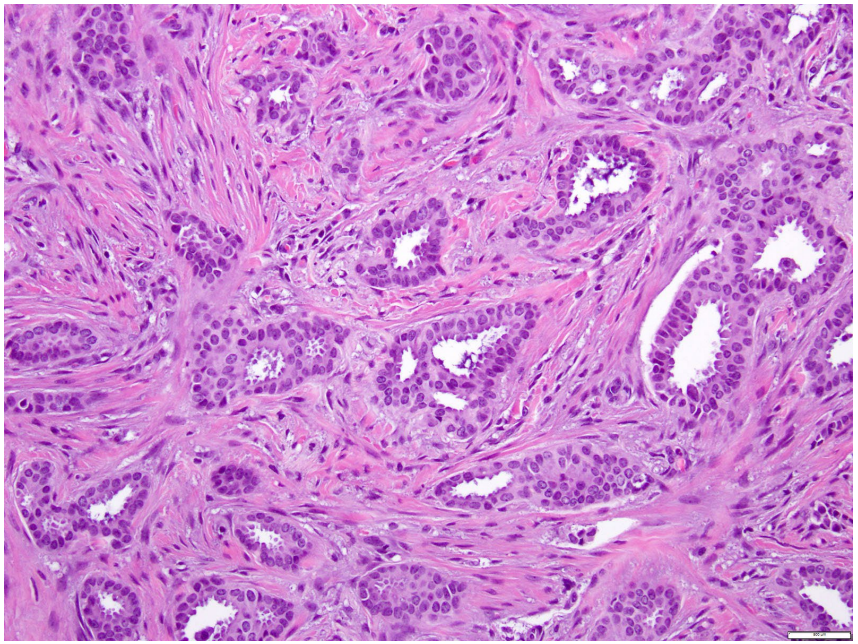
| Low grade adenosquamous carcinoma | Radial scar |
| --- | --- |



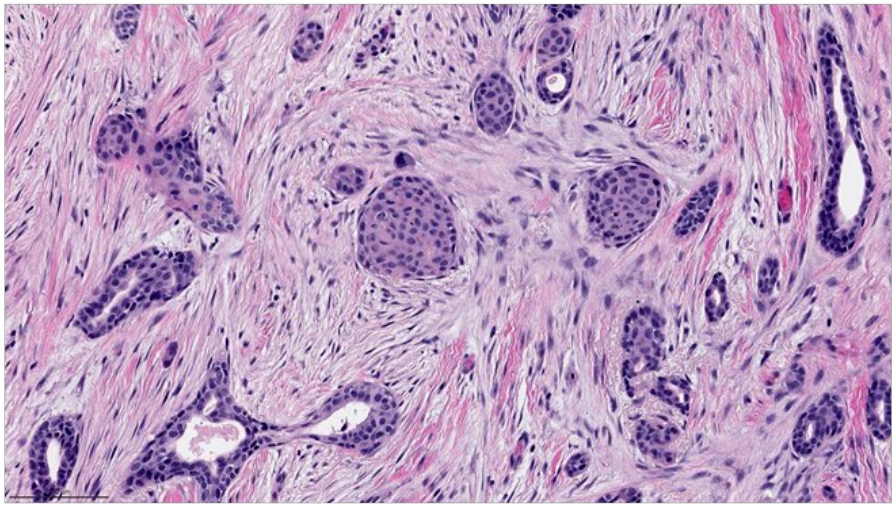


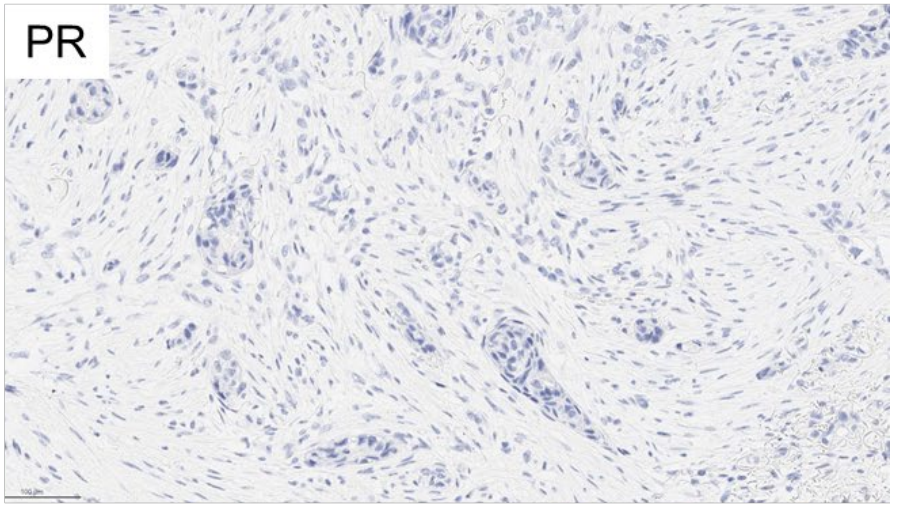
# Differential diagnosis: LGASC vs invasive NST

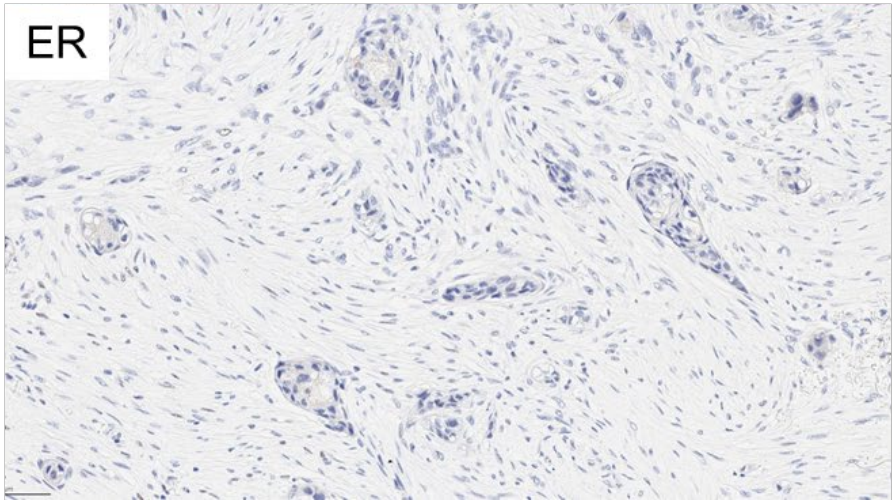


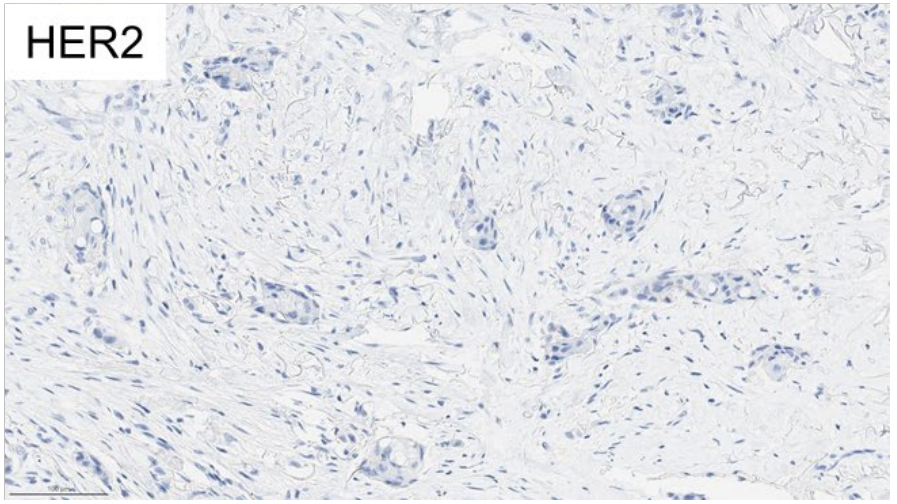



# LGASC: ER/PR/HER2-negative



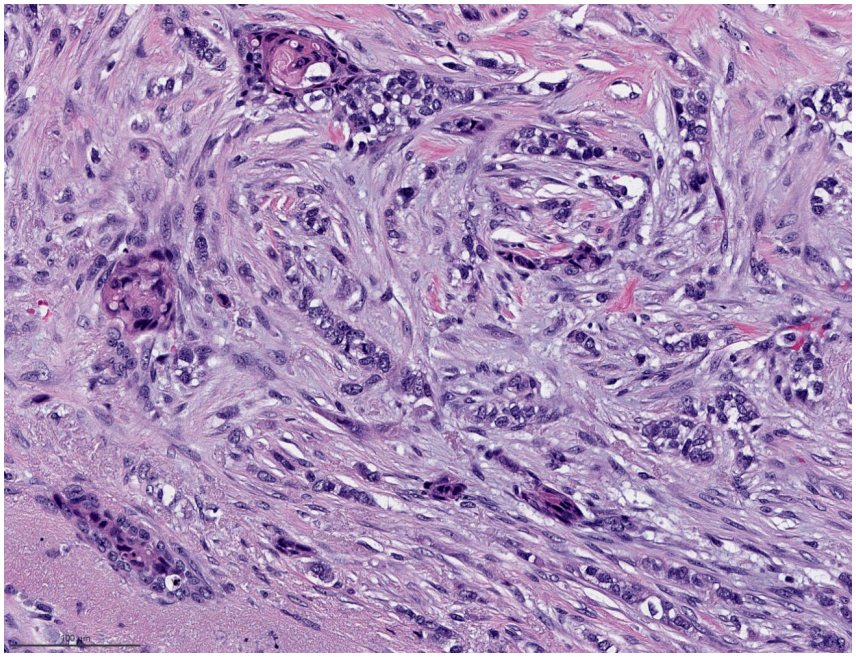


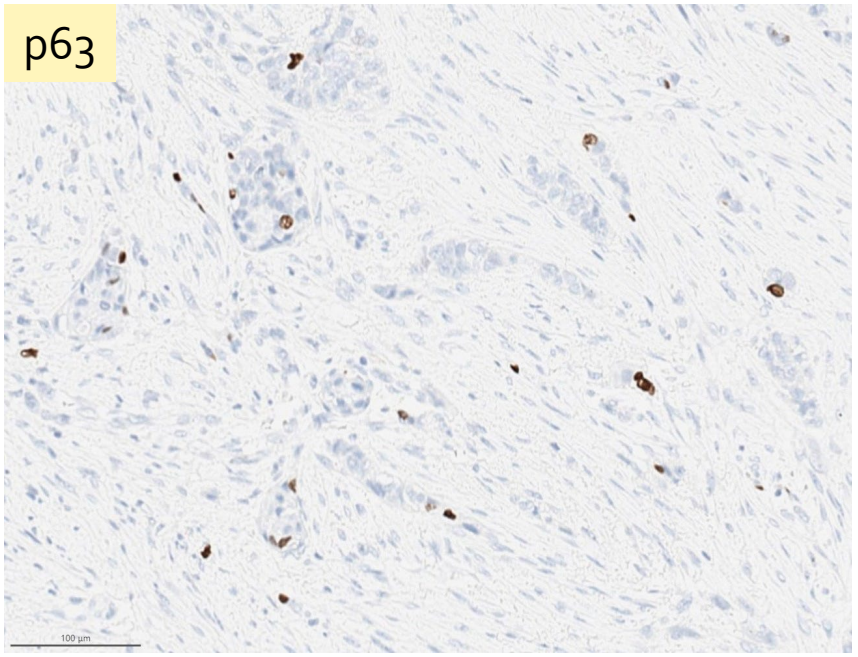



# Immunohistochemical staining for myoepithelial markers

- A spectrum of complete, discontinuous, and absent staining
  - "*The inconsistent staining pattern* in LGASC is consistently and uniquely present in this entity" (*Kawaguchi K and Shin SJ. Am J Surg Pathol. 2012)*
- p63 highlights neoplastic cells with squamous differentiation





# LGASC: a clinicopathologic study of 32 cases

**TABLE 1.** *Treatment and follow-up*

| Age (yr) | Size of primary tumor (cm) | Treatment | Follow-up | Comments |
|---|---|---|---|---|
| 33 | 8.0 | Modified radical mastectomy | AWD <6 mo | Lung metastases at time of mastectomy |
| 36 | 1.6 | Excisional biopsy | NED 1.7 yr | |
| 40 | 3.5 | Modified radical mastectomy | NED <1 mo | * Metastases in one of 33 axillary lymph nodes |
| 42 | 5.0 | Simple mastectomy | NED 5 yr | |
| 42 | 1.3 | Modified radical mastectomy | NED 4 yr | |
| 43 | 3.5 | Excisional biopsy & axillary dissection | n/a | |
| 46 | 0.6 | Excisional biopsy | NED 4.6 yr | |
| 49 | 3.5 | Modified radical mastectomy | NED 3.4 yr | |
| 50 | 2.4 | Excisional biopsy | NED 6.4 yr | Recurred 2 yr later and reexcised |
| 50 | n/a | Excisional biopsy | NED (n/a) | Died of contralateral ductal carcinoma |
| 51 | n/a | Simple mastectomy | NED 3.8 yr | Coexisting lobular carcinoma in situ |
| 51 | 3.2 | Excisional biopsy | NED <1 yr | |
| 51 | 2.4 | Excisional biopsy & axillary dissection | NED 2 yr | |
| 53 | 1.0 | Simple mastectomy | NED 2 yr | Contralateral ductal CA 5 yr earlier |
| 55 | 2.4 | Modified radical mastectomy | NED 5.3 yr | |
| 55 | 8.6 | Radical mastectomy | NED 8 yr | |
| 58 | 7.0 | Excisional biopsy | NED 1 yr | |
| 59 | 0.8 | Excisional biopsy | NED 3.4 yr | Contralateral LGASC 1 yr later |
| 61 | 1.5 | Excisional biopsy | NED 4.9 yr | |
| 61 | 0.8 | Excisional biopsy | NED 3.5 yr | Recurred 1.3 yr later and reexcised |
| 62 | 0.7 | Modified radical mastectomy | NED 1.3 yr | |
| 62 | 1.7 | Excisional biopsy | NED 4.8 yr | Recurred 3 yr later and reexcised |
| 62 | 1.5 | Modified radical mastectomy | NED 5 yr | |
| 65 | 1.5 | Excisional biopsy | NED 2.7 yr | |
| 69 | 2.0 | Excisional biopsy | NED 7 yr | |
| 69 | 2.3 | Excisional biopsy | NED 8.3 yr | Recurred 2.6 yr later and reexcised |
| 70 | 5.7 | Modified radical mastectomy | NED 1 yr | |
| 73 | 2.1 | Excisional biopsy | DOC 9 mo | |
| 76 | 1.3 | Excisional biopsy | DOD 8.4 yr | Recurred, locally invaded hemithorax |
| 76 | 4.0 | Excisional biopsy | NED 3 yr | |
| 77 | 2.5 | Modified radical mastectomy | NED 3 yr | |
| 88 | 1.5 | Excisional biopsy | NED <1 yr | |

AWD, alive with disease; DOC, died of cancer, no surgical or postmortem pathology to identify origin of lung tumor; DOD, died of disease; n/a, data not available; NED, no evidence of disease.

Distant Metastasis: 1/25

Local Recurrence: 5/25

van Hoeven KH et al. *Am J Surg Pathol*. 1993

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# A retrospective series of 13 LGASC

- No local or distant recurrence, clinical follow-up (mean, 7.5 years, range, 3–17 years)

**Table 1: Clinical characteristics of the cohort of 13 LGASCs of the breast.**

38%

| Case | Age | Previous breast lesion | Family history of cancer | Initial clinical presentation | Size (mm) | Lymph node metastasis | Mastectomy | Chemotherapy | Radiotherapy | Disease-free survival (years) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50 | Benign | none | Palpable mass | 25 | 0/14 | Total | no | no | 17 |
| 2 | 54 | none | Mother (Breast) | Palpable mass | 20 | NA | Partial | no | yes | 13 |
| 3 | 54 | none | Father (Esophagus) | Screening mammography | 10 | 0/10 | Partial | yes | yes | 11 |
| 4 | 85 | none | none | Palpable mass | 12 | NA | Partial | no | no | 11 |
| 5 | 54 | none | Father (Colon) | Palpable mass | 15 | 0/4 | Partial | no | yes | 9 |
| 6 | 56 | Invasive lobular carcinoma | none | Screening mammography | 3.5 | 0/1 | Partial | no | yes | 8 |
| 7 | 66 | none | none | Palpable mass | 20 | 0/19 | Partial | no | yes | 6 |
| 8 | 81 | Invasive ductal carcinoma | Mother (Breast) | Palpable mass | 35 | 10/15* | Partial | yes | yes | 5 |
| 9 | 46 | none | none | Palpable mass | 34 | NA | Partial | no | no | 5 |
| 10 | 66 | none | none | Screening mammography | 10 | 0/12 | Partial | yes | yes | 4 |
| 11 | 62 | none | none | Screening mammography | 14 | 0/19 | Partial | yes | yes | 3 |
| 12 | 58 | Benign | Mother (Breast) | Palpable mass | 70 | 0/10 | Partial | yes | yes | 3 |
| 13 | 28 | none | Mother (Breast) | Palpable mass | 11 | 0/2 | Partial | no | yes | 3 |

Legend: *: lymph node metastasis of contralateral ER-positive invasive ductal carcinoma (i.e. invasive carcinoma of no special type); NA: not available.

Bataillon G et al *Histopathology.* 2018; 73: 273-283

# LGASC: a retrospective review of 34 cases at MSKCC

| Case | Age (yrs) | Tumor size (mm) | *Lymph node involvement* | Follow-up (Months) |
|---|---|---|---|---|
| 1 | 44 | 5 | None | NED, 1 |
| 2 | 38 | 6 | None | NED, 1 |
| 3 | 70 | 5 | None | NED, 1 |
| 4 | 66 | 1.5 | None | NED, 9 |
| 5 | 64 | 1.5 | None | NED, 10 |
| 6 | 60 | 15 | None | NED, 11 |
| 7 | 40 | 7 | None | NED, 22 |
| 8 | 54 | 14 | None | NED, 34 |
| 9 | 49 | 8 | None | NED, 35 |
| 10 | 54 | 1.7 | None | NED, 54 |
| 11 | 60 | 10 | None | NED, 68 |
| 12 | 69 | 13 | ITCs from concurrent IDC NST (ipsilateral, separate tumor) | NED, 73 |
| 13 | 37 | 6 | None | Local recurrence, 81 |
| 14 | 66 | 20 | None | NED, 83 |
| 15 | 40 | 24 | None | NED, 84 |
| 16 | 52 | 10 | None | NED, 104 |

Colon-Cartagena L et al. USCAP 2022

# Treatment: locoregional treatment

- Systemic therapies do not appear to be warranted

| | |
|---|---|
| ***LGASC (11)*** | |
| Radiation therapy | 9 ( 82%) |
| Chemotherapy | 3 (27%) |
| No additional therapy | 2 (18%) |
| ***LGASC with concurrent IDC, NST and DCIS (4)*** | |
| Radiation therapy | 4 (100%) |
| Chemotherapy | 4 (100%) |
| Endocrine therapy | 2 (50%) |

Colon-Cartagena L et al. USCAP 2022

# Genomic alterations in LGASC

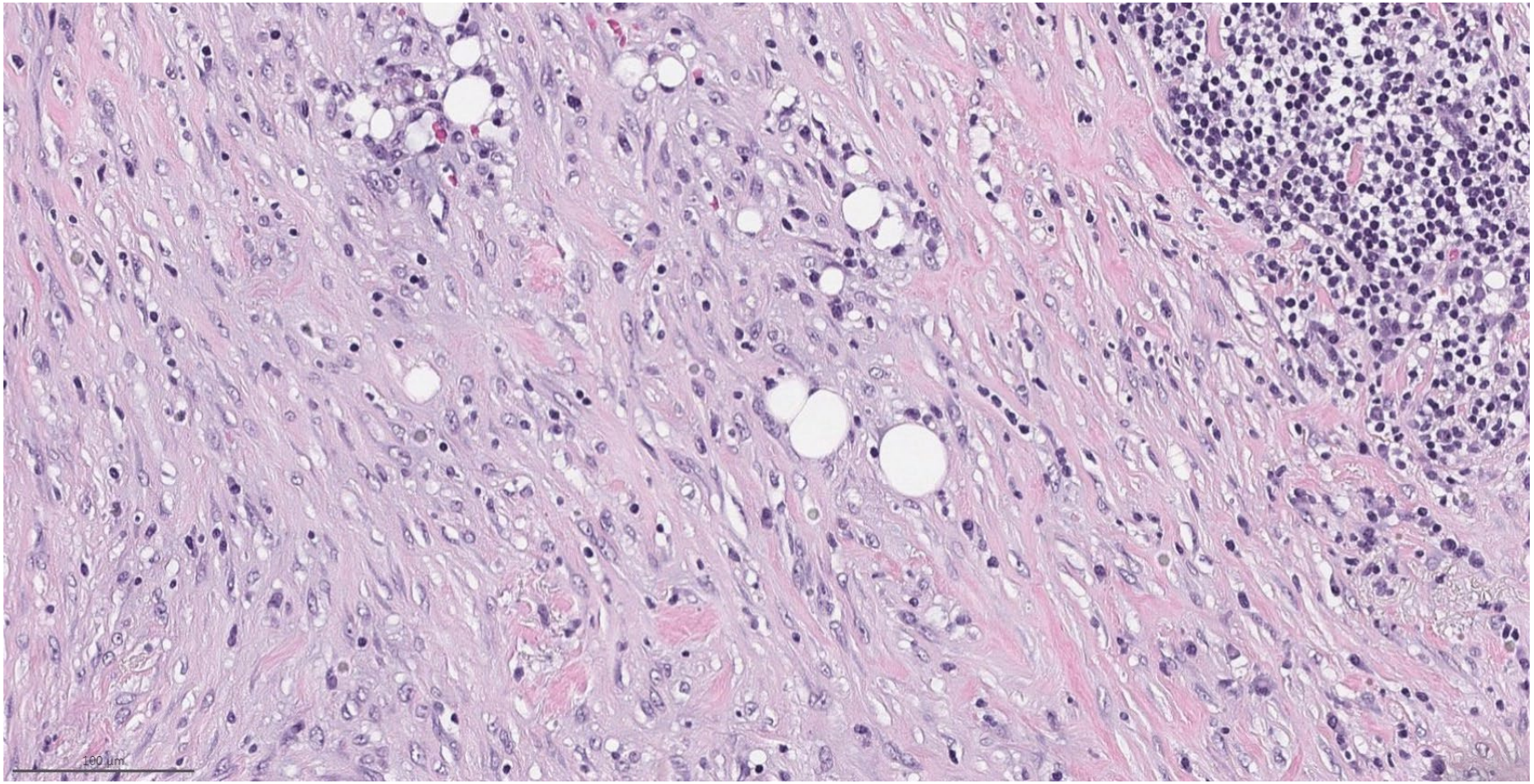
High rate of *PIK3CA* mutations (52%)

No *TP53* mutations

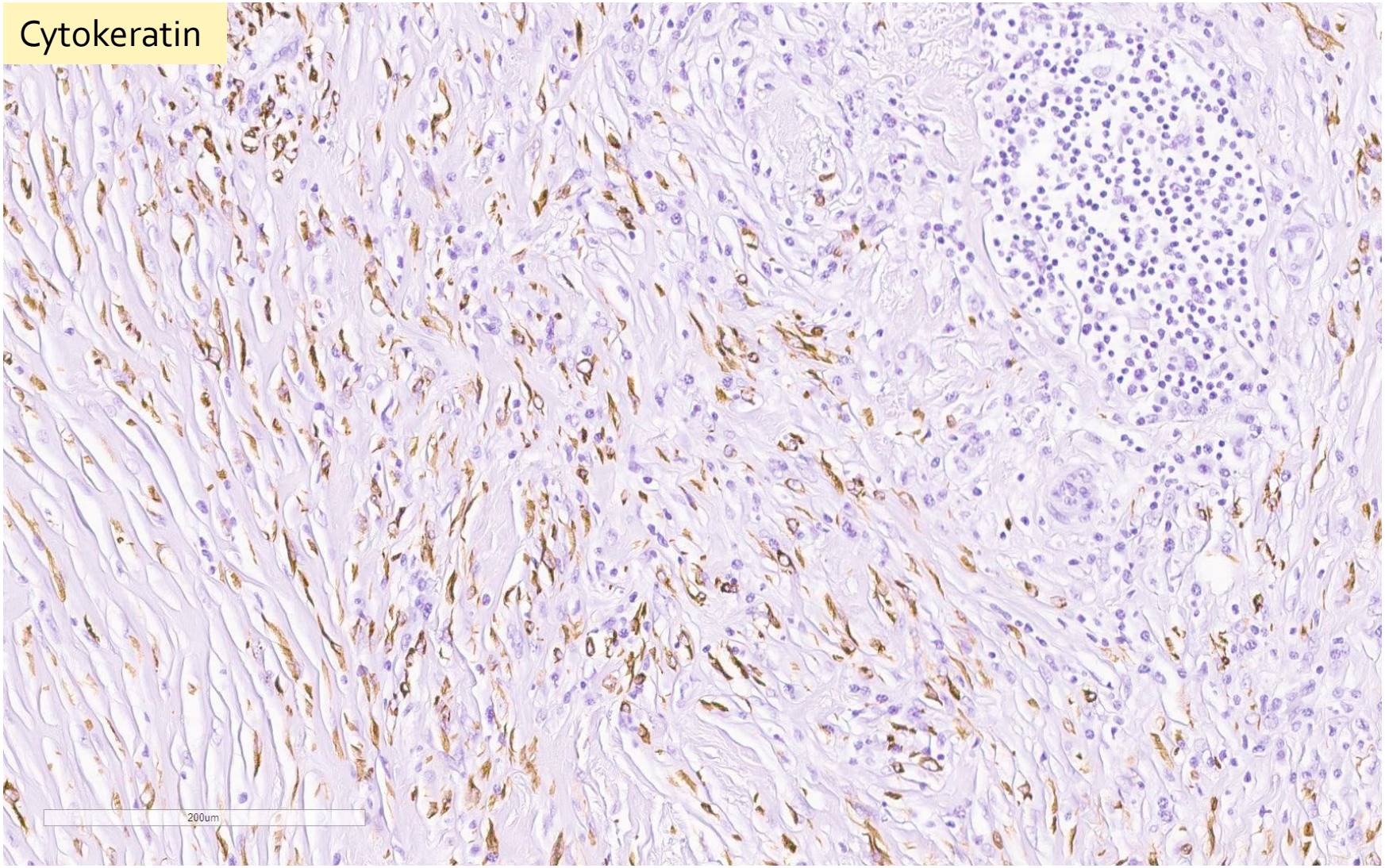
Bataillon G et al *Histopathology.* 2018; 73: 273-283

# Fibromatosis-like metaplastic carcinoma

- Bland spindle cells, resembling fibromatosis. Atypia is absent or minimal



# Fibromatosis-like metaplastic carcinoma

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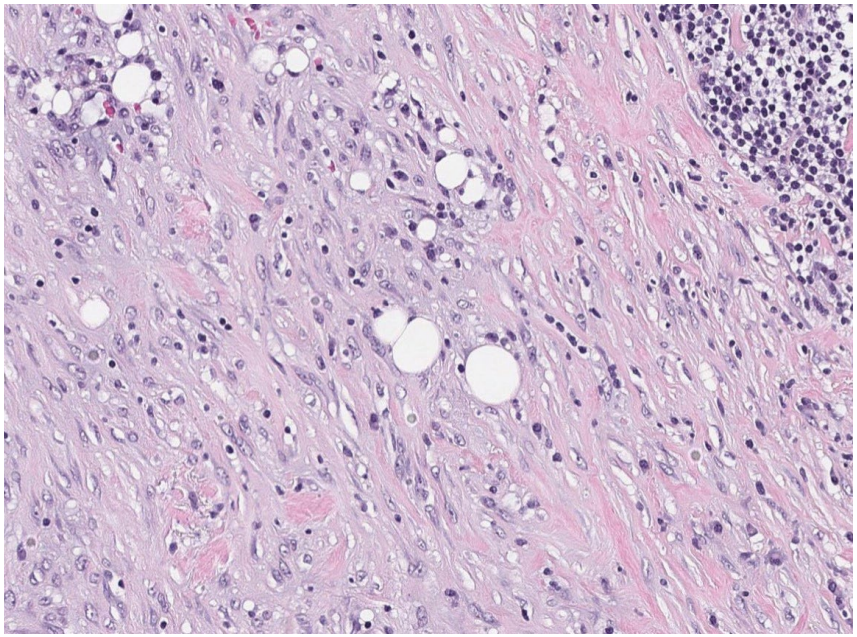
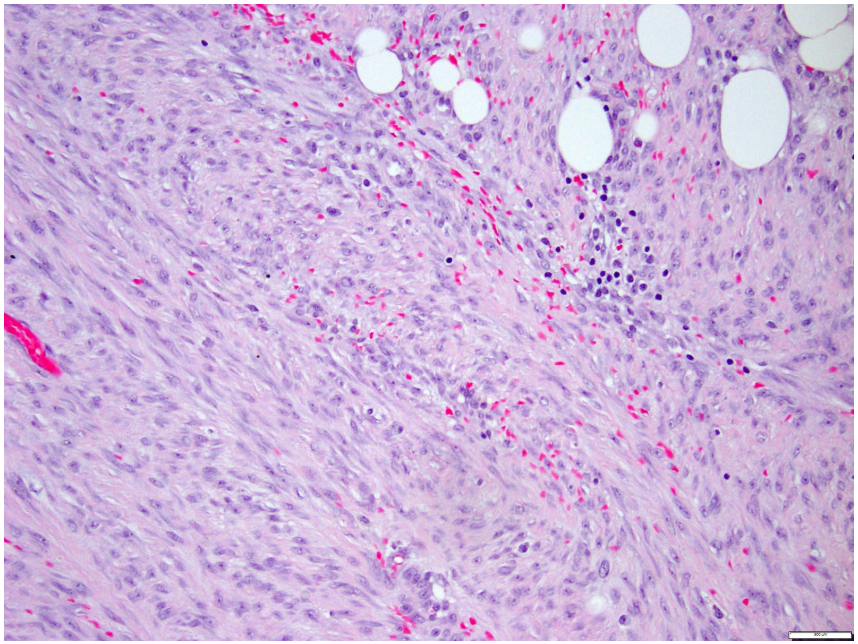
# Differential diagnosis

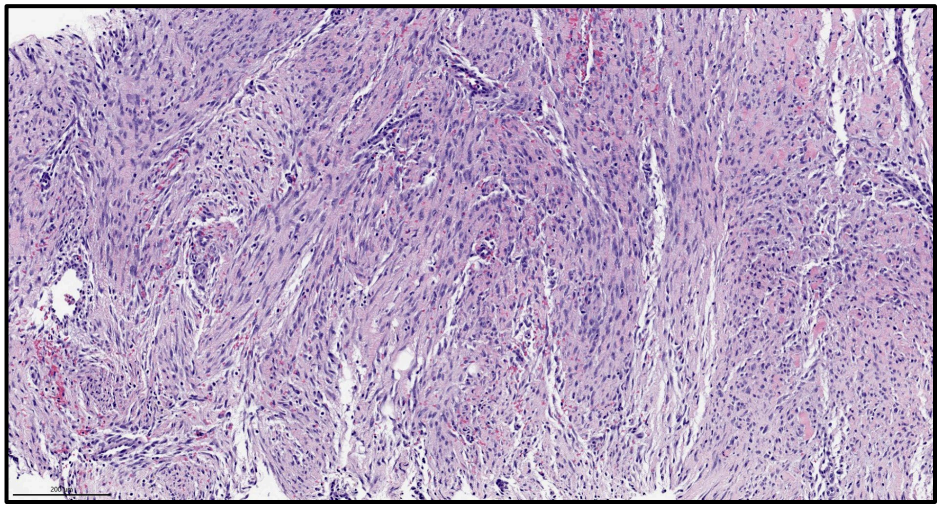
## Fibromatosis-like metaplastic carcinoma



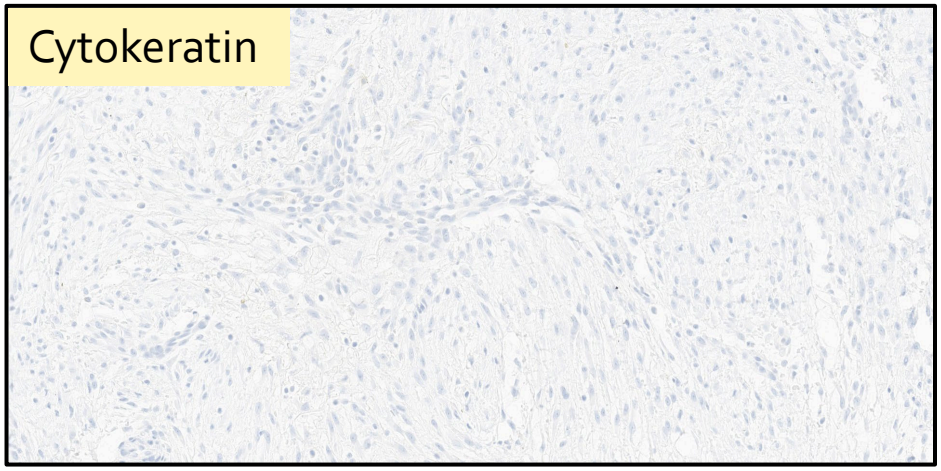
## Fibromatosis



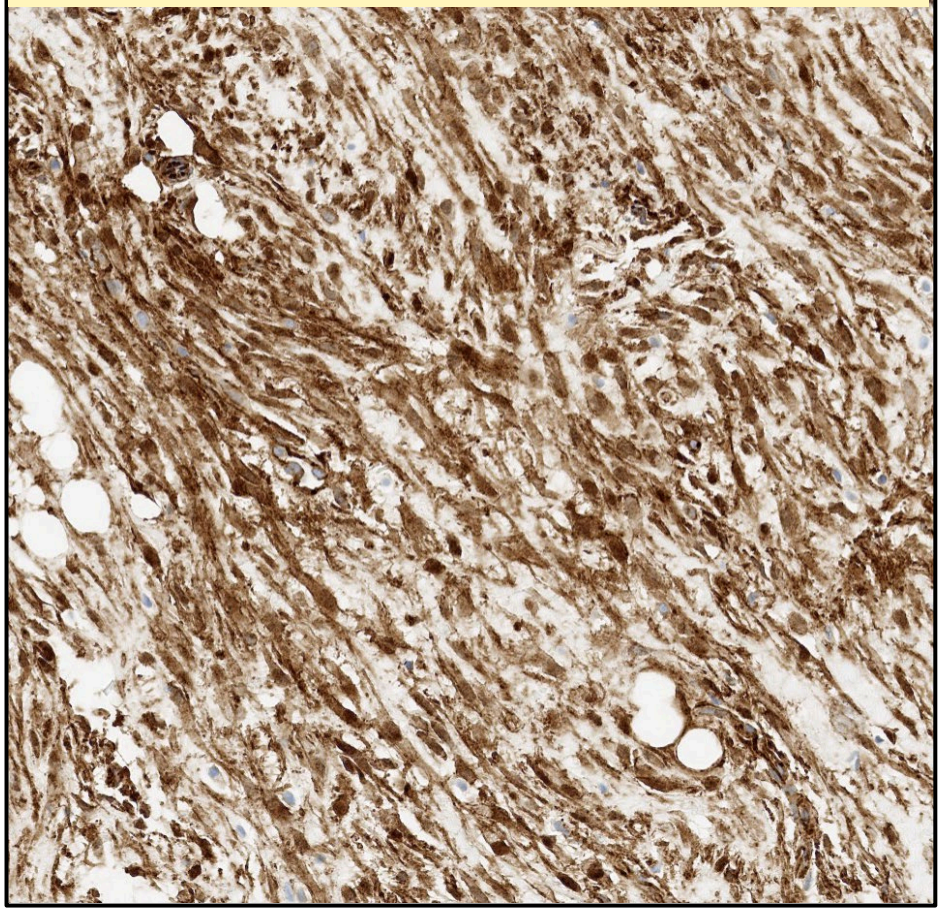
# Fibromatosis



Cytokeratin



Beta-catenin: nuclear staining

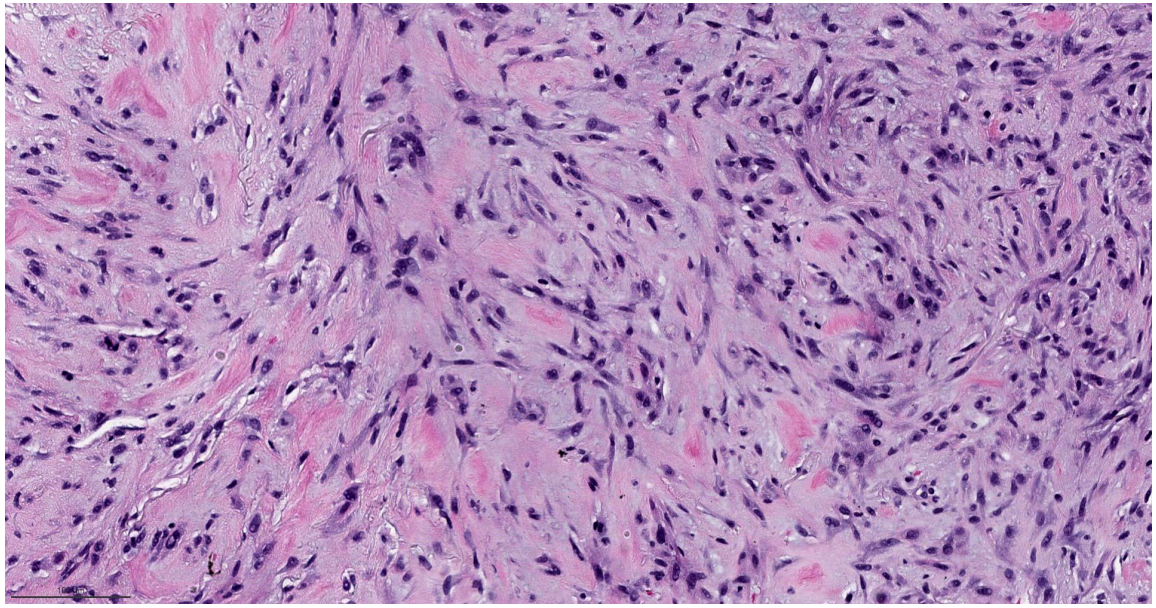


# Capable of local recurrence, distant metastasis is rare

| Study (year) | Gobbi (Cancer 1999) | Sneige (AJSP 2001) |
|---|---|---|
| Number of patients | 30 | 24 |
| Age, mean (range), years | 63 (35-80) | 66 (55-85) |
| Tumor size, median (range), mm | 27 (12-70) | 28 (10-50) |
| Axillary lymph node involvement | 0/11 | 0/15 |
| Excisional biopsy | 8/23 (35%) | 5/20 (25%) |
| Breast conserving surgery | 10/23 (43%) | 1/20 (5%) |
| Mastectomy | 5/23 (22%) | 14/20 (70%) |
| Radiation | 3/23 (13%) | 5/20 (25%) |
| Chemotherapy | 2/23 (9%) | 1/20 (5%) |
| Median follow-up (months) | 27 (6-88) | 33 (8-90) |
| Local recurrence | 8/18 (44%)* | 2/16 (12.5%) |
| Distant metastasis | 0 | 2/16 (12.5%) |
| Died of disease | 0 | 2/16 (12.5%) |

*7 out of the 8 cases in the recurrence group were not recognized as metaplastic carcinoma in the initial biopsy

# Molecular pathology



54-year-old woman s/p mastectomy and chemotherapy for fibromatosis like MBC, developed lung metastasis

POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS

- 1. DROSHA (NM_013235) exon4 p.Y172* (c.516T>G)
- 2. PIK3R1 (NM_181523) exon13 p.L531Vfs*7 (c.1589dupA)
- 3. PIK3R1 (NM_181523) exon13 p.L570R (c.1709T>G)
- 4. TERT (NM_198253) promoter variant (g.1295228C>T)
- 5. PIK3R1 (NM_181523) rearrangement: c.1745+32_c.1815-230del

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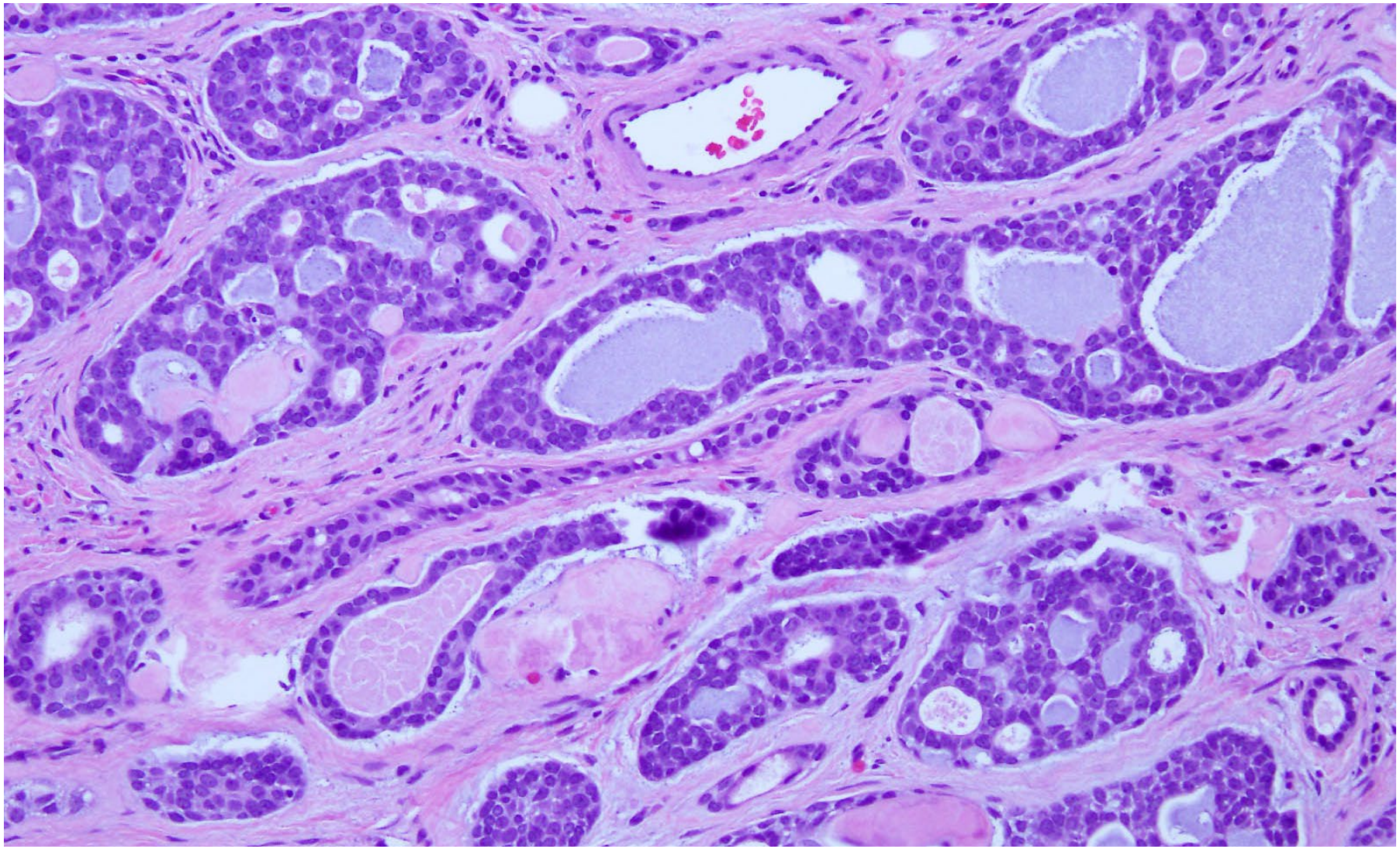
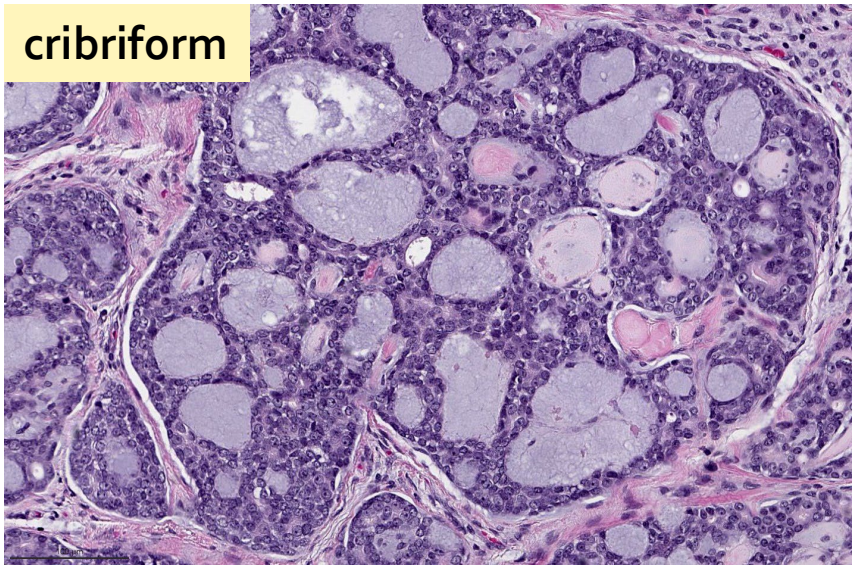
# Adenoid cystic carcinoma

# Adenoid cystic carcinoma (AdCC)

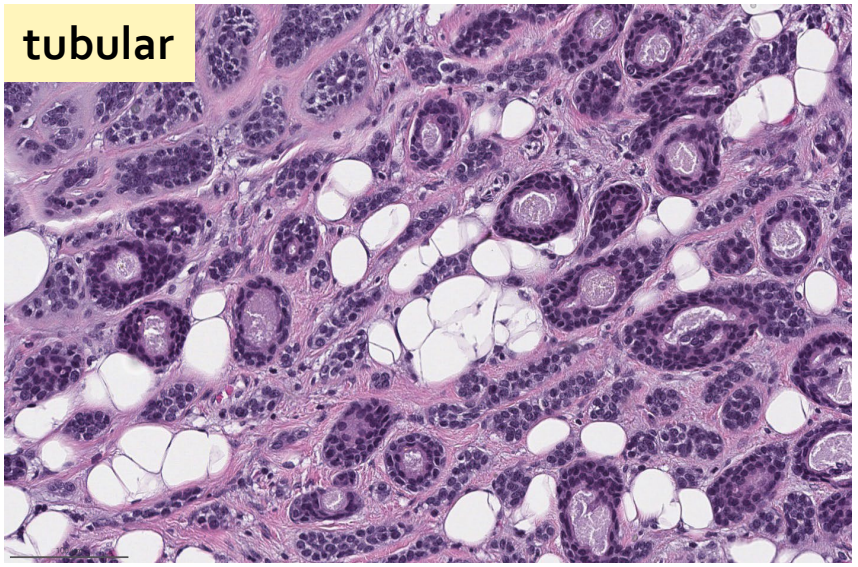


# Histologic patterns

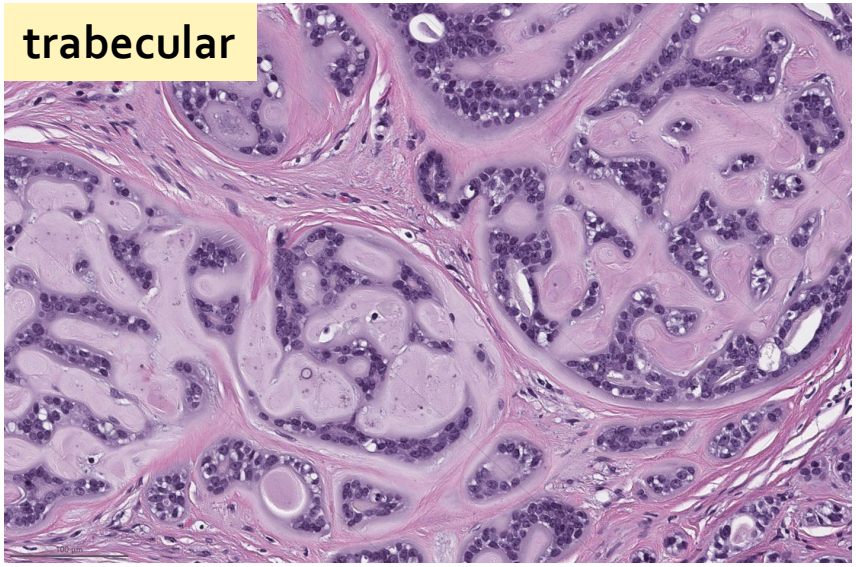
cribriform



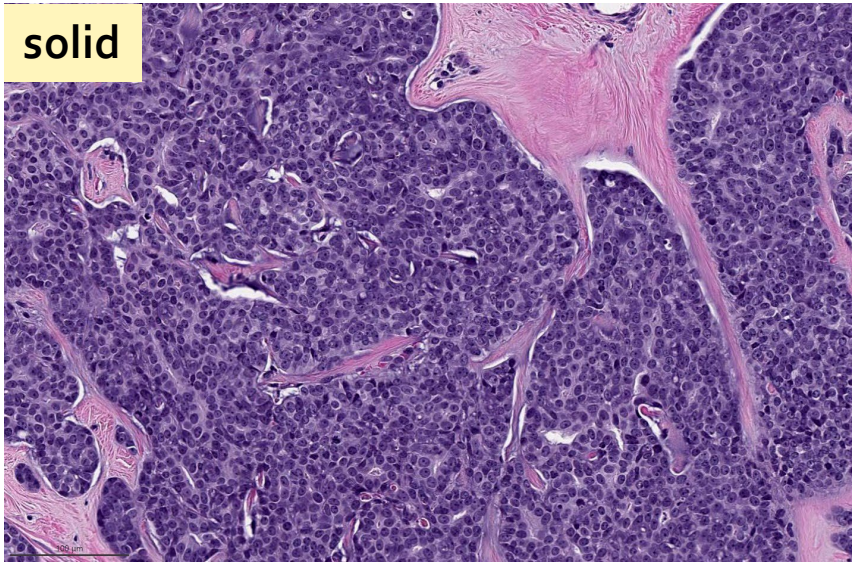
tubular



trabecular

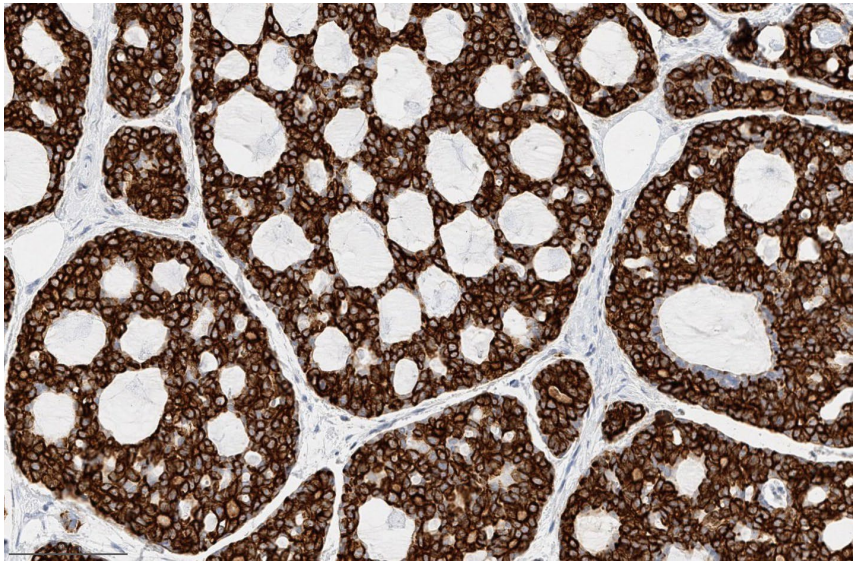


solid

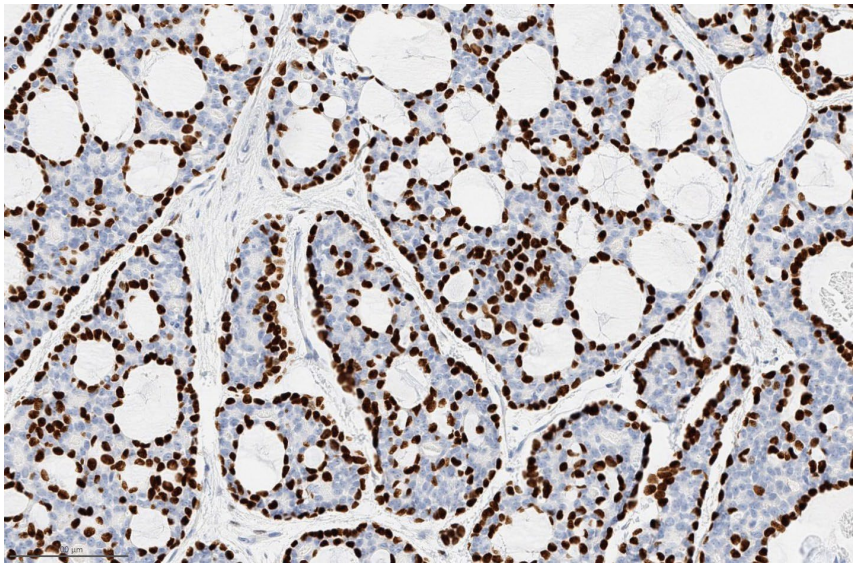


# Biphasic tumor: epithelial and myoepithelial cells

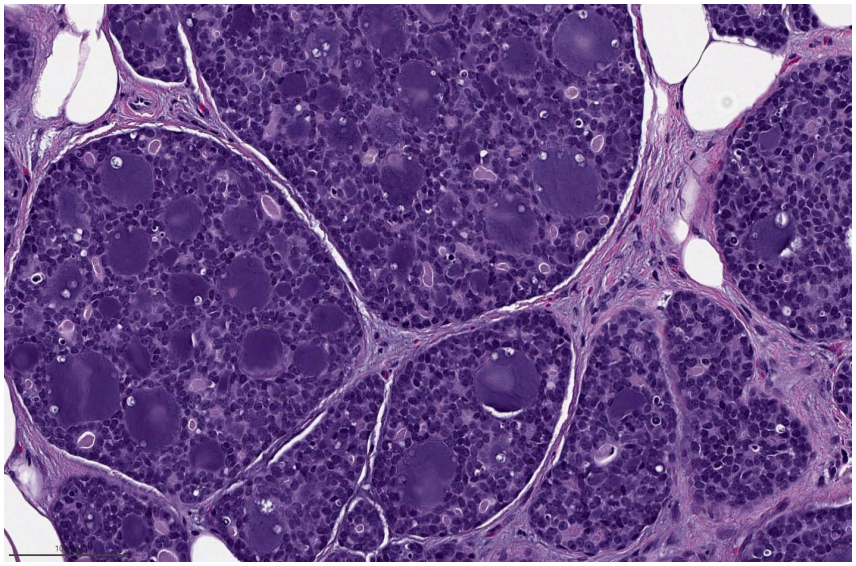
CK7

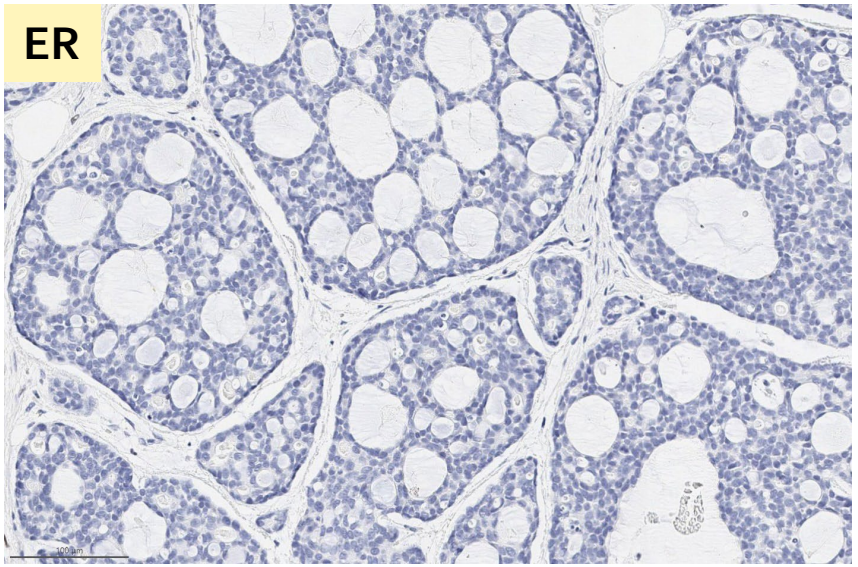


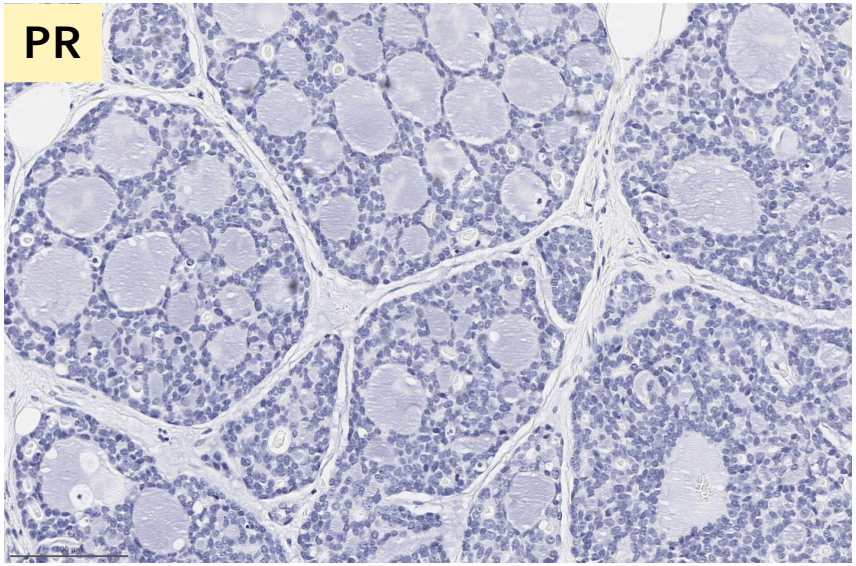
p63

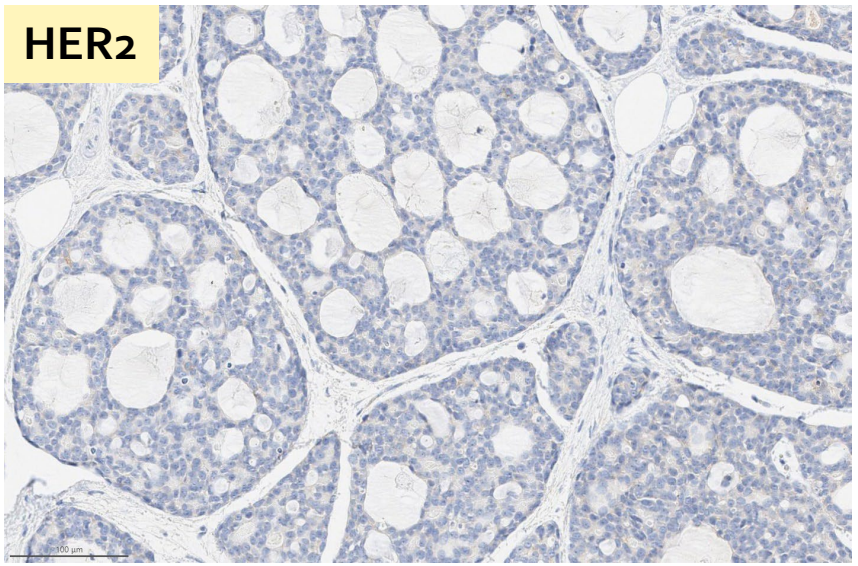


# AdCC: usually triple negative



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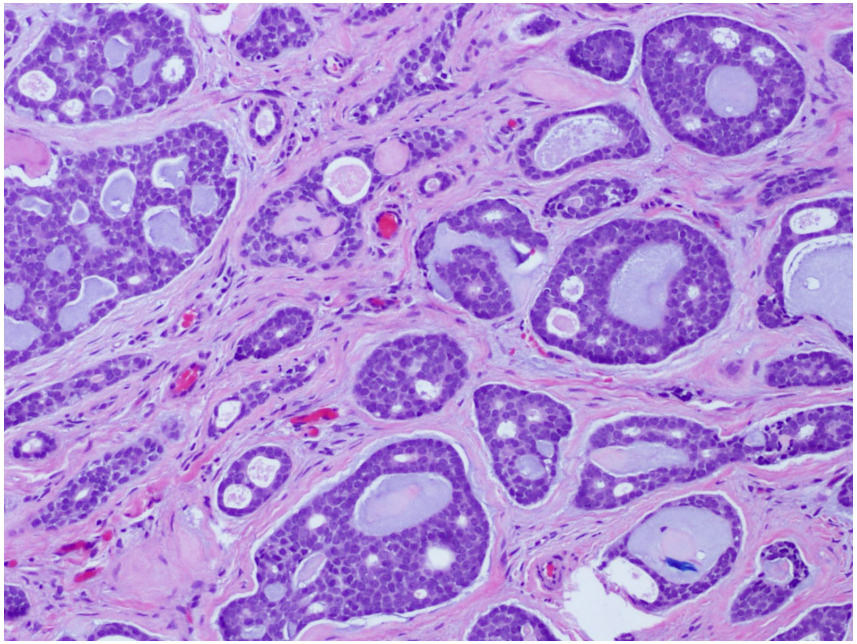
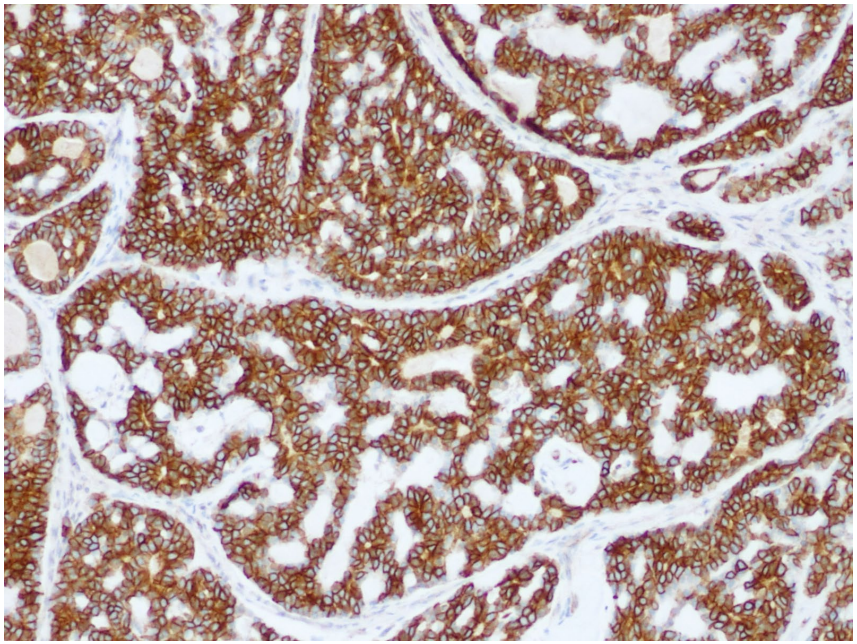
# Immunohistochemistry

**H&E**



**C-kit (CD117)**

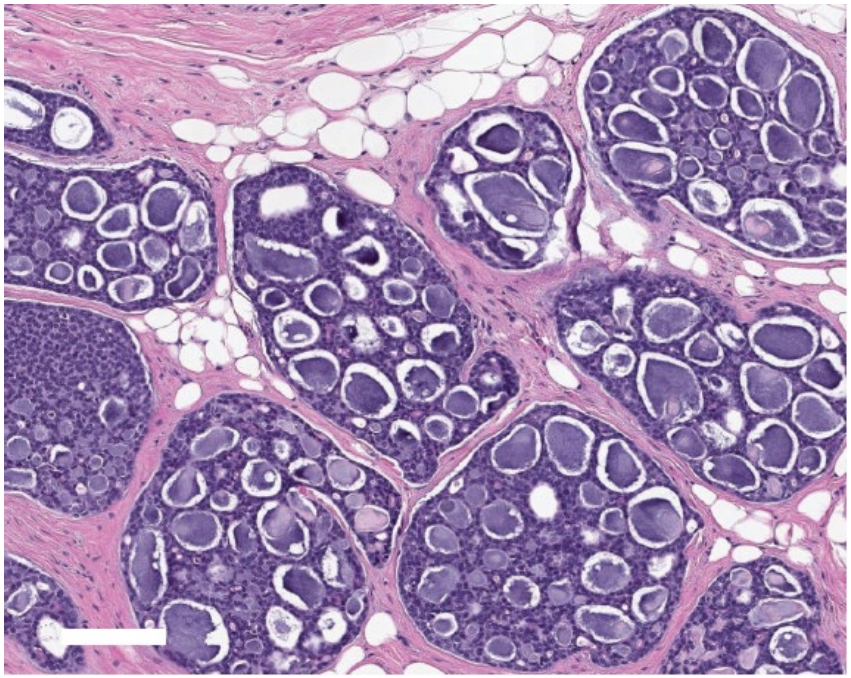


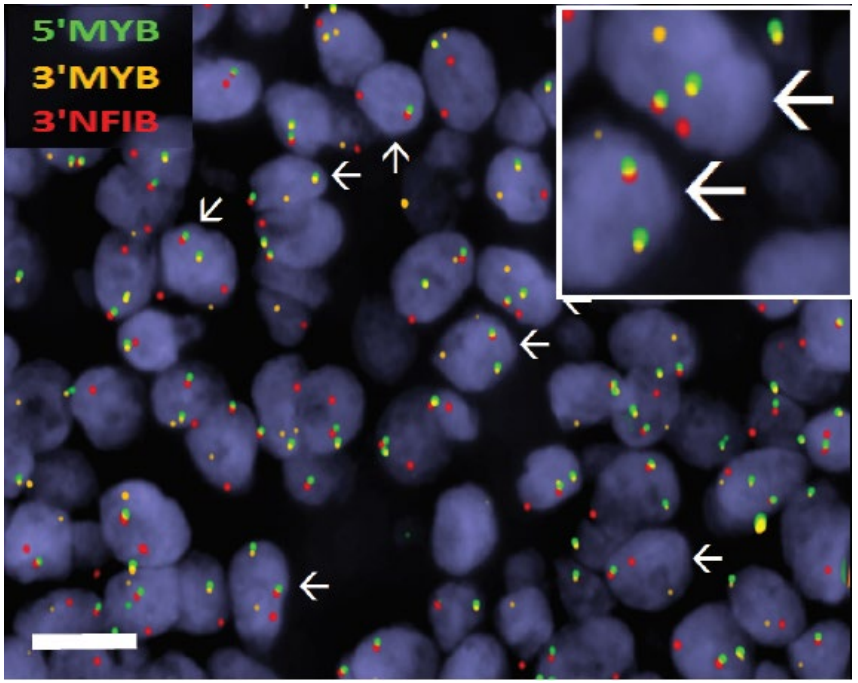
# Genomic alterations

- t(6::9) >> *MYB-NFIB* fusion
- Other genetic alterations
  - *MYB* rearrangement with other partners
  - *MYBL1* rearrangement
  - *MYB* amplification
- Whole exome sequencing
  - Low mutation rate
  - Lacks mutations in *TP53* and *PIK3CA (*unlike TNBC NST*)*

Persson M et al. *Proc Natl Acad Sci U S A*. 2009; 106:18740-18744
Kim J et al. *J Pathol*. 2018; 244:143-150
Martelotto LG et al. *J Pathol* 2015;237:179-189

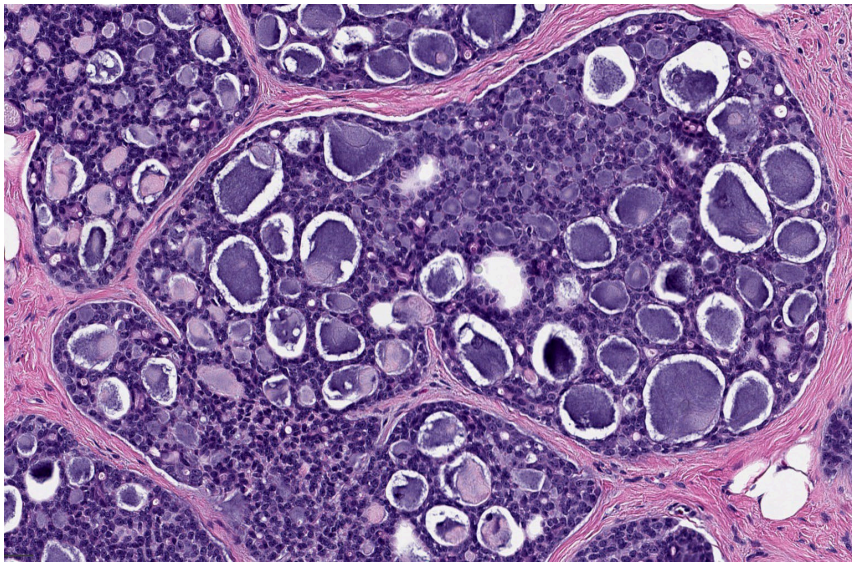
# FISH for *MYB* rearrangement

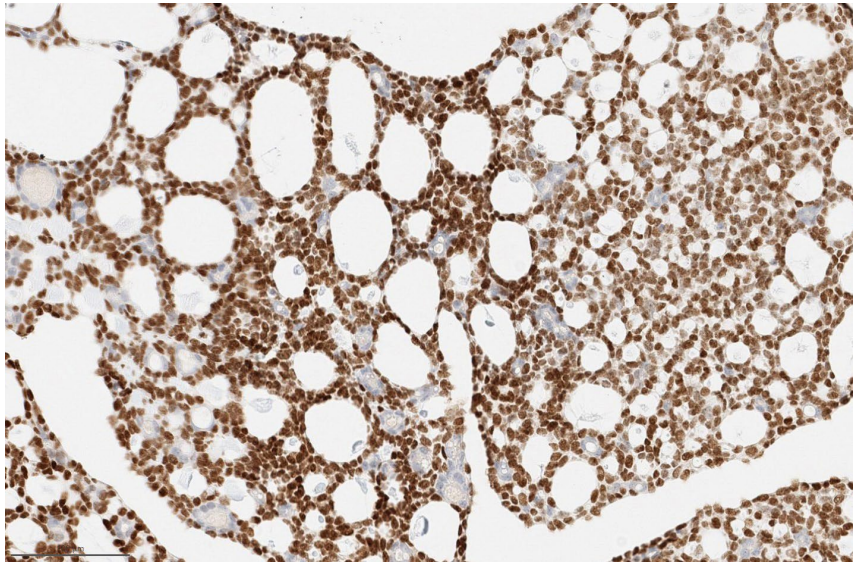





*MYB* break-apart probe

# MYB immunohistochemistry





- MYB expression detected in both fusion-positive and fusion-negative AdCC

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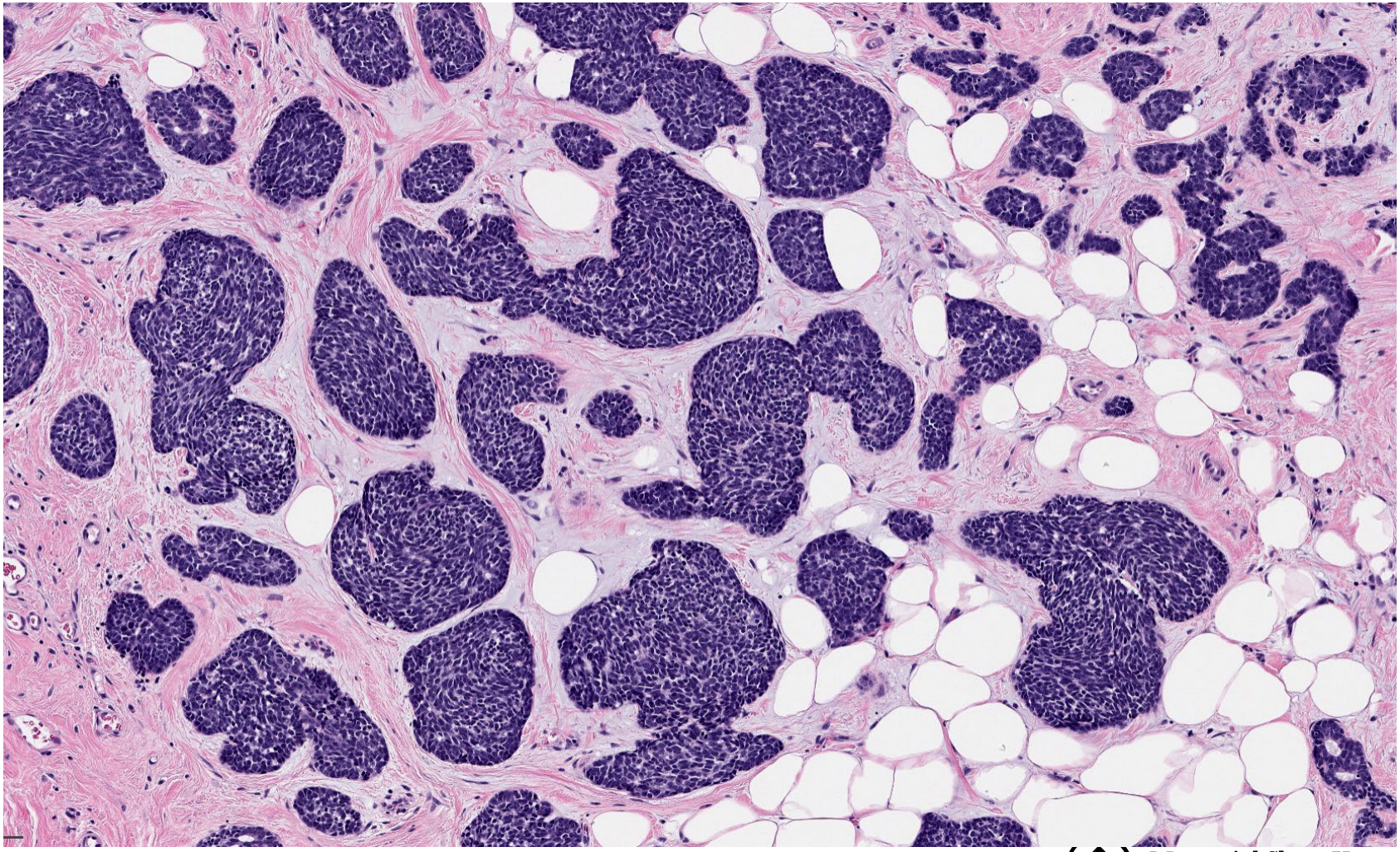
# Adenoid cystic carcinoma solid basaloid variant

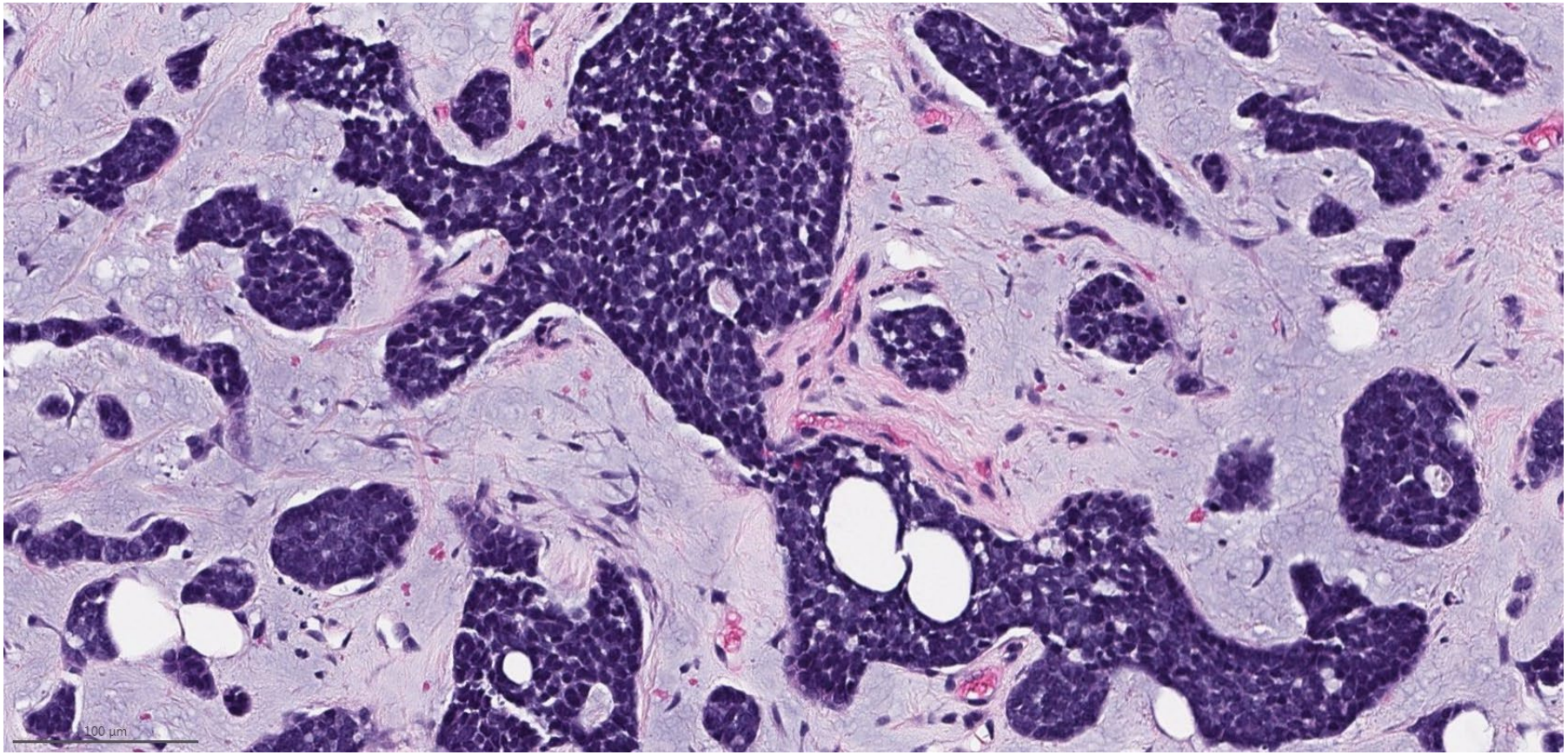
# Solid basaloid variant of adenoid cystic carcinoma (SB-AdCC)

- ***Solid*** (>90%) growth pattern



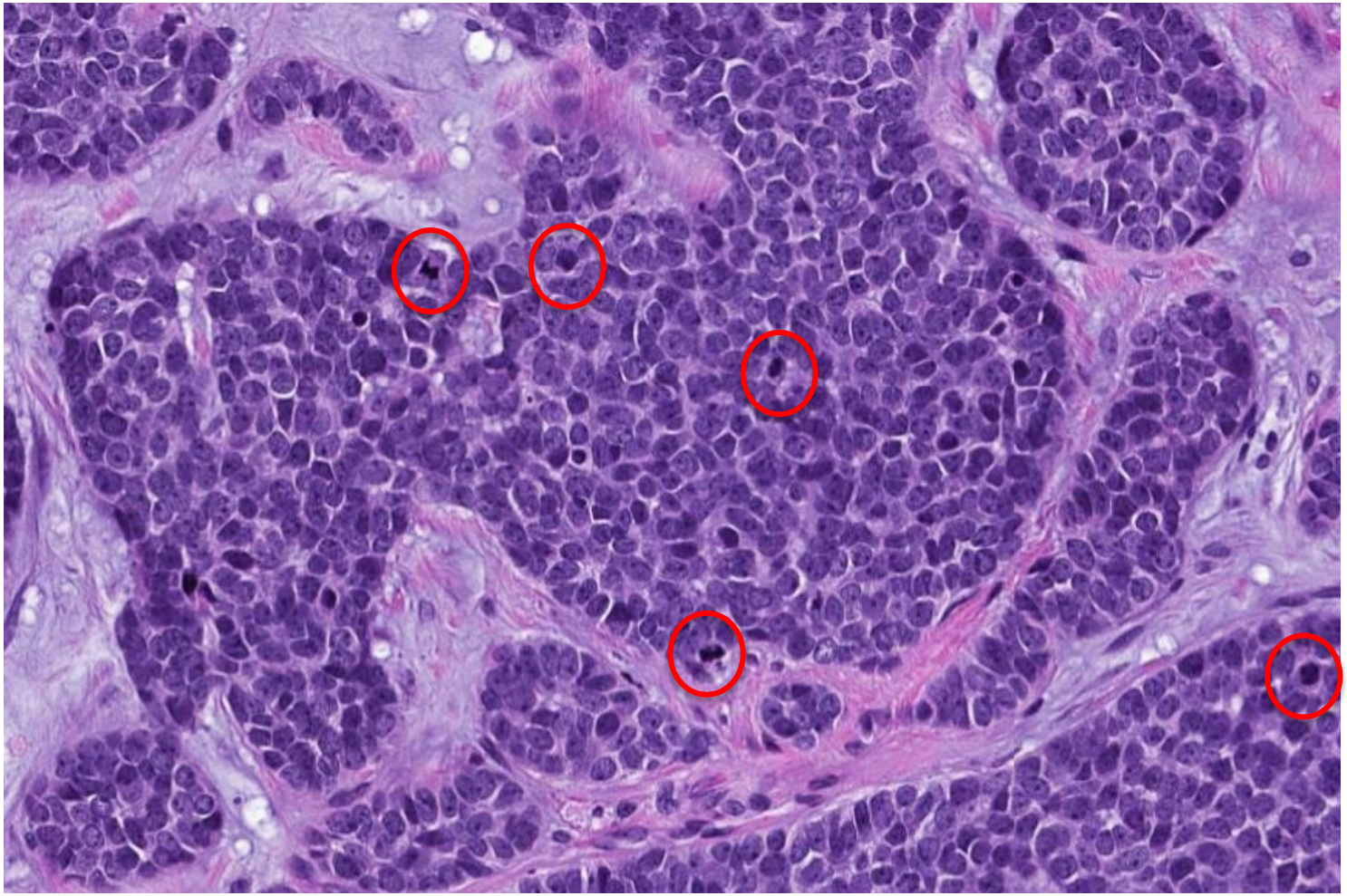
# Adenoid cystic carcinoma solid basaloid variant

- ***Basaloid*** cells, myxoid or hyalinized stroma



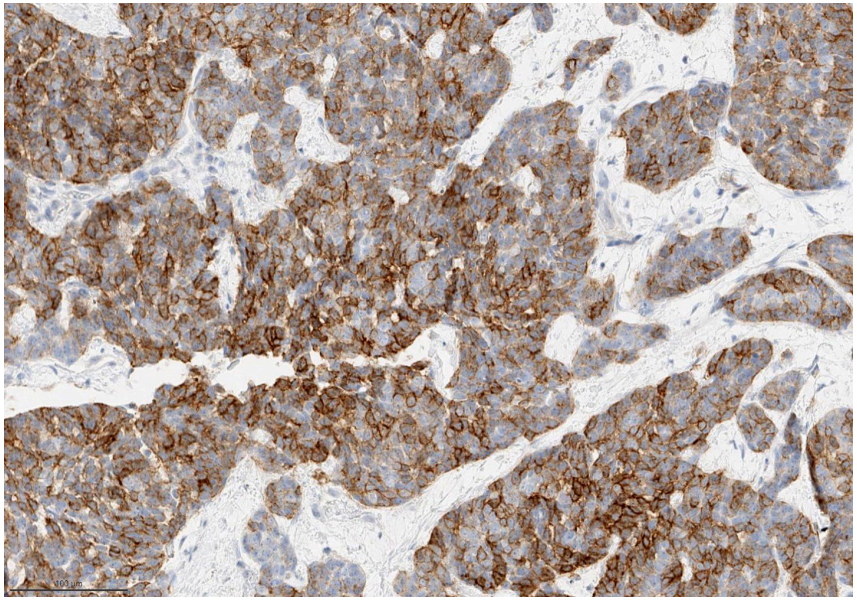
# Adenoid cystic carcinoma solid basaloid variant

- Moderate to marked nuclear atypia, some with brisk mitotic activity

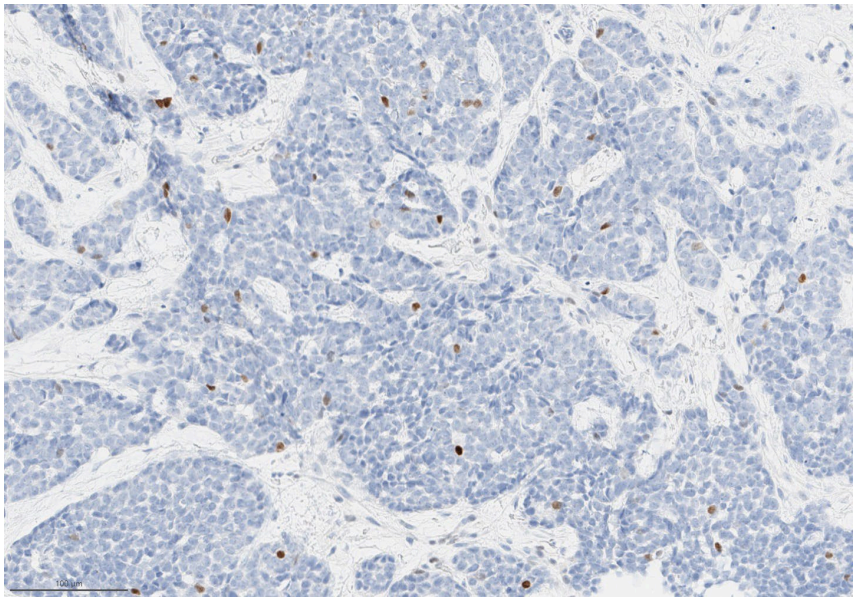


# Adenoid cystic carcinoma solid basaloid variant

CD117



p63



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# SB-AdCC: more frequent lymph node metastasis than C-AdCC

- Classic AdCC: excellent prognosis
  - Lymph node involvement is rare
- SB-AdCC: more frequent lymph node metastasis than C-AdCC

**TABLE 2.** *Solid variant of mammary adenoid cystic carcinoma with basaloid features: clinical summary*

| Age (y)/sex* | Date of diagnosis | Size (cm) | Nodes | Therapy 1°/subsequent | Follow-up (mo) | Status | Comments |
|---|---|---|---|---|---|---|---|
| 37/F | 7/91 | 1.5 | ND | EXBX/none | ? | ? | Clear cell features; solid DCIS |
| 51/F | 12/98 | 1.1 | 0/2 | EXBX/none | 17 | NED | Squamous diff; in-situ ACC |
| 51/F | 8/89 | 5.0 | 1/25 | EXBX/MX | 88 | NED† | |
| 52/F | 6/00 | 2.0 | 0/15 | EXBX/partial MX | 10 | NED | In-situ ACC |
| 68/F | 1/99 | 2.1 | 0/1 (SN) | NC/EXBX | 13 | NED | Solid DCIS |
| 77/F | 6/97 | 2.8 | 0/37 | NC/partial MX | 36 | NED | In-situ ACC |
| 78/F | 11/90 | 1.4 | 0/10 | EXBX/none | 37 | NED | In-situ ACC |
| 81/F | 12/99 | 2.3 | ND‡ | EXBX/none‡ | 2 | NED | |
| 83/F | 3/93 | 15 | 1/12 | EXBX/MR-MX | 21 | NED | DOC |

Shin SJ and Rosen PP. *Am J Surg Pathol* 2002; 26:413-420



**ARTICLE**

# The clinical behavior and genomic features of the so-called adenoid cystic carcinomas of the solid variant with basaloid features

Christopher J. Schwartz[1], Edi Brogi[1], Antonio Marra[1], Arnaud F Da Cruz Paula[2], Gouri J. Nanjangud[3], Edaise M. da Silva[1], Sujata Patil[4], Shreena Shah[2], Katia Ventura[1], Pedram Razavi[5], Larry Norton[5], Timothy D'alfonso[1], Britta Weigelt[1], Fresia Pareja[1✉], Jorge S. Reis-Filho[1✉] and Hannah Y. Wen[1✉]

Schwartz CJ et al. *Mod Pathol*. 2022; 35: 193-201

# Clinicopathologic characteristics

**Table 1.** Clinicopathologic parameters of breast adenoid cystic carcinoma cohort.

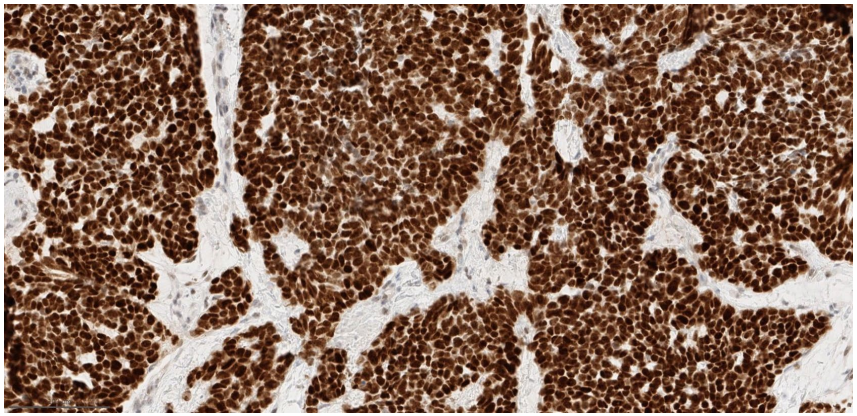
| | C-AdCC $N = 75$ | SB-AdCC $N = 29$ | *P* value |
|---|---|---|---|
| Age at diagnosis | | | <0.05 |
| Range | 36.0–78.0 | 44.0–88.0 | |
| Median | 55.5 | 63.0 | |
| Q1, Q3 | 51.0, 64.5 | 55.5, 75.3 | |
| Average tumor size (cm) | 1.94 | 2.13 | 0.29 |
| T Stage | | | 0.68 |
| 1A | 2/52 (3.8%) | 0/20 (0.0%) | |
| 1B | 9/52 (17.3%) | 2/20 (10.0%) | |
| 1C | 21/52 (40.4%) | 9/20 (45.0%) | |
| 2 | 20/52 (38.5%) | 9/20 (45.0%) | |
| Nottingham Grade | | | <0.05 |
| 1 | 25/63 (40%) | 0/29 (0%) | |
| 2 | 38/63 (60%) | 6/29 (21%) | |
| 3 | 0/63 (0%) | 23/29 (79%) | |
| LVI | 2/63 (3%) | 8/29 (28%) | <0.05 |
| PNI | 6/63 (10%) | 6/29 (21%) | 0.10 |
| Nodal metastasis | 0/56 (0%) | 3/21 (14%) | <0.05 |

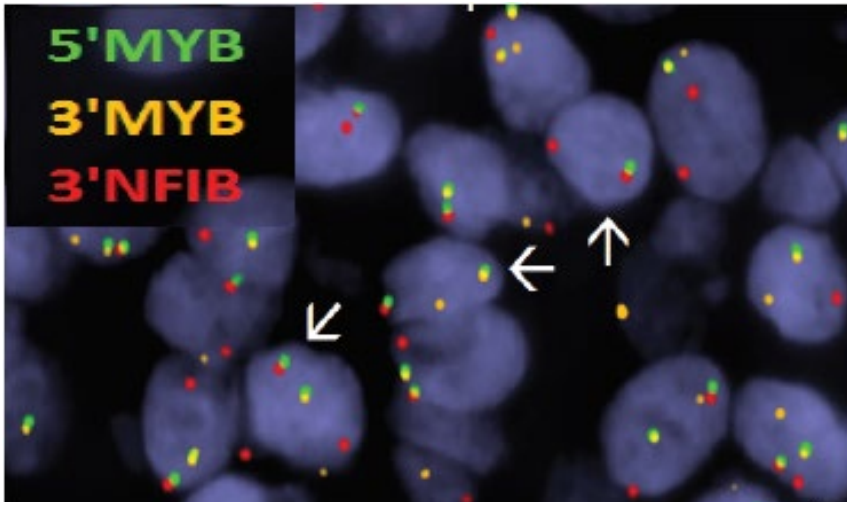
Schwartz CJ et al. *Mod Pathol*. 2022; 35: 193-201

# MYB expression by IHC and rearrangement by FISH

**Table 2.** MYB status in breast adenoid cystic carcinomas.

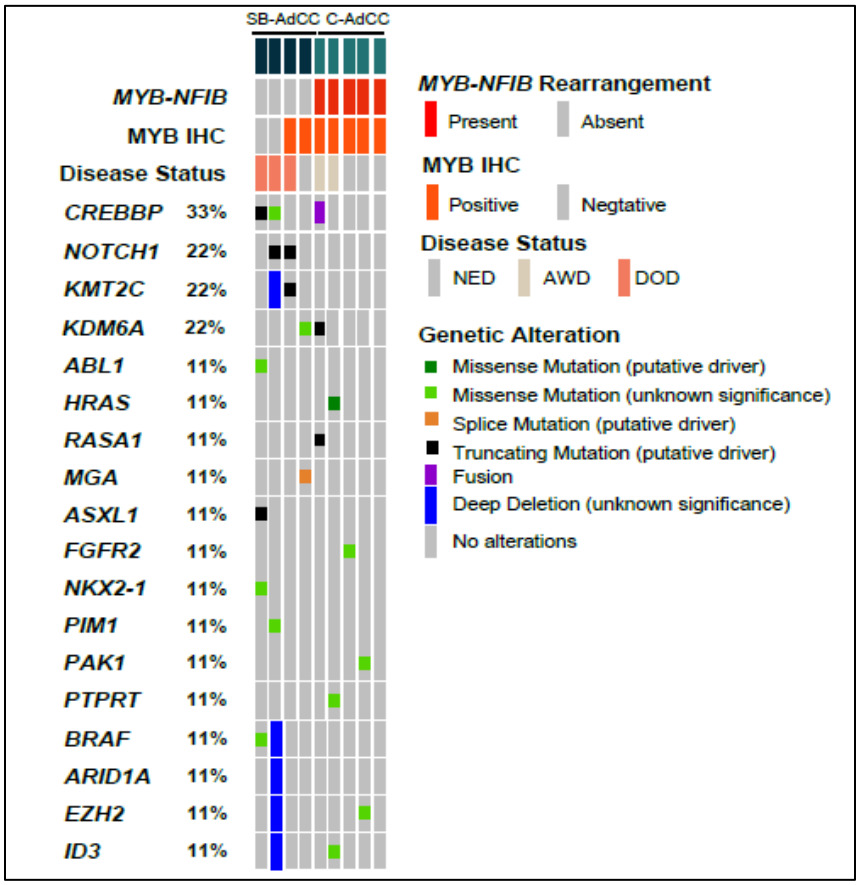
| | C-AdCC *N* = 20 | SB-AdCC *N* = 14 | *P* value |
|---|---|---|---|
| MYB IHC | | | |
| Positive | 19/20 (95%) | 9/14 (64%) | 0.07 |
| Focal | 9/19 (47%) | 3/9 (33%) | |
| Diffuse | 10/19 (53%) | 6/9 (66%) | |
| FISH studies | | | |
| *MYB-NFIB* | 16/20 (80%) | 1/14 (7%) | <0.05 |
| *MYB* unknown partner | 0/20 (0%) | 2/14 (14%) | 1.0 |
| *MYBL1* rearrangement | 1/4 (25%) | 0/11 (0%) | 0.25 |
| *MYB* or *MYBL1* rearrangement | 17/20 (85%) | 3/14 (21%) | <0.05 |






Schwartz CJ et al. *Mod Pathol*. 2022; 35: 193-201

# Targeted sequencing: *CREBBP*, *NOTCH1*, *KMT2C*, *KDM6A*




- Somatic mutations in *CREBBP*, *NOTCH1*, *KMT2C*, and *KDM6A*
- Differed from TNBC NST
  - No *TP53* mutations
  - Low mutation burden

Schwartz CJ et al. *Mod Pathol*. 2022; 35: 193-201

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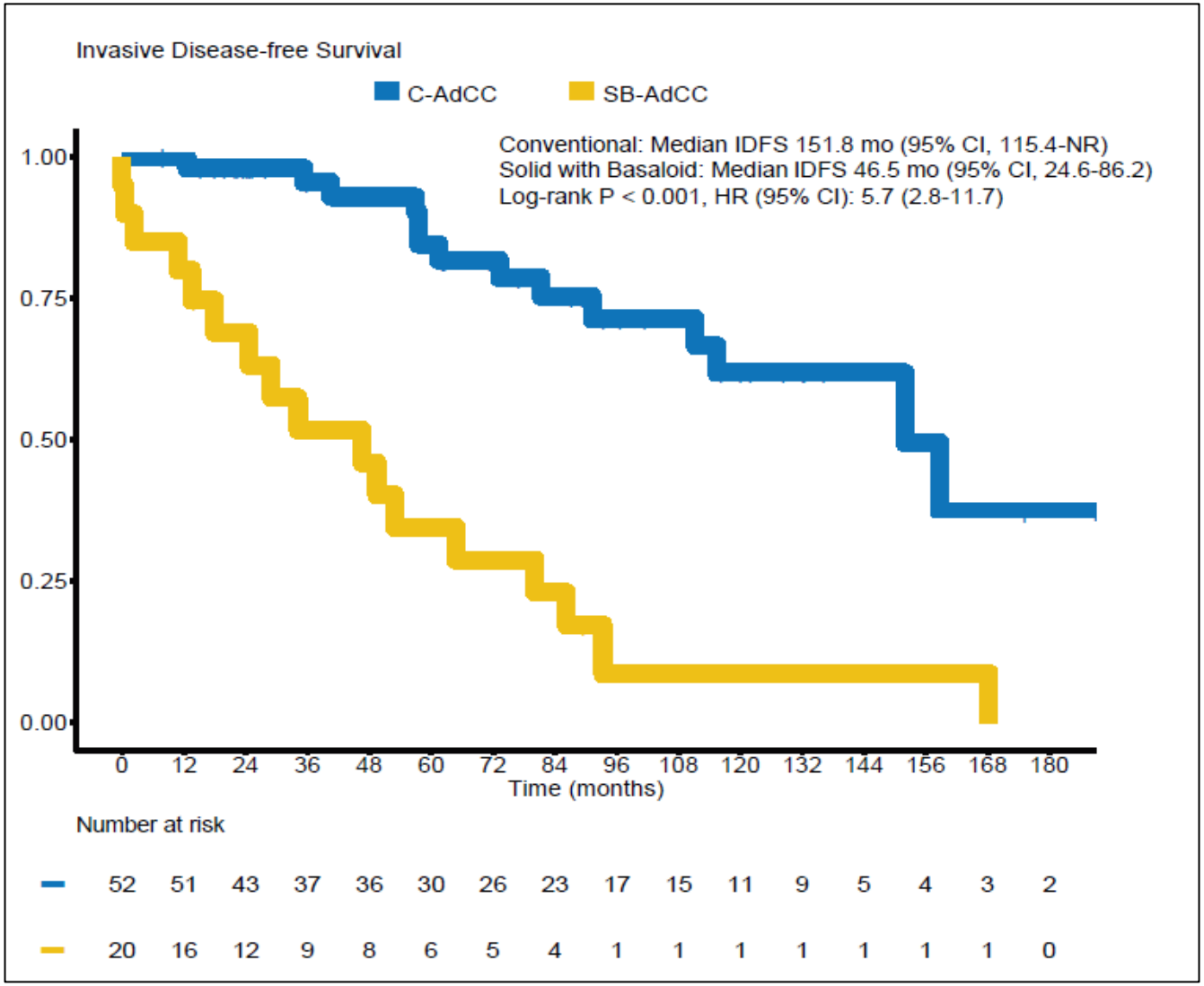
# SB-AdCCs: a shorter invasive disease-free survival than C-AdCCs




Masse J et al. *Mod Pathol 2020; 33: 1041-1055*

Memorial Sloan Kettering Cancer Center

Modern Pathology (2020) 33:1041–1055
https://doi.org/10.1038/s41379-019-0425-3

USCAP

ARTICLE

# Solid-type adenoid cystic carcinoma of the breast, a distinct molecular entity enriched in *NOTCH* and *CREBBP* mutations

Julie Massé[1,2] · Caroline Truntzer[3] · Romain Boidot[3] · Emmanuel Khalifa[1] · Gaëlle Pérot[4,5] · Valérie Velasco[1] · Laétitia Mayeur[1] · Claire Billerey-Larmonier[1] · Larry Blanchard[1] · Hélène Charitansky[6] · Isabelle Soubeyran[1] · Richard Iggo[2,7] · Laurent Arnould[3] · Gaëtan MacGrogan[1,7]

- 33 AdCC of the breast:
  - 16 Classic-AdCC (C-AdCC), 17 Solid basaloid-AdCC (SB-AdCC)
- MYB expression by IHC:
  - 82% (14/17) of SB-AdCC
- MYB rearrangement:
  - 19% (3/16) SB-AdCC, 56% (9/16) C-AdCC

Masse J et al. *Mod Pathol 2020; 33: 1041-1055*

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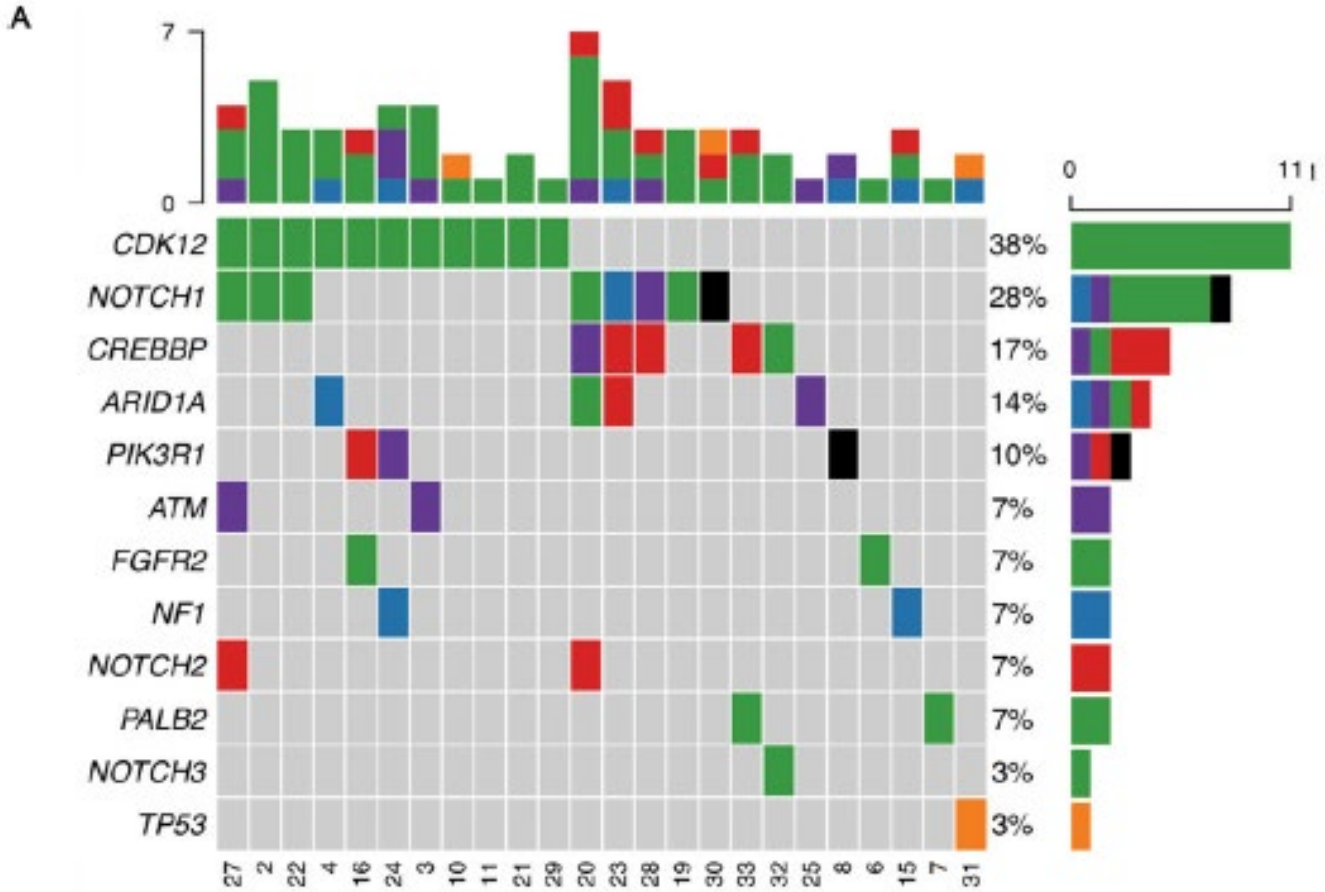
# Somatic mutations

- The most frequent somatic mutations: CDK12 in 11/29 (38%), NOTCH1 in 8/29(28%) , CREBBP in 5/29 (27%), ARID1A in 4/29 (14%) of cases




Masse J et al. *Mod Pathol 2020; 33: 1041-1055*

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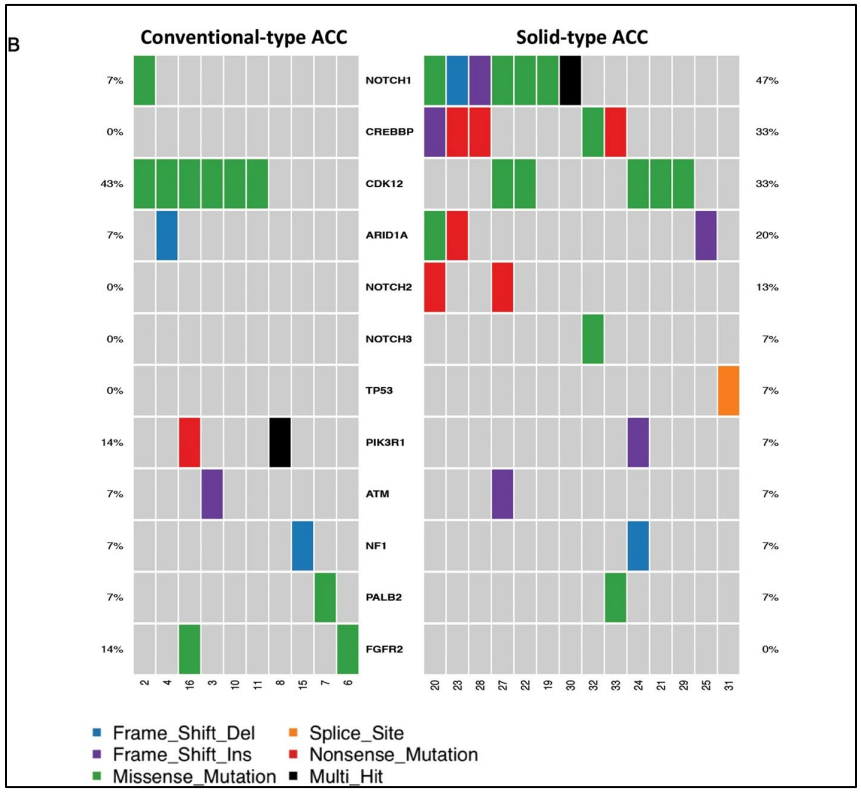
# SB-AdCC: a distinct molecular entity within AdCC

- *CREBBP* mutations and *NOTCH* activating mutations were only present in SB-AdCC
  - NOTCH mutations: 8/16 (50%) SB-AdCC
  - CREBBP mutations: 5/16 (31%) SB-AdCC




Masse J et al. *Mod Pathol 2020; 33: 1041-1055*

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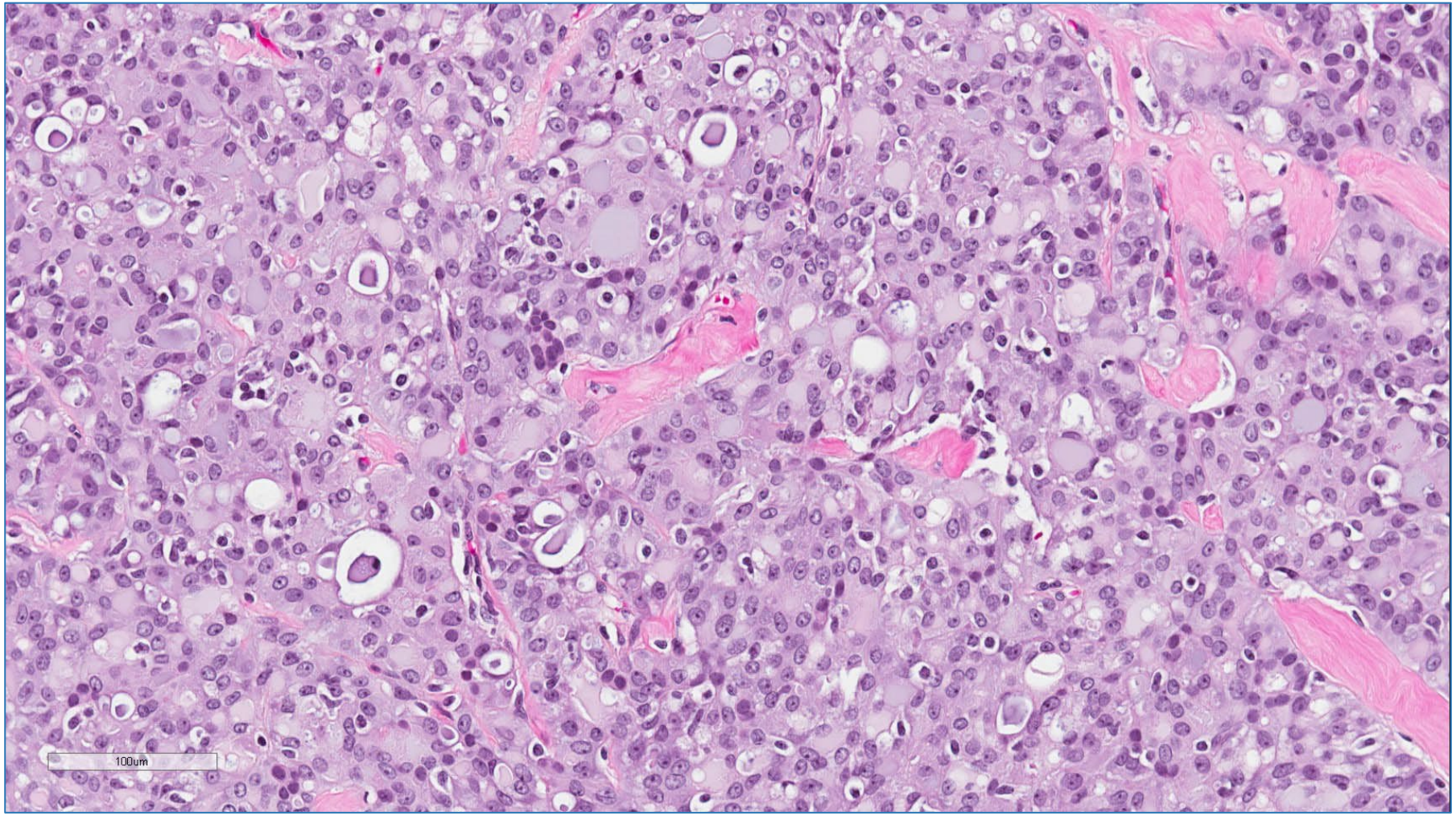
# Secretory carcinoma

# Secretory carcinoma

- Exceptionally rare, <0.15% of all breast cancers
- Occurs in both children and adults, median age 25 years (range, 3-87 years)
- Occurs in both female and male
- Excellent prognosis

# Secretory carcinoma




- Solid, microcystic, or tubular growth pattern
- with abundant intracellular and extracellular secretory material

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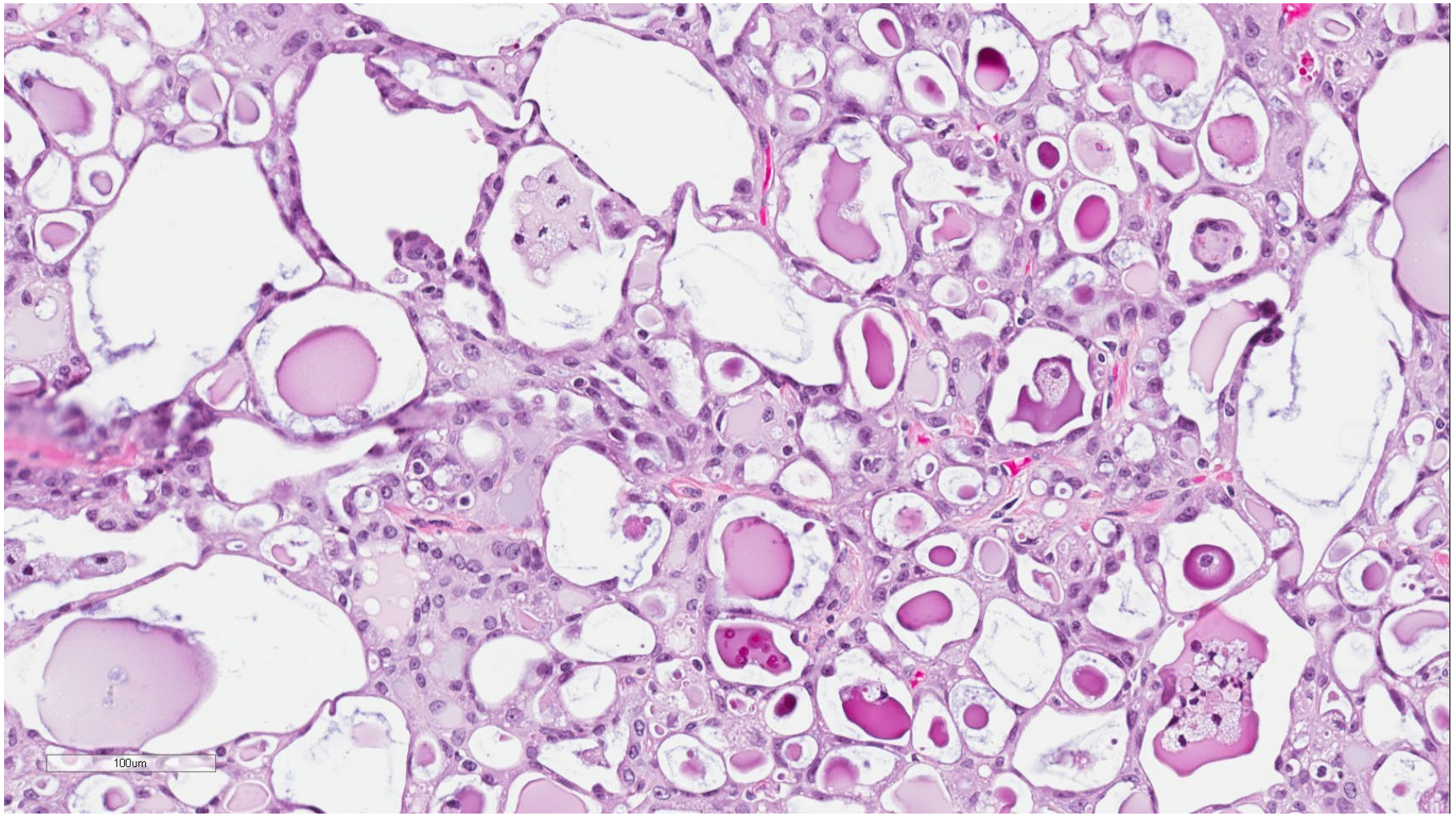


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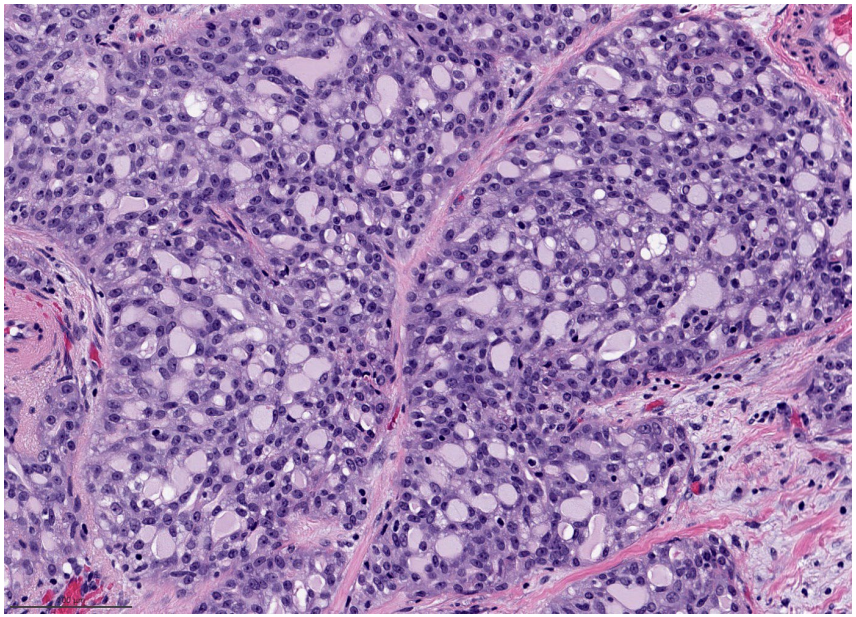
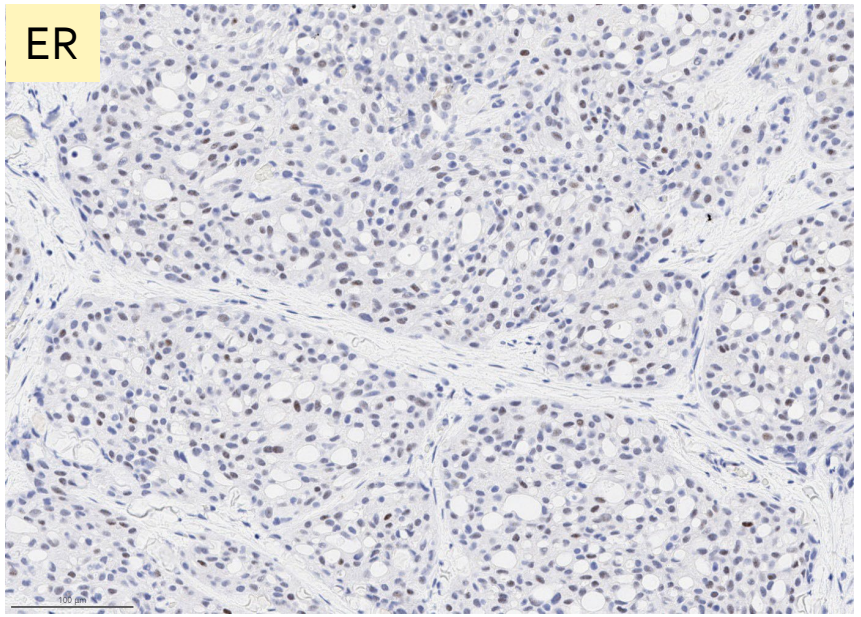
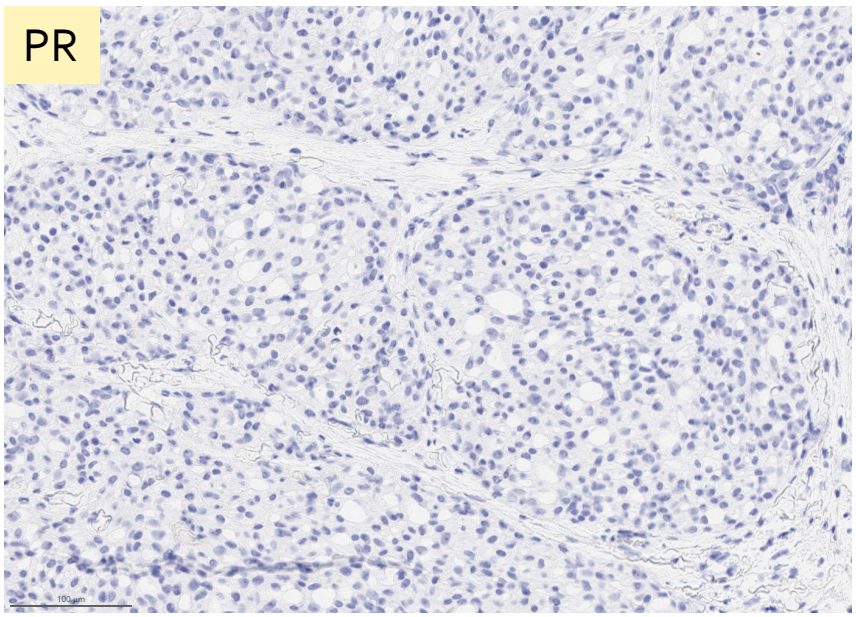
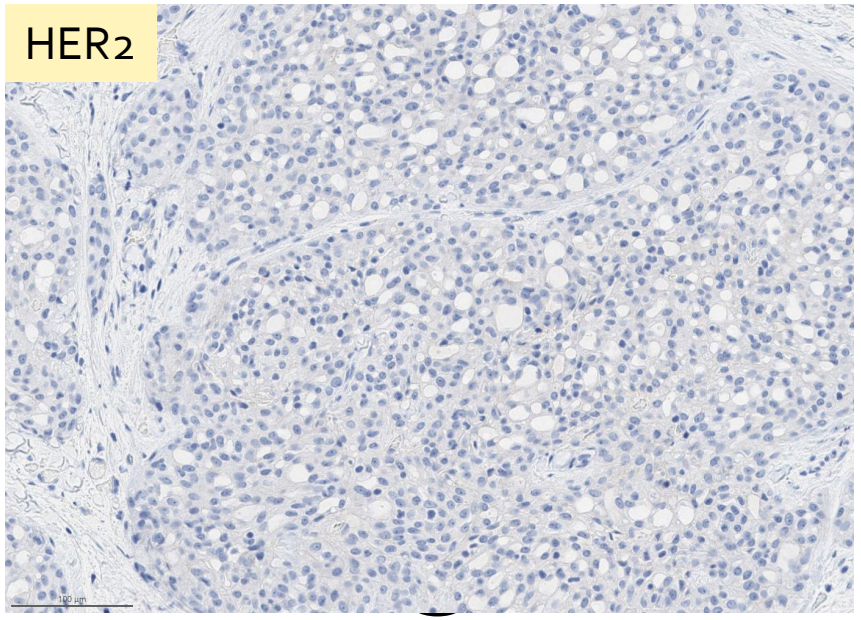
# Secretory carcinoma: triple negative or low ER+

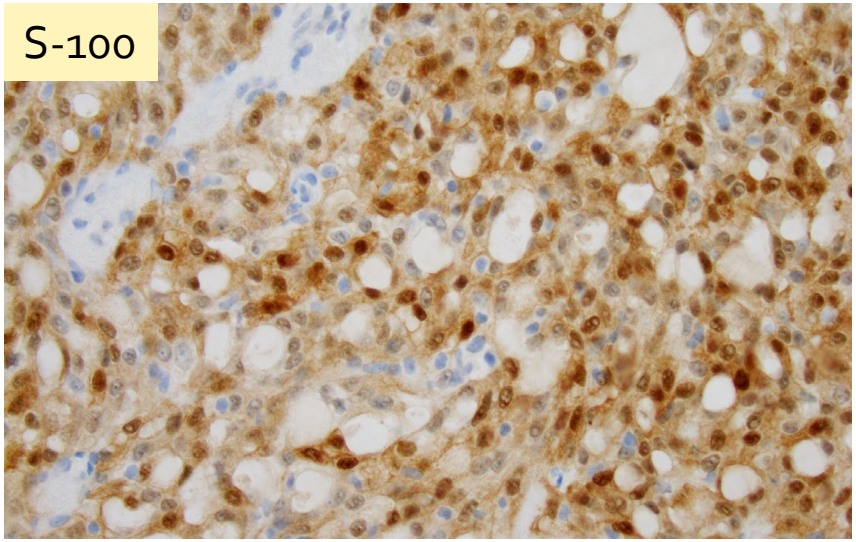




# Secretory carcinoma: immunohistochemical profile




- S-100 (+)
- Mammaglobin (+)
- SOX-10 (+)
- GATA3 (+/-)
- CK5/6 (+)
- EGFR (+)
- Pan-Trk (+)

# Cytogenetics

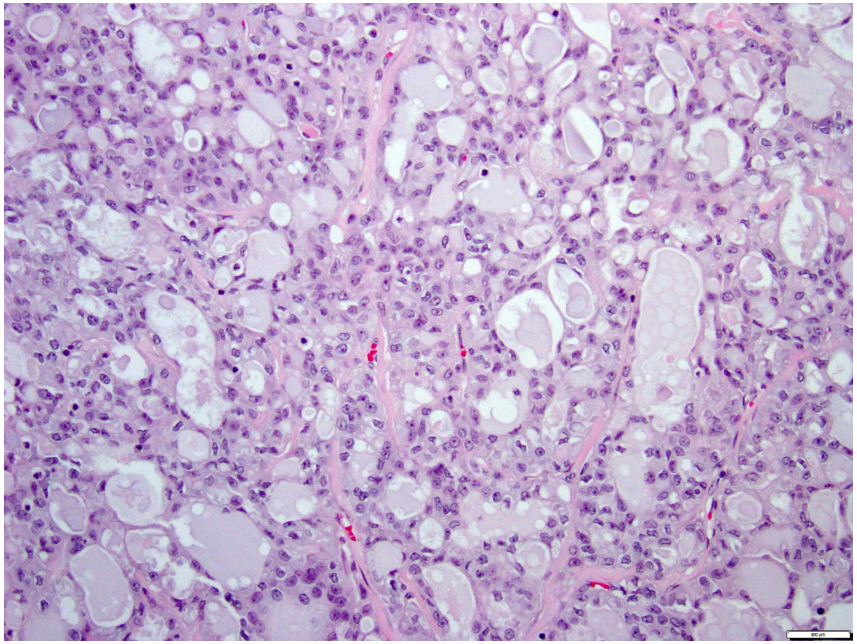
- t(12::15) creates *ETV6-NTRK3* fusion

- A very low mutation burden
- No additional pathogenic mutations

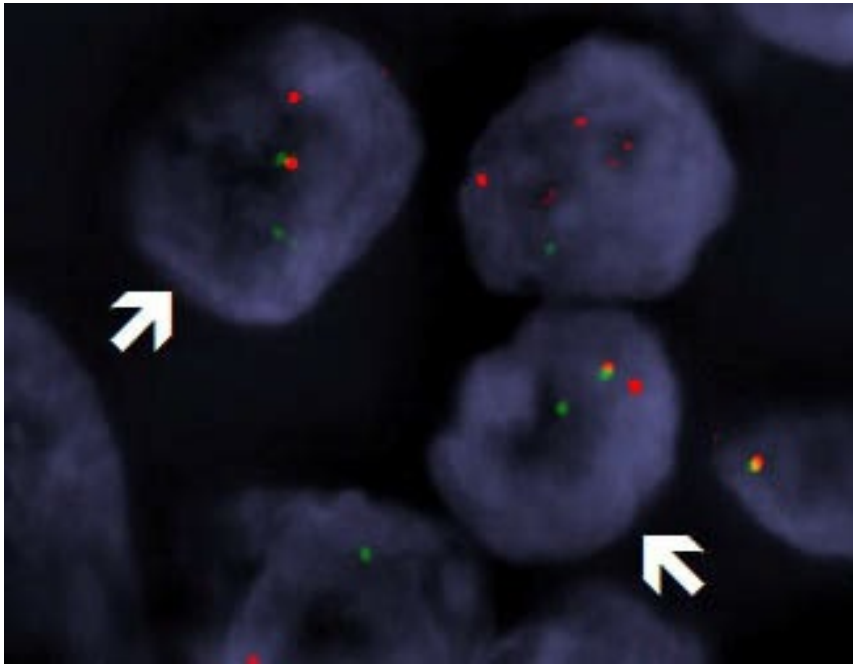
Tognon C et al. Cancer Cell 2002; 2:367-376
Krings G et al. Mod Pathol. 2017;30:1086-1099

# t(12::15) translocation >> *ETV6-NTRK3* gene fusion

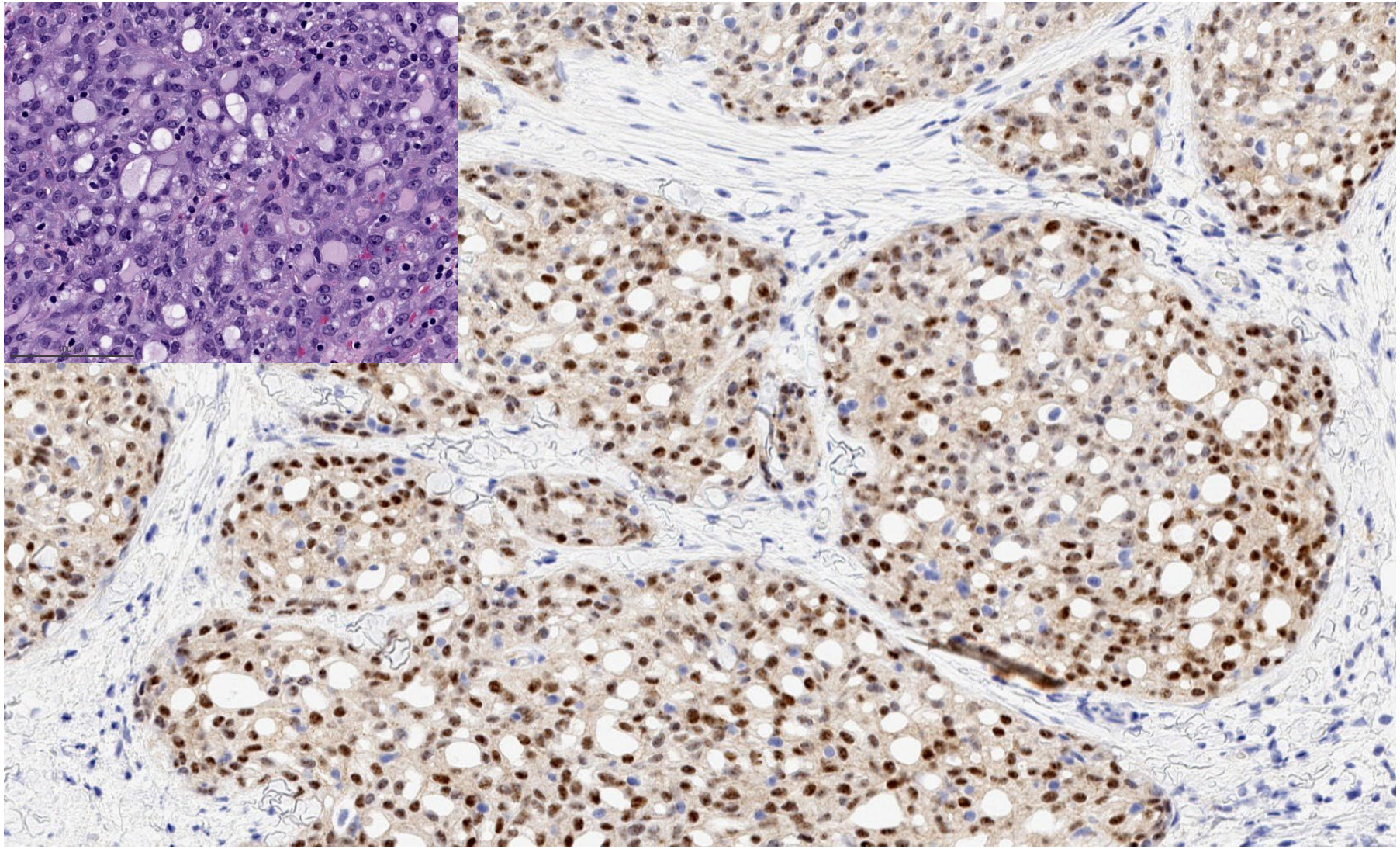
**H&E**



**FISH (*ETV6* break apart probe)**



# Immunohistochemistry for pan-Trk



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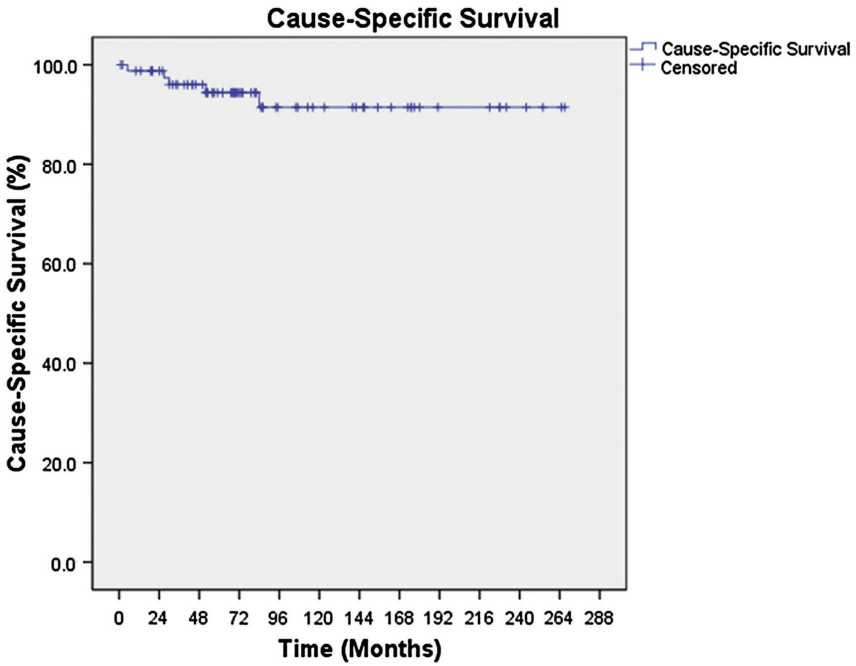
Original article

# Secretory carcinoma of the breast: Results from the survival, epidemiology and end results database

David P. Horowitz*, Charu S. Sharma, Eileen Connolly, Daniela Gidea-Addeo, Israel Deutsch




- The SEER database: 83 patients with secretory carcinoma of the breast 1983-2007
- Median follow-up 70 months
- 10-year cause specific survival was 91.4%.

Horowitz DP. et al. *Breast* 2012; 21-350-353

# *NTRK3* fusion is an actionable target

- *TRK* fusions defined a unique molecular subgroup of solid tumors in children and adults in whom Larotrectinib, a selective TRK inhibitor, is highly effective

**Table 2. Overall Response Rate, According to Investigator and Central Assessment.***

| Response | Investigator Assessment (N=55) | Central Assessment (N=55) |
|---|---|---|
| | *percent* | |
| Overall response rate (95% CI)† | 80 (67–90) | 75 (61–85) |
| Best response | | |
| Partial response | 64‡ | 62 |
| Complete response | 16 | 13 |
| Stable disease | 9 | 13 |
| Progressive disease | 11 | 9 |
| Could not be evaluated | 0 | 4 |

Drilon A. et al. *N Engl J Med* 2018; 378:731-739

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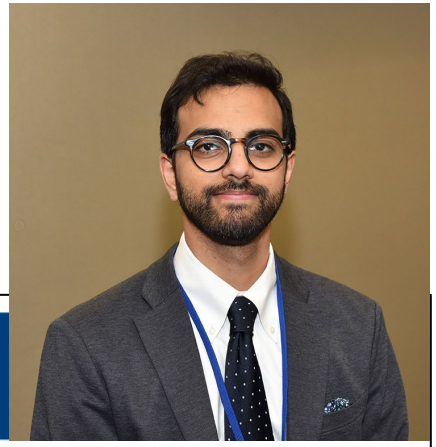


Histopathology

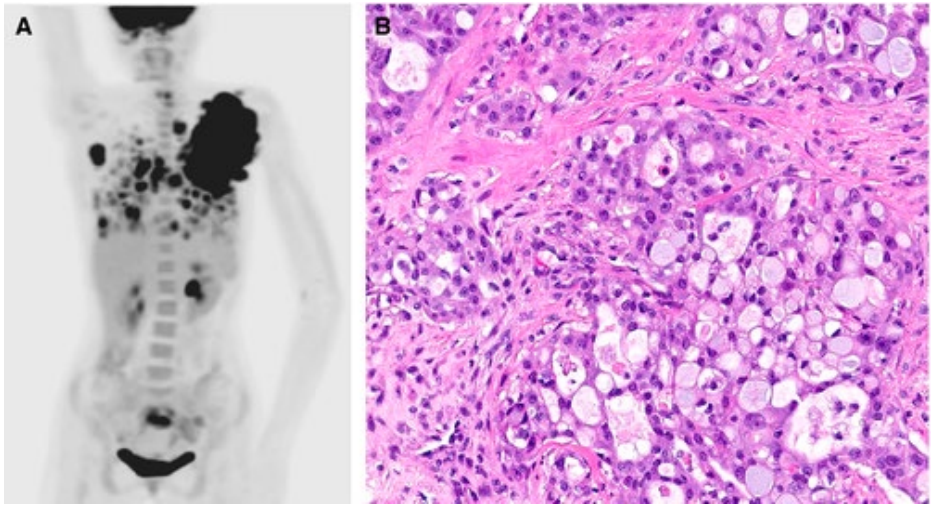
*Histopathology* 2019, **75**, 213–224. DOI: 10.1111/his.13879

# Secretory carcinoma of the breast: clinicopathologic profile of 14 cases emphasising distant metastatic potential

Raza S Hoda,[1] Edi Brogi,[2] Fresia Pareja,[2] Gouri Nanjangud,[3] Melissa P Murray,[2] Britta Weigelt,[2] Jorge S Reis-Filho[2] & Hannah Y Wen[2]

# Favorable prognosis. Distant metastasis is rare

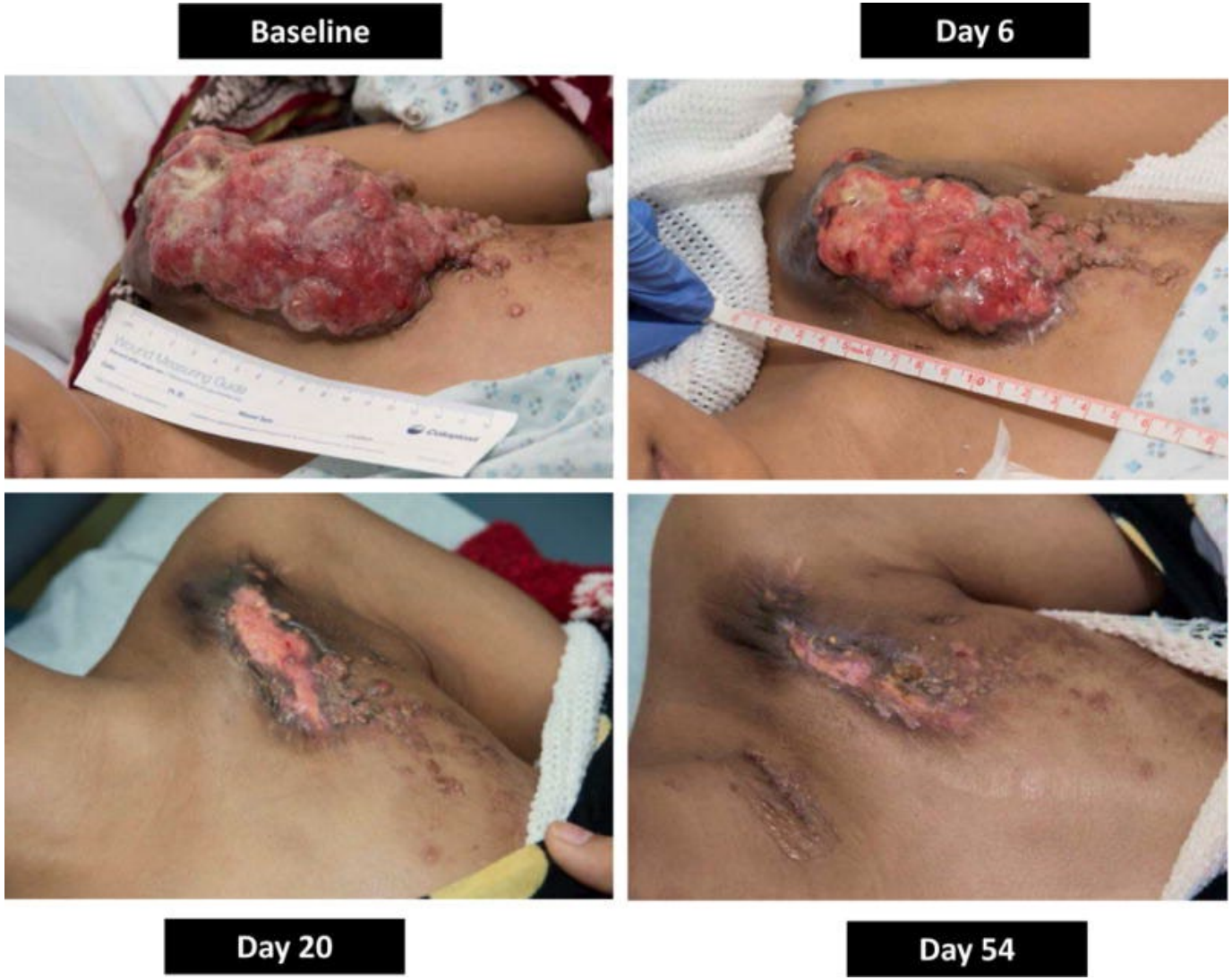
- 14-year-old girl, h/o secretory carcinoma, mastectomy and chemotherapy
- Presented with chest wall mass, distant metastasis to the lungs and bone




- Sequencing analysis of the chest wall recurrence:
  - *ETV6-NTRK3* fusion t(12::15)(p13.2;q25.3)
  - *TERT* promoter variant (g.1295228C>T)
- Treated with pan-Trk inhibitors: Larotrectinib (LOXO-101), Selitrectinib (LOXO-195)

Hoda RS et al. *Histopathology*. 2019; 75:213-224

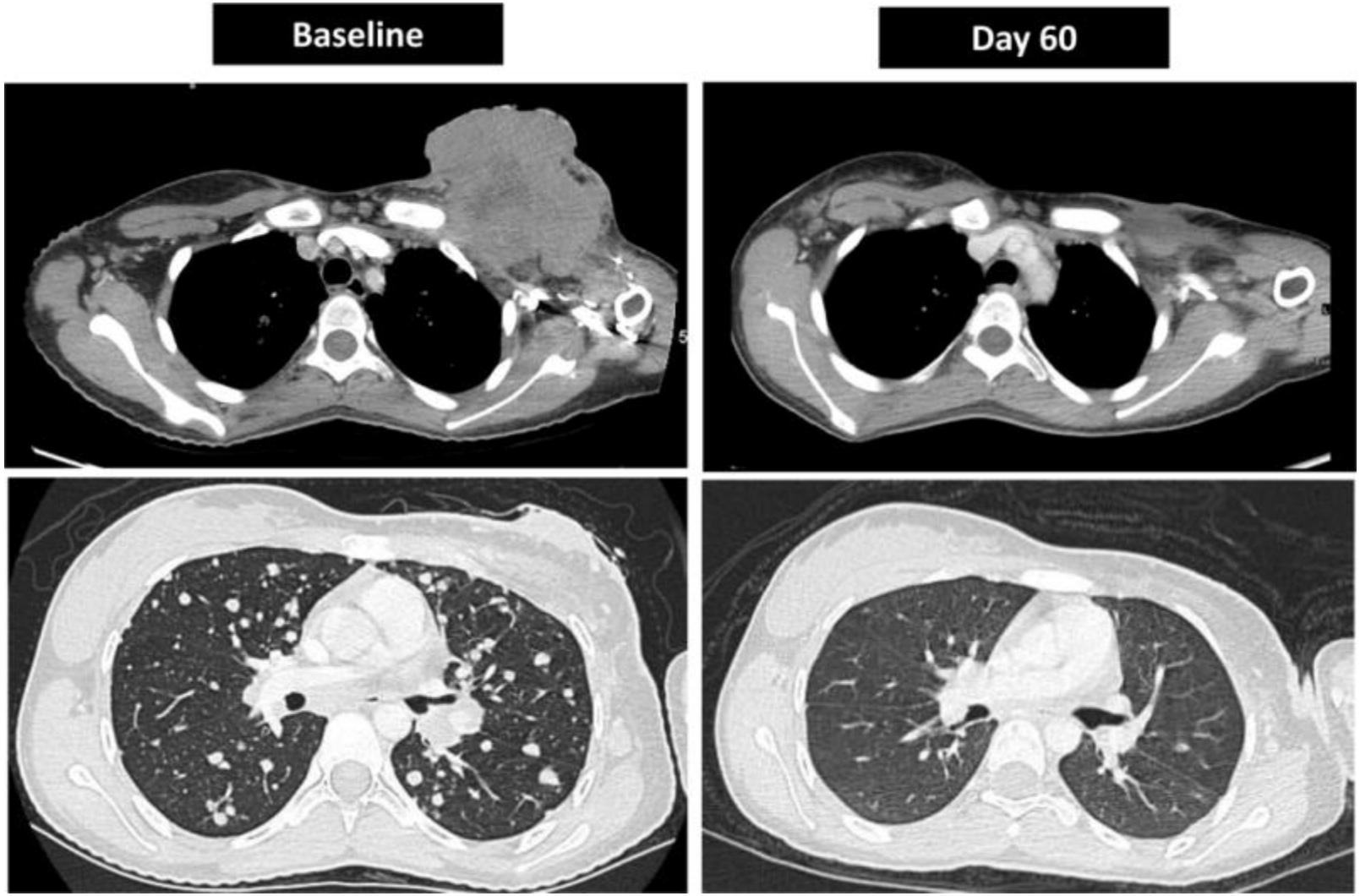
# Targeted therapy with larotrectinib (LOXO-101)




Shukla N et al. *JCO Precis Oncol*. 2017;2017

Memorial Sloan Kettering Cancer Center

# Targeted therapy with larotrectinib (LOXO-101)




Shukla N et al. *JCO Precis Oncol*. 2017;2017

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# Tall cell carcinoma with reverse polarity

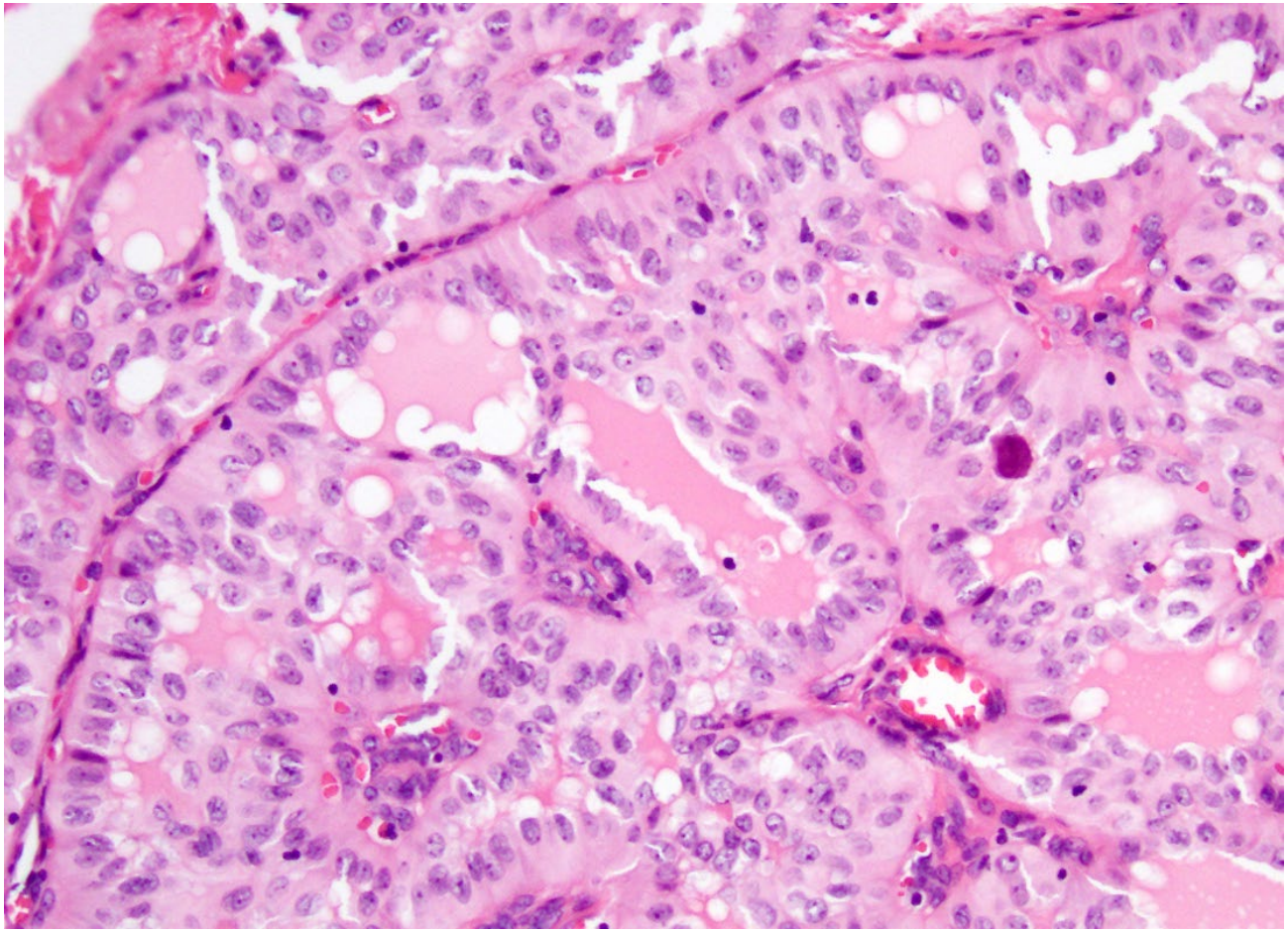
# Tall cell carcinoma with reverse polarity

- Related terminology:
  - Breast tumor resembling the tall cell variant of papillary thyroid carcinoma
  - Solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid carcinoma
  - Tall cell variant of papillary breast carcinoma
  - Solid papillary carcinomas with reverse polarity
- Median age 64 years (45-80)
- Triple negative or low-ER positivity, AR-negative, CK5/6 (+)
- Indolent behavior

Eusebi V et al Am J Surg Pathol. 2003; Chiang S et al. Cancer Res. 2016
Foschini MP et al. Am J Surg Pathol 2017; Lozada JR et al. Histopathology. 2018

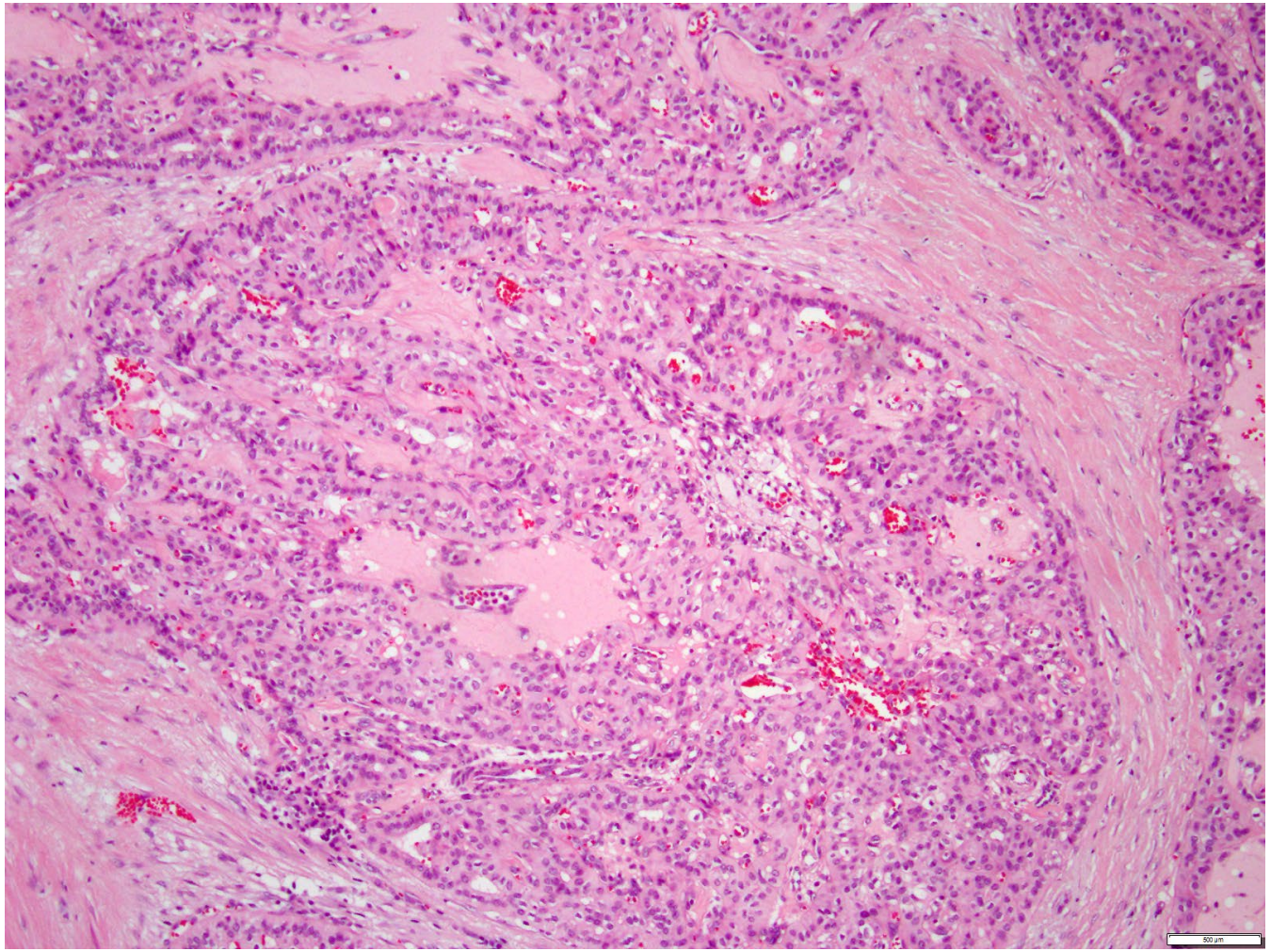
# Tall cell carcinoma with reverse polarity

- Tall columnar cells with reversed nuclear polarity: the nuclei are at the apical rather than the basal poles of the columnar epithelial cells



# Tall cell carcinoma with reverse polarity

- Solid and solid papillary patterns



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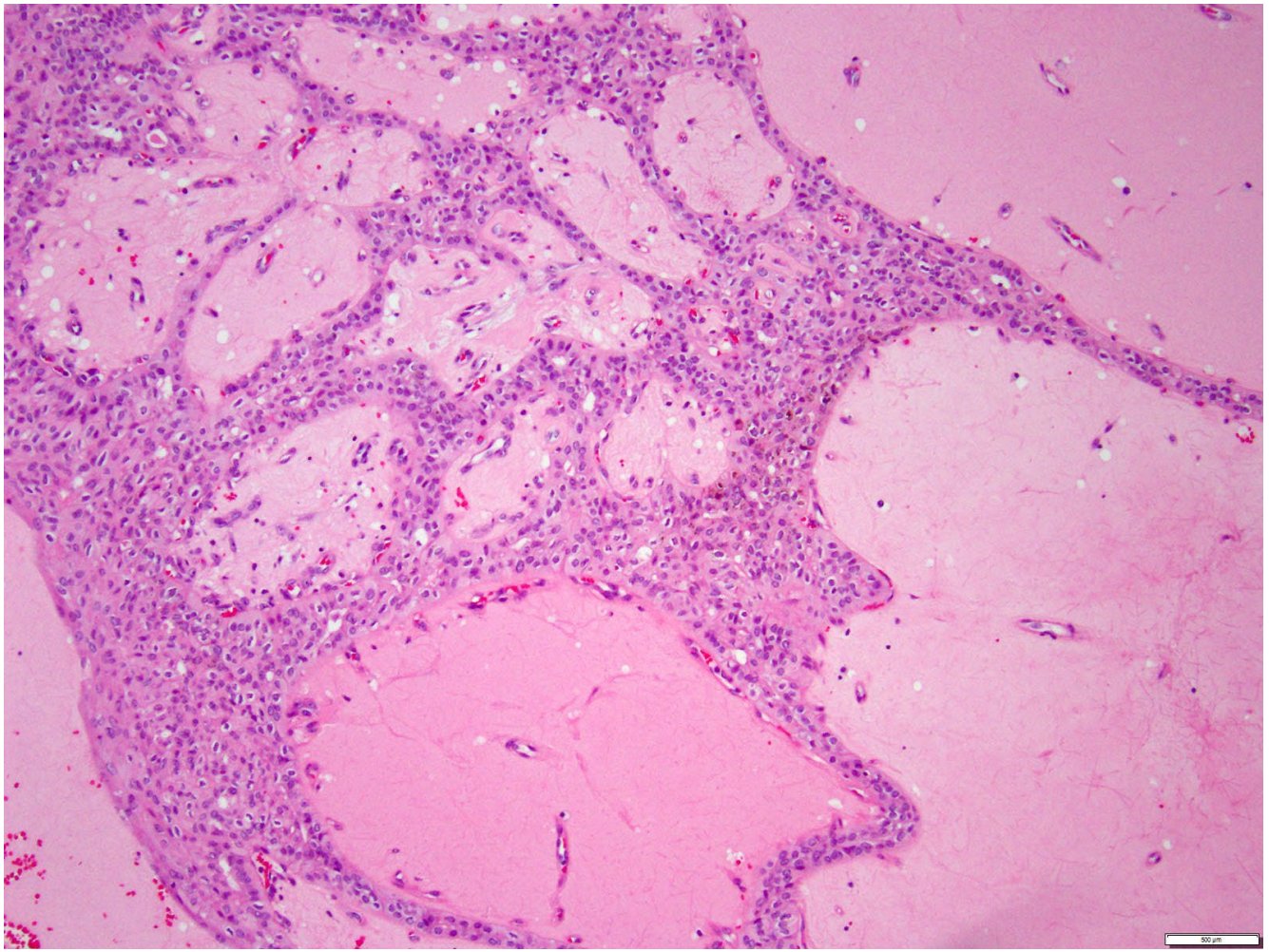
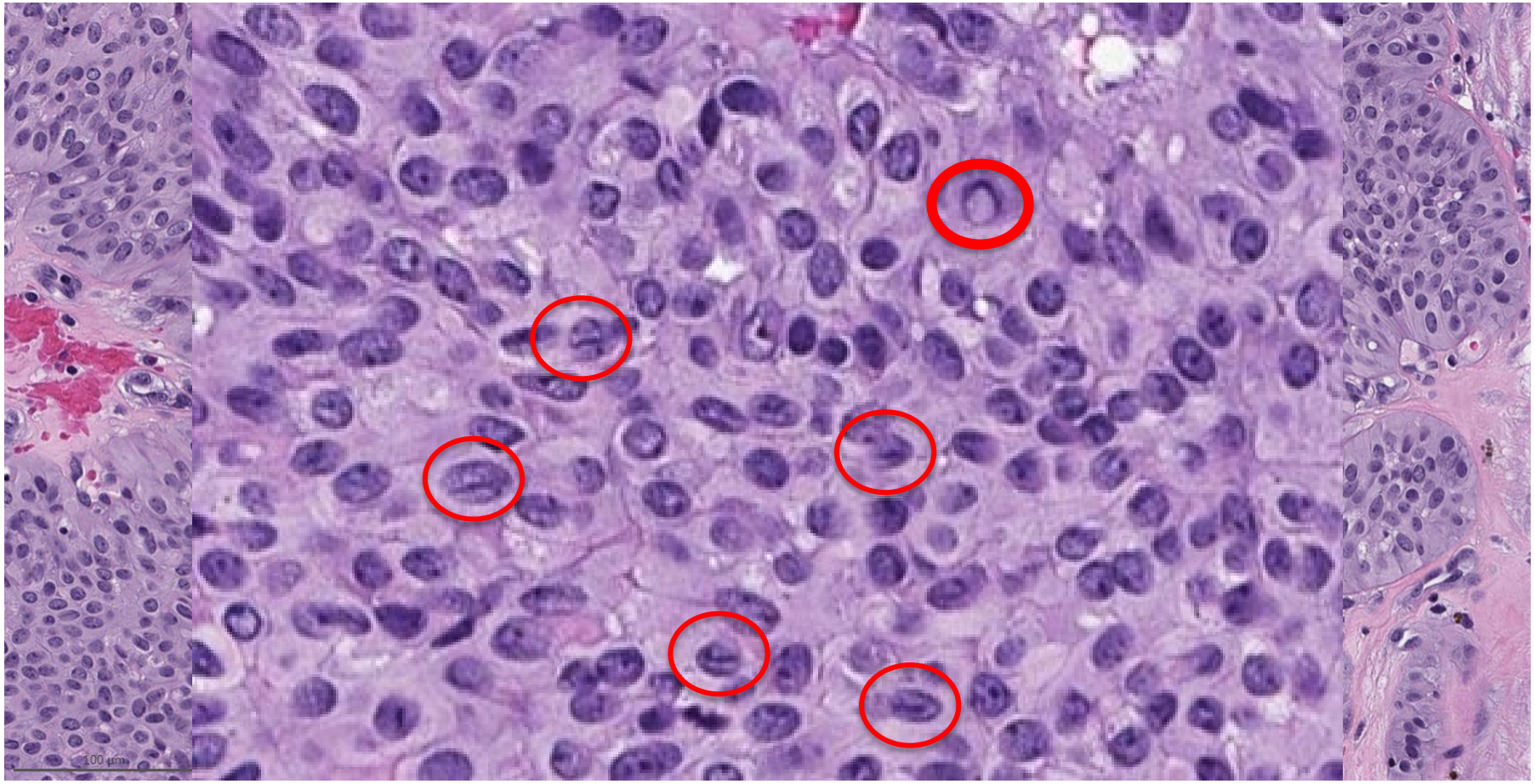
# Tall cell carcinoma with reverse polarity

- Colloid-like material can be observed



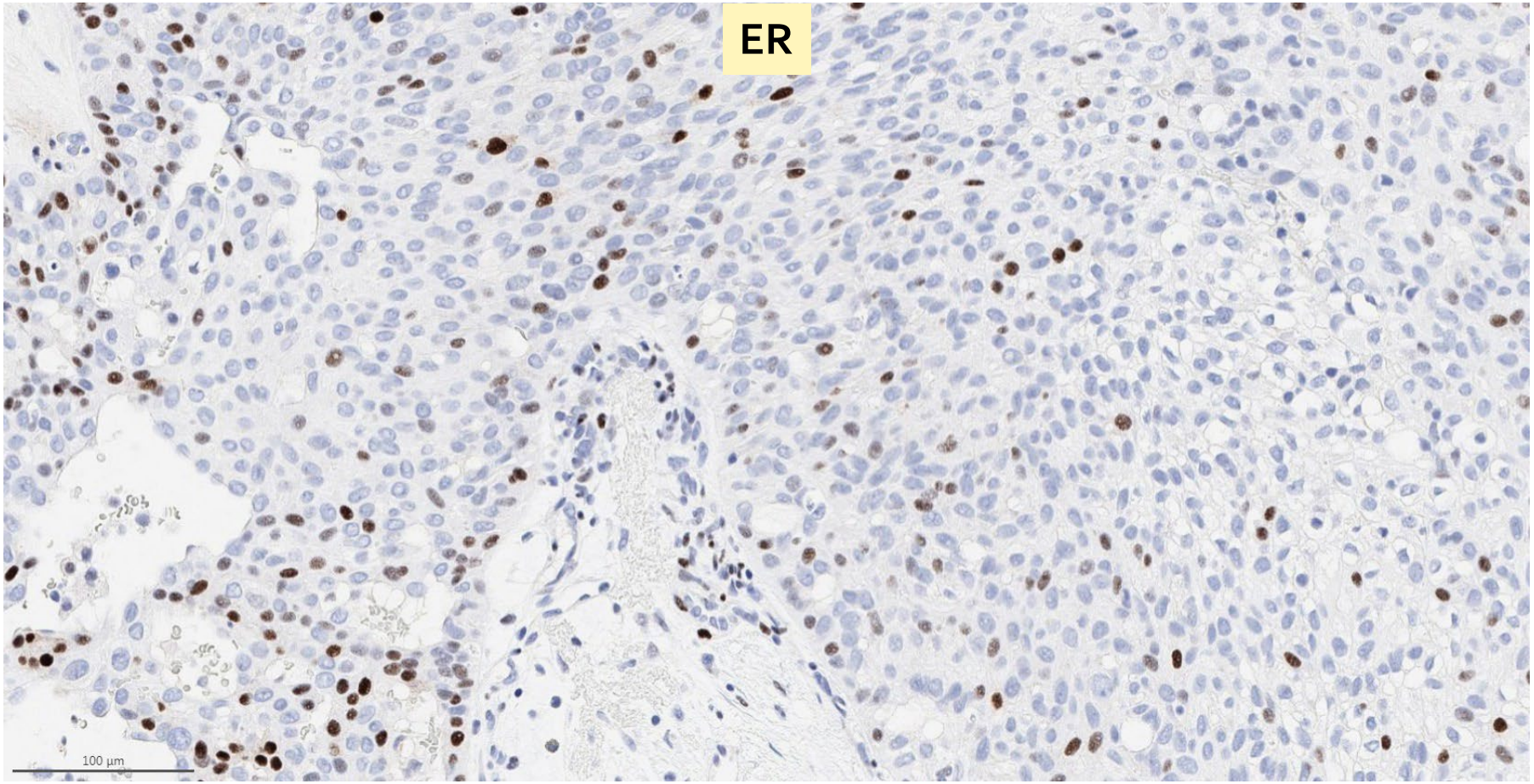
# Tall cell carcinoma with reverse polarity

- Nuclear grooves and inclusions



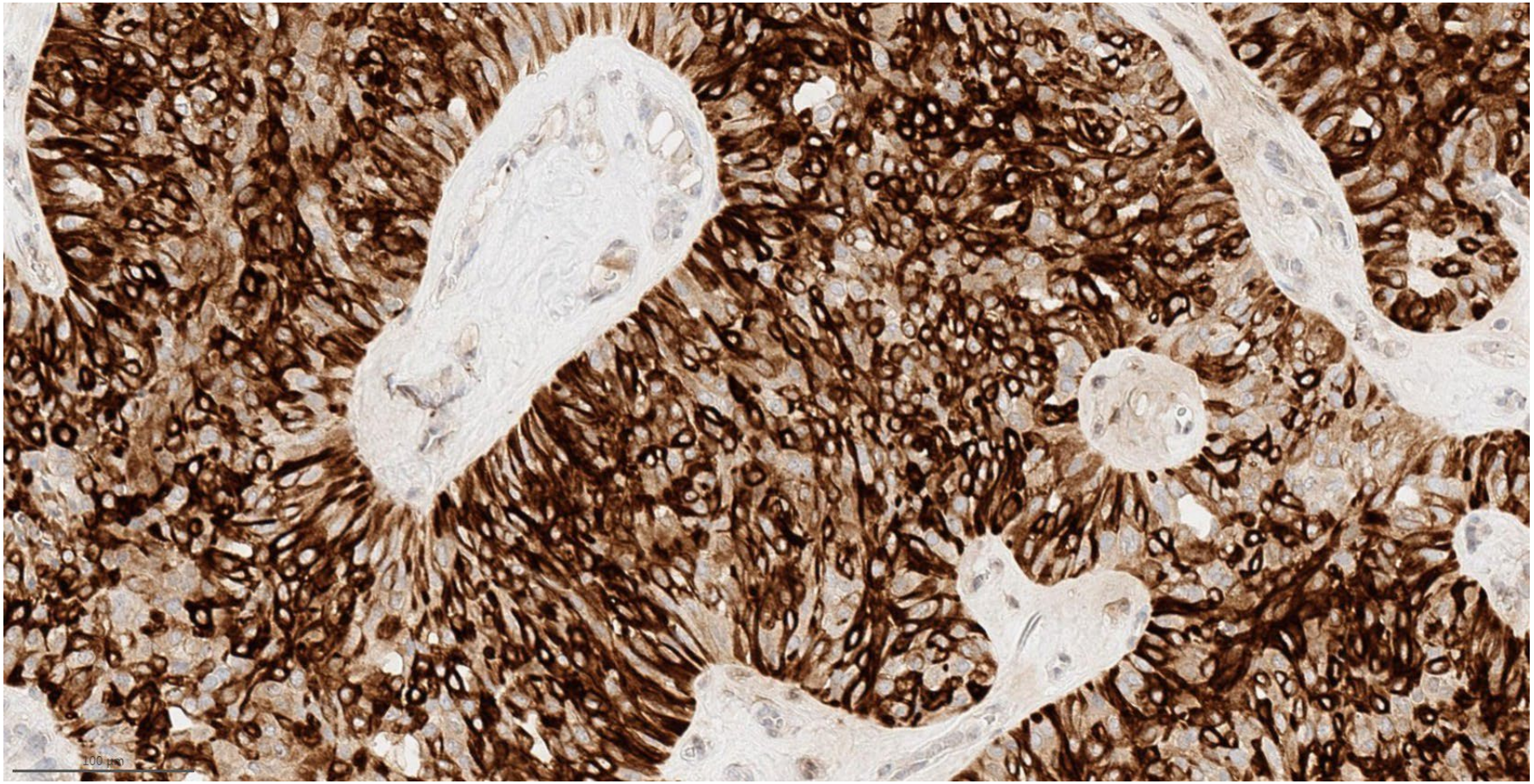
# Immunohistochemical stains

- Triple negative, or low ER/PR expression, TTF-1 negative

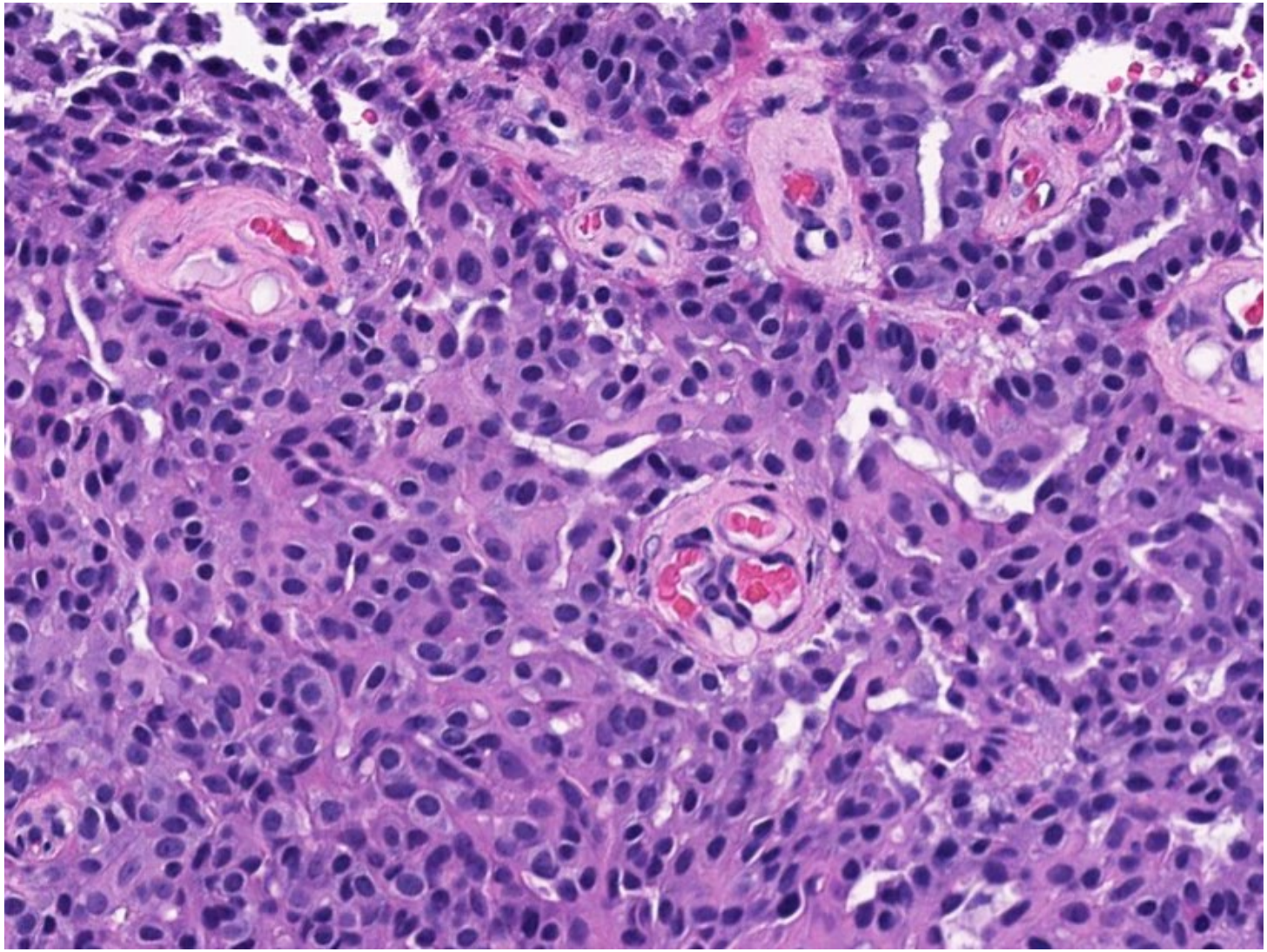


# Immunohistochemical stains

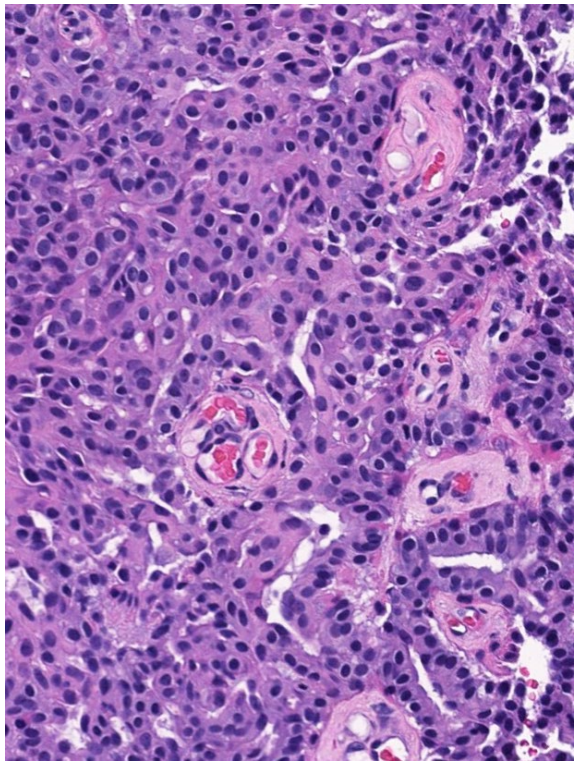
- Express basal cytokeratin CK5/6

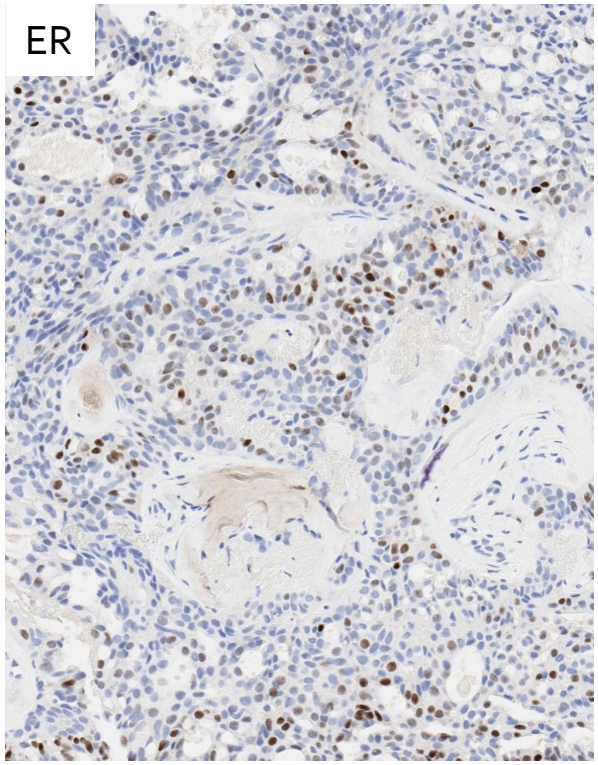


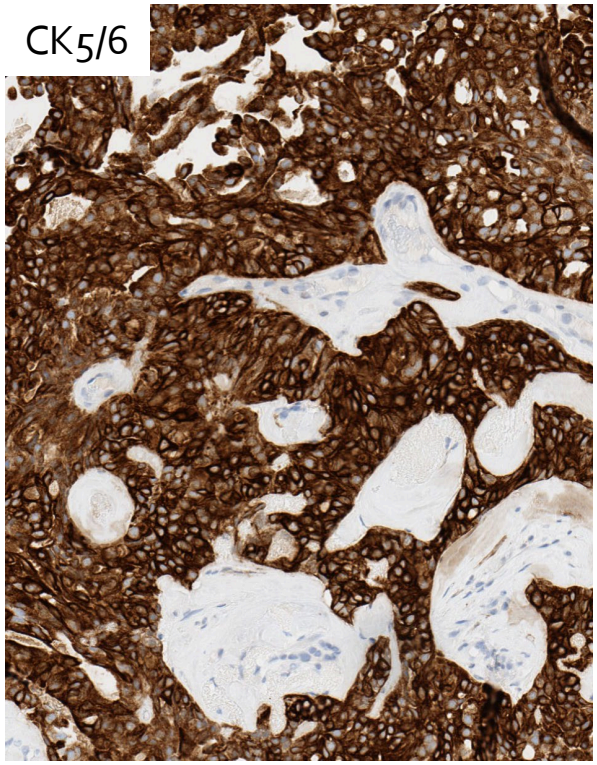
# Differential diagnosis: intraductal papilloma



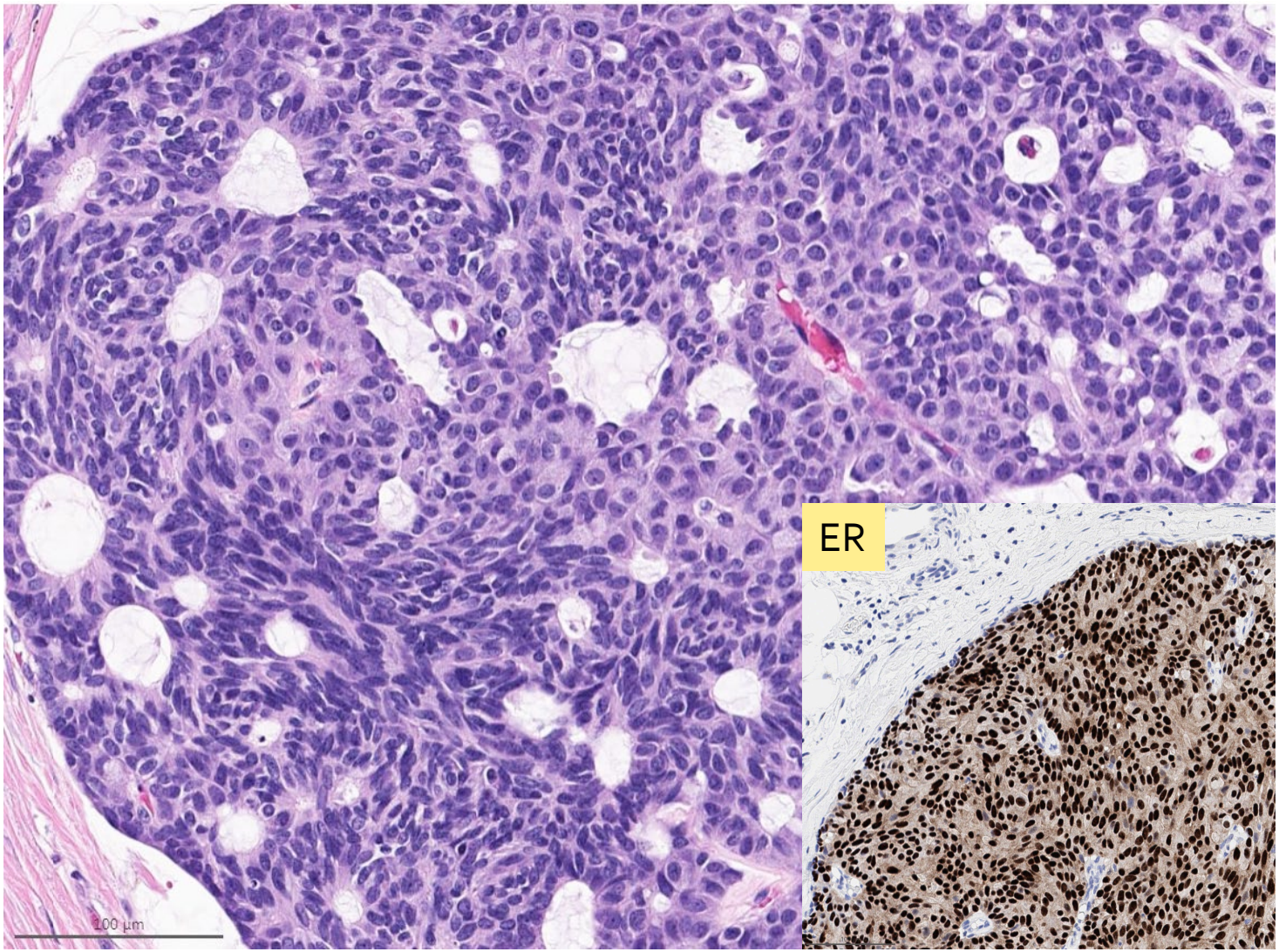
# Intraductal papilloma: no tall columnar cells, no reverse polarity





# Differential diagnosis: solid-papillary carcinoma

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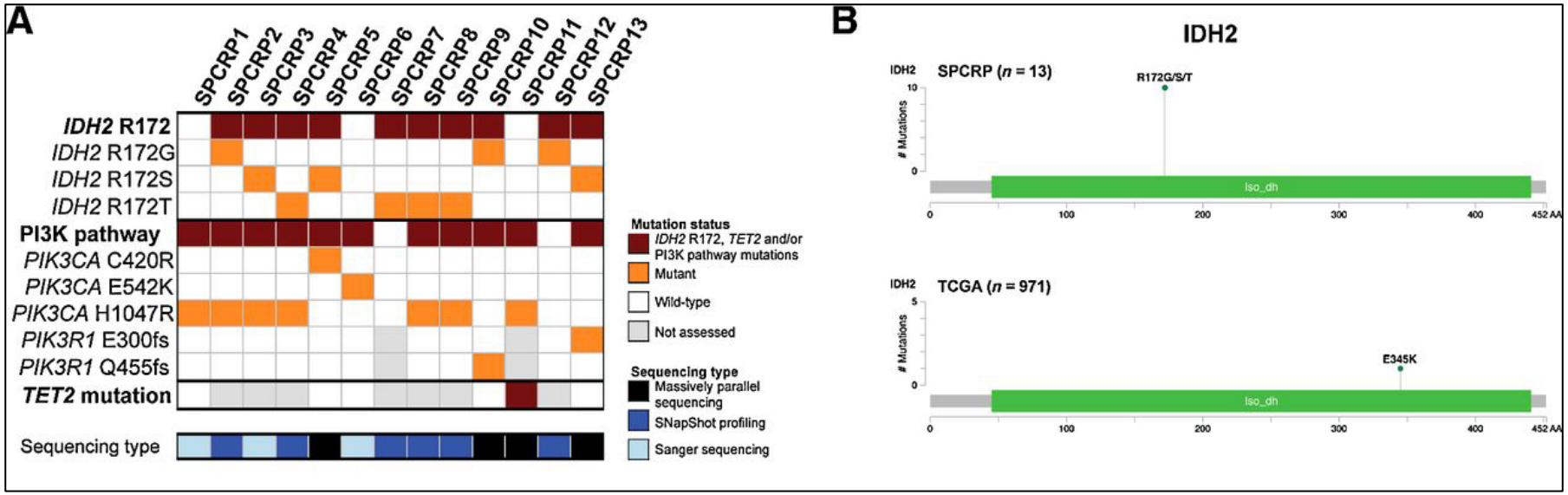
# Tall cell carcinoma with reverse polarity

- *IDH2* and PI3K pathway mutations
  - *IDH2* mutations at hotspot R172: 10 of 13 (77%) cases
  - 8 of 10 with *IDH2* mutations had concurrent pathogenic mutations of *PIK3CA* or *PIK3R1*




Chiang S et al. *Cancer Res*. 2016;76:7118-7129.

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Modern Pathology (2020) 33:1056–1064
https://doi.org/10.1038/s41379-019-0442-2

ARTICLE

# Immunohistochemical analysis of *IDH2* R172 hotspot mutations in breast papillary neoplasms: applications in the diagnosis of tall cell carcinoma with reverse polarity

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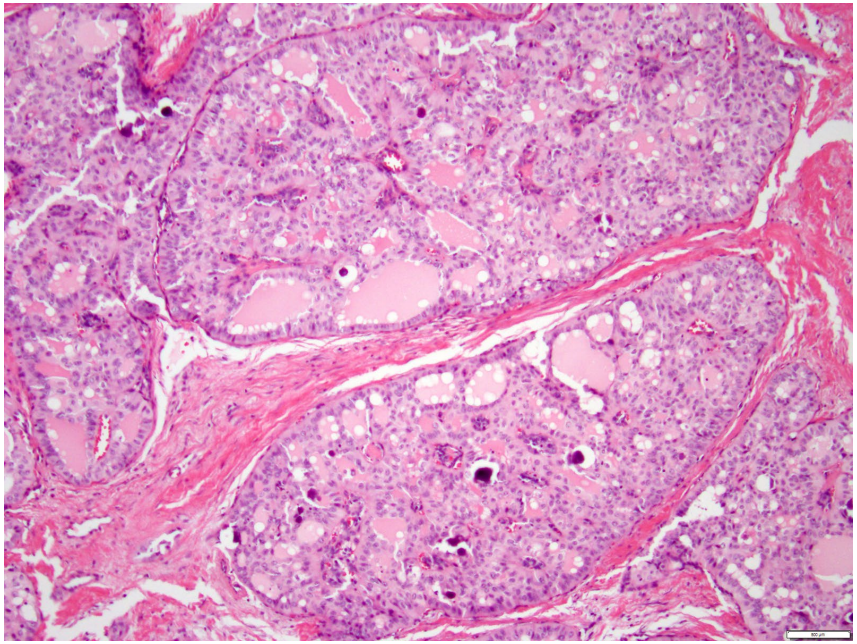
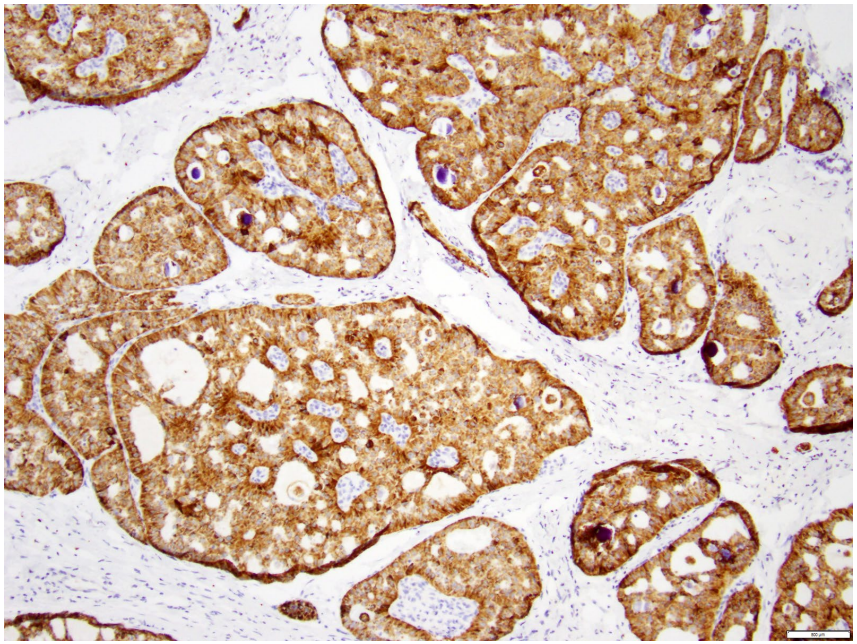
Pareja F et al. Mod Pathol. 2020; 33:1056-1064.

# Immunohistochemistry for *IDH2* R172 mutation

| H&E | IDH2 R172S |
| --- | --- |





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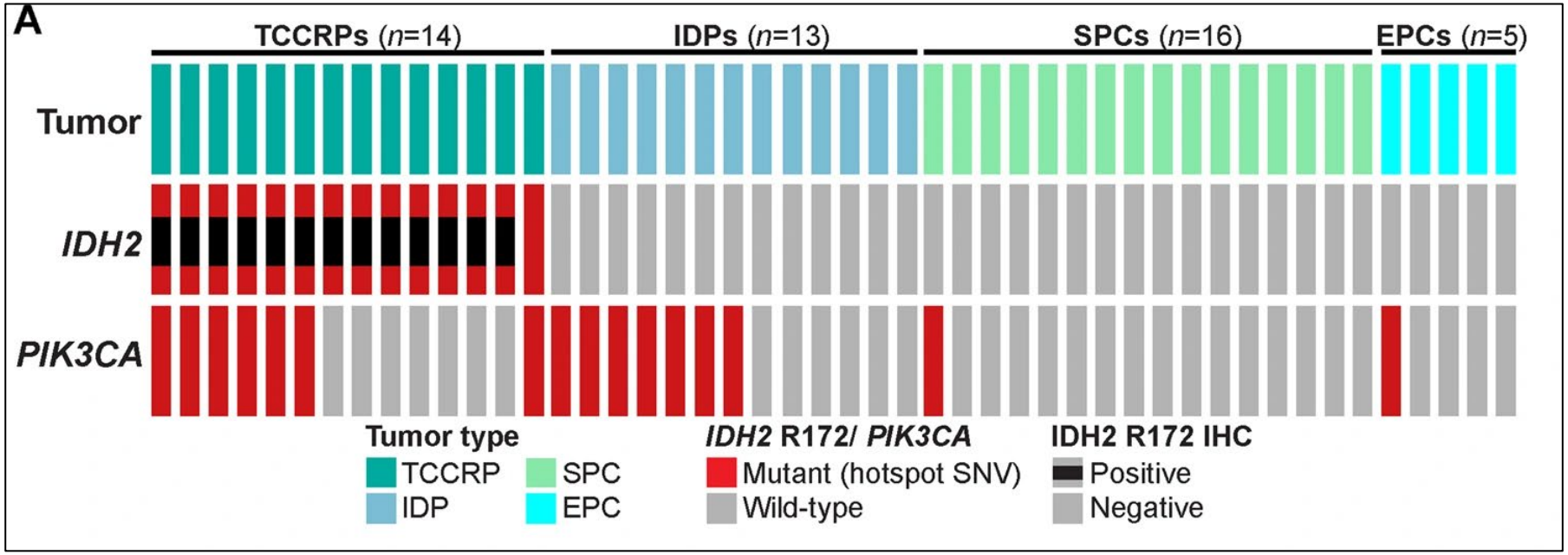
# Immunohistochemical analysis of *IDH2* R172 hotspot mutations

- *IDH2* R172 mutations are unique, not found in other breast cancer subtypes or other papillary lesions




Pareja F et al. Mod Pathol. 2020; 33:1056-1064.

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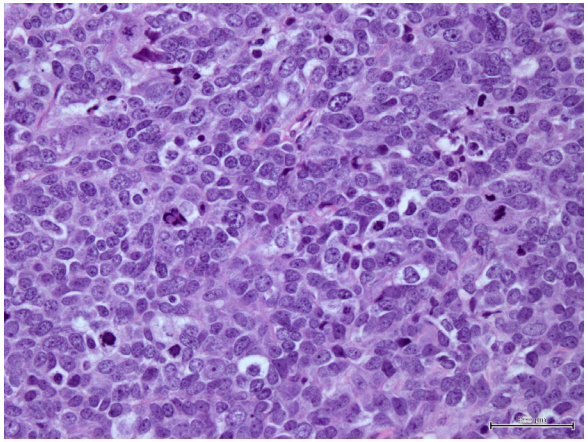
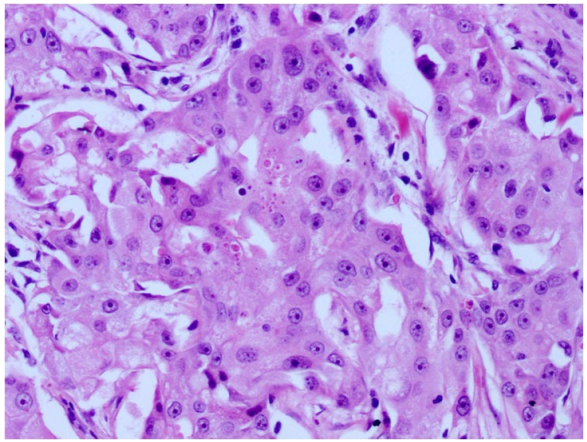
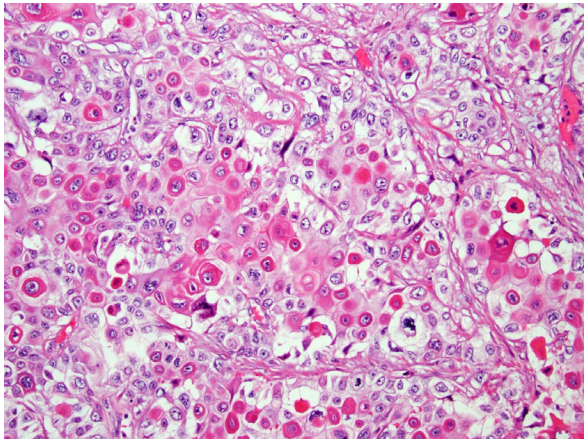
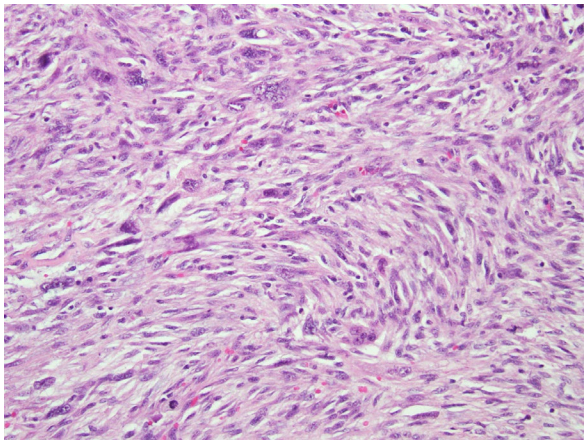
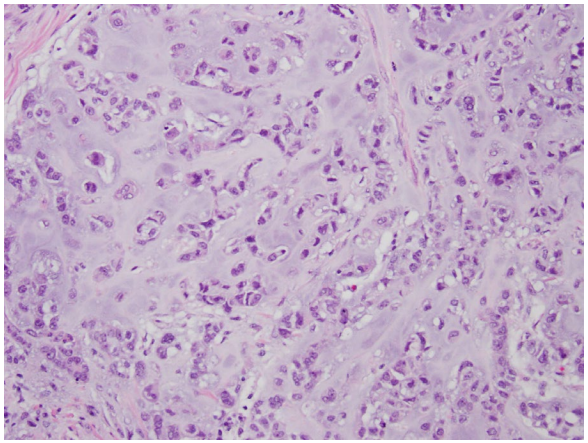
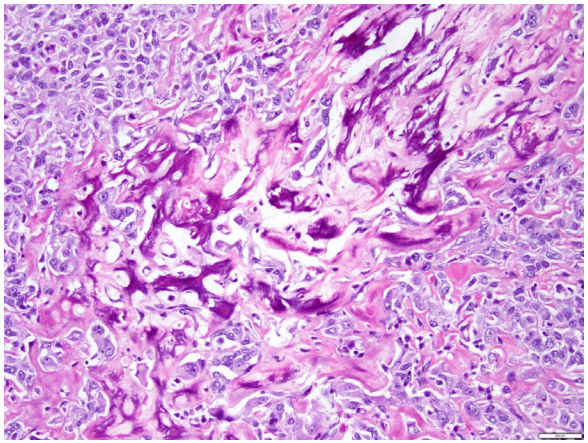
# Summary

# Summary: TNBC is a heterogenous group

- High grade histologic types

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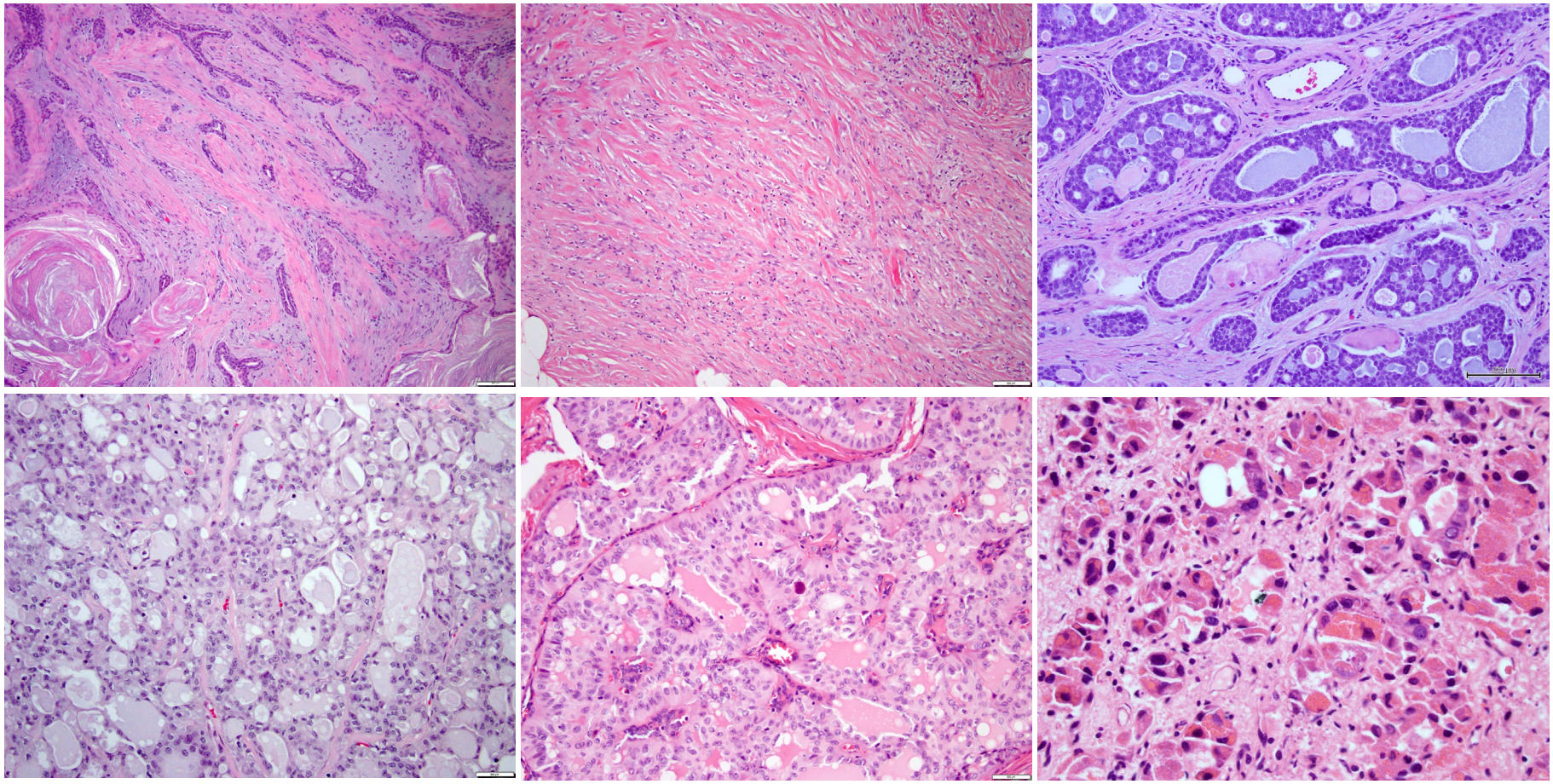
# Summary: TNBC is a heterogenous group

- Low grade special histologic subtypes with indolent clinical course



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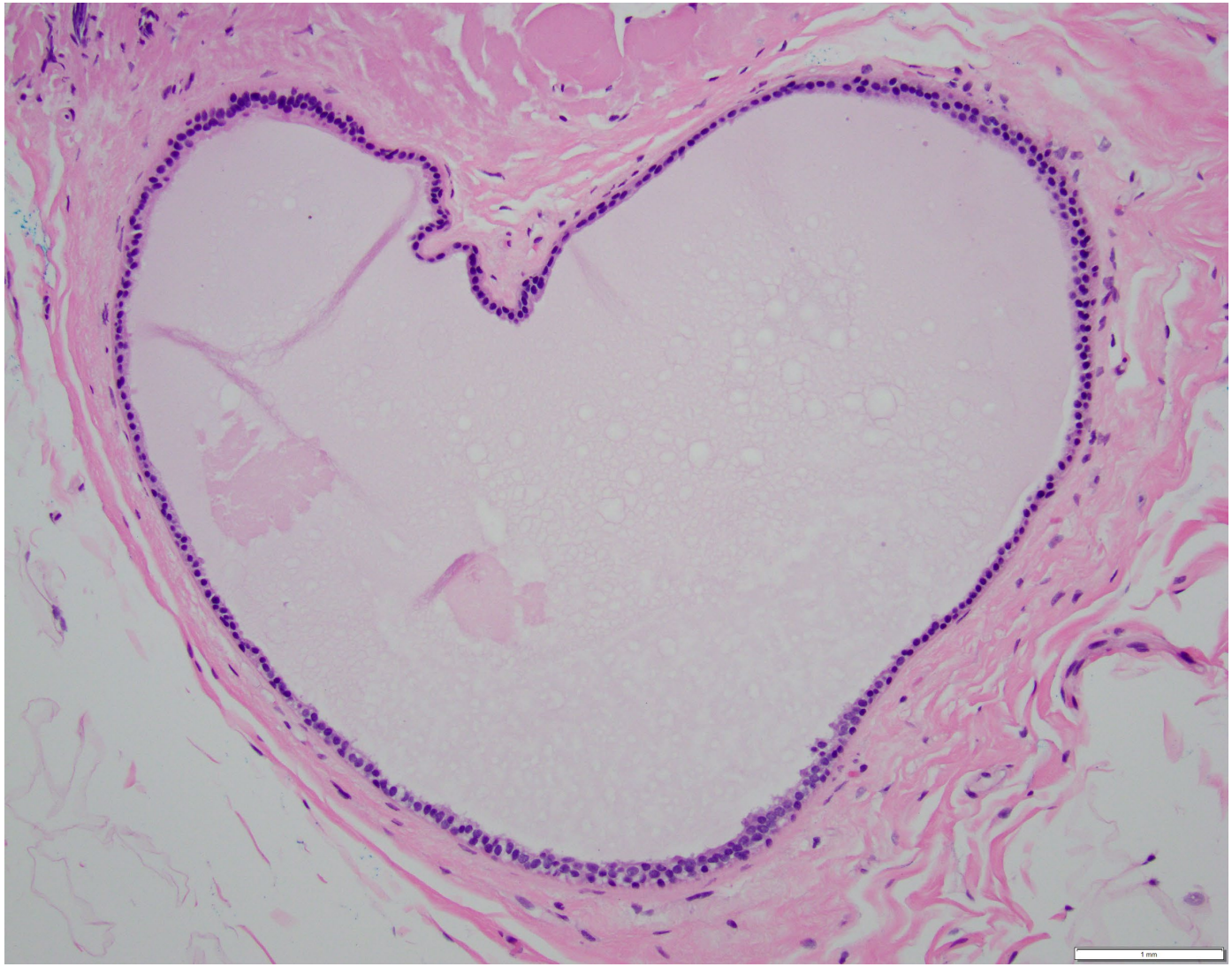
# Thank you



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