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Low Grade Triple Negative Breast Tumours

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Translational Medical Sciences, University of Nottingham

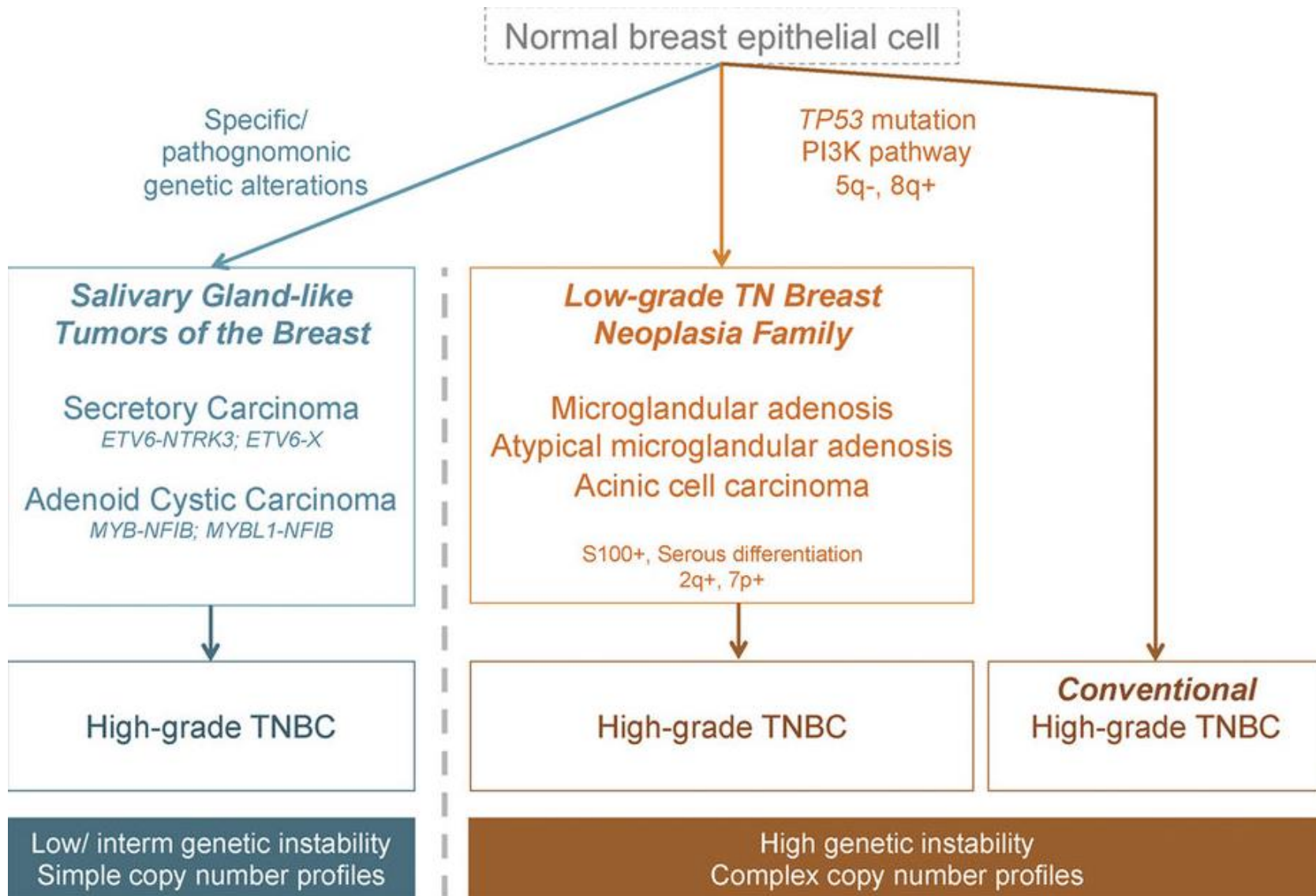
Department of Histopathology, Nottingham University Hospitals NHS Trust

WHO 2019

Rare Breast and Salivary Cancers

- Acinic Cell
- Adenoid Cystic
- Secretory
- Mucoepidermoid
- Polymorphous adenocarcinoma
- Tall cell carcinoma with reversed polarity

Triple Negative Breast Cancer



Low Grade TN BC

1. Salivary gland-like tumors of the breast
2. Low-grade TN breast neoplasia family
3. Rare additional subtypes of uncertain nature

Low Grade TN BC

1. Salivary gland-like tumors of the breast

Adenoid cystic carcinoma (AdCC)

MYB-NFIB fusion gene

Secretory

ETV6-NTRK3 fusion-gene

Vare rare subtypes:

Polymorphous carcinoma

Mucoepidermoid carcinoma

Adenomyoepithelioma

Low Grade TN BC

2. Low-grade TN breast neoplasia family

Microglandular adenosis (MGA)

Atypical MGA (AMGA) and

Acinic cell carcinoma (ACC)

Low Grade TN BC

3. Rare Additional Types of uncertain nature

- Low-grade variants of Metaplastic Breast Cancer, incl infiltrative epitheliosis
- Tall cell carcinoma with reversed polarity (Solid papillary carcinoma with reversed polarity (SPCRP)). *IDH2 p.Arg172 mutations*

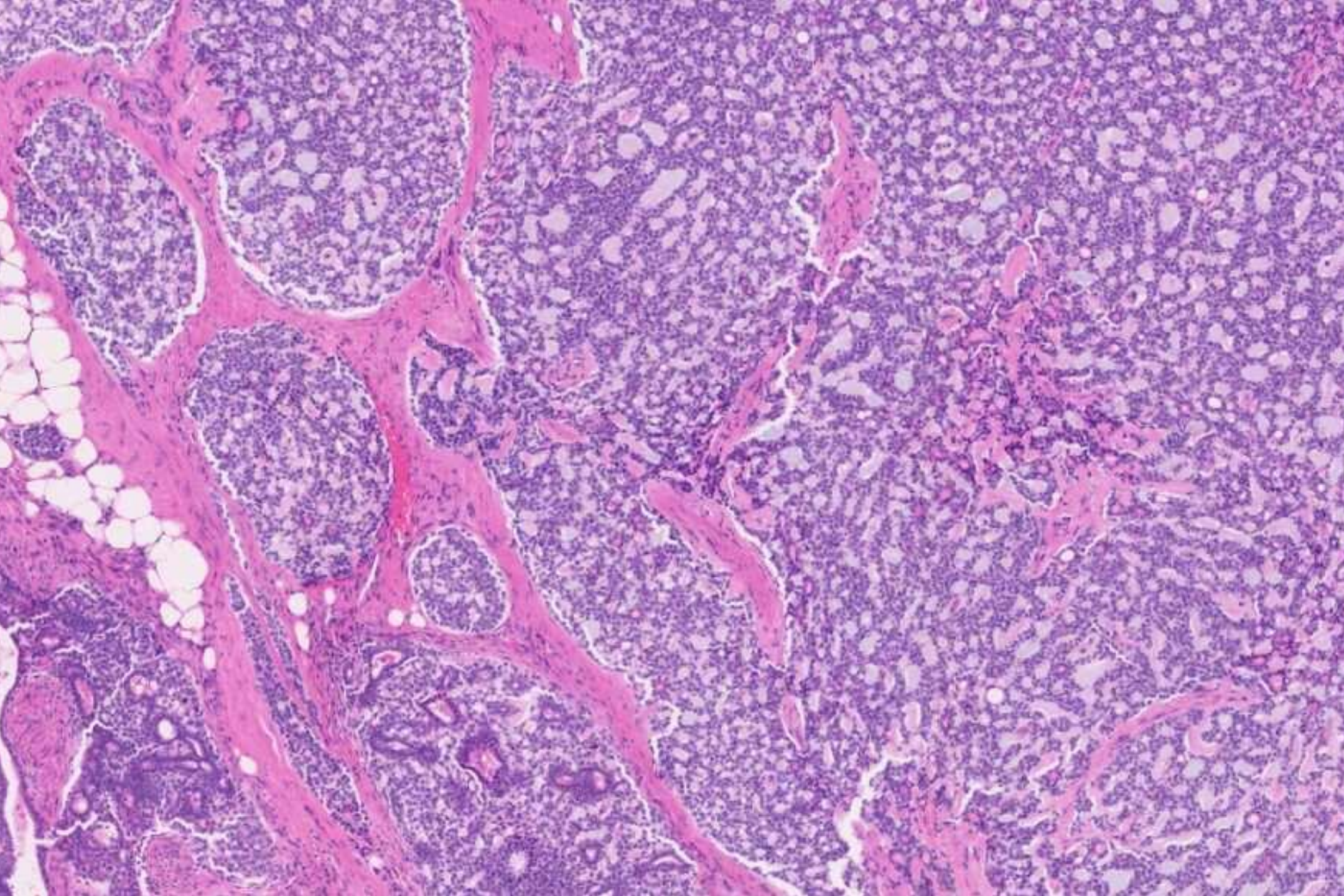
WHO 2019

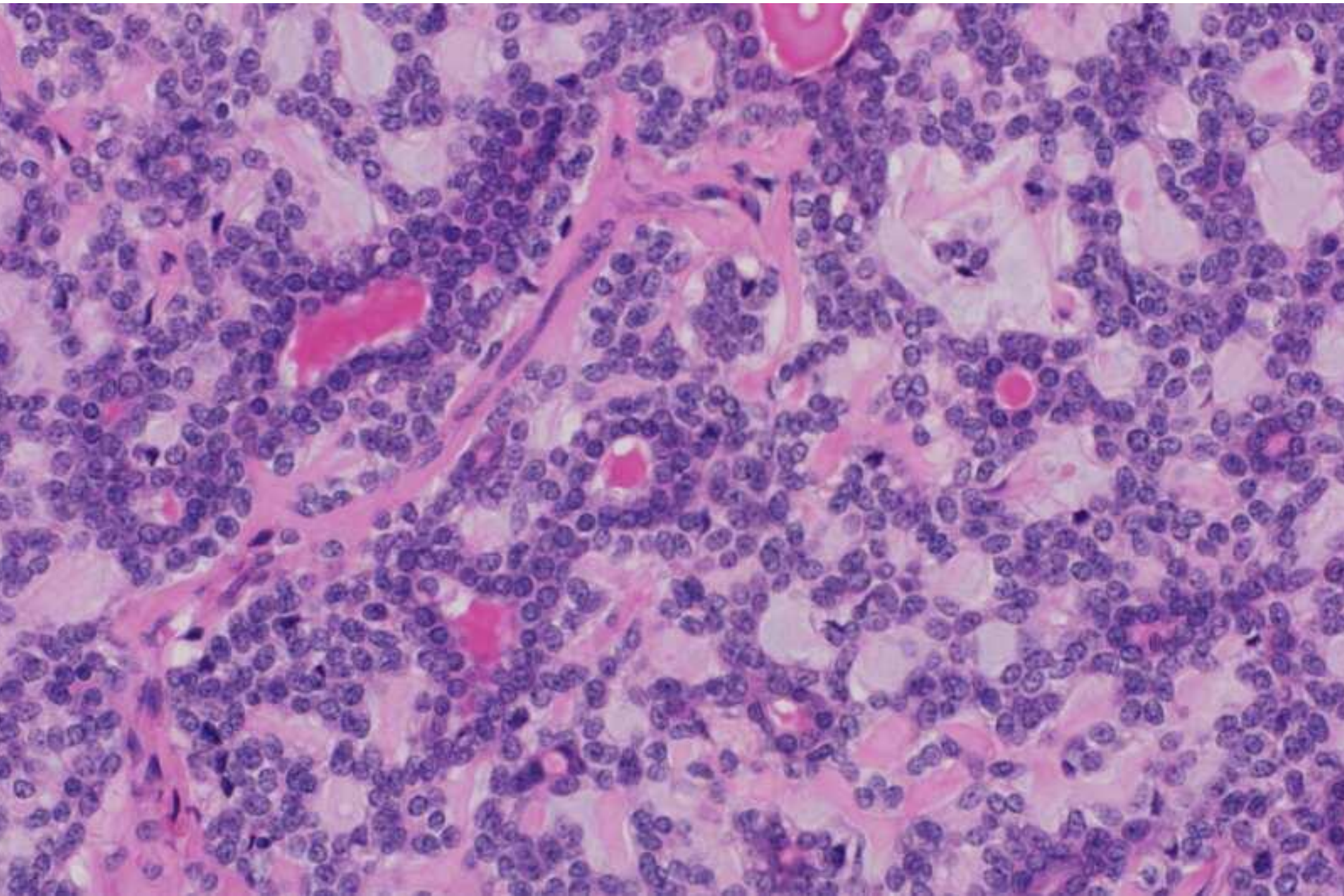
Adenoid cystic carcinoma

- Adenoid cystic carcinoma (AdCC) is an invasive carcinoma composed of epithelial and myoepithelial neoplastic cells arranged in tubular, cribriform, and solid patterns associated with basophilic matrix and reduplicated basement membrane material
- Frequently associated with MYB-NFIB fusion (similar to salivary counterpart)

Adenoid cystic carcinoma

- 0.1 – 1% of breast cancers
- Wide age range
- Mass lesion, often periareolar, may be painful
- Well defined
- Excellent long term prognosis ->90-100% 10 year survival (cf salivary gland tumours)

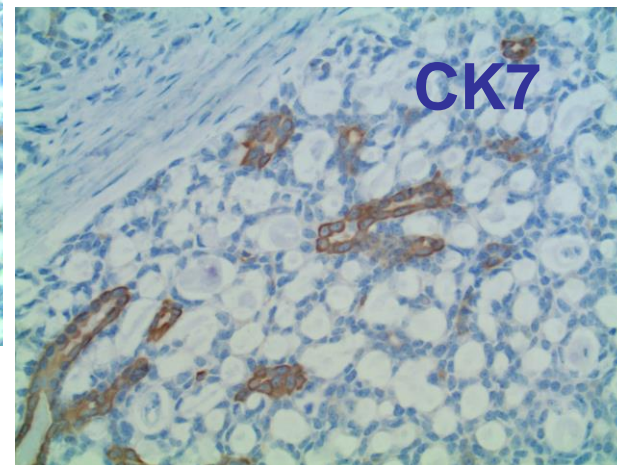
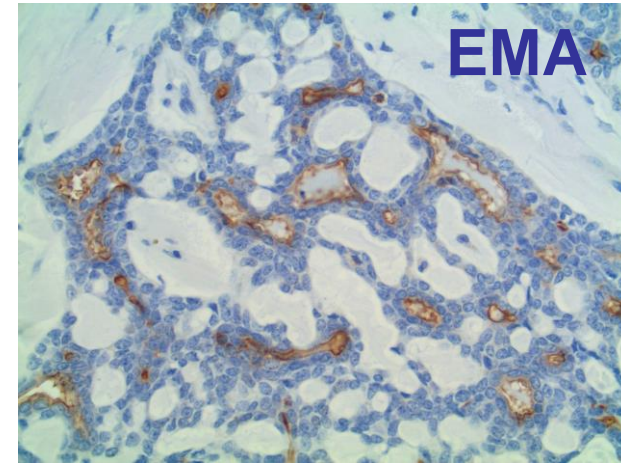
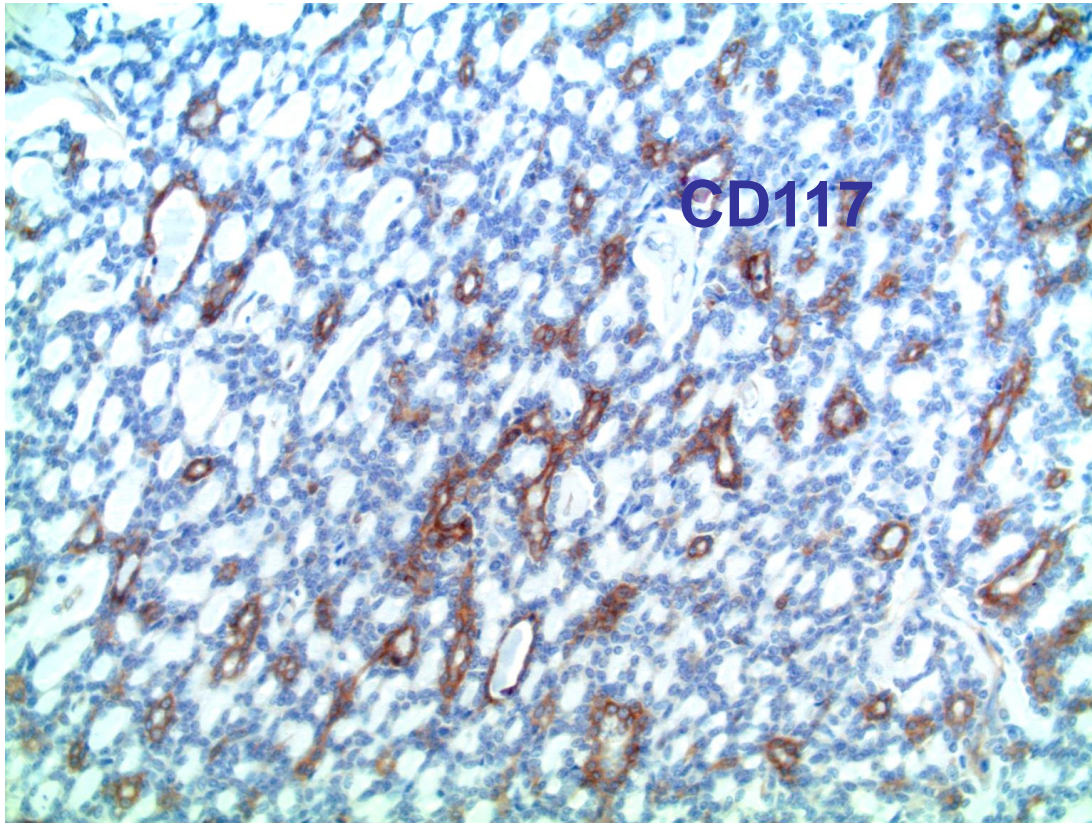




Epithelial cells



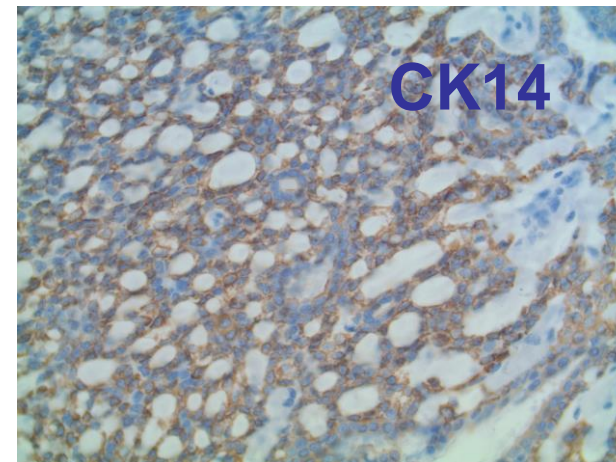
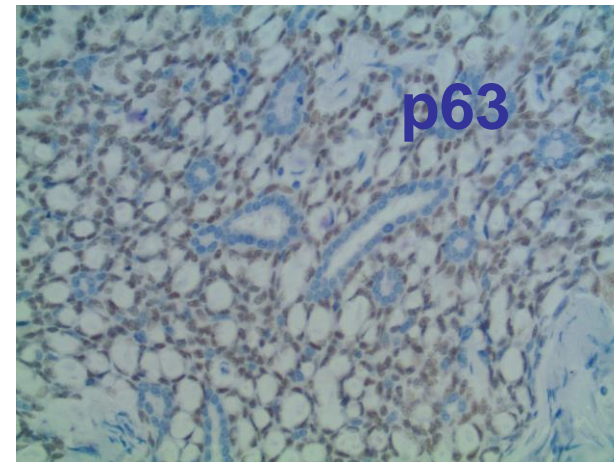
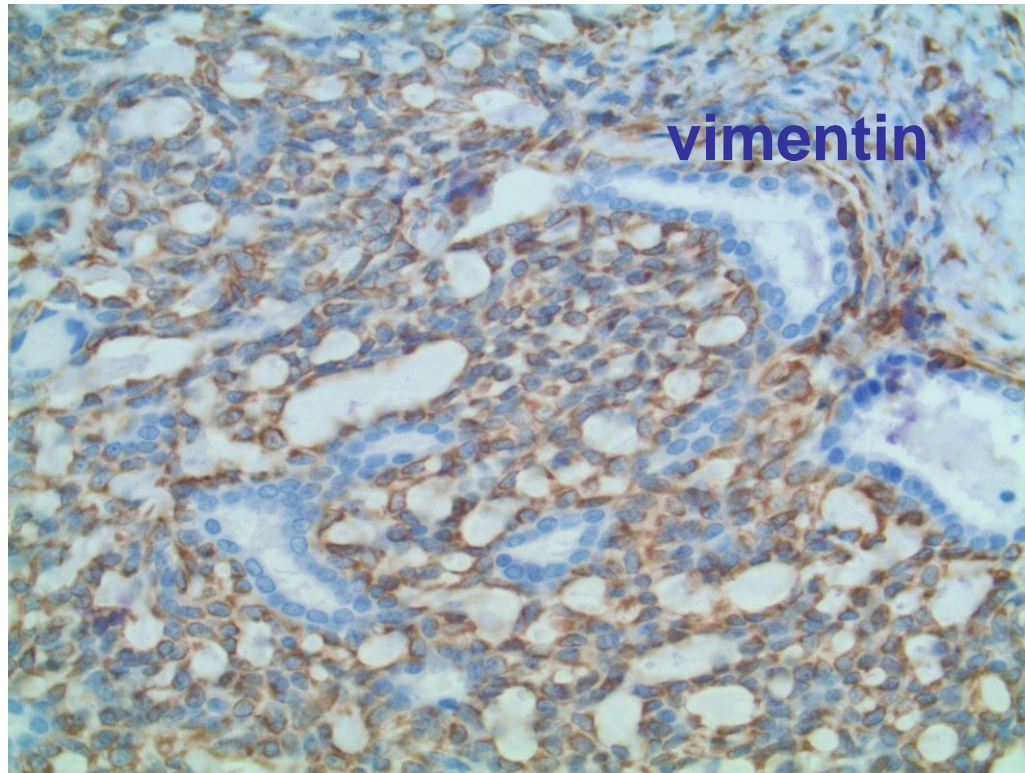
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Basaloid cells



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Adenoid cystic carcinoma

- Cribriform, solid, tubular, reticular, basaloid patterns
- Dual population: epithelial and basaloid cells
- Epithelial: CK7, CEA, EMA, CD117
- Basaloid: CK14, CD17, vimentin, S100, actin, calponin, p63
- May be associated with microglandular adenosis

Adenoid cystic carcinoma molecular pathology

- Clusters with metaplastic and medullary carcinomas – triple negative
- Translocation t (6;9) (q22-23; p23-24) – similar to salivary and other adenoid cystic carcinomas

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Adenoid cystic carcinoma

Three subtypes have been defined, on the basis of architectural and cytological features:

- Classic AdCC
- Solid-basaloid AdCC (SB-AdCC)
- AdCC with high-grade transformation

WHO 2019

Adenoid cystic carcinoma

Classic AdCC:

- At low magnification, this subtype shows a central cribriform area surrounded by a peripheral area with predominant tubular architecture.
- Both areas show the same cellular composition, namely epithelial and myoepithelial cells.
- The glandular spaces in both areas are lined by epithelial-type

WHO 2019

Adenoid cystic carcinoma

Solid Basaloid-AdCC:

- Classic features of AdCC with solid nests composed of basaloid cells, with marked nuclear atypia, high mitotic count, and necrosis.
- Perineural invasion is a frequent finding in this subtype.
- SB-AdCC should be differentiated from carcinomas with basaloid morphology and small cell neuroendocrine carcinoma

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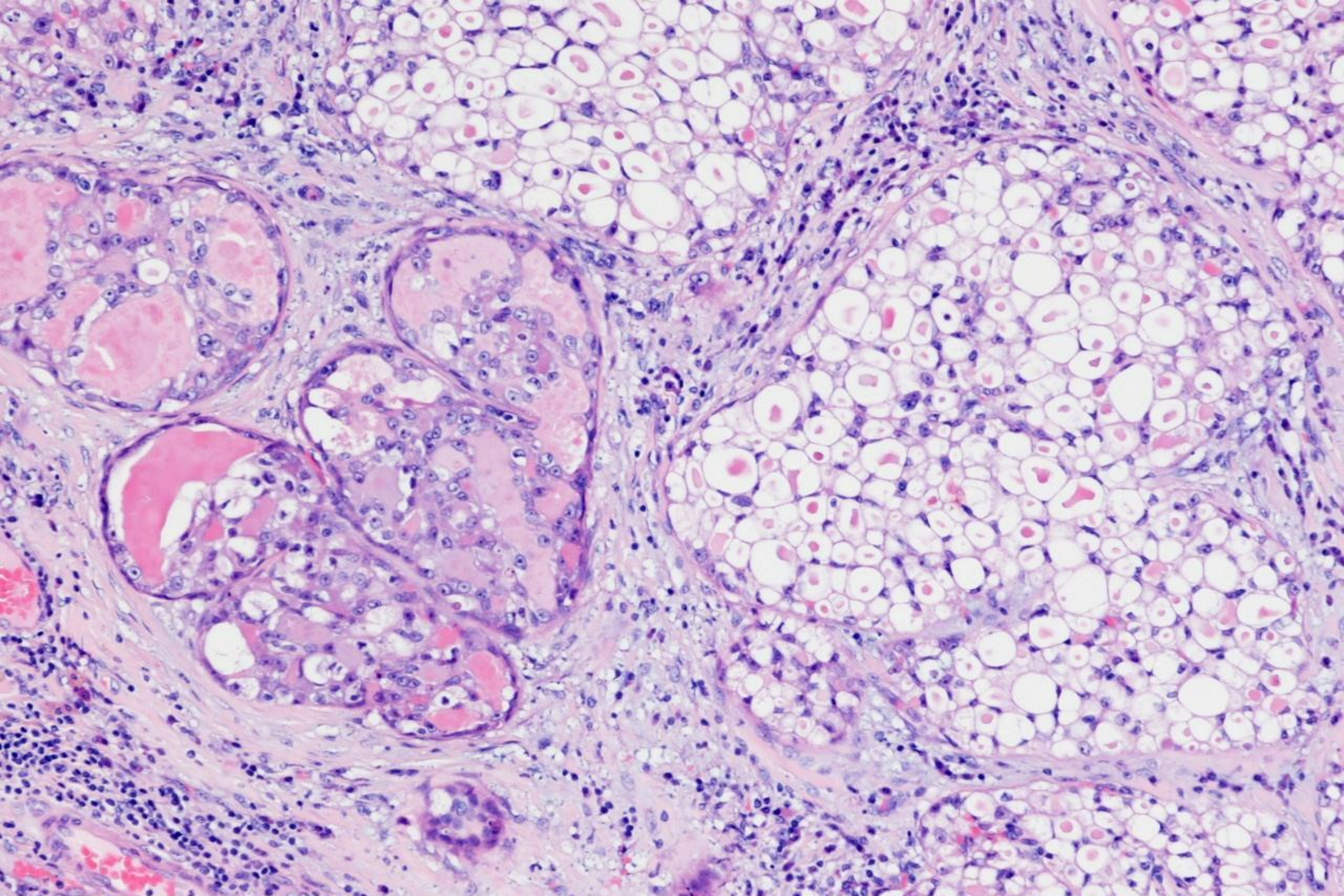
Adenoid cystic carcinoma

- **AdCC with high-grade transformation:**
- Well delineated in the salivary glands v rare in breast
- AdCC showing multiple areas of differentiation, small cell carcinoma, invasive ductal carcinoma, and malignant adenomyoepithelioma described

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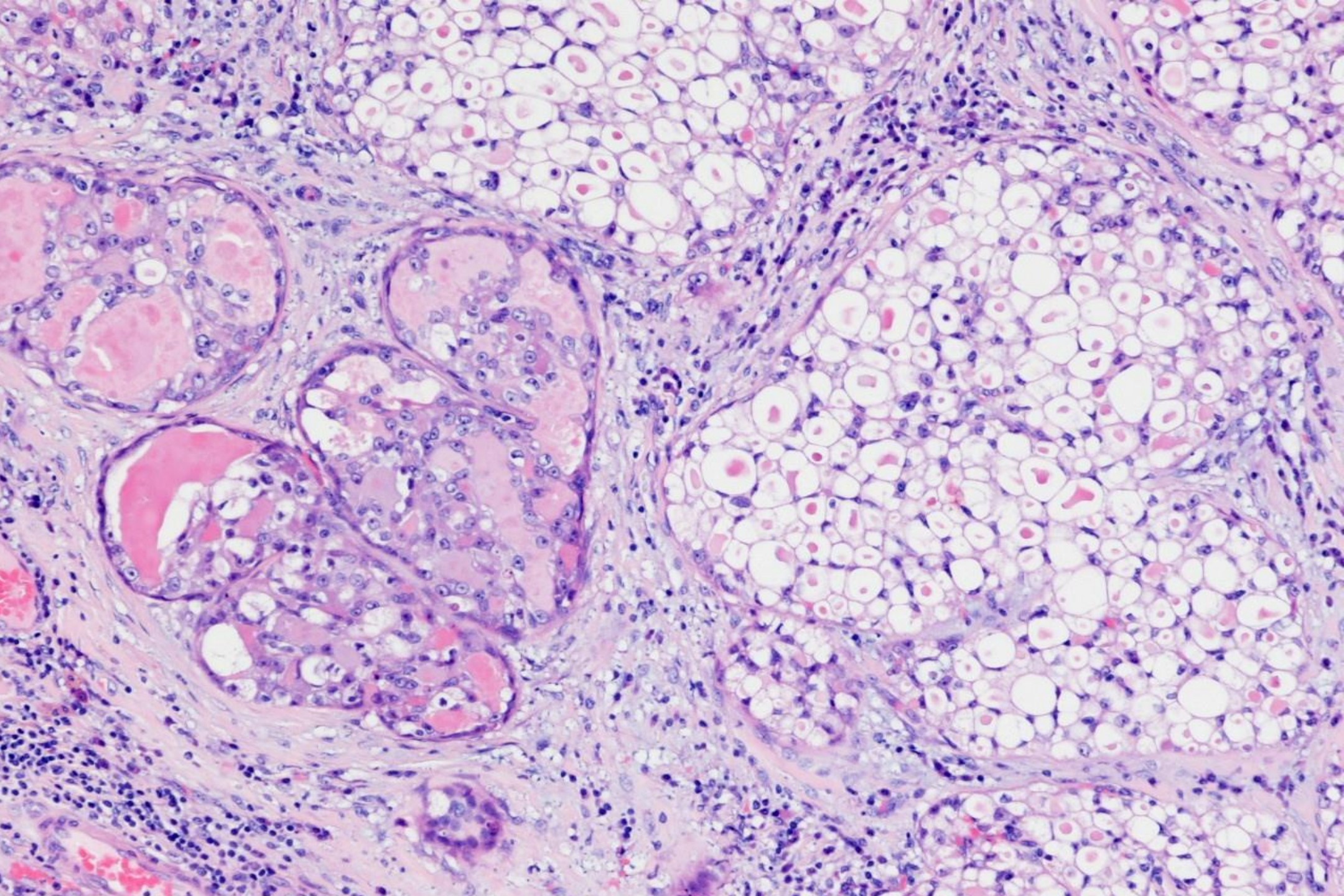
Adenoid cystic carcinoma

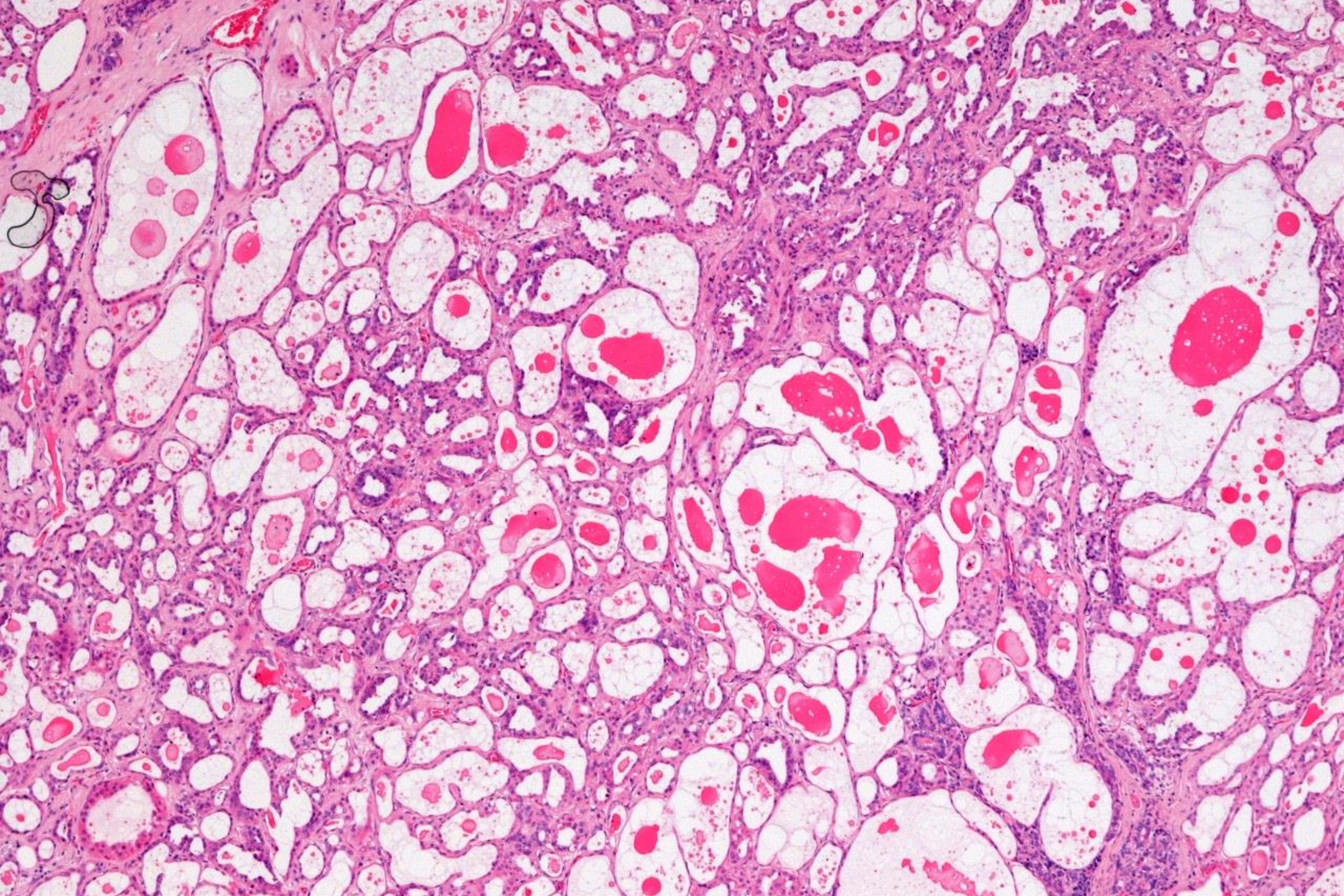
- **AdCC with high-grade transformation:**
- Case of AdCC described in association with an invasive ductal carcinoma, similar molecular alterations shared by the two components;
- mitochondrial DNA analysis demonstrated a clonal relationship between the two components
- Implies that AdCC neoplastic cells can acquire aggressive potential

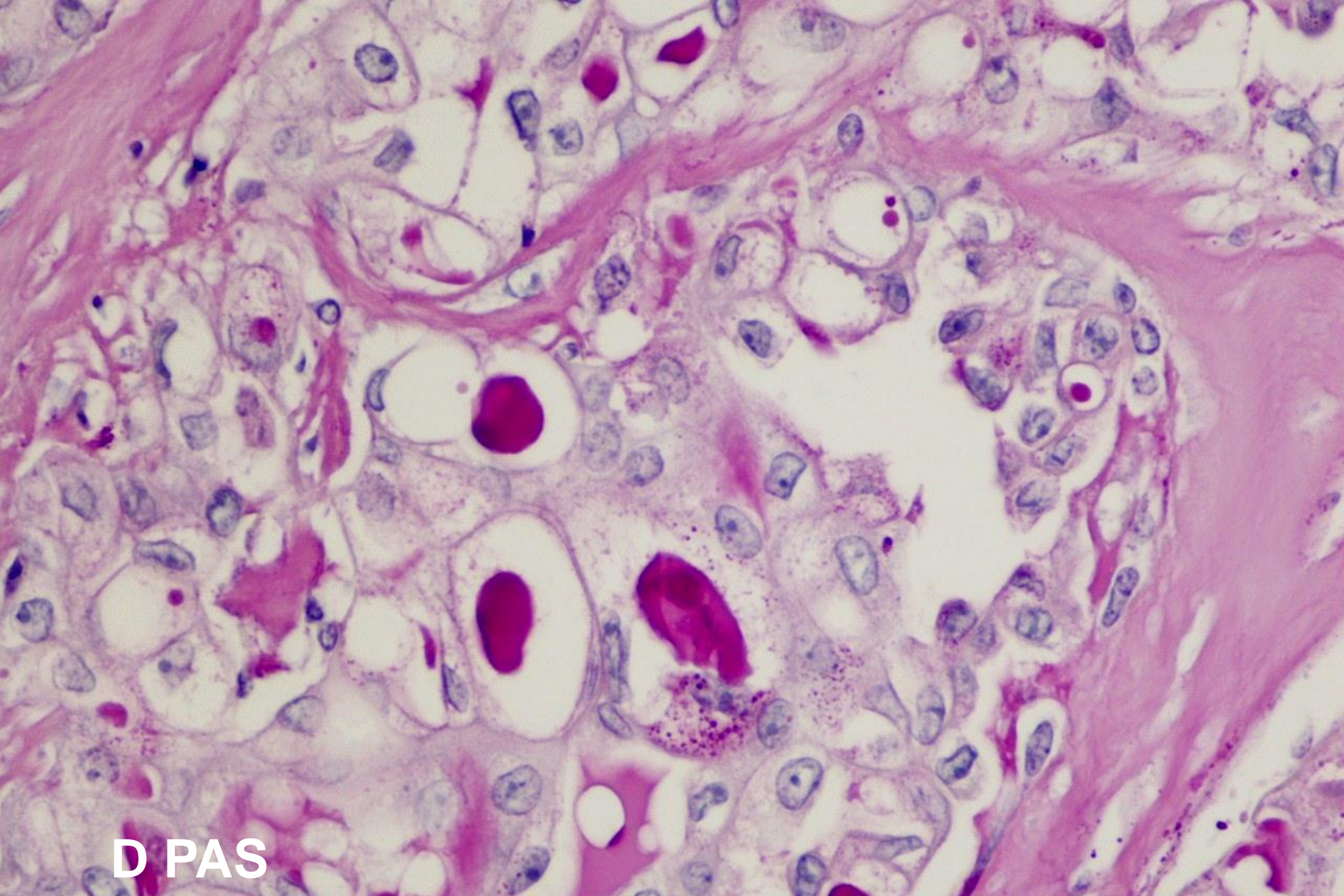


Secretory carcinoma

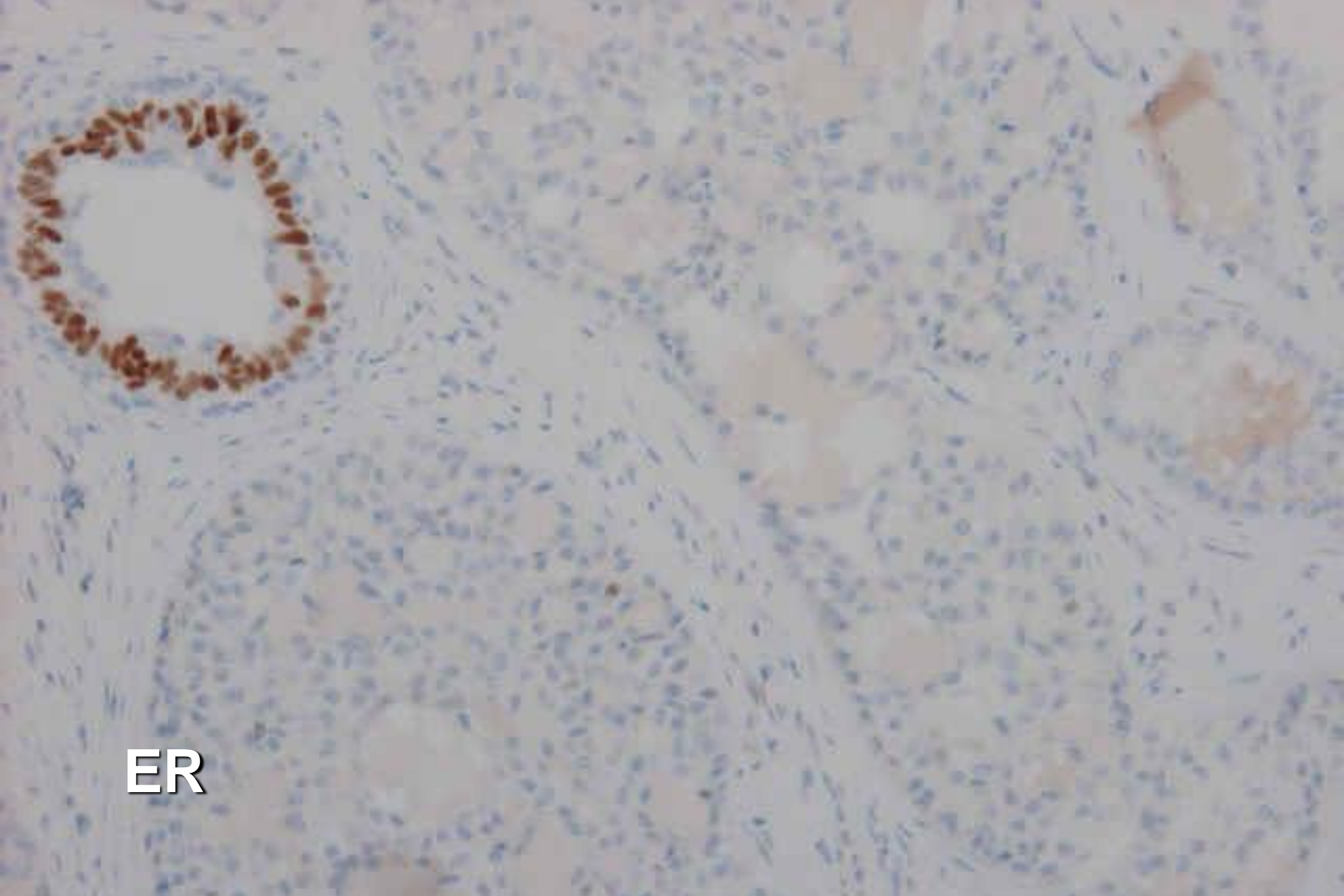
- First identified by McDivitt & Stewart in 1966 as a children's breast cancer but later recognised as also occurring in young, and a few adults. Male association
- Usually present as a well defined sub-areolar mass
- Prognosis is favourable and is thought to be better in children than in adults
- Local recurrences, if developed, are late
- Lymph node metastasis are uncommon
- Distant metastasis are exceedingly rare
- Death is unusual, but has been reported



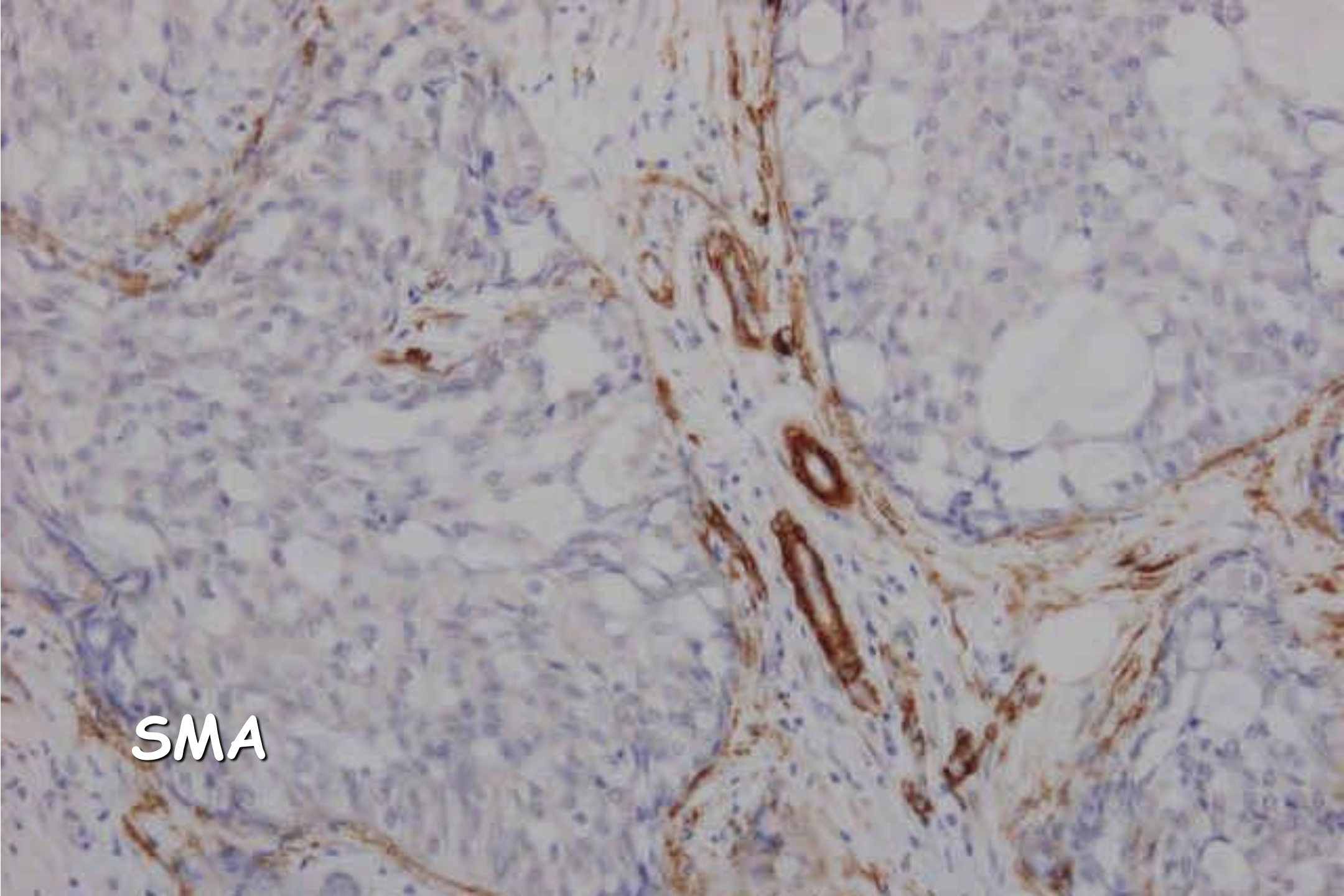




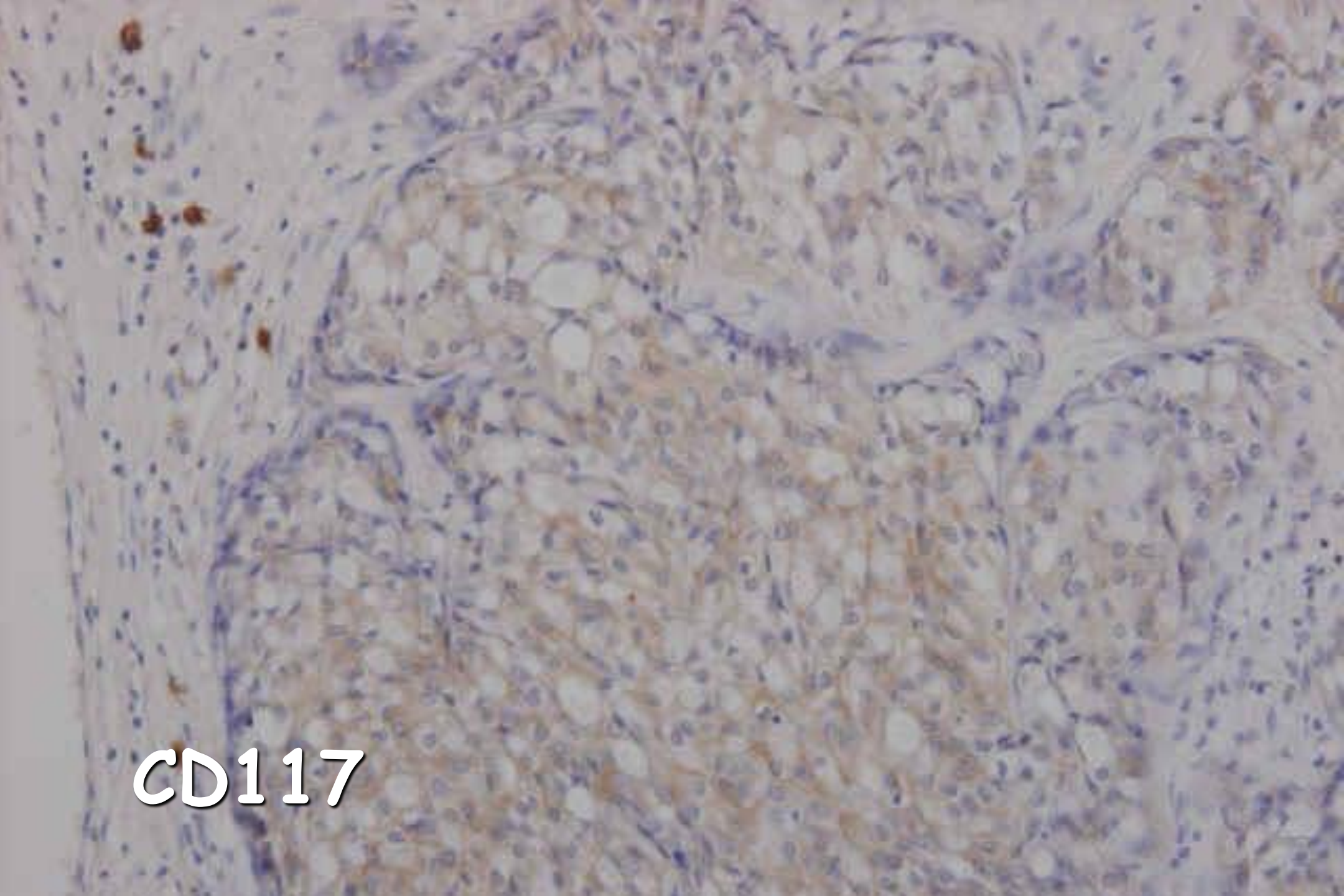
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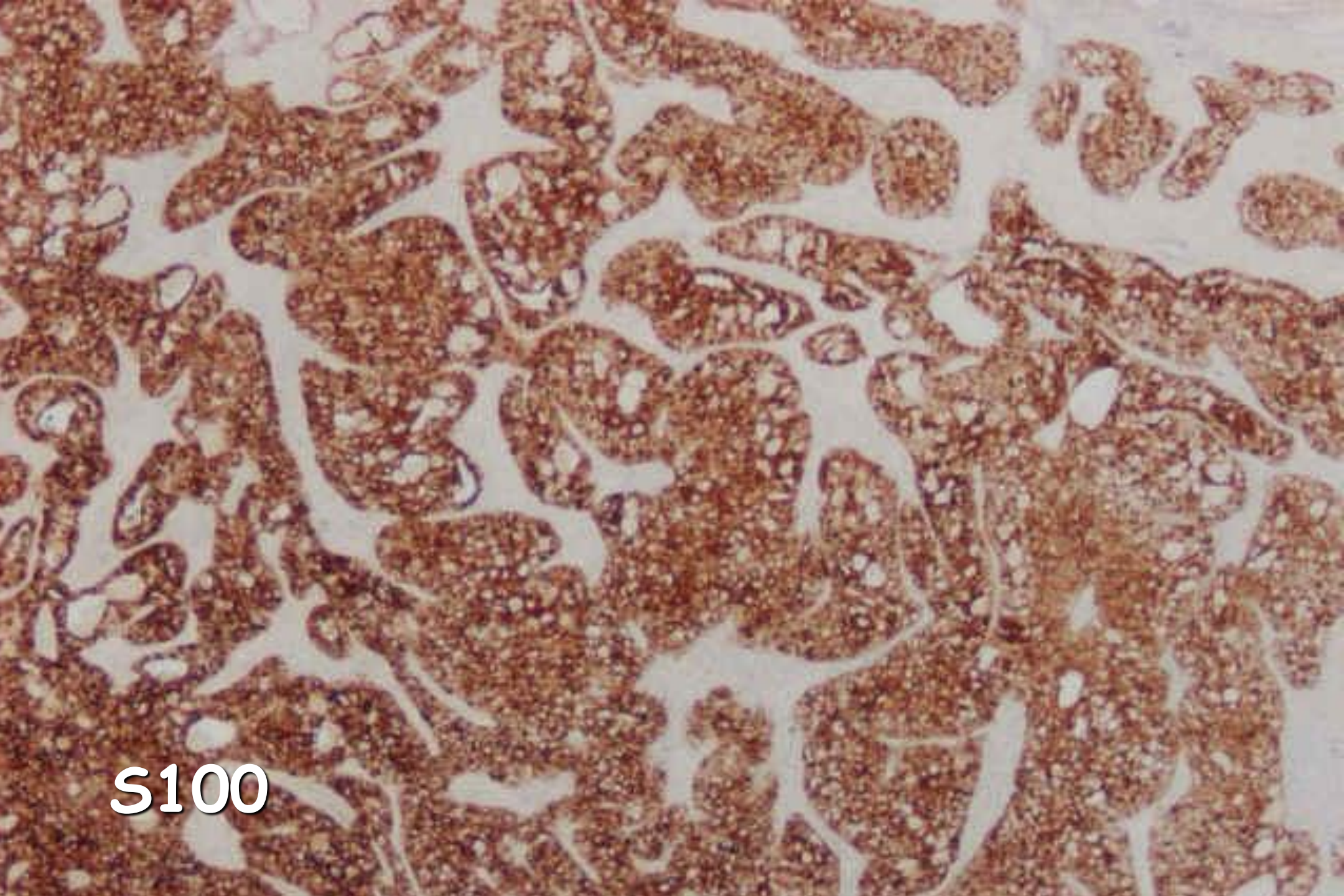
ER



SMA



CD117



S100

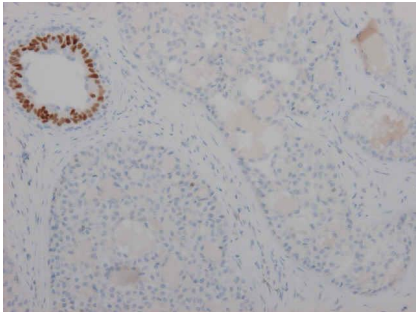
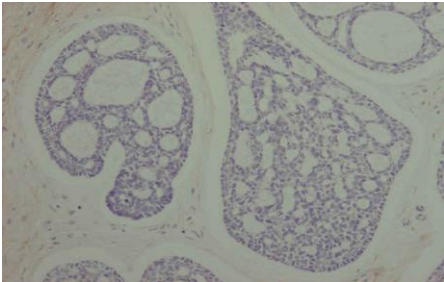
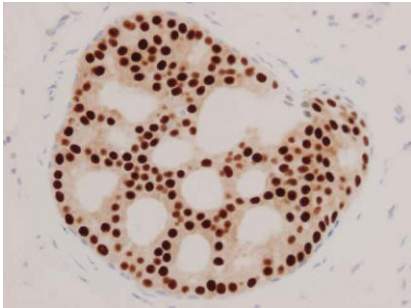
Secretory carcinoma

- Low nuclear grade with vacuolated cytoplasm which may contain eosinophilic secretion arranged in cribriform patterns with the spaces containing eosinophilic secretions
- Typically, they show strong reactivity with S100
- They are mostly triple negative
- Express basal cytokeratins, and belong to the basal-like molecular group of breast cancers
- Genetically they are characterised by the presence of a chromosomal translocation $t(12;15)(p13;q25)$ which results in the formation of ETV6-NTRK3 fusion gene

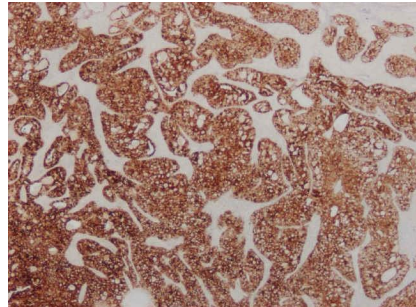
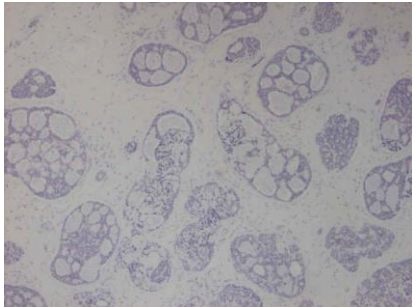
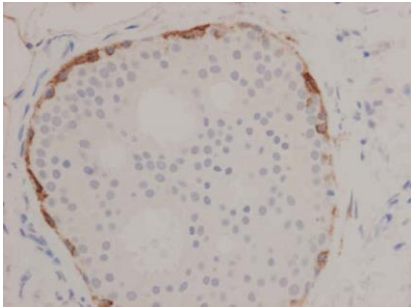
Differential diagnosis:



ER



S100



**+Basal CKs
p63**

Negative
ME cells

Positive
Diffuse or patchy

Negative
Negative

Cribriform carcinoma

Adenoid cystic carcinoma

Secretory carcinoma

CD117+

t(12;15)(p13;q25) ETV6-
NTRK3 fusion gene

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Secretory carcinoma

- Secretory carcinoma is an invasive carcinoma composed of epithelial cells with intracytoplasmic secretory vacuoles and extracellular eosinophilic, bubbly secretions, arranged in a variable architecture
- frequently associated with ETV6-NTRK3 fusion.

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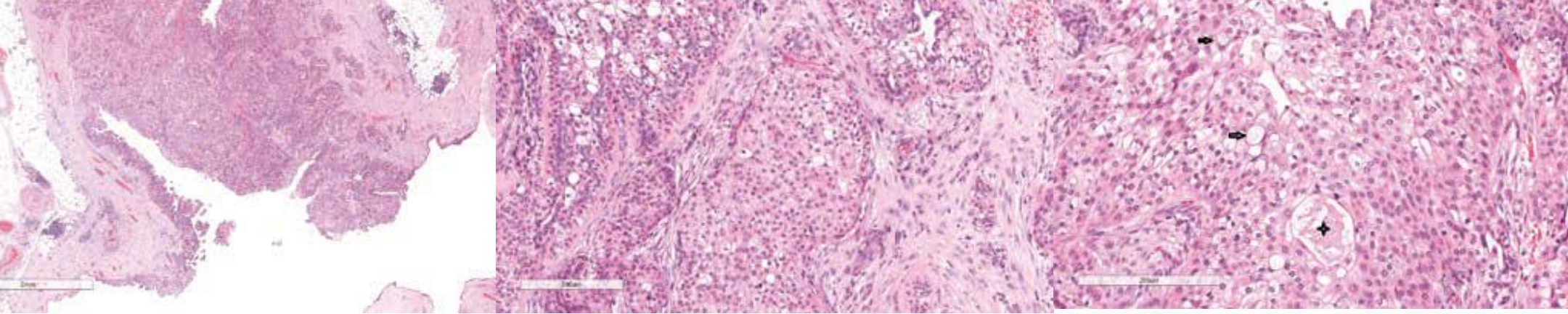
Secretory carcinoma

- ETV6-NTRK3 alteration in both invasive and in situ component i.e. an early event
- also identified in mammary analogue secretory carcinomas arising in other sites, such as the salivary glands, thyroid, and skin

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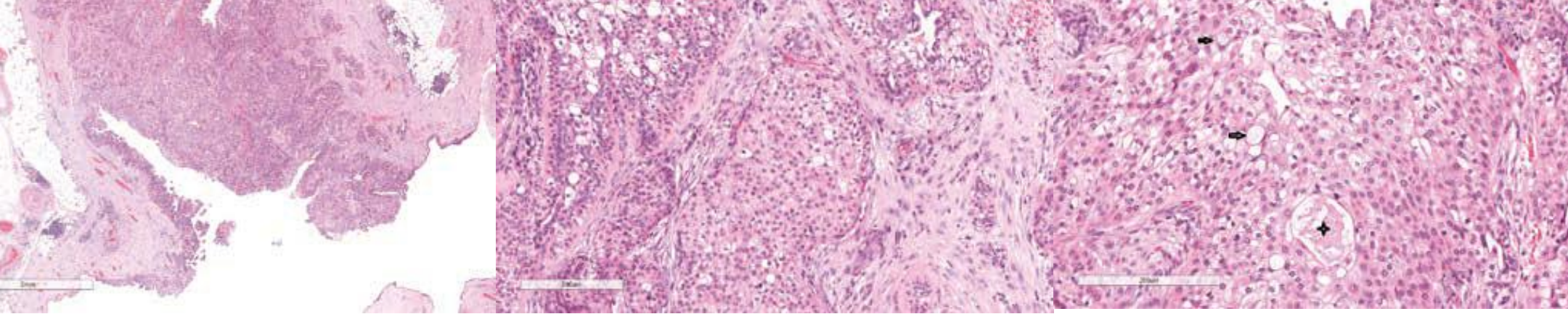
Mucoepidermoid carcinoma

- Mucoepidermoid carcinoma (MEC) is an invasive carcinoma composed of mixed mucinous, intermediate (transitional), and squamoid neoplastic cells arranged in solid and cystic patterns.
- < 40 cases reported to date
- wide range of histological features, spanning from low-grade to high-grade lesions
- Low and Int grade - very good prognosis
- High grade – poor prognosis



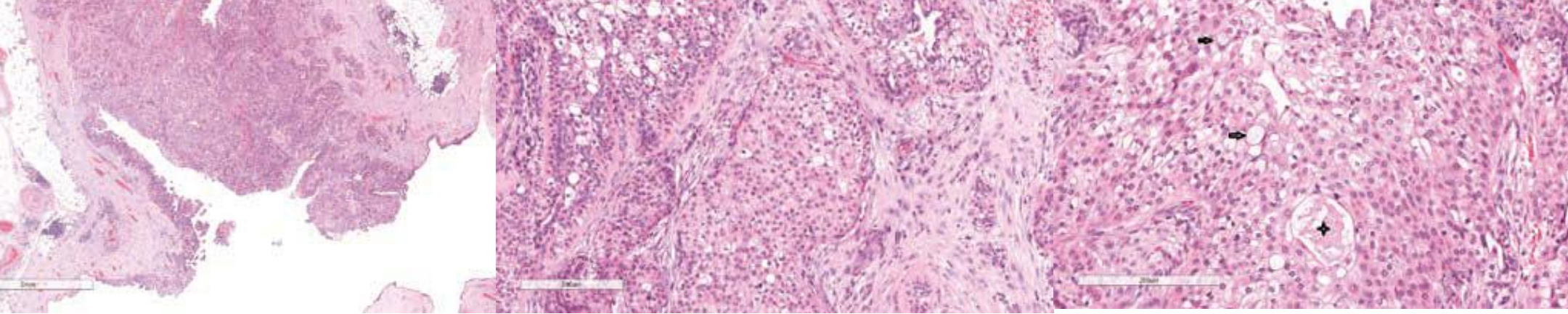
WHO 2019 - Mucoepidermoid

- Wide range of histological features, spanning from low-grade to high-grade lesions
- Grading by salivary gland or breast systems



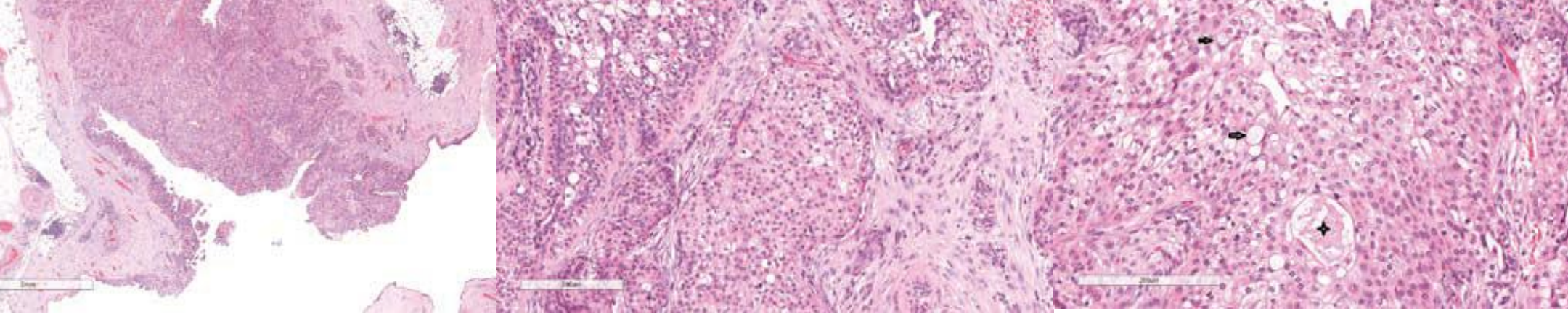
WHO 2019 - Mucoepidermoid

- **Low-grade MEC** more frequent cystic
- Cystic spaces are lined by mucous cells intermingled with eosinophilic cells
- Solid areas have peripheral layer of basaloid cells merging in groups of epidermoid cells and mucous cells.



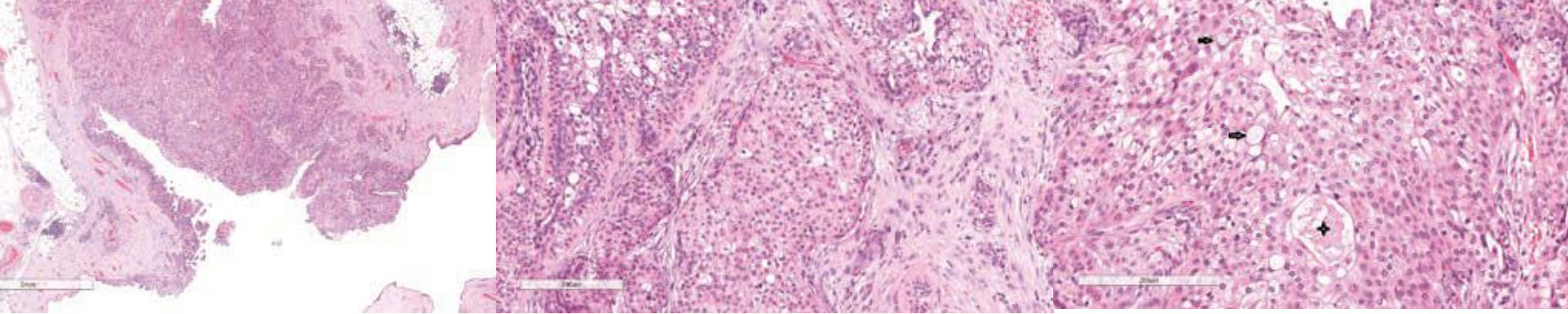
WHO 2019 - Mucoepidermoid.

- **High-grade MEC** more frequently solid, and show same cell composition as low-grade
- Cytological atypia is present
- Mitotic figures numerous
- Necrosis can be present.



WHO 2019 - Mucoepidermoid.

- **Intermediate-grade** breast MEC has been occasionally reported.
- An intraductal component can be present.
- True keratinization with squamous pearls does not occur with any grade



WHO 2019 - Mucoepidermoid

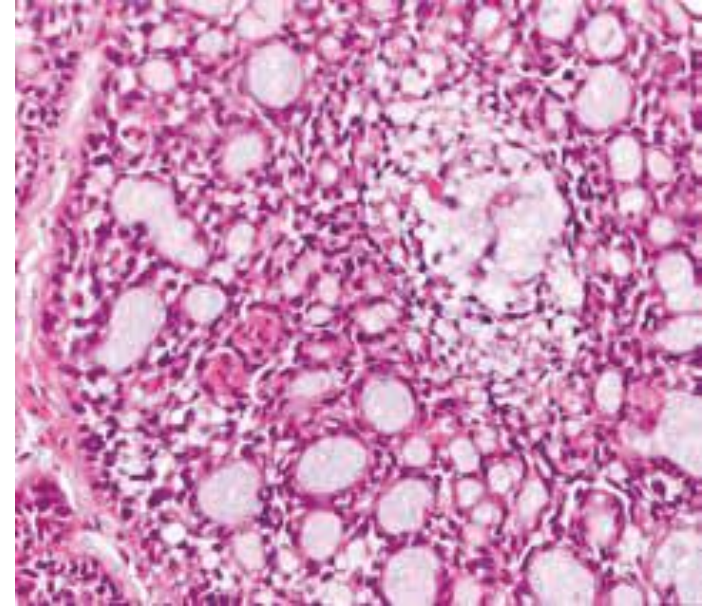
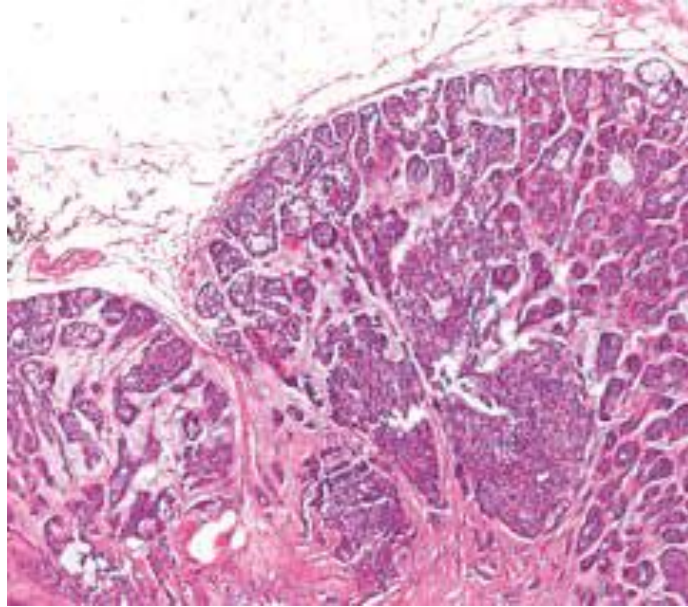
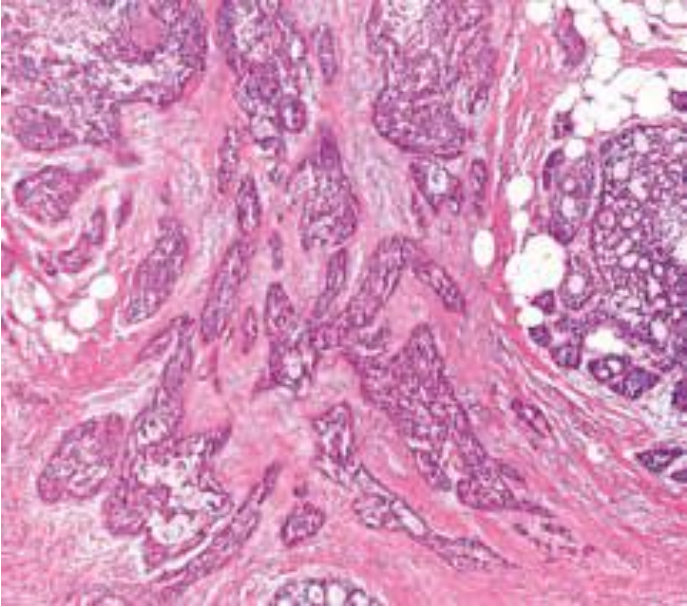
IHC

- Triple negative ER PR HER2
- Basal epidermoid cells – High MW Ck & p63 +ve
- Muroid cells – Low MW Ck +ve
- GATA 3 and Mammaglobin +ve

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Polymorphous adenocarcinoma

- Polymorphous adenocarcinoma (PmA) invasive malignant tumour similar to PmA of the salivary glands
- monotonous neoplastic cells with architectural diversity, incl. large nests surrounded by cords and single files (single-cell infiltration).
- Only 3 breast cases reported to date
- 1 of the 3 cases reported had widespread metastases with death at 3 years
- The term “low-grade” should not be used for this breast tumour.



WHO 2019 - Polymorphous adenocarcinoma

- **Essential:** typical architectural pattern composed of a centrally located large solid area surrounded by thin strands of uniform and monotonous neoplastic cells.
- **Desirable:** focal and weak immunopositivity for CK7 and E-cadherin
- negative ER, PR, and HER2. *Note: bcl2 +ve*

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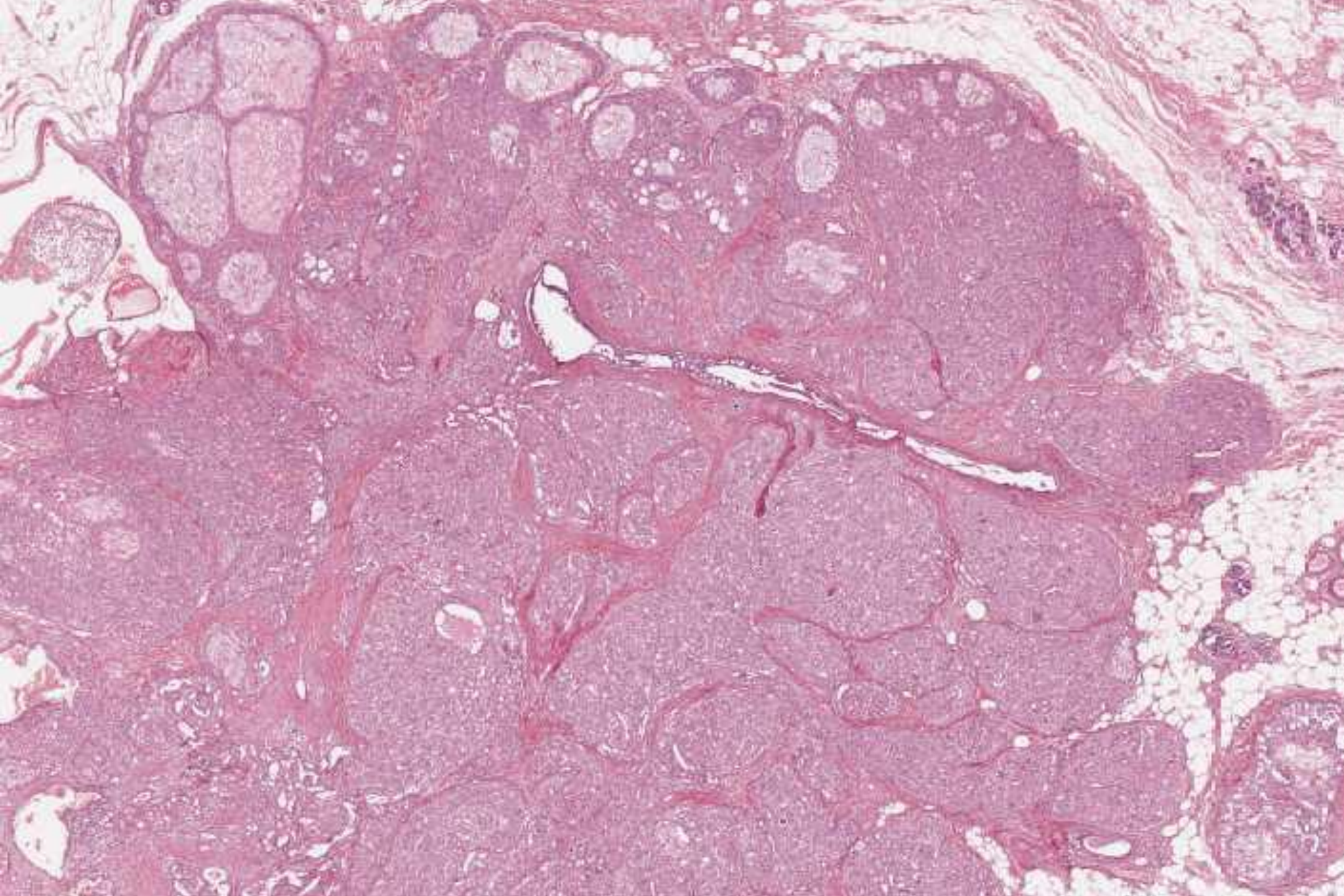
Tall cell carcinoma with reversed polarity

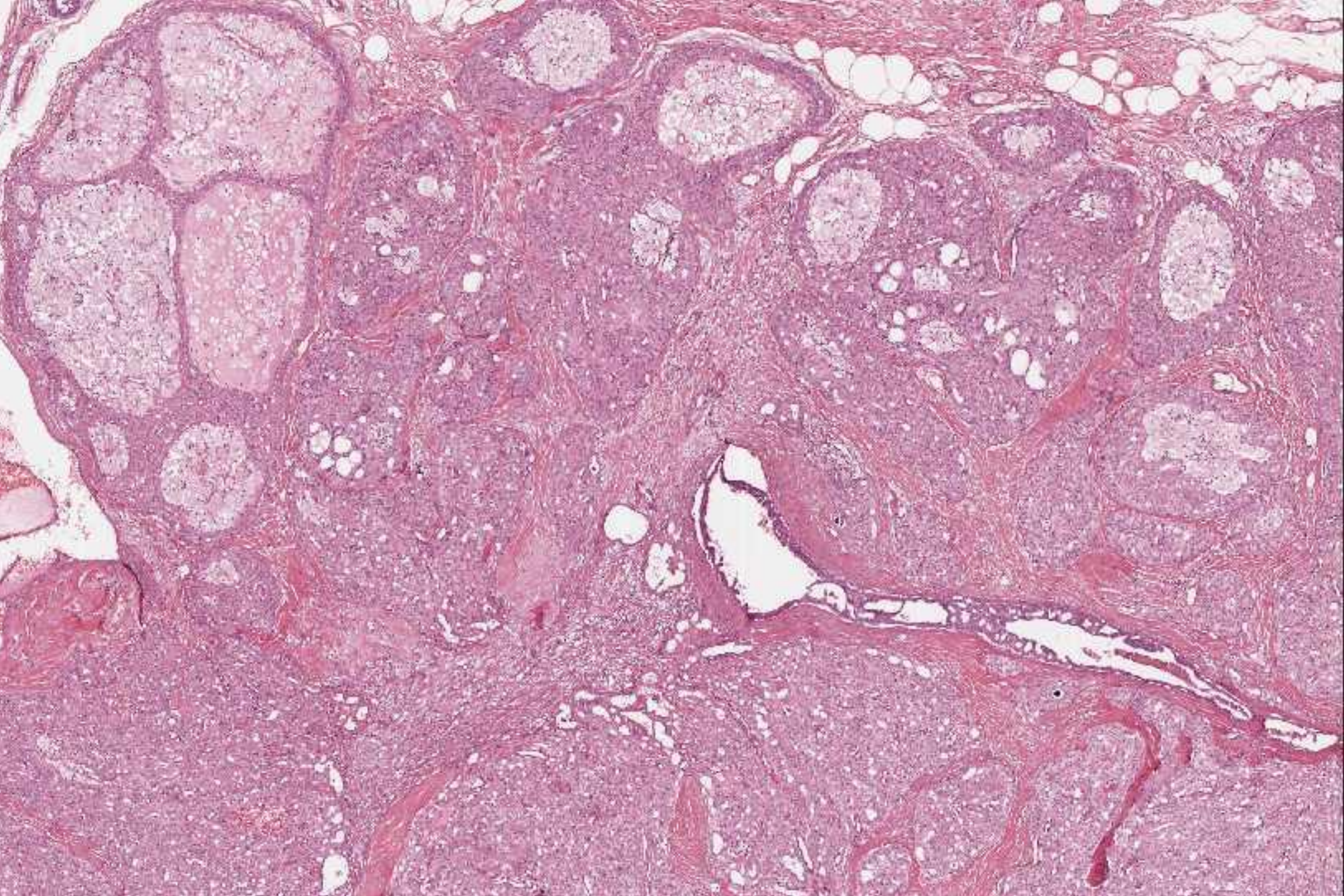
- New name, previous names:
 - solid papillary carcinoma resembling the tall cell variant of papillary thyroid carcinoma
 - solid papillary carcinoma with reverse polarity

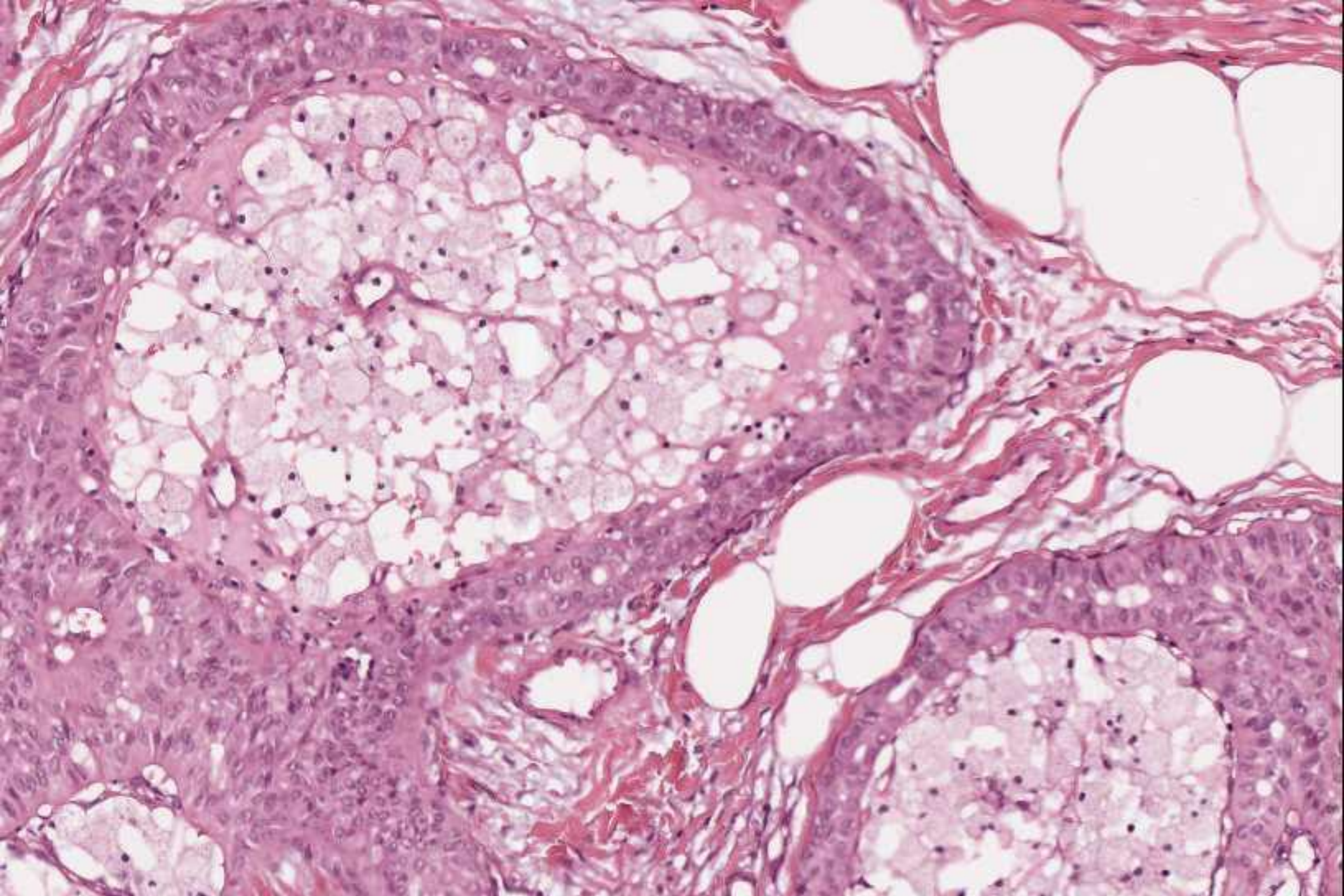
WHO 2019

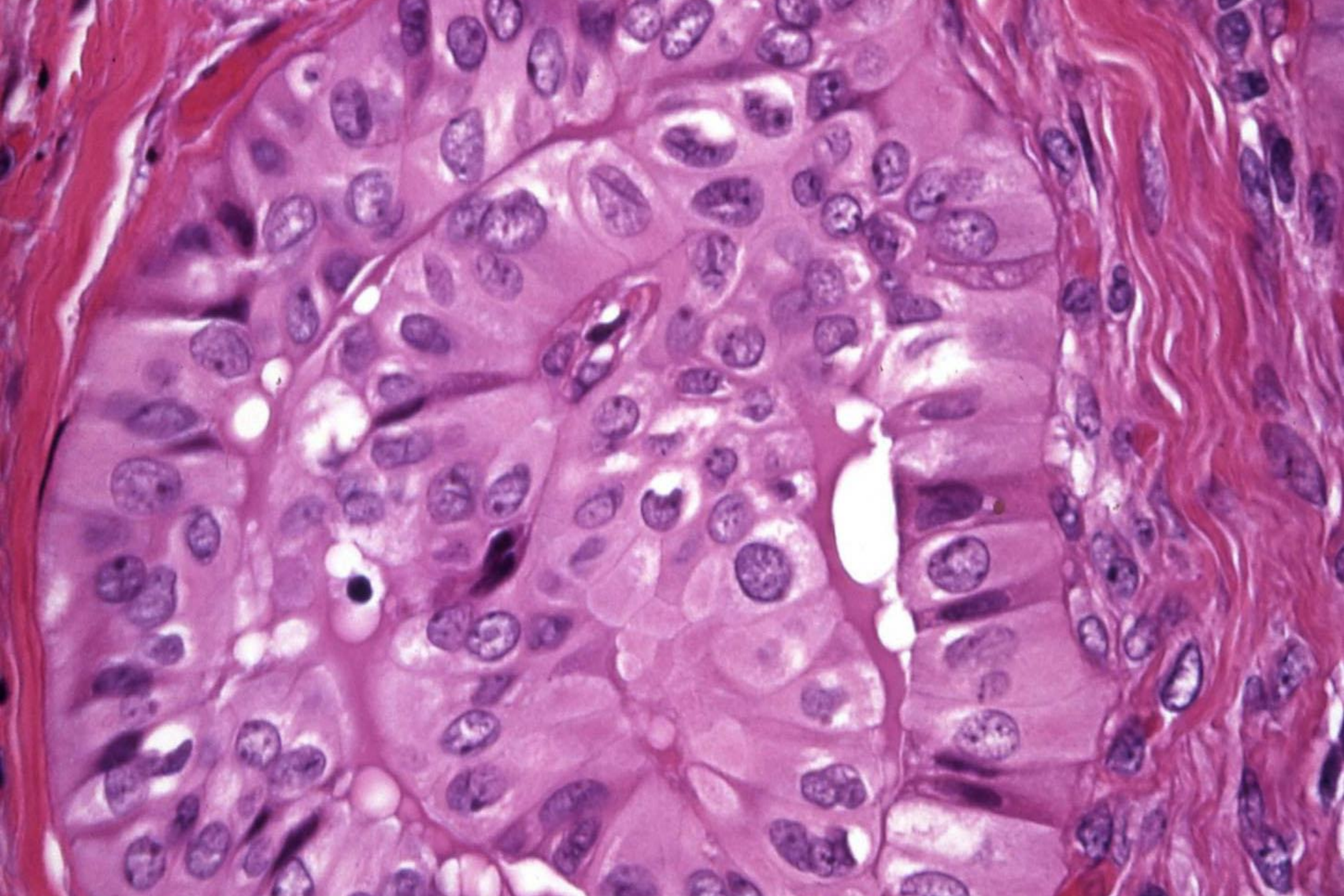
Tall cell carcinoma with reversed polarity

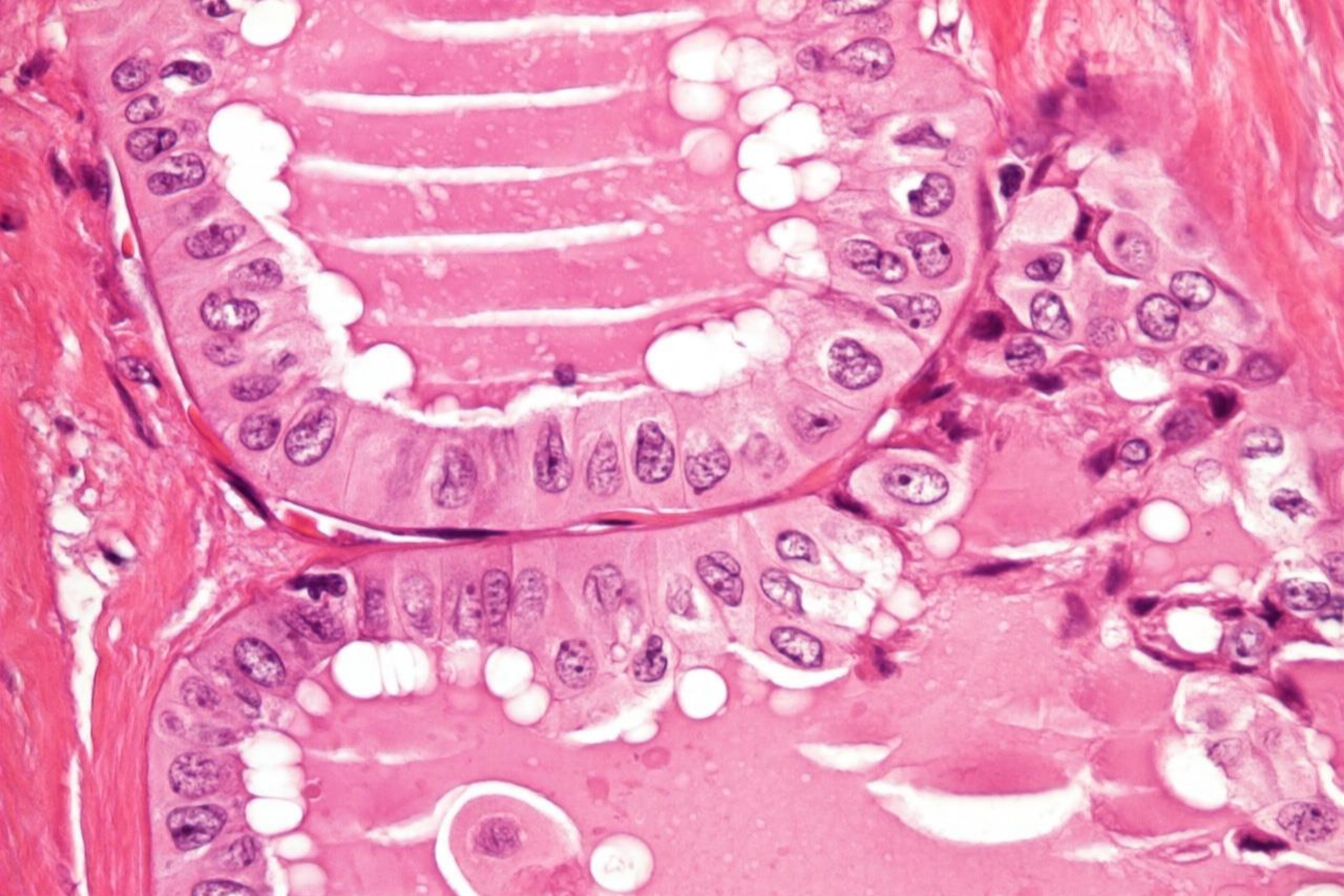
- rare subtype of invasive breast carcinoma characterized by tall columnar cells with reversed nuclear polarity, arranged in solid and solid papillary patterns
- most commonly associated with IDH2 p.Arg172 hotspot mutations.

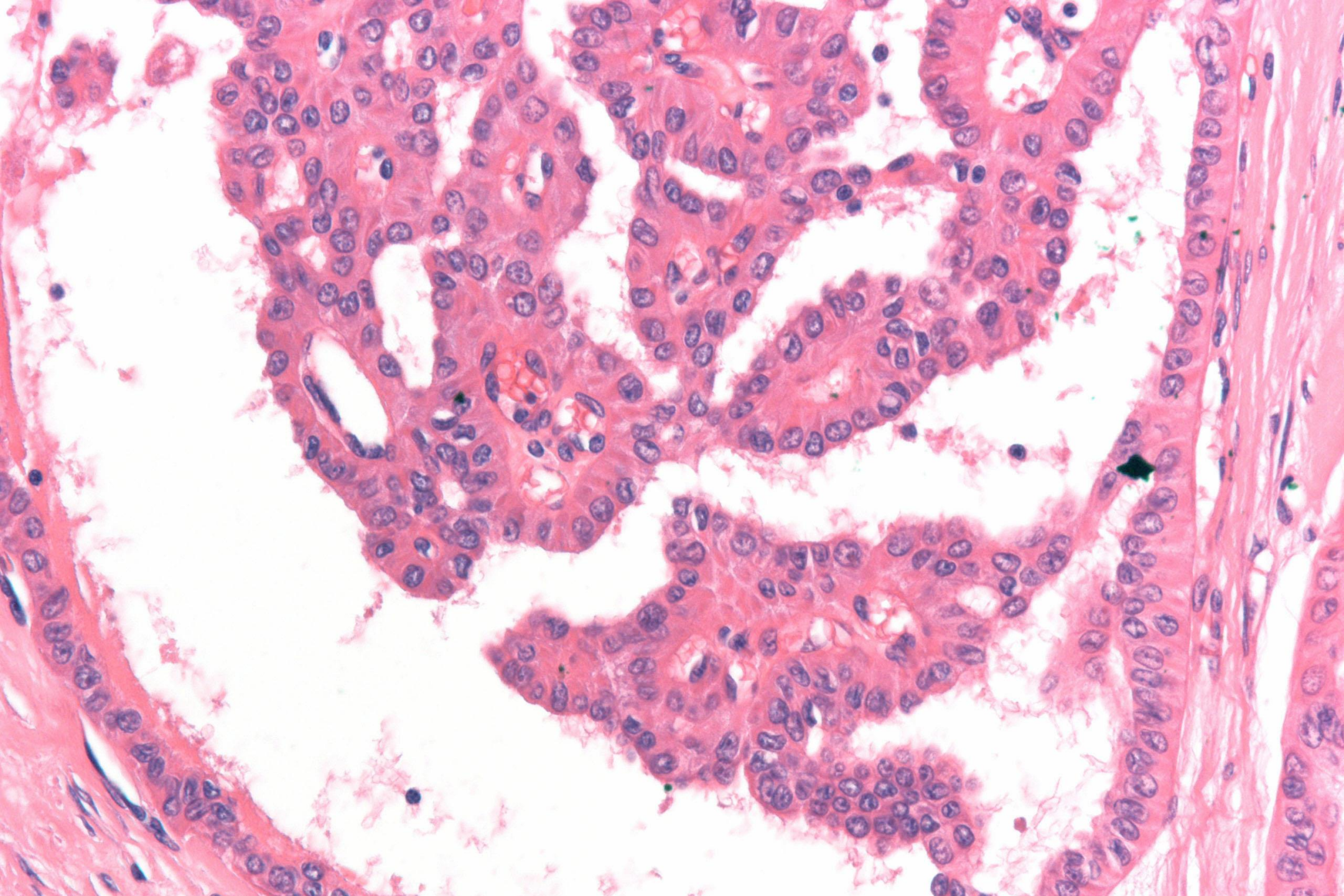


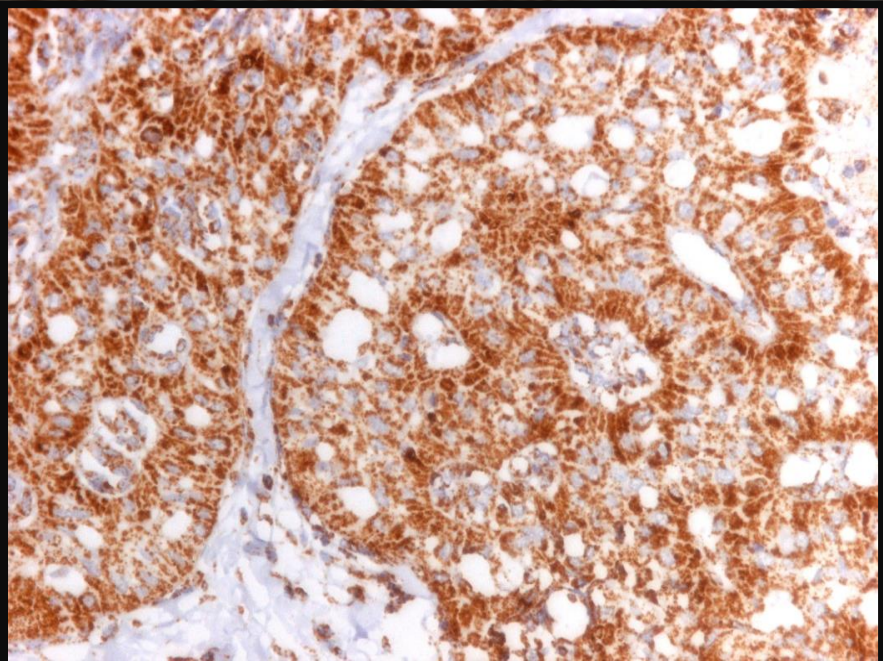
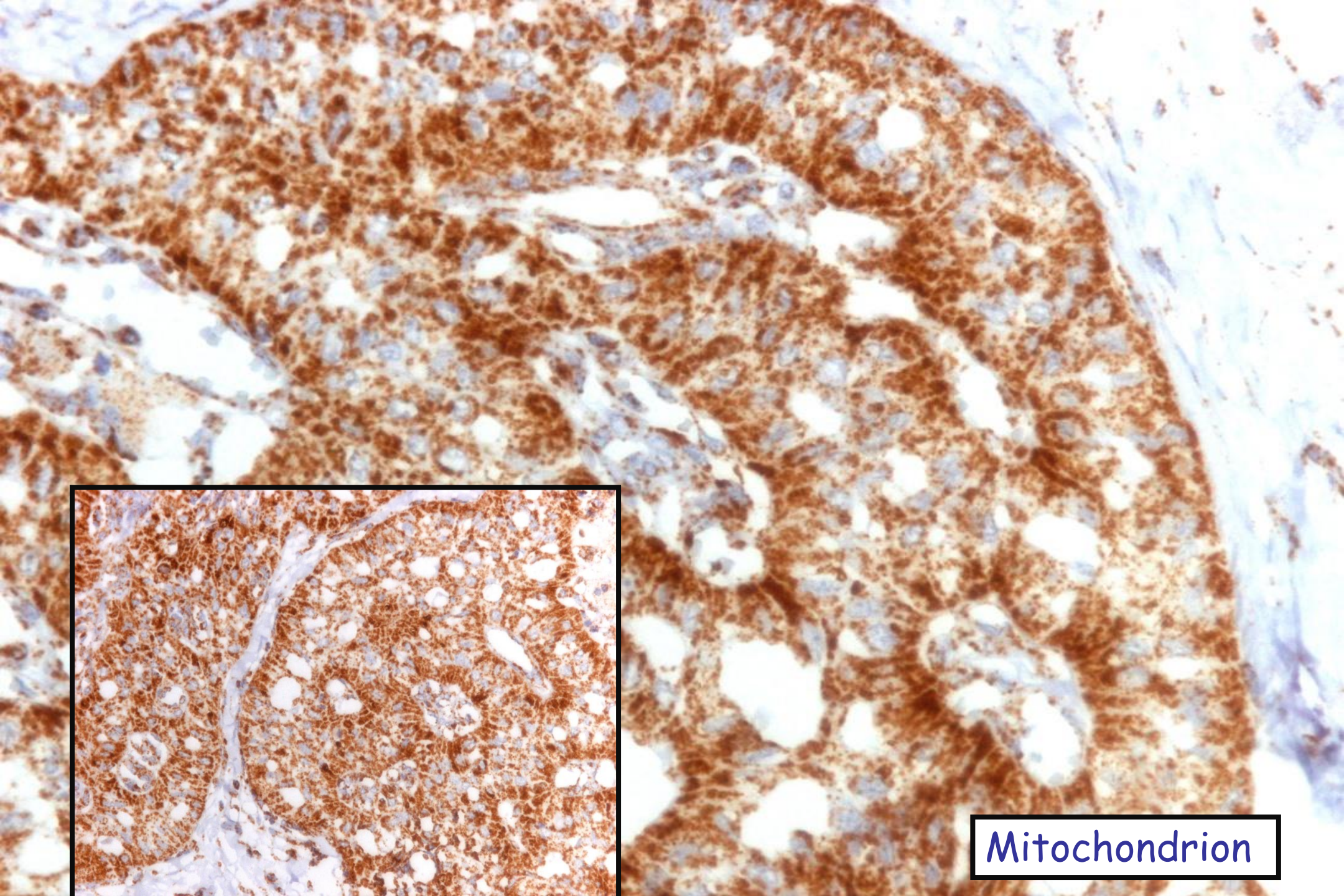












Mitochondrion



Breast Tumor Resembling the Tall Cell Variant of Papillary Thyroid Carcinoma

Report of 5 Cases

V. Eusebi, M.D., F.R.C.Path., S. Damiani, M.D., I. O. Ellis, M.D., F.R.C.Path.,
J. G. Azzopardi, M.D., F.R.C.Path., and J. Rosai, M.D., F.R.C.Path.

Imunohistochemical Findings (10 Cases)

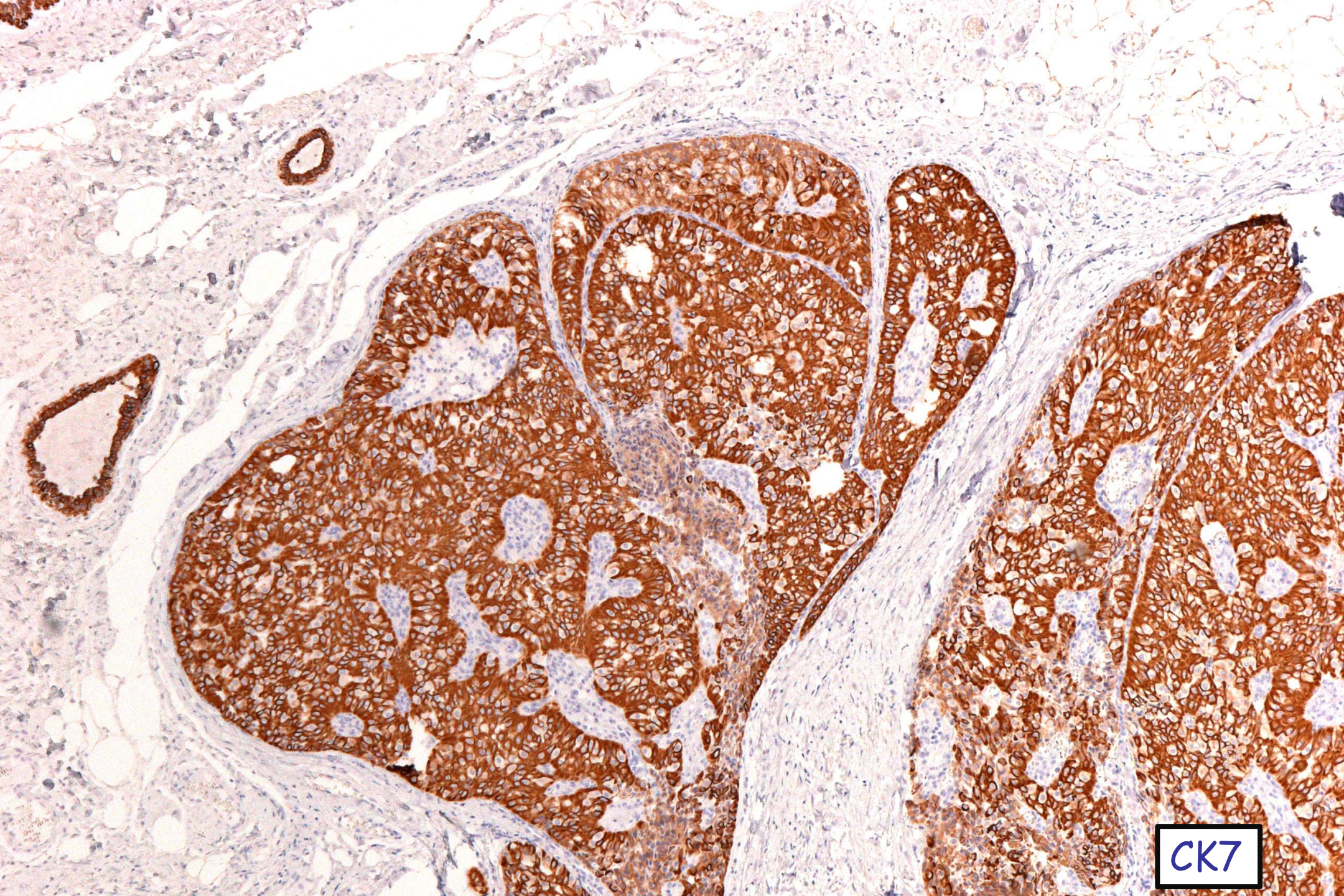
CK 7	Positive	10/10
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Mitochondria	Positive	9/10
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P 63	Negative	10/10
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ER / PGR / AR / Herb2	Negative	10/10
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TTF-1 / Thyroglobulin	Negative	10/10
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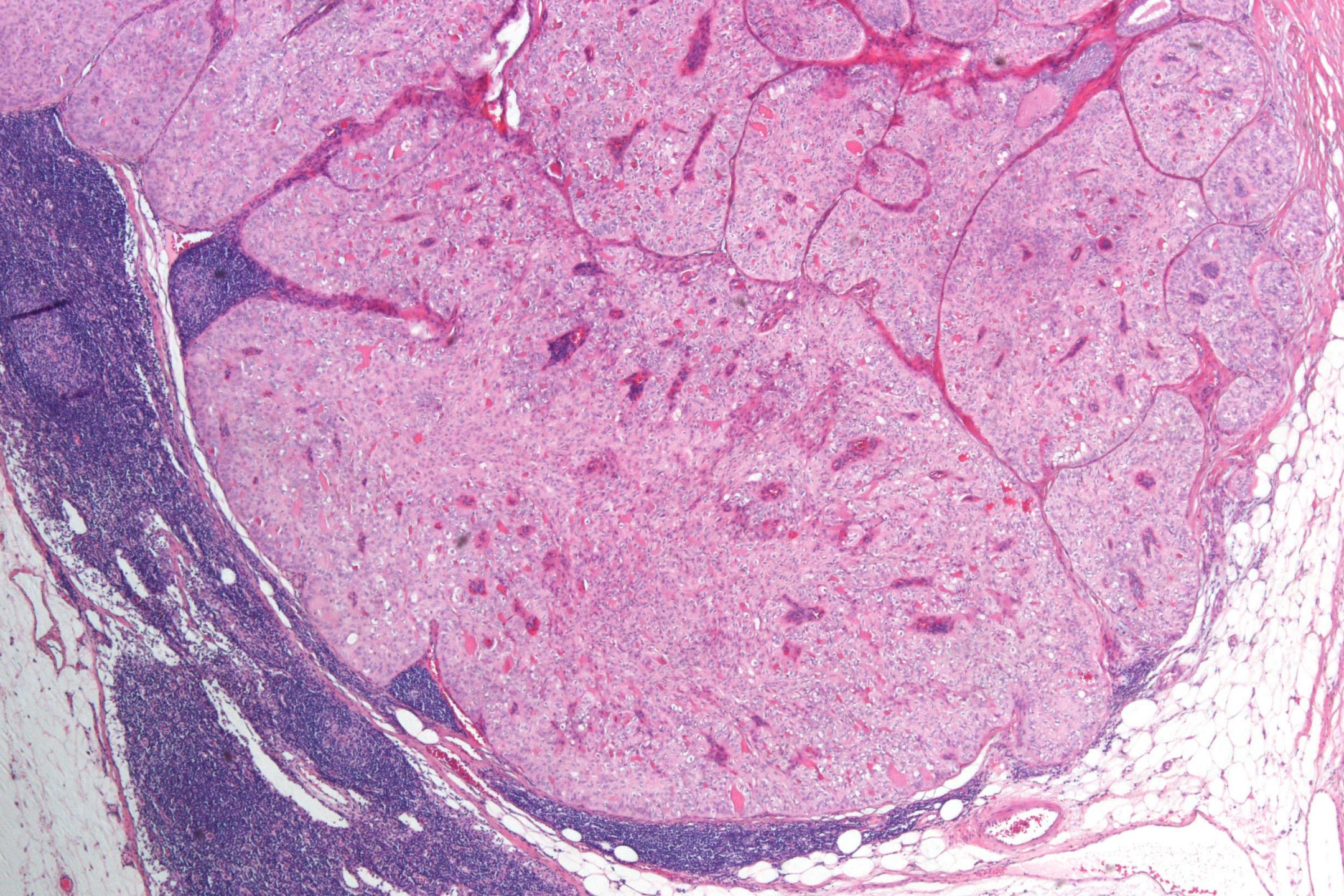


CK7

Follow-Up (FU)

(range 24 mos- 14.5 years)
(mean 7,72 years)

1 Patient	Lost FU
8 Patients	Alive and well (A&W)
1 Patient A&W (12,3 years)	9,4 years: local recurrence and 1 axillary lymph node metastasis



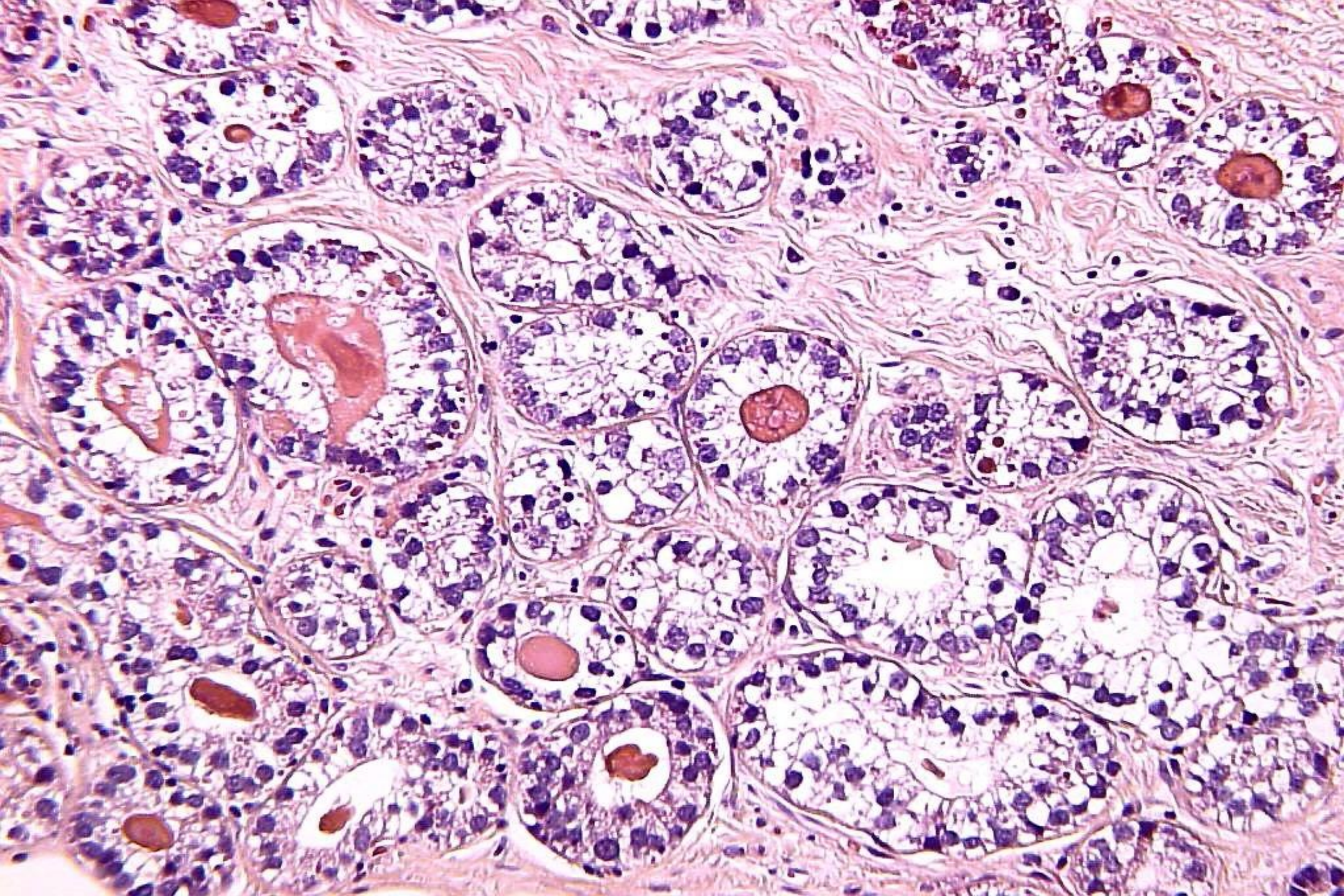
***IDH2* Mutations Define a Unique Subtype of Breast Cancer with Altered Nuclear Polarity**

Sarah Chiang¹, Britta Weigelt¹, Huei-Chi Wen¹, Fresia Pareja¹, Ashwini Raghavendra¹, Luciano G. Martelotto¹, Kathleen A. Burke¹, Thais Basili¹, Anqi Li¹, Felipe C. Geyer¹, Salvatore Piscuoglio¹, Charlotte K.Y. Ng¹, Achim A. Jungbluth¹, Jörg Balss², Stefan Pusch², Gabrielle M. Baker³, Kimberly S. Cole⁴, Andreas von Deimling^{2,5}, Julie M. Batten⁶, Jonathan D. Marotti⁷, Hwei-Choo Soh⁸, Benjamin L. McCalip⁹, Jonathan Serrano¹⁰, Raymond S. Lim¹, Kalliopi P. Siziopikou¹¹, Song Lu¹², Xiaolong Liu¹³, Tarek Hammour¹⁴, Edi Brogi¹, Matija Snuderl¹⁰, A. John Iafrate^{6,15}, Jorge S. Reis-Filho¹, and Stuart J. Schnitt^{15,16}

19 of 13 (77%) SPCRPs harbored hotspot mutations at R172 *IDH2*

Of which 8 of 10 displayed concurrent pathogenic mutations affecting *PIK3CA* or *PIK3R1*

First report of *IDH2* hotspot mutations in breast cancer



WHO 2019

Acinic cell carcinoma

- Acinic cell carcinoma is a malignant epithelial neoplasm composed of clear and granular epithelial cells, some of which contain intracytoplasmic zymogen granules, arranged in microglandular and solid patterns.

WHO 2019

Acinic cell carcinoma

Essential diagnostic criteria:

- neoplastic cells with eosinophilic and basophilic granular cytoplasm and PASD-positive intracytoplasmic granules
- immunohistochemical positivity for EMA and markers of serous acinar differentiation.

Acinic Cells Carcinoma(AcCC)

Clinicopathological features

- First report by Roncaroli 1996

Acinic cell-like carcinoma of the breast.

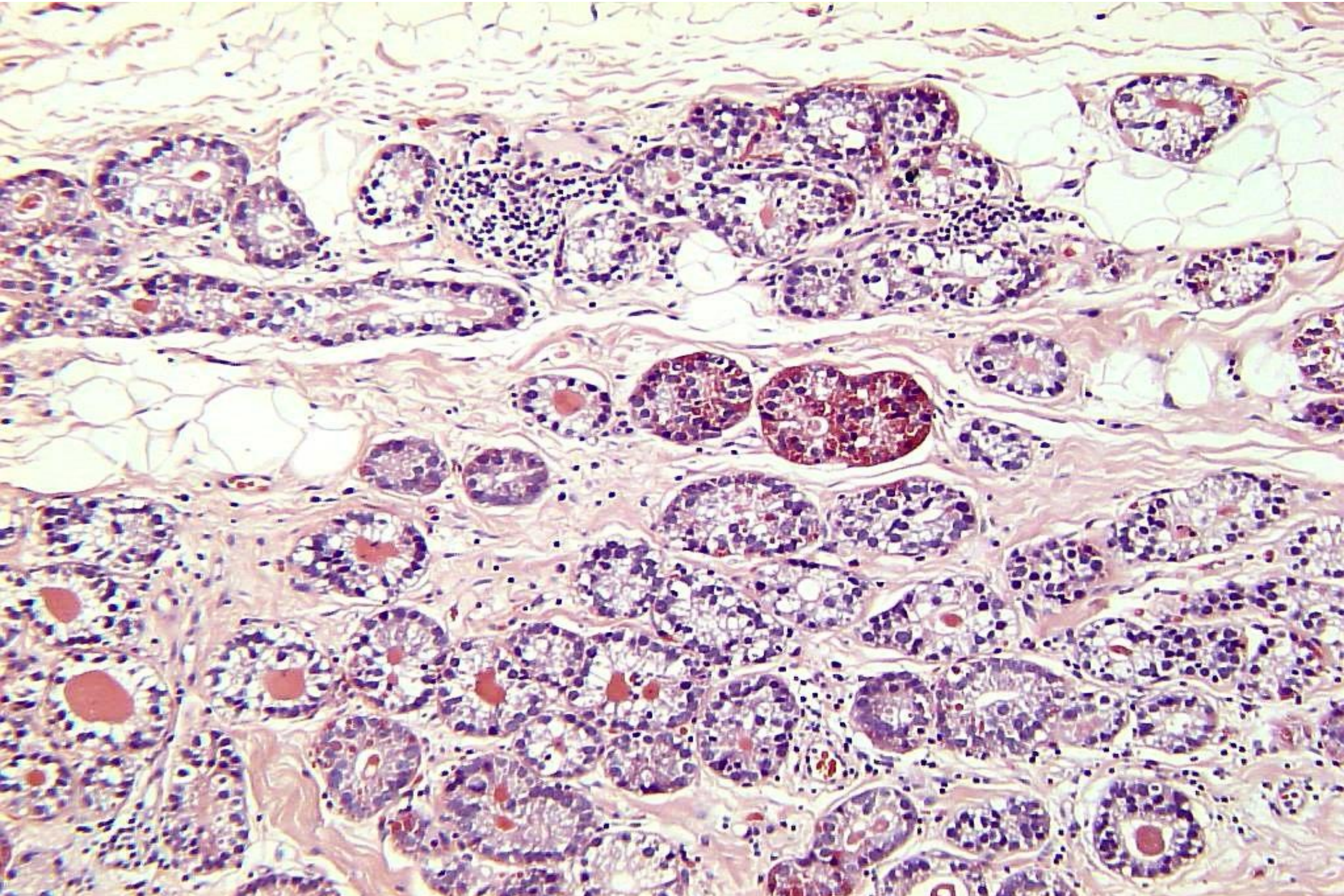
Virchows Arc 1996;429:69-74

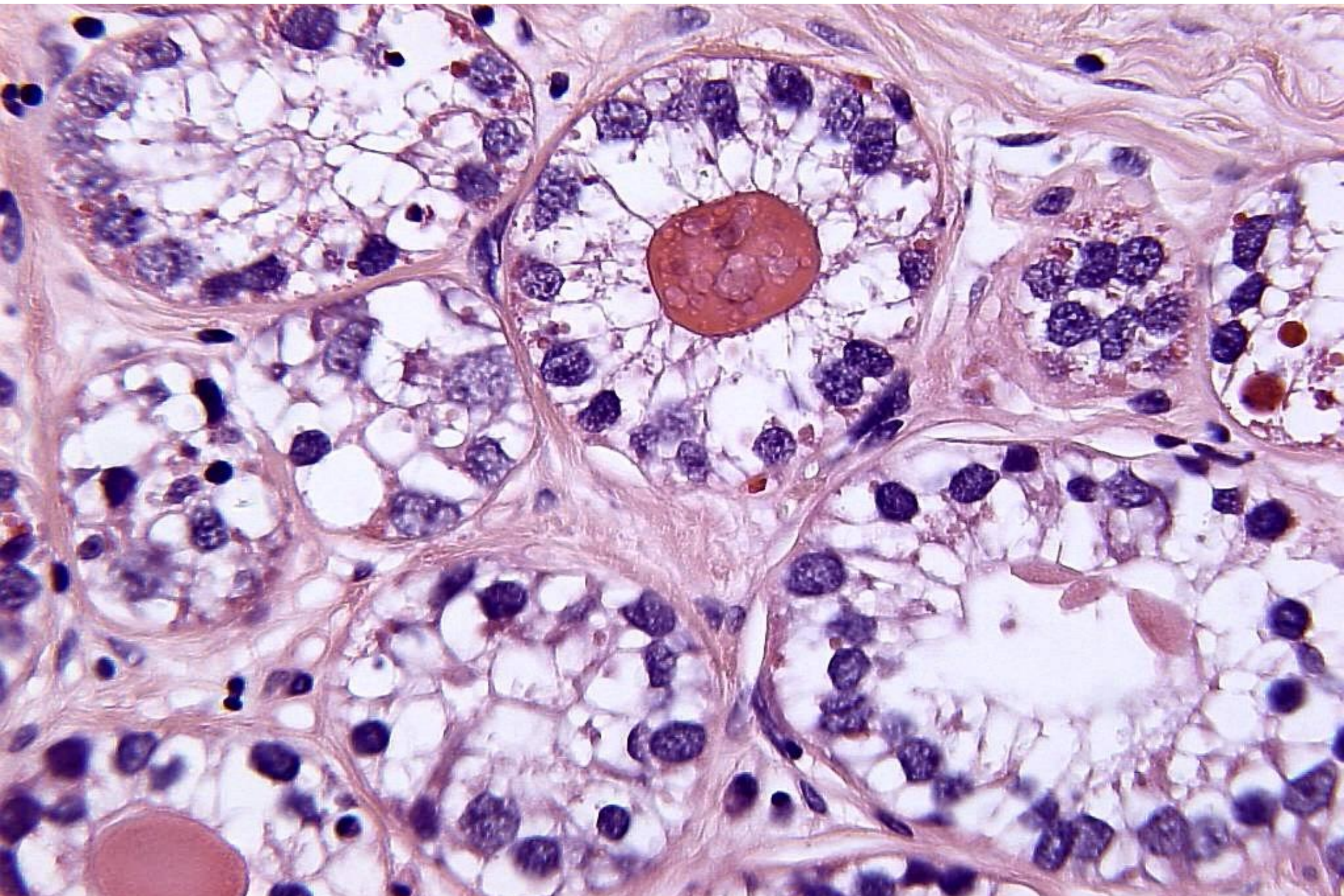
- Defined by serous differentiation
- Infiltrative margin
- Microglandular areas merging with solid aggregates
- Intraluminal inspissated secretion
- Stroma can be fibro-fatty without desmoplasia

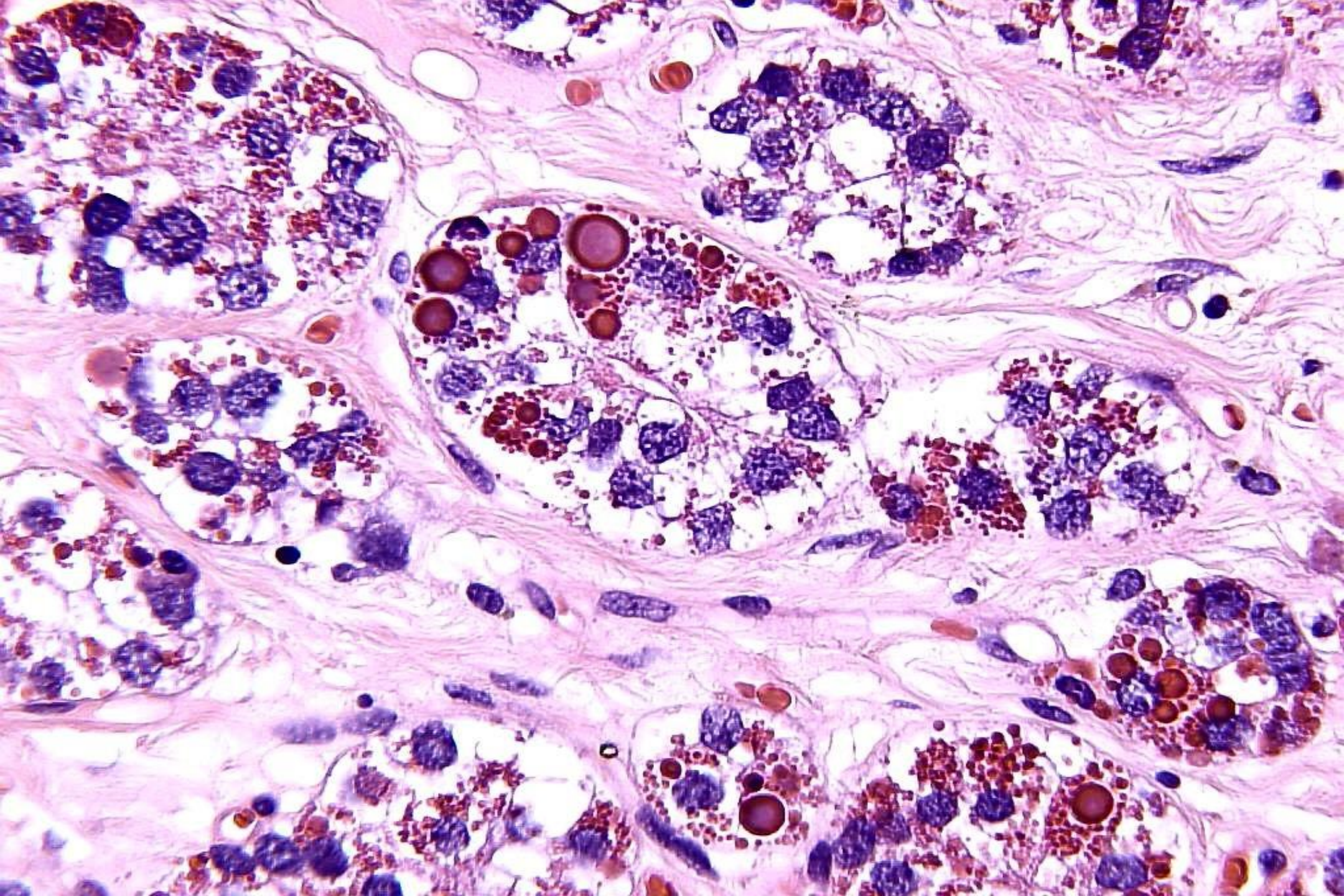
AcCC of the breast

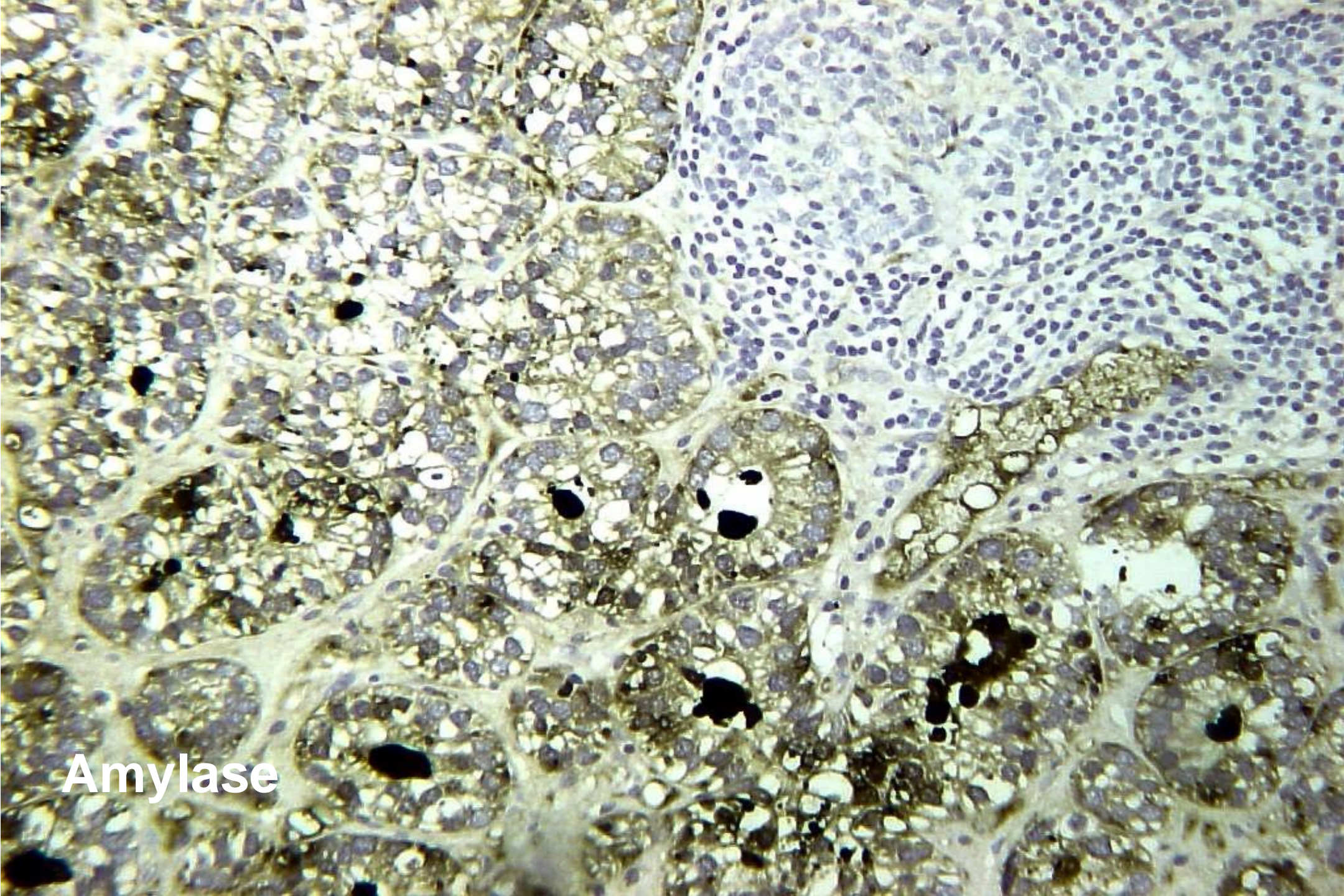
Morphology II

- Abundant eosinophilic or amphophilic granular cytoplasm
- Variable mitotic count
- Immunohistochemistry:
 - + Luminal cytokeratins, S100, Lysosyme, alfa 1-antitrypsin, alfa-amylase(focal, scanty), IgA, E Cadherin
 - Basal cytokeratins, ER, PR, HER 2, GCDFP
- EM: membrane bound zymogen granules 0.08-0.9um

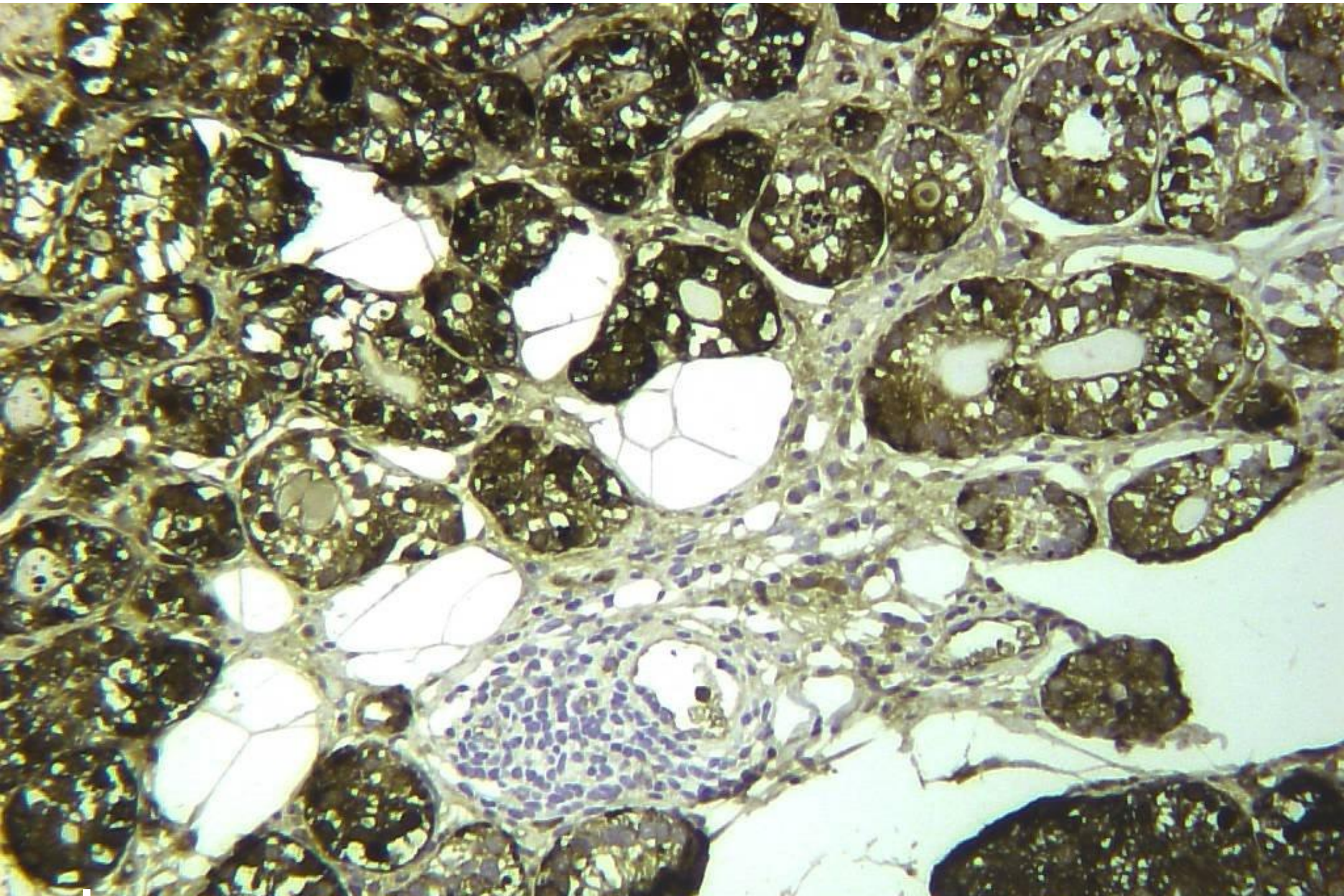


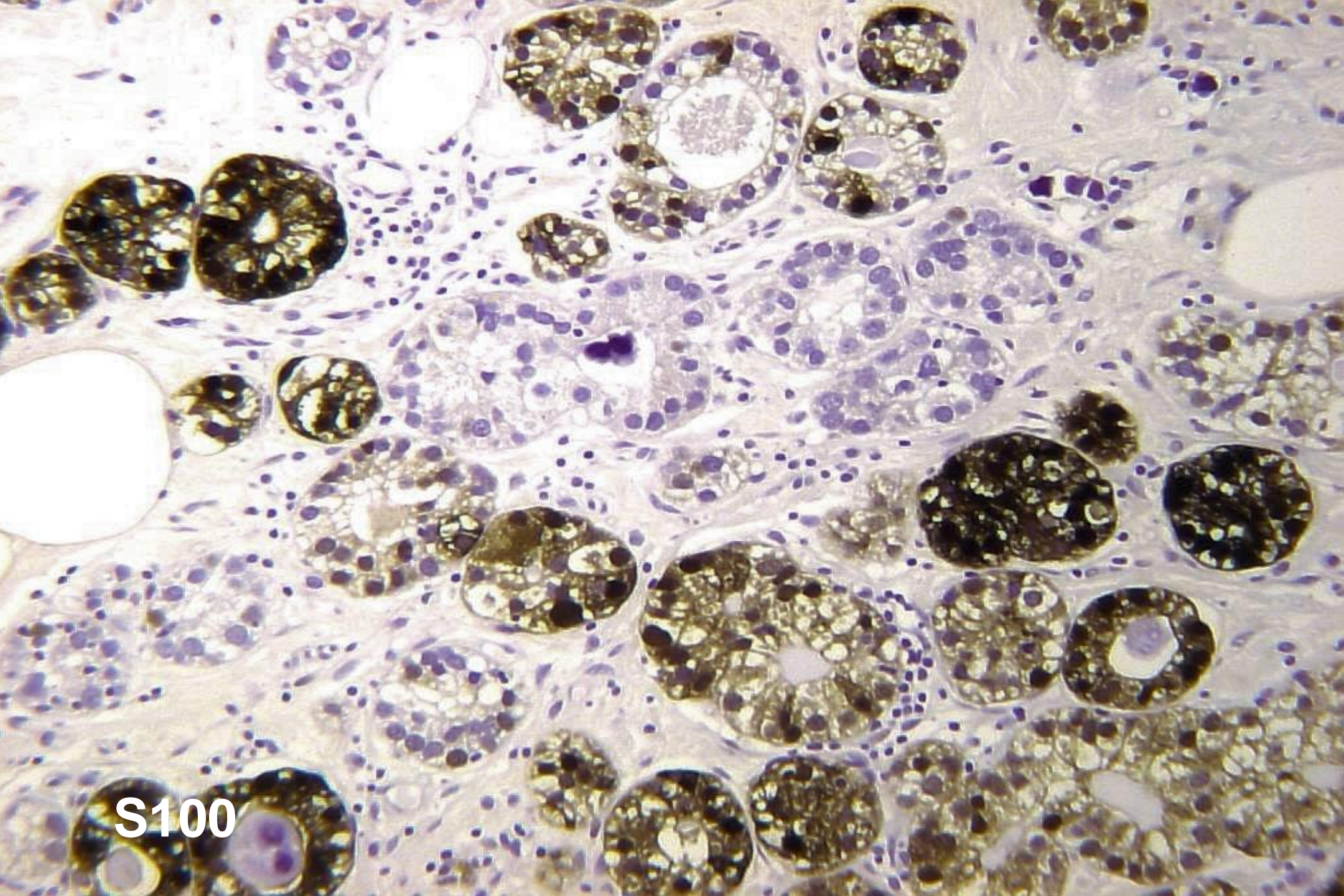




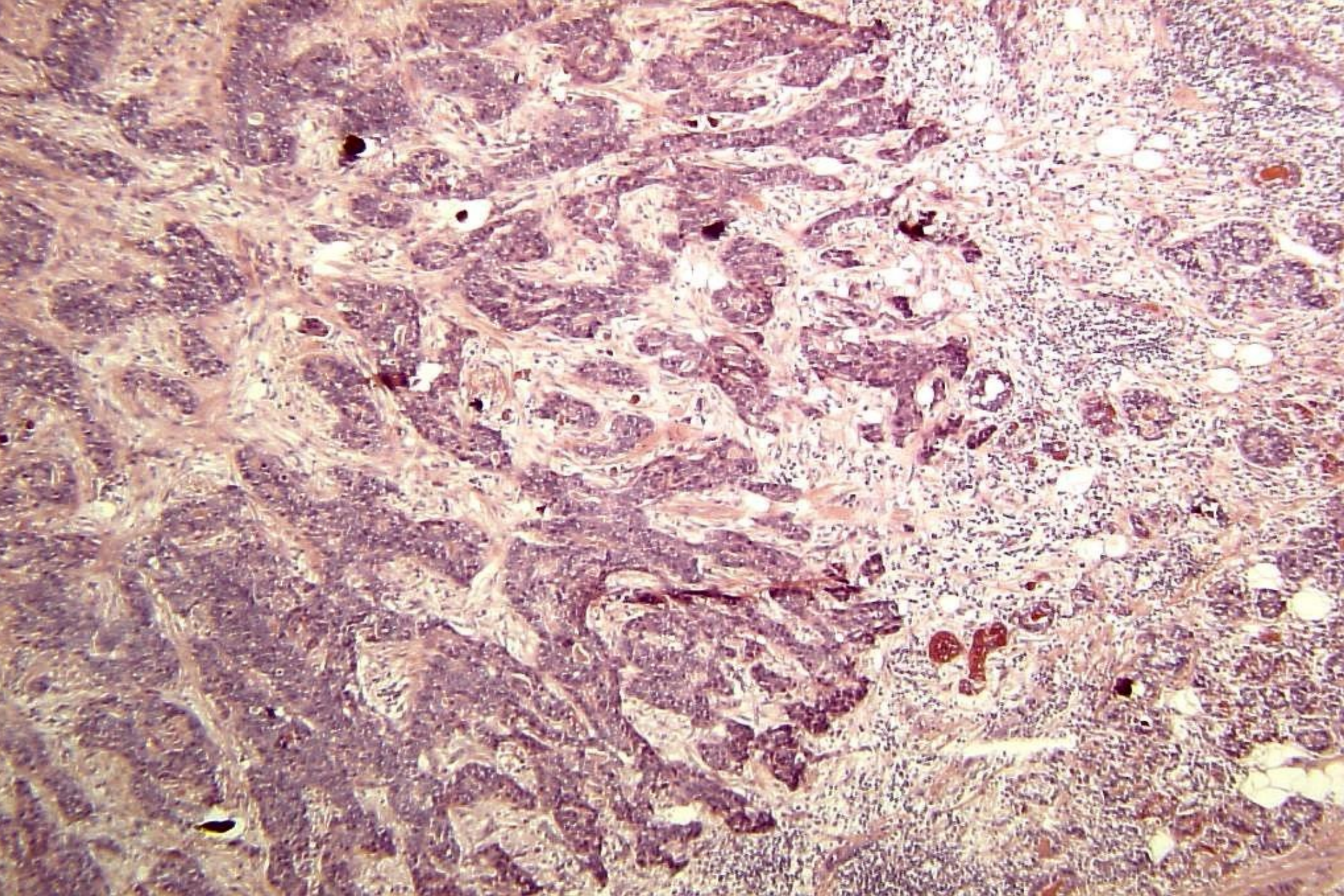


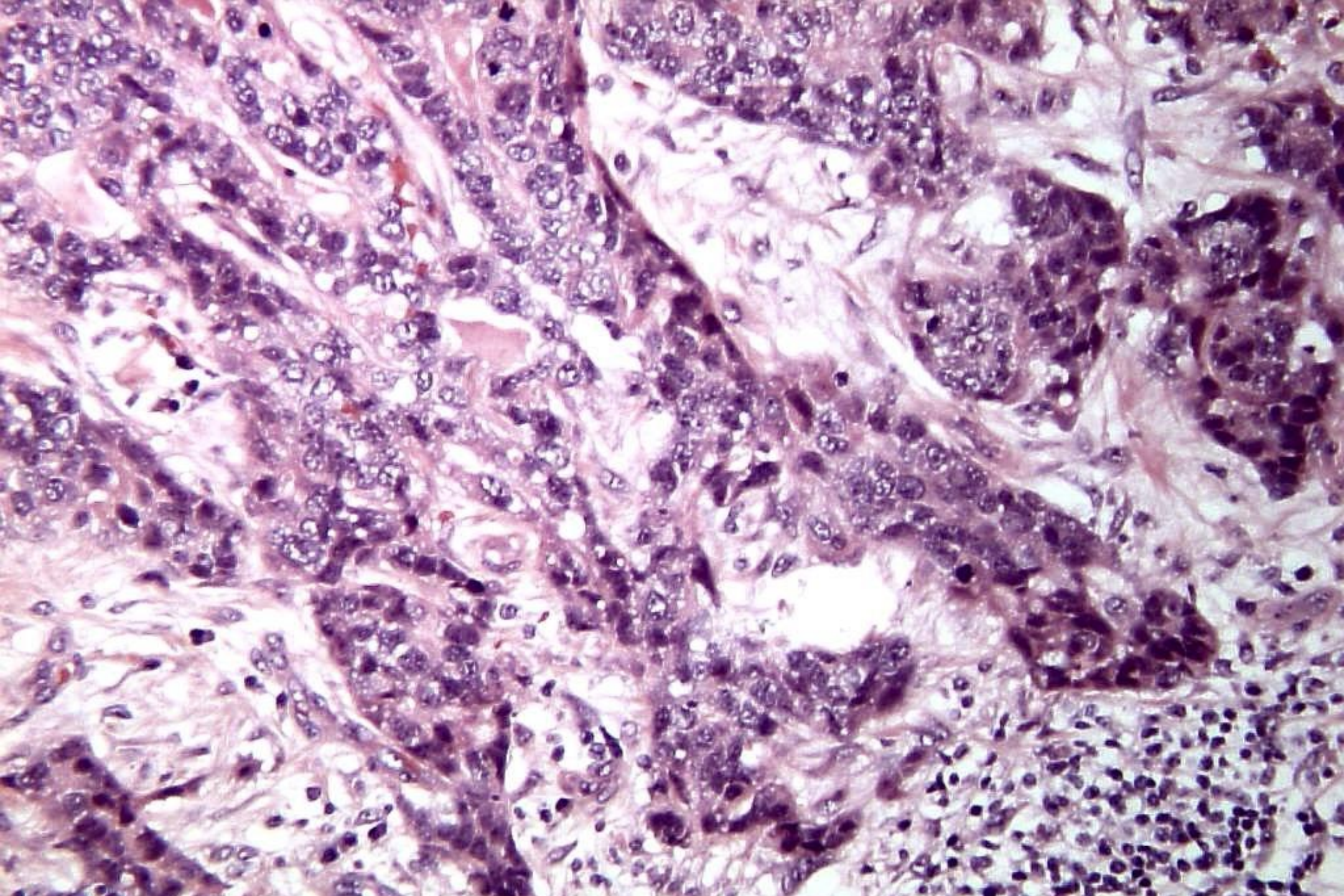
Amylase





S100





Differential diagnosis

Tumours with granular cytoplasm

- Neuroendocrine carcinoma – ICH
- Oncocytic tumours – mitochondria
- Apocrine carcinoma – GCDFP 15

Tumours with architectural similarities

- Microglandular adenosis
- Secretory carcinoma

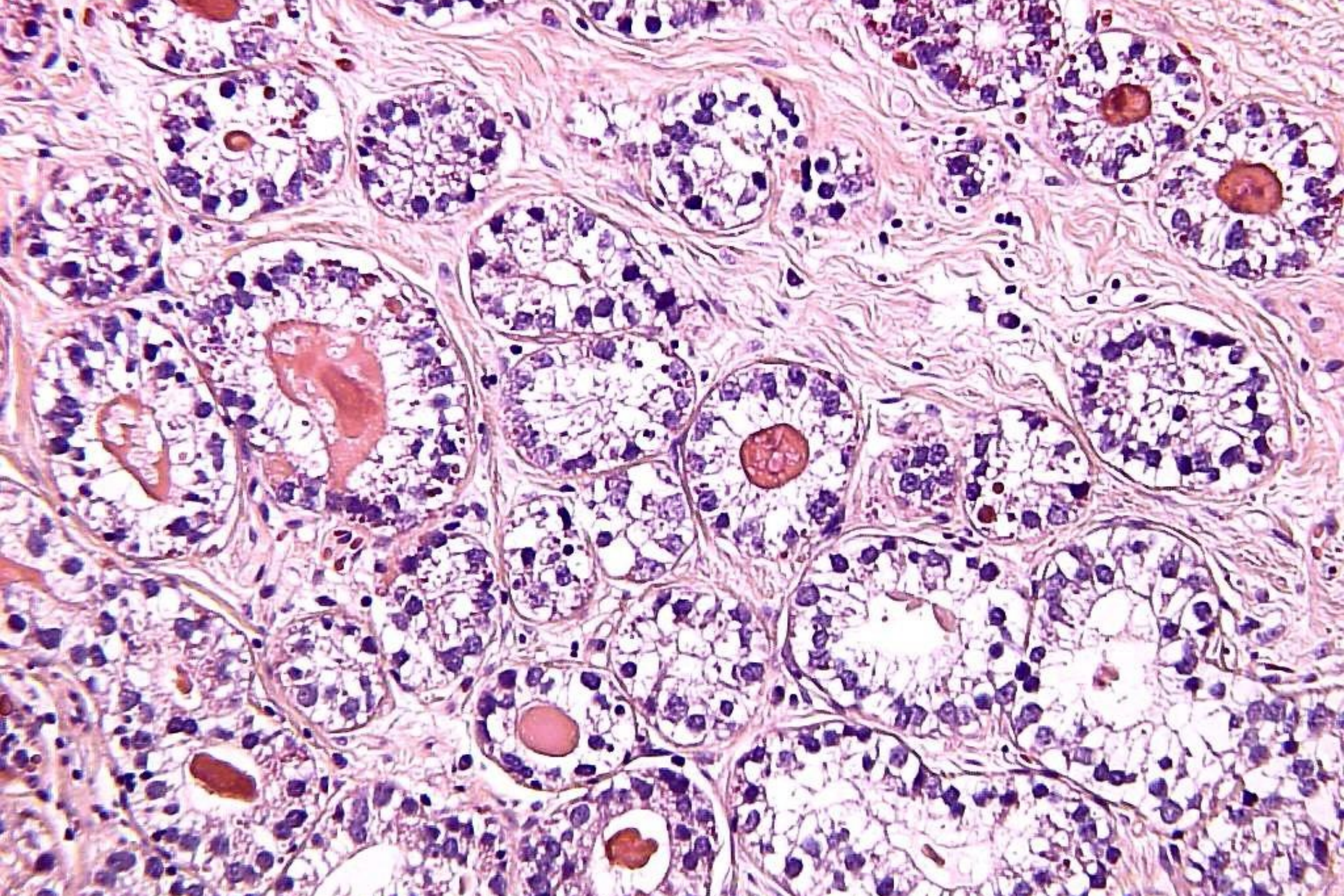
AcCC v MGA

- Overlapping architectural features-small glandular/acinar structure without myoepithelial layer
- IHC similarities- CK,S100,Lysosyme, ER, Her2
- Morphological similarities between MGA and AcCC
- Transitional forms do exist
- Reported carcinomas associated with MGA retain the acinar architecture
- High rate of invasive carcinoma also reported with MGA

AcCC v MGA

But

- AcCC usually with solid areas
- Lack of BM
- IHC differences-EMA, ?Amylase
- Zymogen granules on EM



AcCC v MGA

- Overlapping architectural features
 - small glandular/acinar structure without myoepithelial layer
- IHC similarities
 - CK, S100, ER, Lysosyme, Her2,

But

- AcCC usually with solid areas
- Lack of BM
- IHC differences
 - EMA, ?Amylase
- Zymogen granules on EM

Acinic cell carcinoma

Journal of Pathology

J Pathol 2015; **237**: 166–178

Published online 29 July 2015 in Wiley Online Library

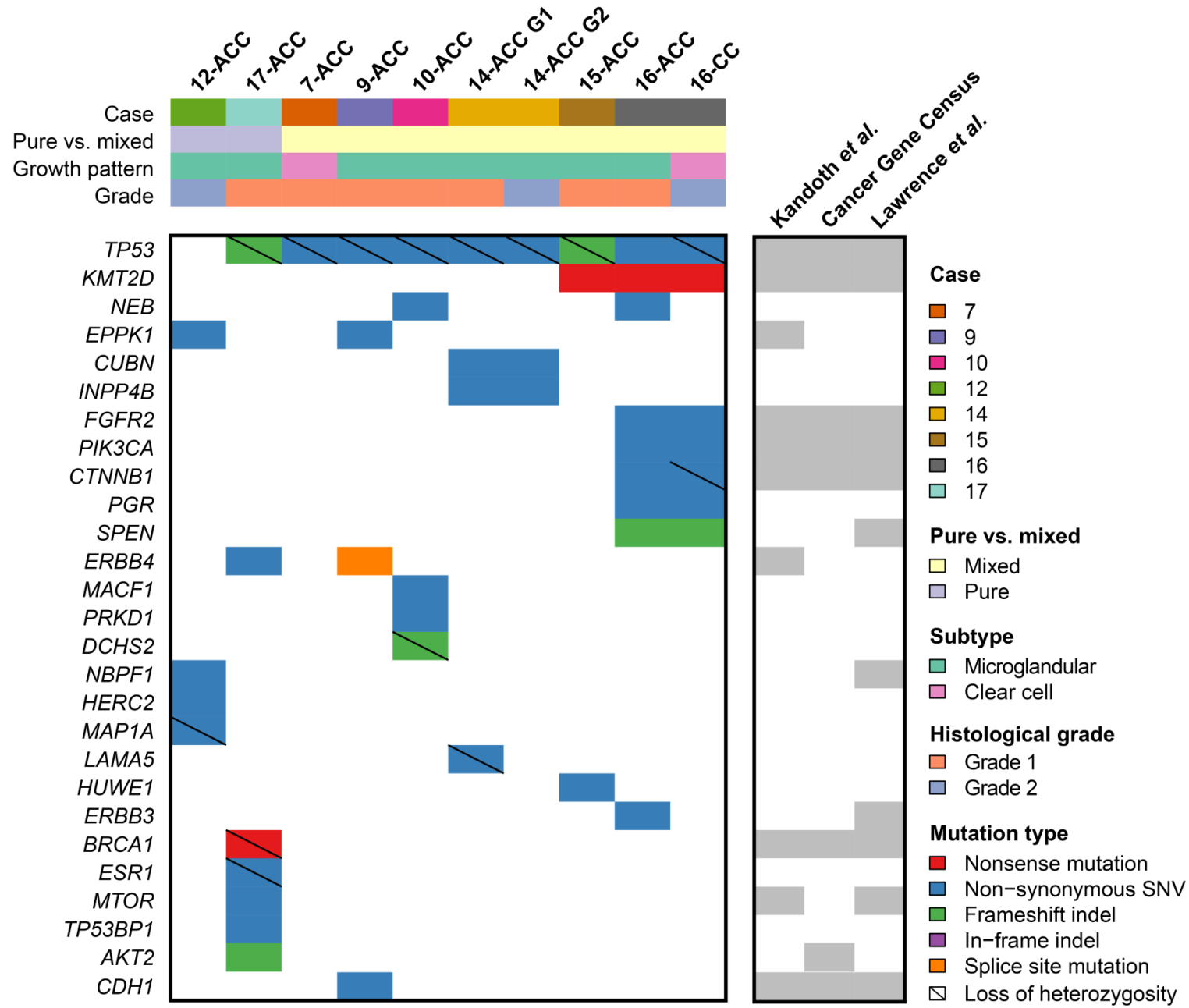
(wileyonlinelibrary.com) DOI: 10.1002/path.4566

ORIGINAL PAPER

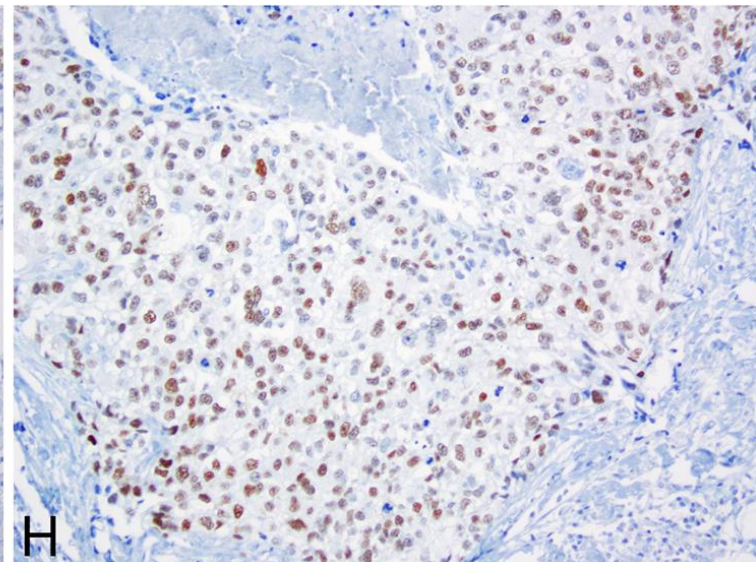
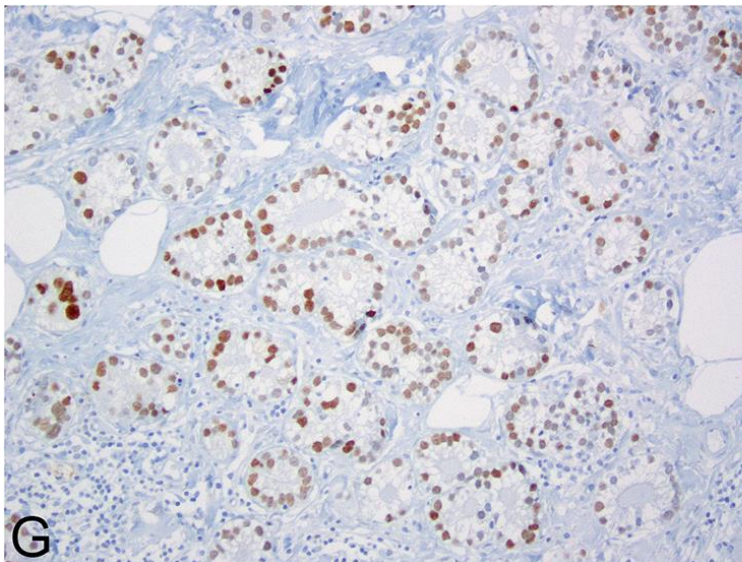
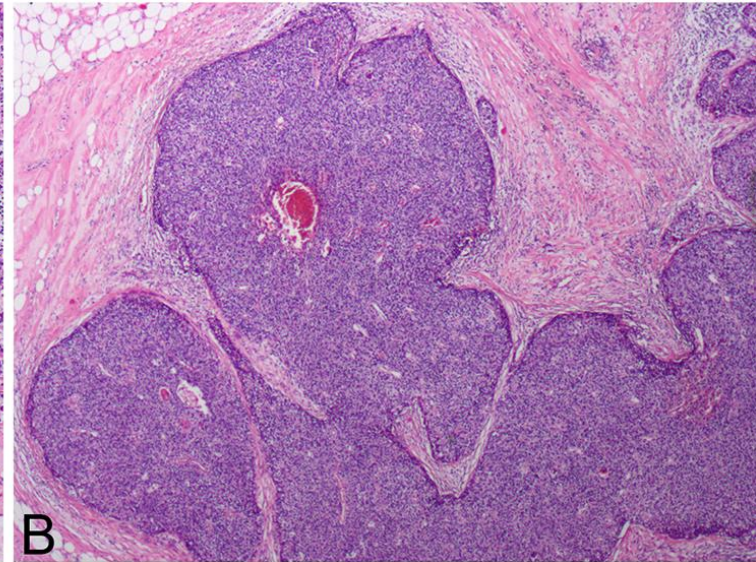
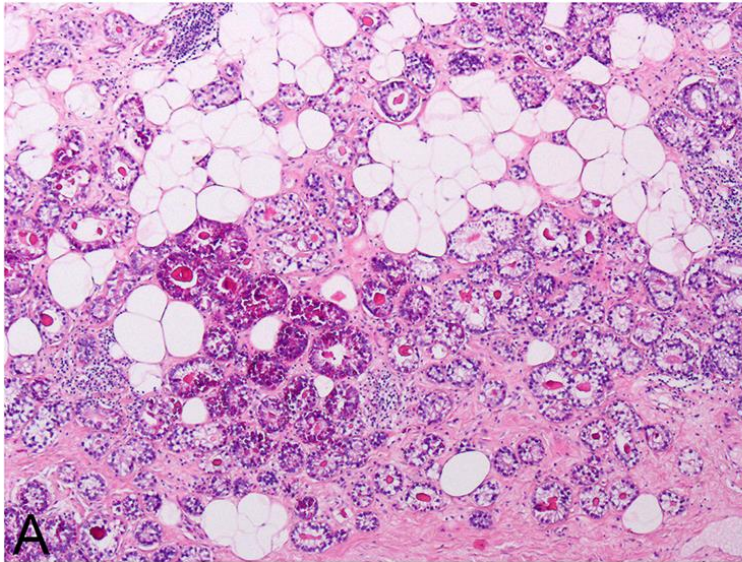
The repertoire of somatic genetic alterations of acinic cell carcinomas of the breast: an exploratory, hypothesis-generating study

Elena Guerini-Rocco,^{1,2†} Zsolt Hodi,^{3†} Salvatore Piscuoglio,^{1†} Charlotte KY Ng,^{1†} Emad A Rakha,³ Anne M Schultheis,¹ Caterina Marchiò,^{1,4} Arnaud da Cruz Paula,¹ Maria R De Filippo,¹ Luciano G Martelotto,¹ Leticia De Mattos-Arruda,^{1,5} Marcia Edelweiss,¹ Achim A Jungbluth,¹ Nicola Fusco,^{1,2} Larry Norton,⁶ Britta Weigelt,^{1*} Ian O Ellis^{3*} and Jorge S Reis-Filho^{1*}

Landscape of somatic genetic alterations



ACCs and high grade TNBCs share identical *TP53* mutations and p53 expression



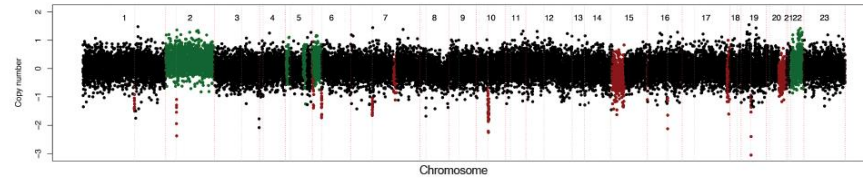
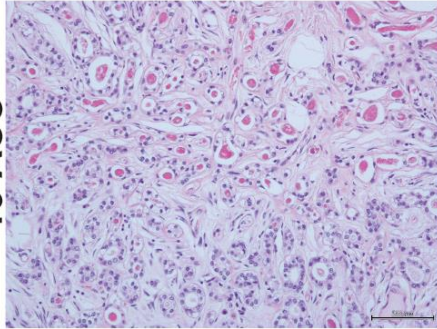
Classic and clear cell ACC and metaplastic breast cancer: parallel progression and convergent phenotypes

H&E

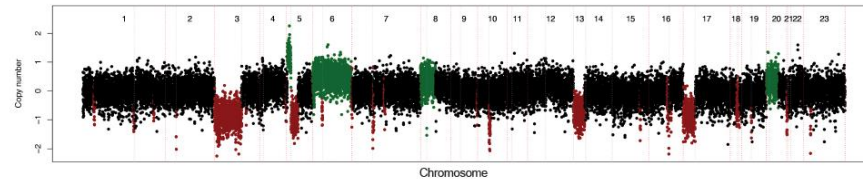
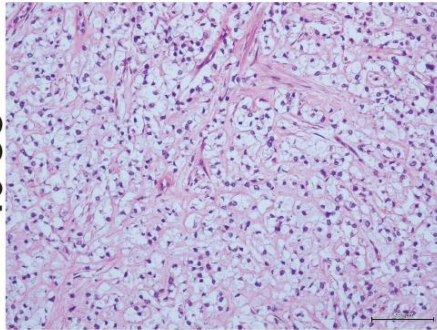
Genome plot

Mutational profile

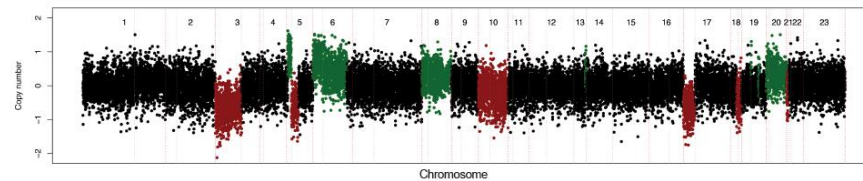
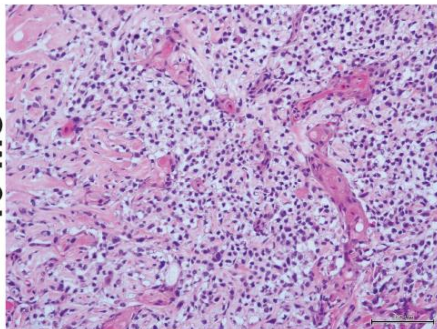
16-ACC



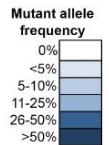
16-CC



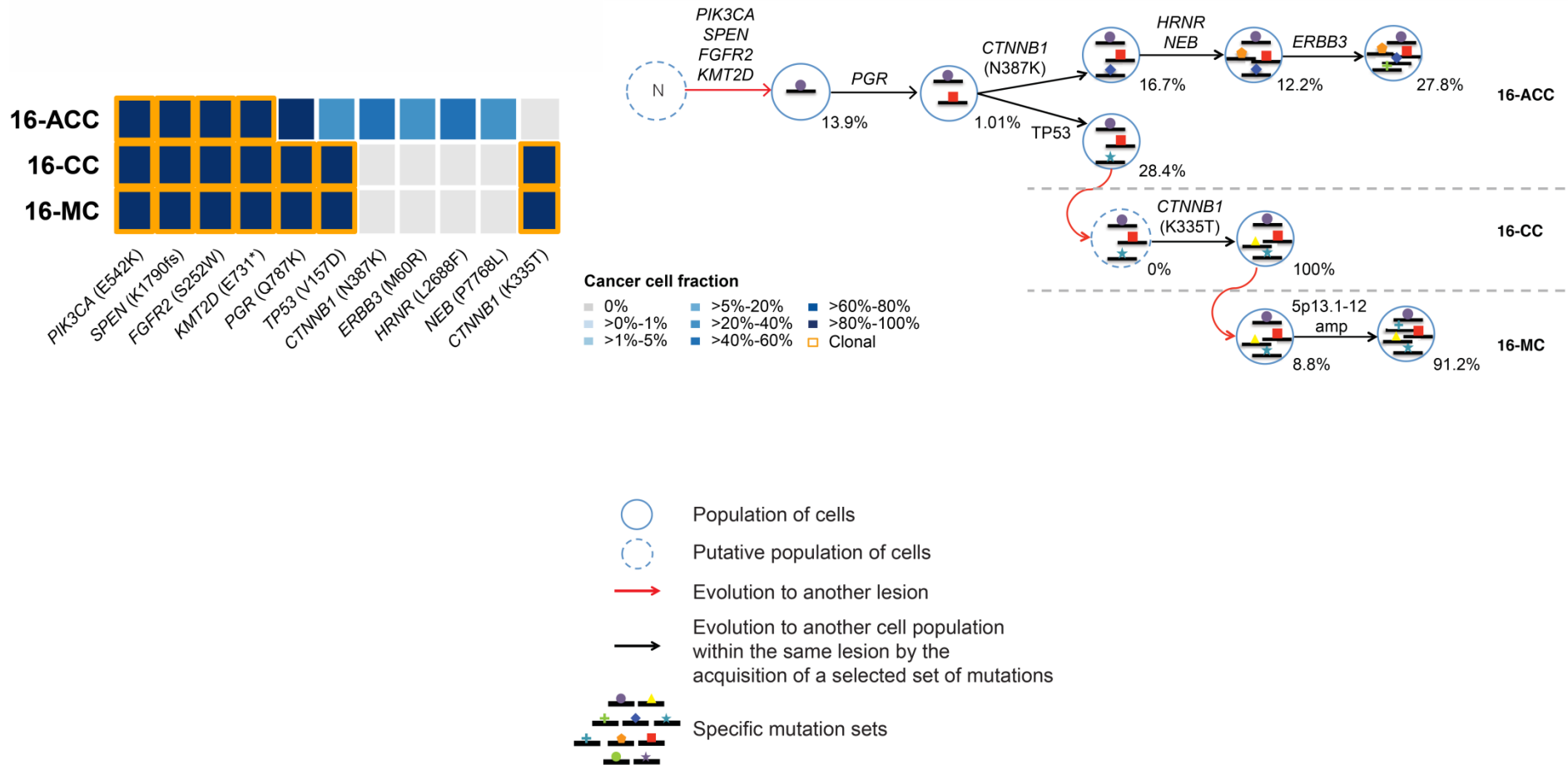
16-MC



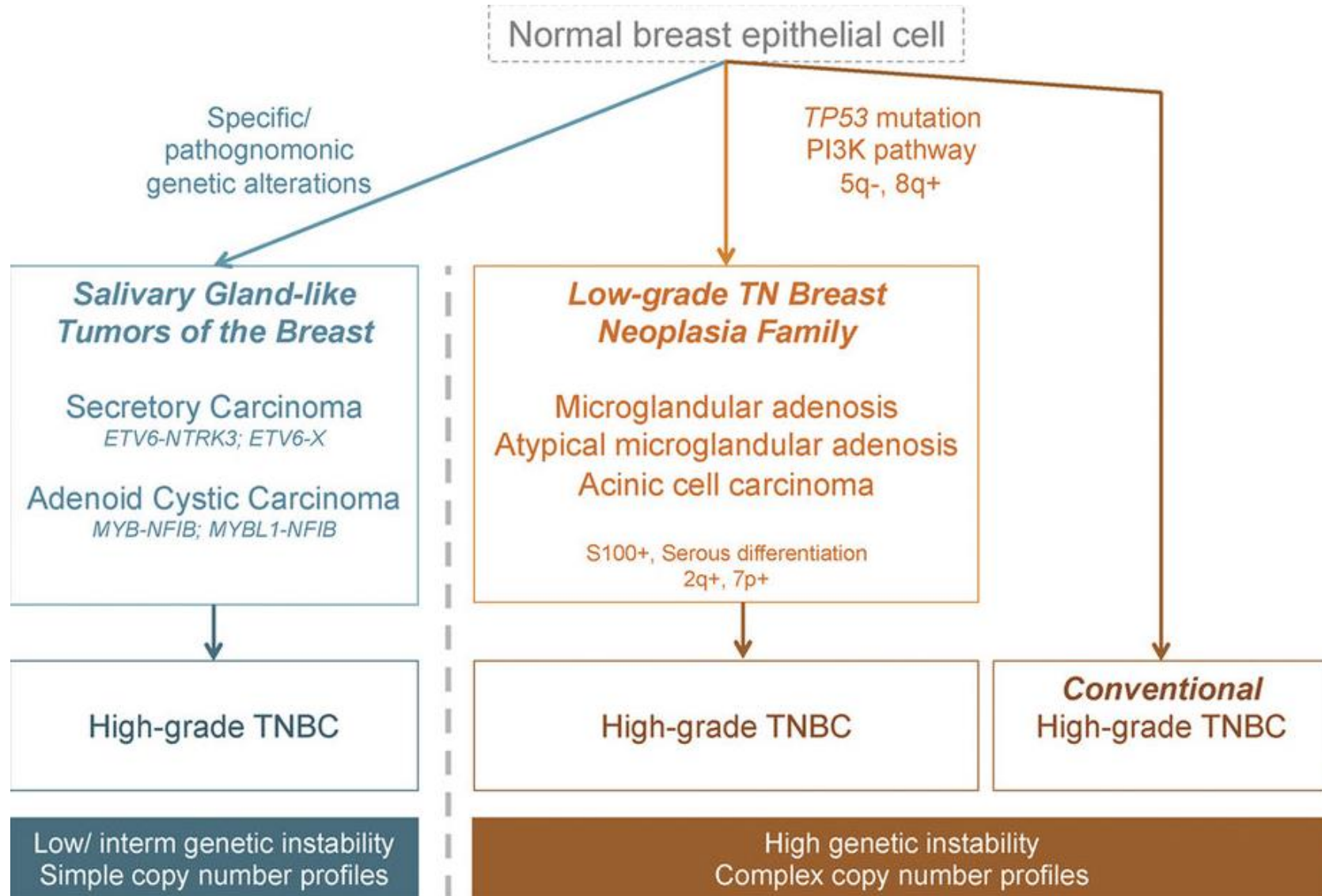
Mutation	16-ACC	16-CC	16-MC
<i>SPEN</i>	Dark Blue	Dark Blue	Dark Blue
K1790fs	Dark Blue	Dark Blue	Dark Blue
<i>FGFR2</i>	Dark Blue	Dark Blue	Dark Blue
S252W	Dark Blue	Dark Blue	Dark Blue
<i>KMT2D</i>	Dark Blue	Dark Blue	Dark Blue
E731*	Dark Blue	Dark Blue	Dark Blue
<i>PIK3CA</i>	Dark Blue	Dark Blue	Dark Blue
E542K	Dark Blue	Dark Blue	Dark Blue
<i>PGR</i>	Dark Blue	Dark Blue	Dark Blue
Q787K	Dark Blue	Dark Blue	Dark Blue
<i>TP53</i>	Dark Blue	Dark Blue	Dark Blue
V157D	Dark Blue	Dark Blue	Dark Blue
<i>CTNNB1</i>	Light Blue	Light Blue	Light Blue
N387K	Light Blue	Light Blue	Light Blue
<i>HRNR</i>	Light Blue	Light Blue	Light Blue
L2688F	Light Blue	Light Blue	Light Blue
<i>NEB</i>	Light Blue	Light Blue	Light Blue
P7768L	Light Blue	Light Blue	Light Blue
<i>ERBB3</i>	Light Blue	Light Blue	Light Blue
M60R	Light Blue	Light Blue	Light Blue
<i>CTNNB1</i>	White	Dark Blue	Dark Blue
K335T	White	Dark Blue	Dark Blue



Classic and clear cell ACC and metaplastic breast cancer: parallel progression and convergent phenotypes



Triple Negative Breast Cancer



WHO 2019

Rare Breast and Salivary Cancers

- Acinic Cell
- Adenoid Cystic
- Secretory
- Mucoepidermoid
- Polymorphous adenocarcinoma
- Tall cell carcinoma with reversed polarity

Thank you





The image shows the exterior of the Nottingham Breast Institute. The building is a modern structure with a curved glass facade and a brick section. The brick section is on the left, and the glass section is on the right. The sky is clear and blue. There are some trees and a paved area in the foreground.

Nottingham
Breast Institute

NHS