Salivary Gland Type Tumours of the Breast: Insights and updates

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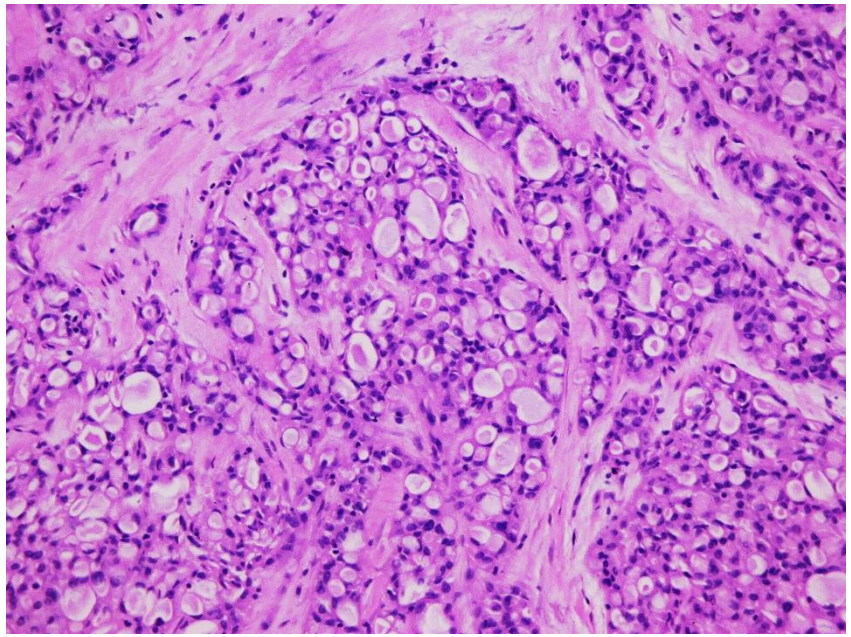
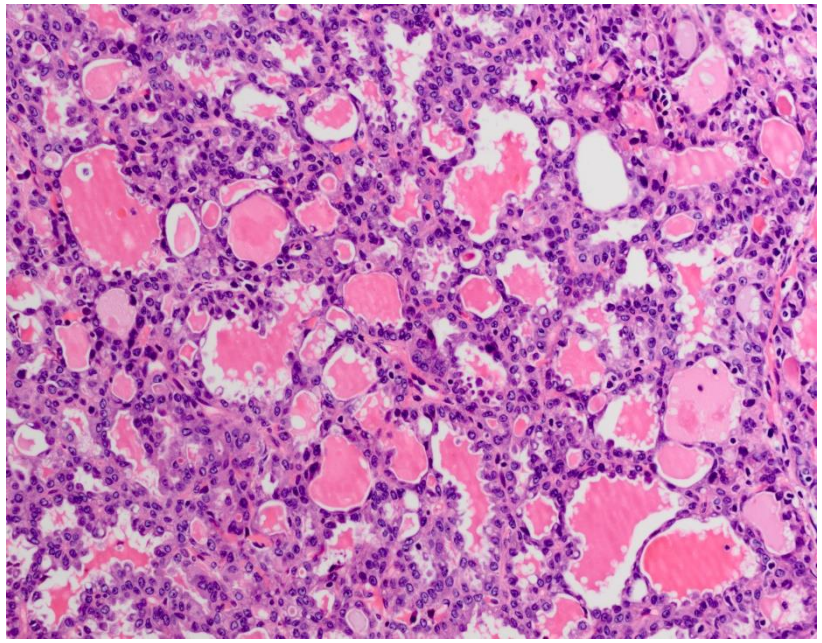
Salivary gland-type tumors of breast

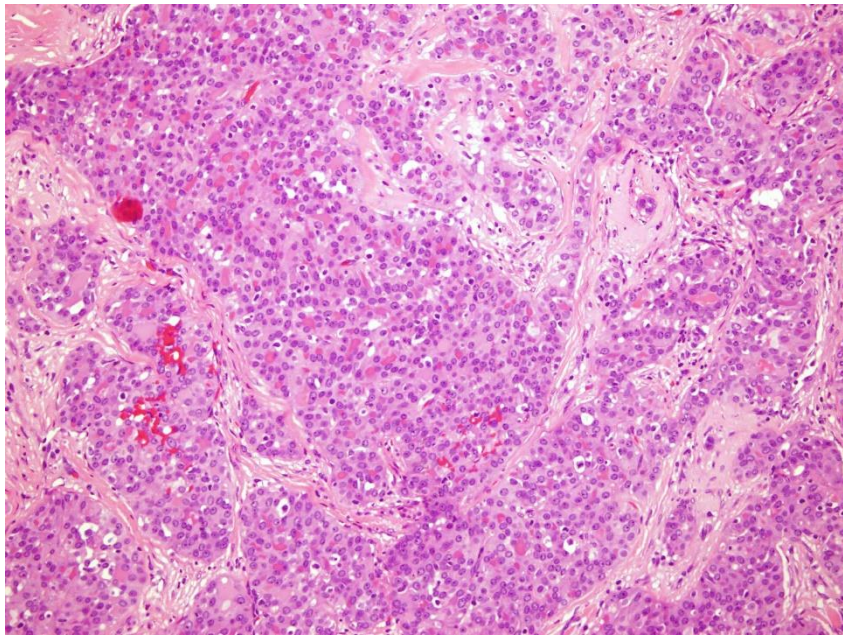
Salivary gland-type tumors
Acinic cell carcinoma
Adenoid cystic carcinoma
Secretory carcinoma
Mucoepidermoid carcinoma
Polymorphous adenocarcinoma
Pleomorphic adenoma
Adenomyoepithelioma and malignant adenomyoepithelioma

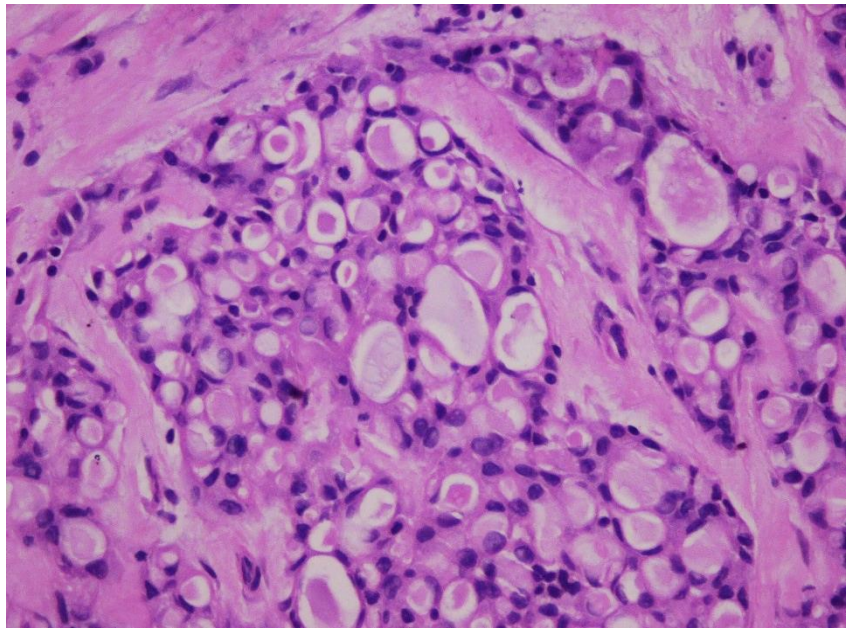
Secretory Carcinoma

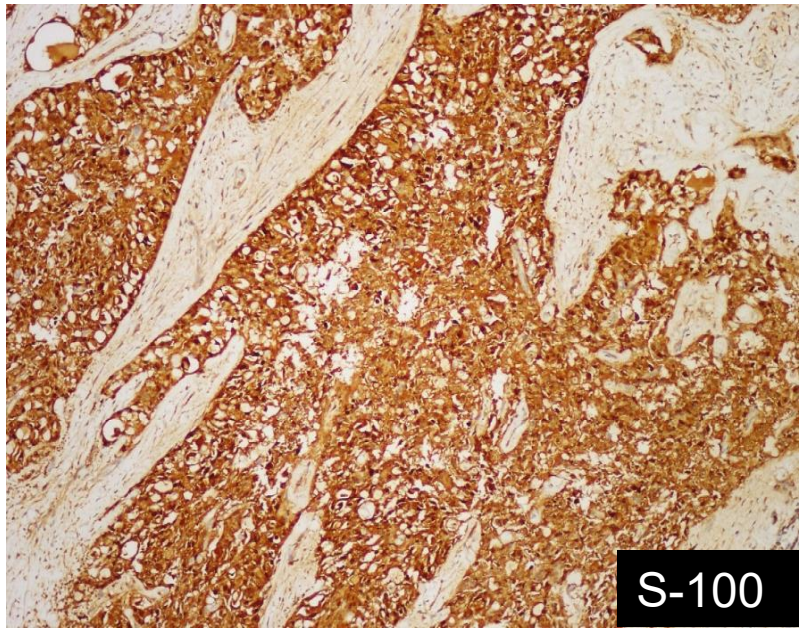
- Tumor cells with eosinophilic granular or vacuolated cytoplasm, round to oval nuclei
- Microcystic/honeycomb, solid, tubular, papillary growth pattern
- In situ component may be present; typically cribriform or solid with low or intermediate nuclear grade
- either triple-negative or weakly ER/PR-positive
- Characterized by *ETV6::NTRK3* gene fusion
- Generally have an indolent clinical course, even in patients with nodal metastases
- Axillary metastases are reported in 20–35% secretory carcinomas and typically involve no more than three nodes



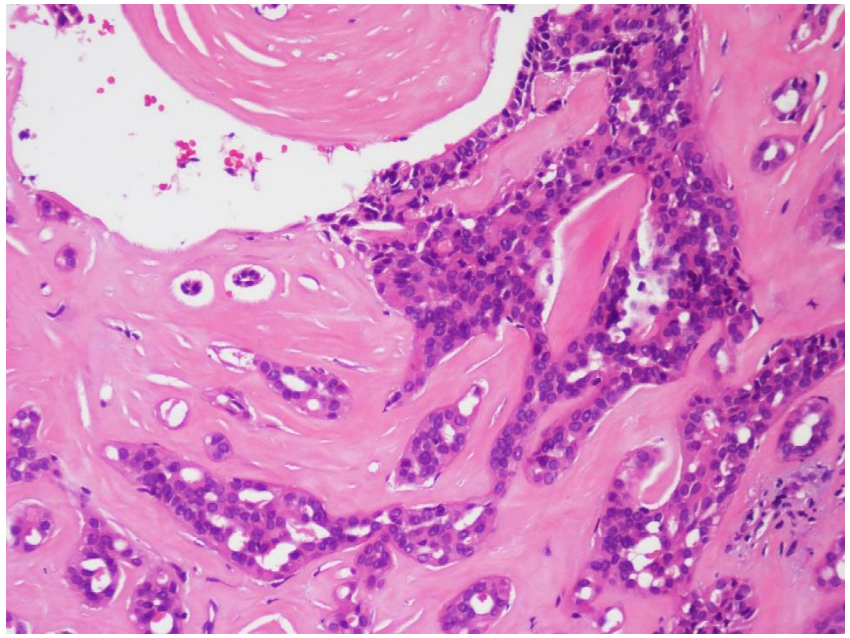
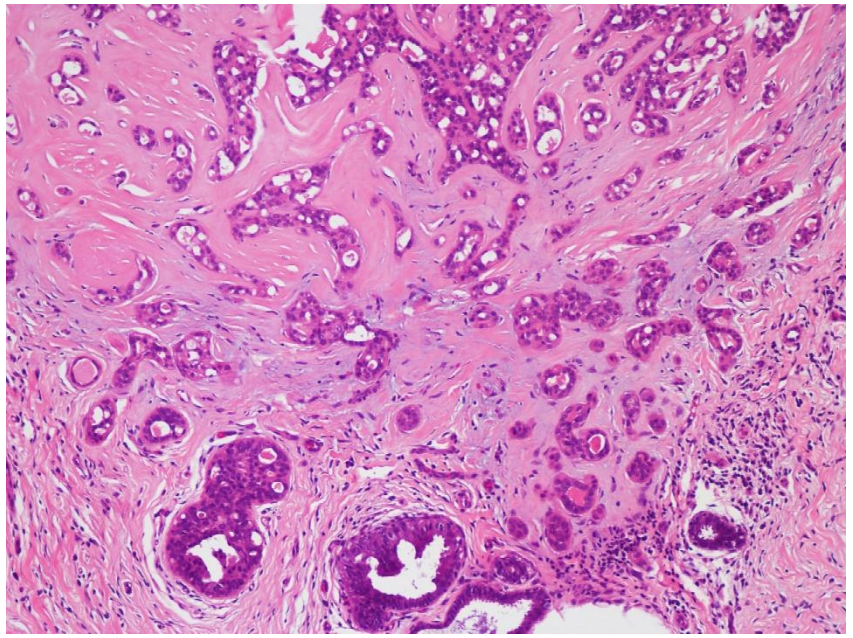
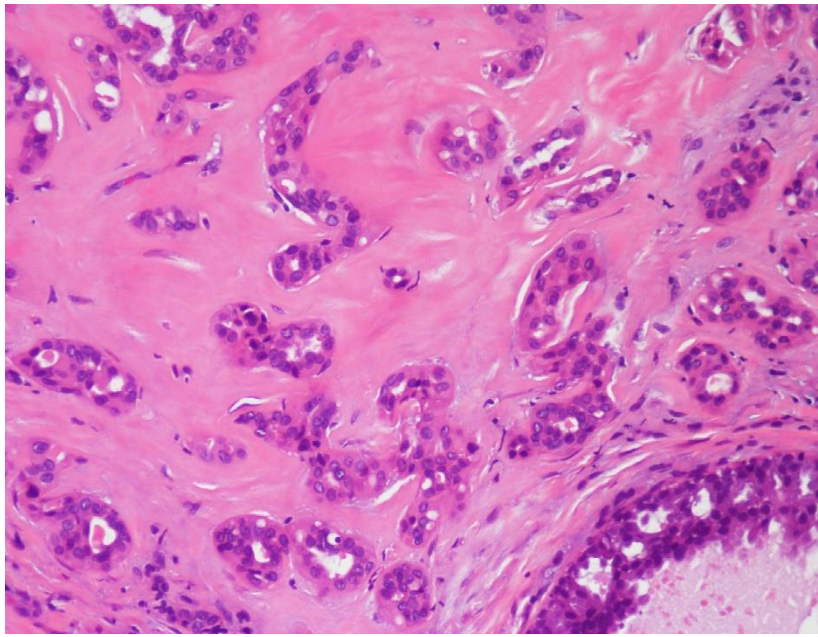
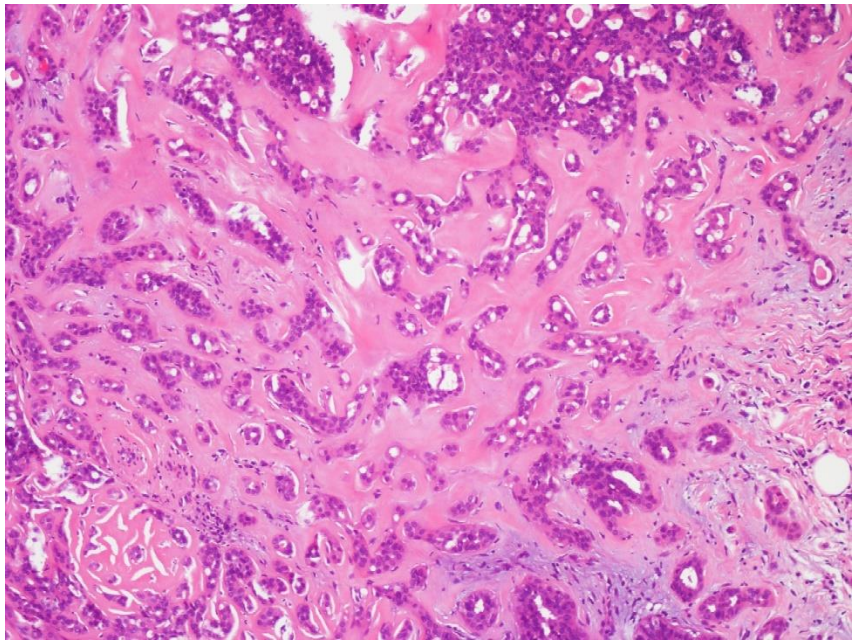
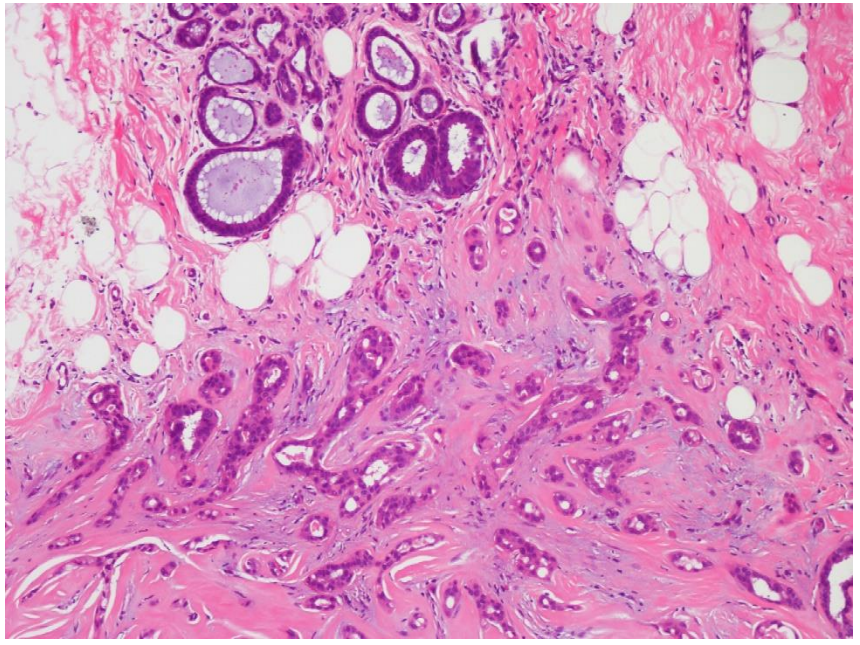
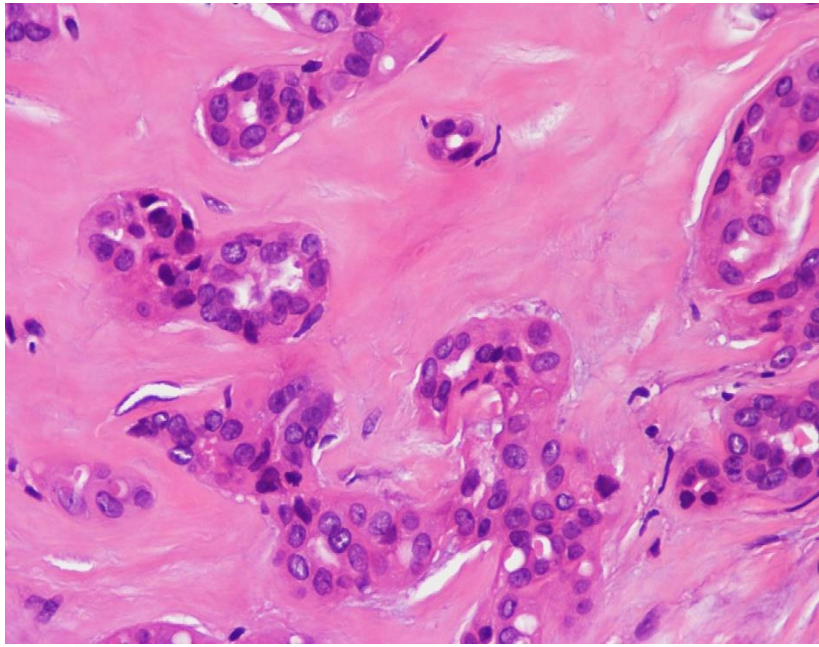


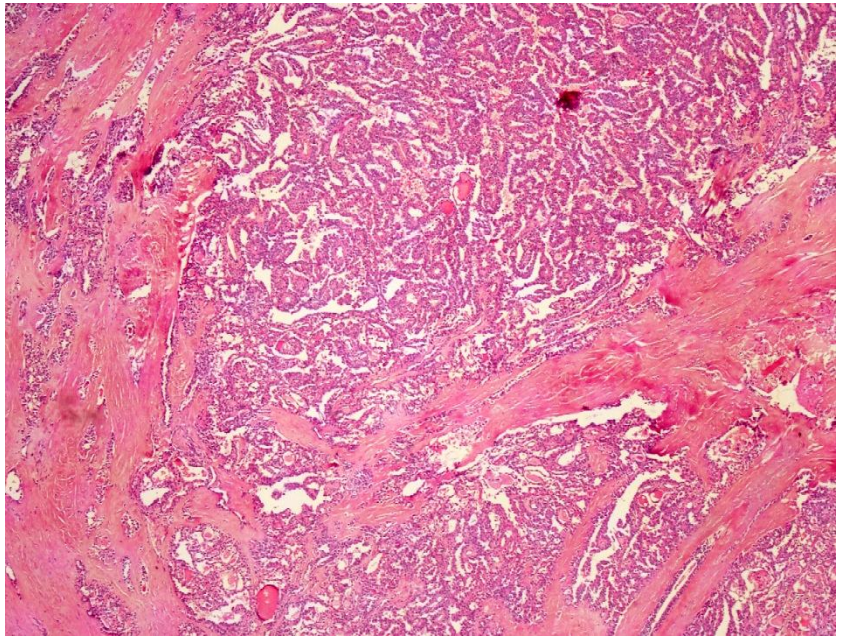
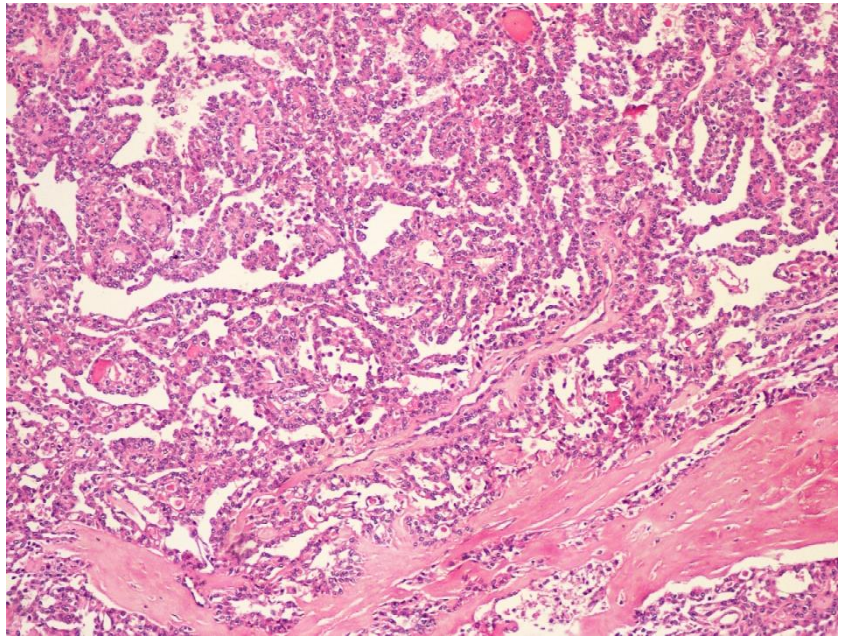
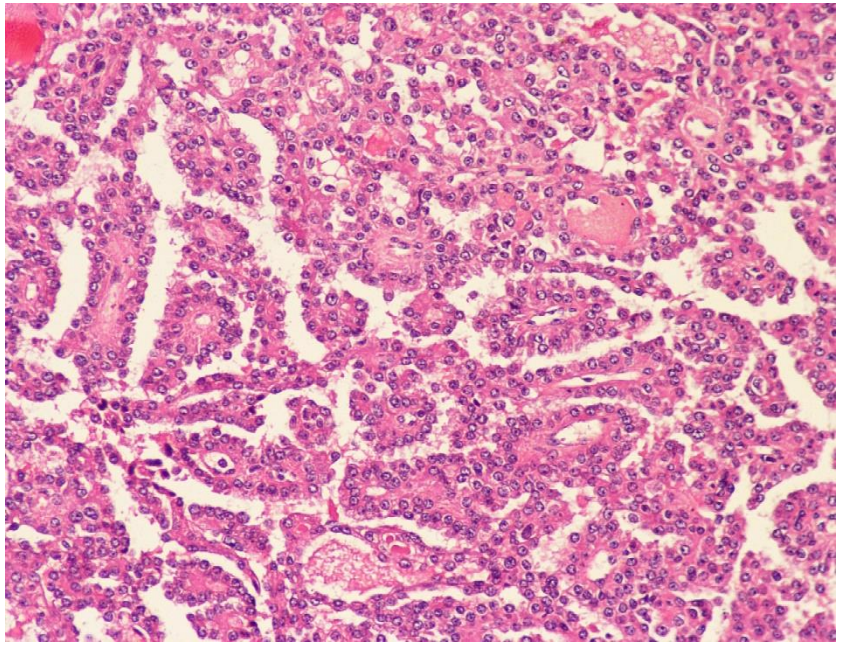
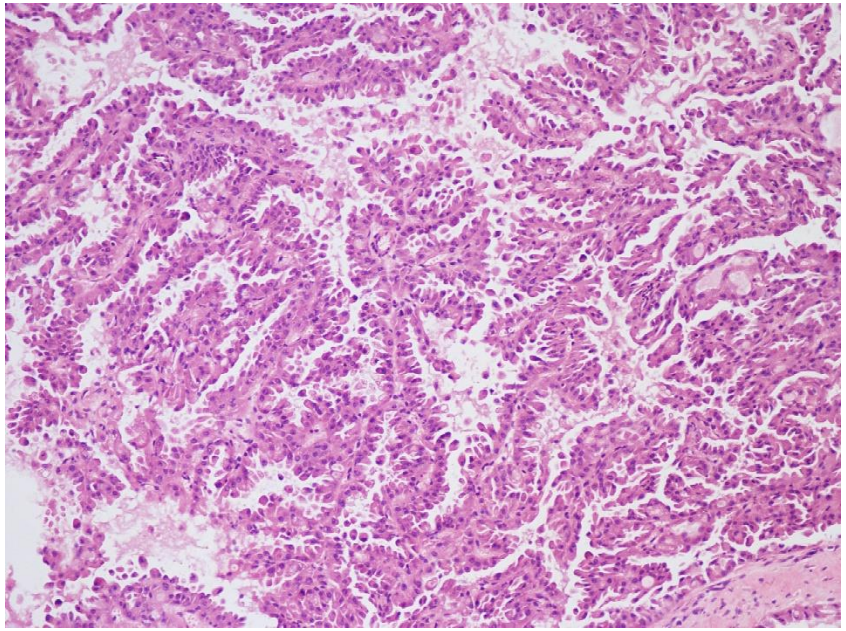
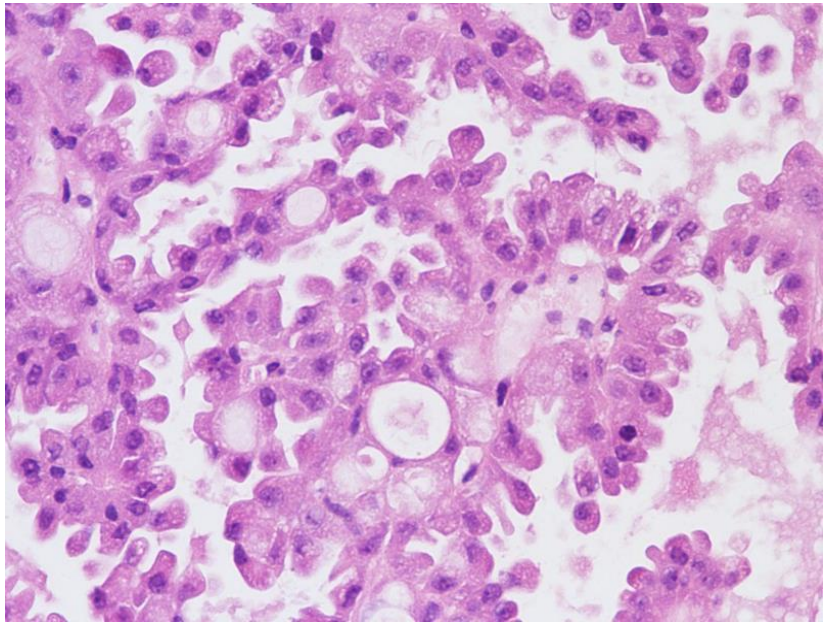
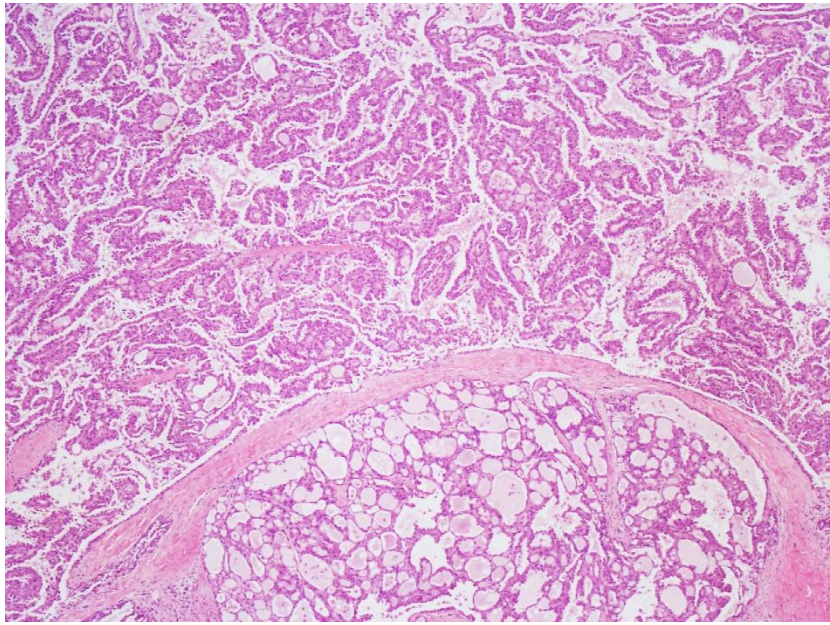




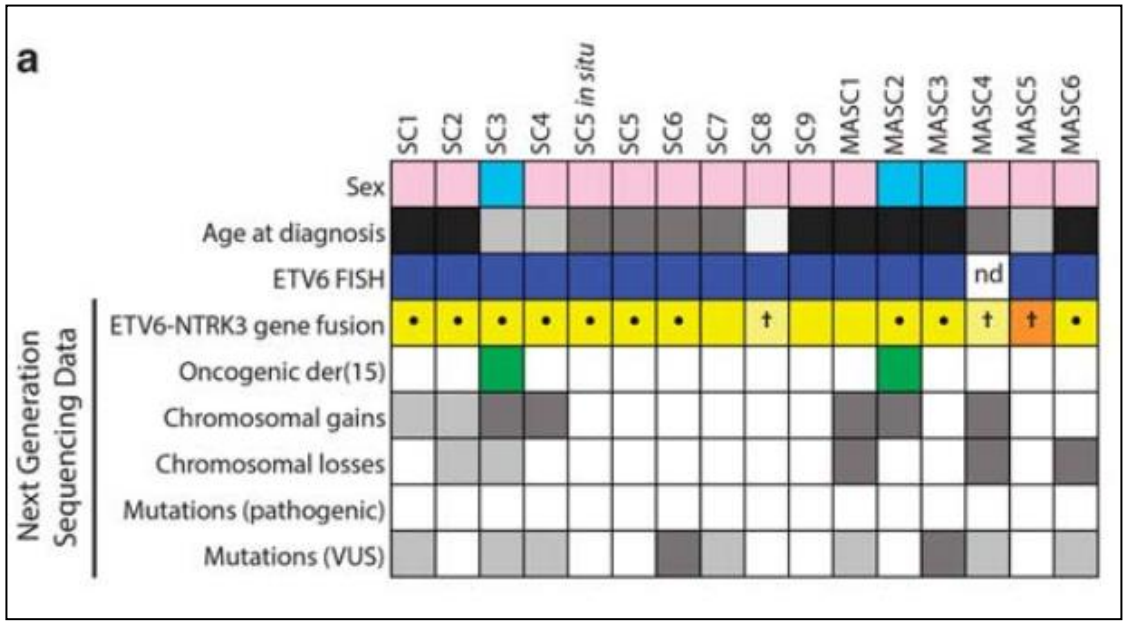


- **TNBC or low HR expression**
- **Low Ki67**
- **S100, SOX10, MUC 4 positive**
- **CK5/6, TRPS1, GCDFP15 may be positive**

Genomic profiling of breast secretory carcinomas reveals distinct genetics from other breast cancers and similarity to mammary analog secretory carcinomas



- **NGS of 510 Tumor-related Genes**
- **IHC: MUC4 and SOX10 (+)**
- **Low mutation burden, lack of copy number variation or minimal copy number variation**
- **Molecular alterations differ from conventional triple-negative breast cancer**
- ***ETV6::NTRK3* is the main molecular abnormality and likely the causative event**

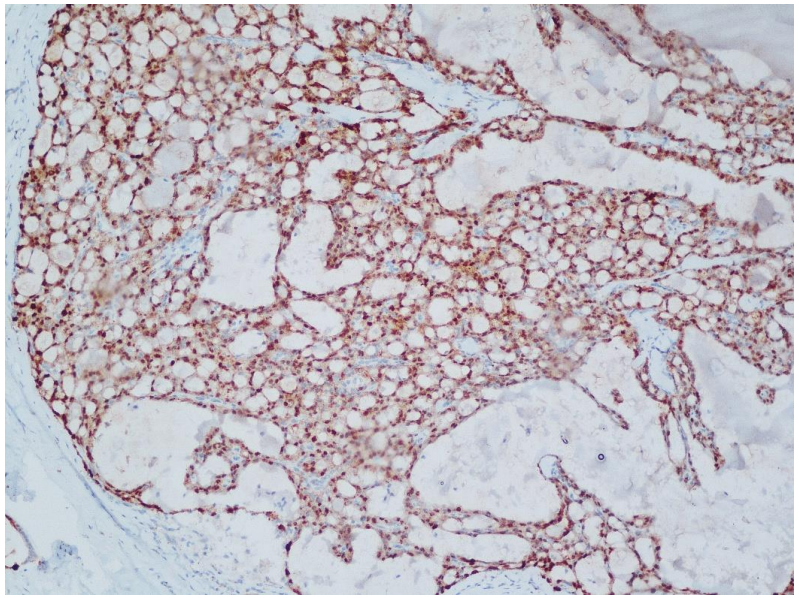
The *ETV6::NTRK3* fusion carries significant clinical value, as patients with aggressive disease may be treated with TRK inhibitors such as**: Larotectinib, entrectinib, selitectinib,repotrectinib**

Mod Pathol 2017;30:1086-1099

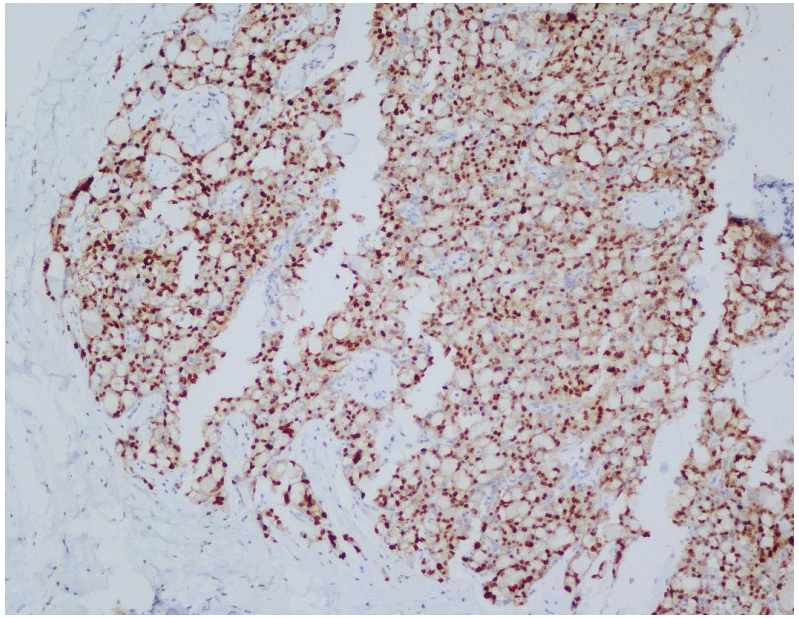
Pan-TRK Immunohistochemistry

A Useful Diagnostic Adjunct For Secretory Carcinoma of the Breast

Beth T. Harrison, MD,† Elizabeth Fowler, MD,*† Gregor Krings, MD, PhD,‡ Yunn-Yi Chen, MD, PhD,‡ Gregory R. Bean, MD, PhD,§ Anne Vincent-Salomon, MD, PhD,‖ Laetitia Fuhrmann, MS,‖ Sandra E. Barnick, MD,¶ Beiyun Chen, MD, PhD,# Elizabeth M. Hosfield, MD,** Jason L. Hornick, MD, PhD,*† and Stuart J. Schnitt, MD*†††*



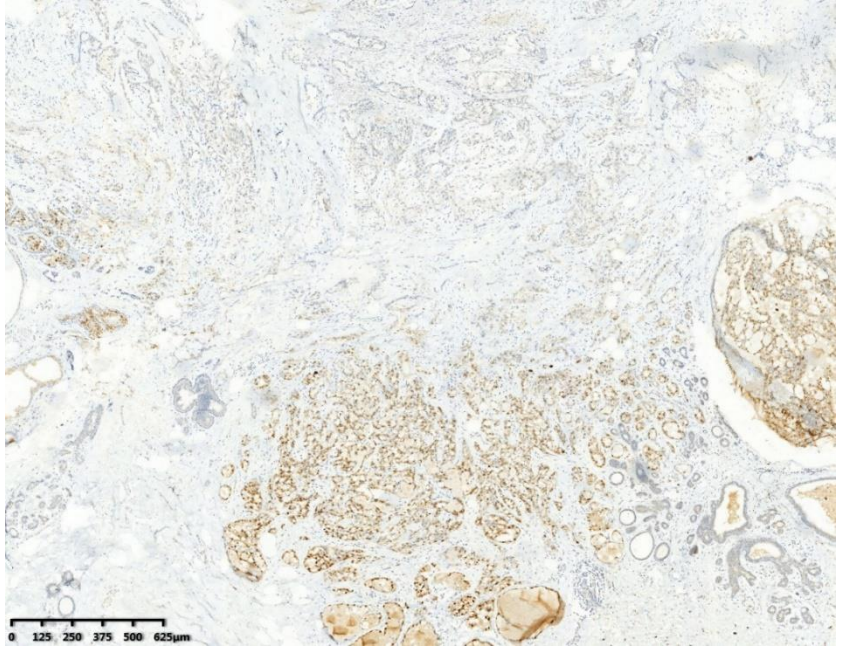
- **Pan-TRK IHC in 24 Breast Secretory Carcinomas**
- **23/24 (95.8%) pan-TRK positive**
  - **19 cases: nuclear staining**
  - **3 cases: mainly nuclear with weak cytoplasmic staining**
  - **1 case: mainly cytoplasmic with focal nuclear staining**
- **203 other breast cancers:**
  - **21 (10.3%) focal weak nuclear staining (<5% tumor cells)**

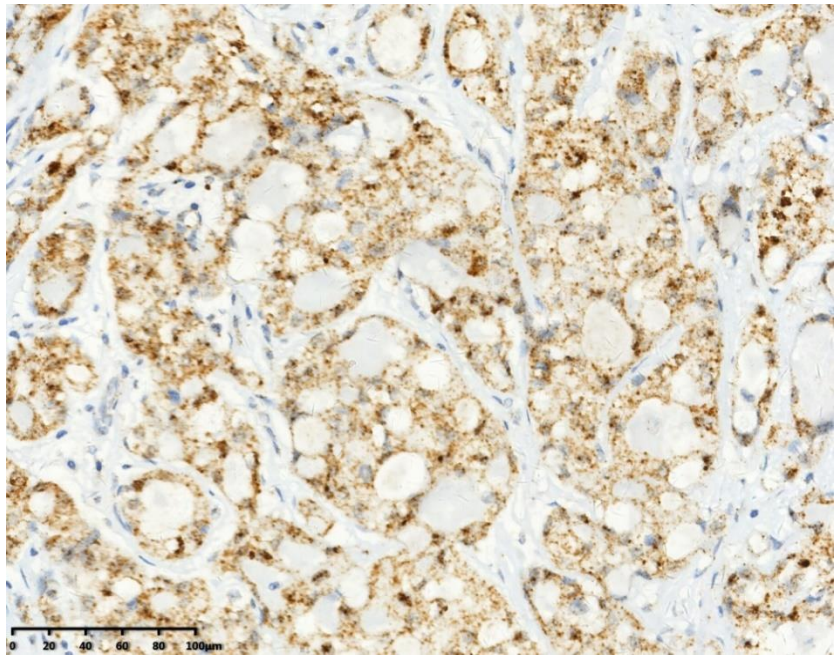


Pan-TRK IHC

- **Simple, fast, inexpensive, require less tumor tissue**
- **Targets C-terminus of 3 TRK proteins which are retained in most fusion proteins**
- **Good sensitivity for NTRK1 and NTRK2, slightly lower for NTRK3**
- **Variable localization depending on fusion type**

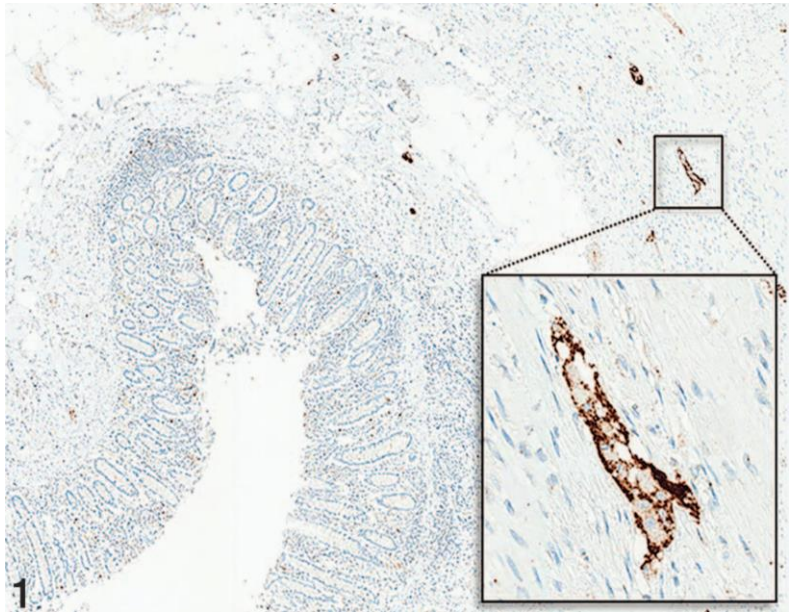
Am J Surg Pathol. 2019;43(12):1693-1700

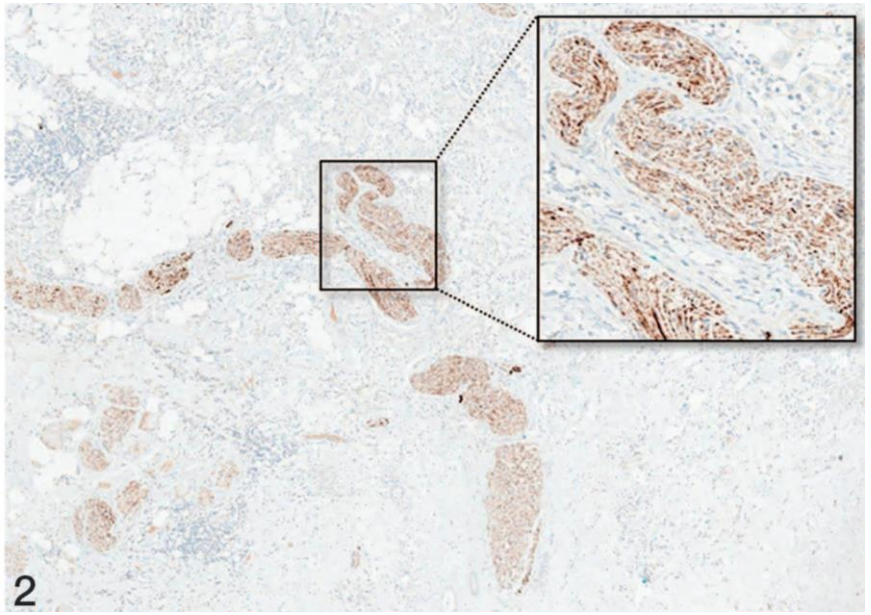




Suboptimal fixation can lead to heterogeneous pan-TRK staining

- **Influence on both staining intensity and percentage**
- **Select best-fixed block (core biopsy vs. surgical specimen)**



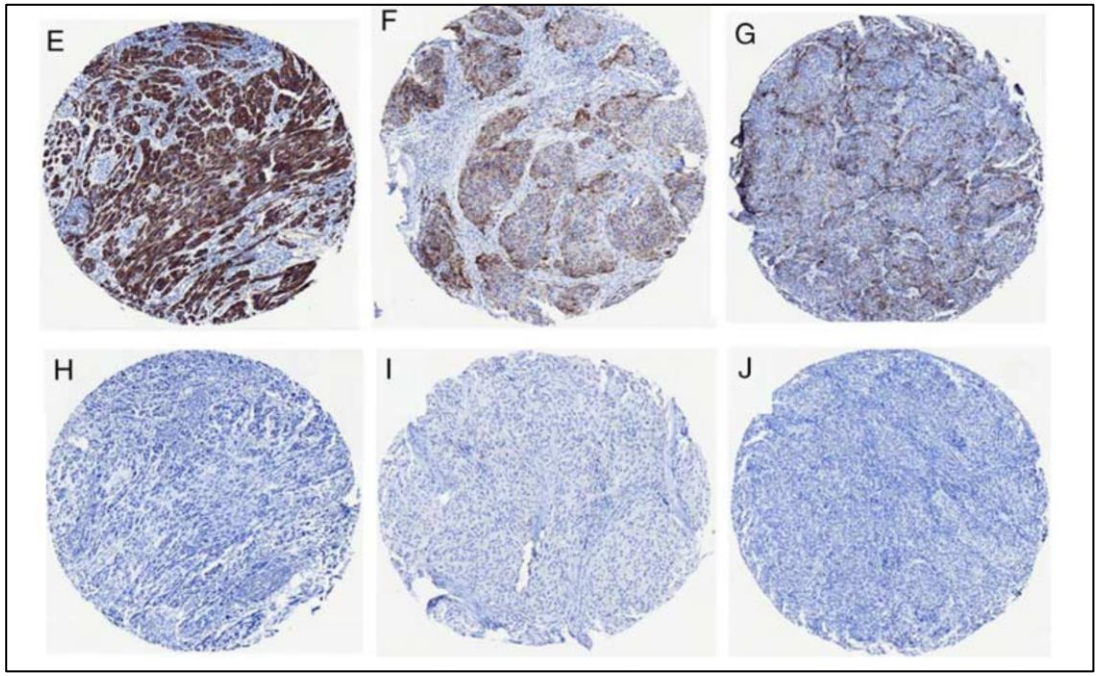


Appendix

- Absence of staining in epithelial cells and muscle and lymphoid tissue
- presence of strong granular cytoplasmic staining in ganglion cells

Cerebellum

- Gray matter (molecular layer) and granular layer: moderate to strong cytoplasmic staining
- White matter: weak or no staining



- A7H6R clone: Four cases positive with no relevant gene rearrangements by FISH
- EPR17341 clone: One case positive and FISH analysis verified the presence of a corresponding gene fusion.
- Conclusion: The EPR17341 clone demonstrates superior specificity.

Appl Immunohistochem Mol Morphol 2020;28:194-196
Appl Immunohistochem Mol Morphol 2020;28: 719

NTRK fusion positive cases

	EPR17341 in house	***EPR17341*** RTU	***A7H6R*** in house	***EP1058Y*** in house
NTRK1	100% (11/11)	100% (11/11)	100% (11/11)	80% (8/10)*
NTRK2	100% (1/1)	100% (1/1)	100% (1/1)	0% (0/1)
NTRK3	100% (8/8)	100% (8/8)	87.5% (7/8)	62.5% (5/8)
Total	**100% (20/20)**	**100% (20/20)**	**95% (19/20)**	**63.2% (12/19)***

All cases harboring an NTRK fusion on molecular testing were immunohistochemically positive with the EPR17341 clone.

Histopathology 2023;82:1003-1012

Pan-TRK IHC

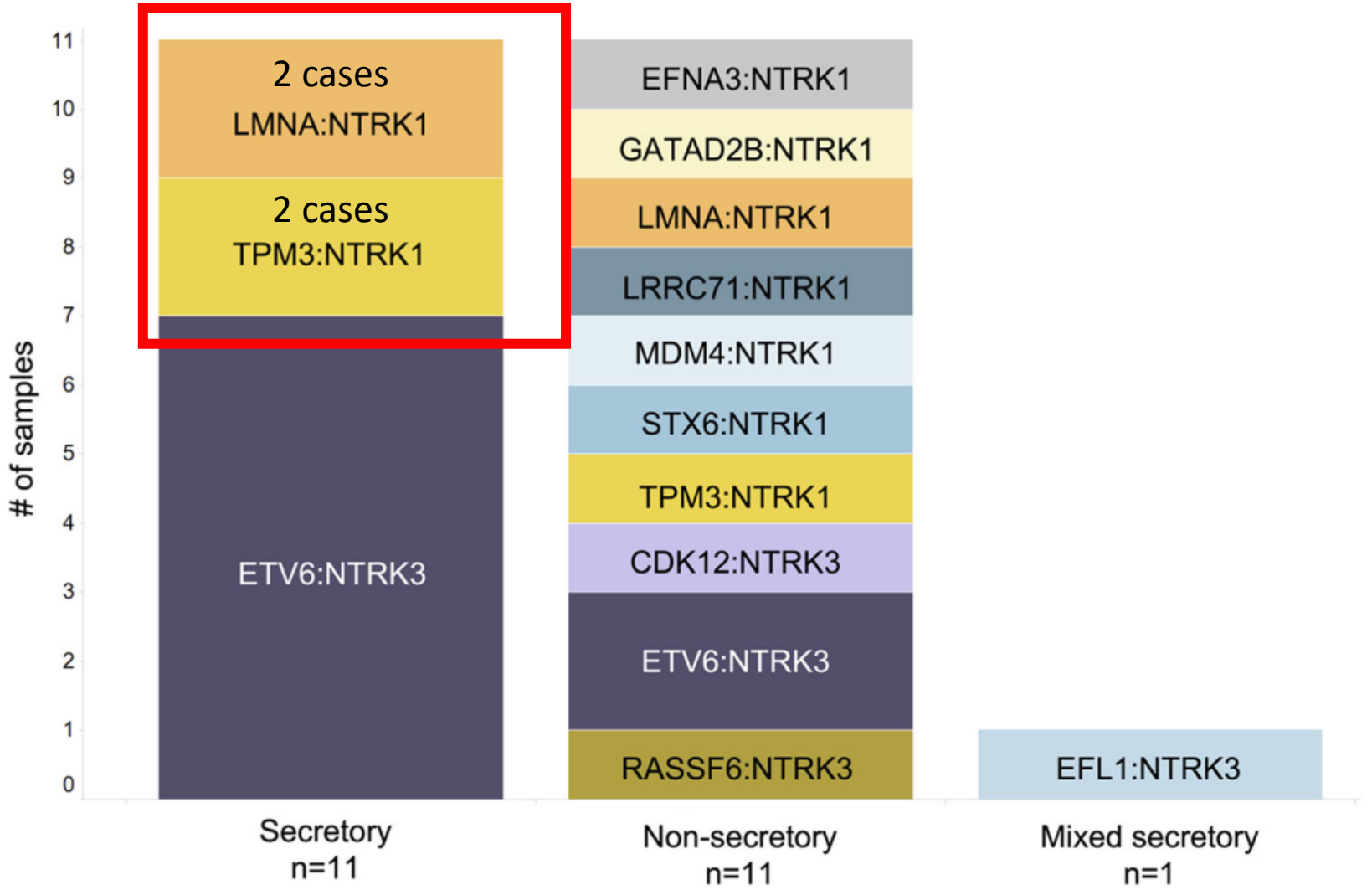
Secretory carcinoma of the salivary gland

Case No.	Age (y)	Sex	Diagnosis	Tumor Site	LD-RT-PCR-NGS	Pan-TRK IHC					
						Nuclear Staining		Cytoplasmic Staining		Membranous Staining	
						Intensity	%	Intensity	%	Intensity	%
19	82	F	SC	Submandibular gland	*ETV6 exon 4-NTRK3 exon 14*	0	0	1	80	0	0
20	57	F	SC	Parotid gland	*ETV6 exon 5-NTRK3 exon 14*	0	0	2	40	0	0
21	36	F	SC	Parotid gland	*ETV6 exon 5-NTRK3 exon 14*	0	0	3	70	0	0
22	51	F	SC	Parotid gland	*ETV6 exon 5-NTRK3 exon 14*	0	0	2	70	0	0
23	56	M	SC	Parotid gland	*ETV6 exon 5-NTRK3 exon 14*	0	0	0	0	0	0
24	46	F	SC	Parotid gland	*ETV6 exon 6-RET exon 12*	0	0	0	0	0	0
25	22	F	SC	Parotid gland	*ETV6 exon 6-RET exon 12*	0	0	0	0	0	0
26	14	F	SC	Submandibular gland	*ETV6 exon 6-RET exon 12*	0	0	0	0	0	0

- **ETV6 encodes a nuclear transcription factor, ETV6–NTRK3 fusion protein is predominantly localized to the nucleus.**
- **Nuclear pan-TRK immunoreactivity was exclusively detected in cases carrying the fusion of ETV6 exon 5 to NTRK3 exon 15.**
- **Fusion of ETV6 exon 4 or 5 with NTRK3 exon 14 disrupts the nuclear localization signal, with only variable cytoplasmic staining or no staining was observed.**
- **Tumors with ETV6–RET fusion were negative for pan-TRK immunostaining.**

Am J Surg Pathol 2021;45:1487-1498

Other Driver Gene Alterations in Breast Secretory Carcinoma

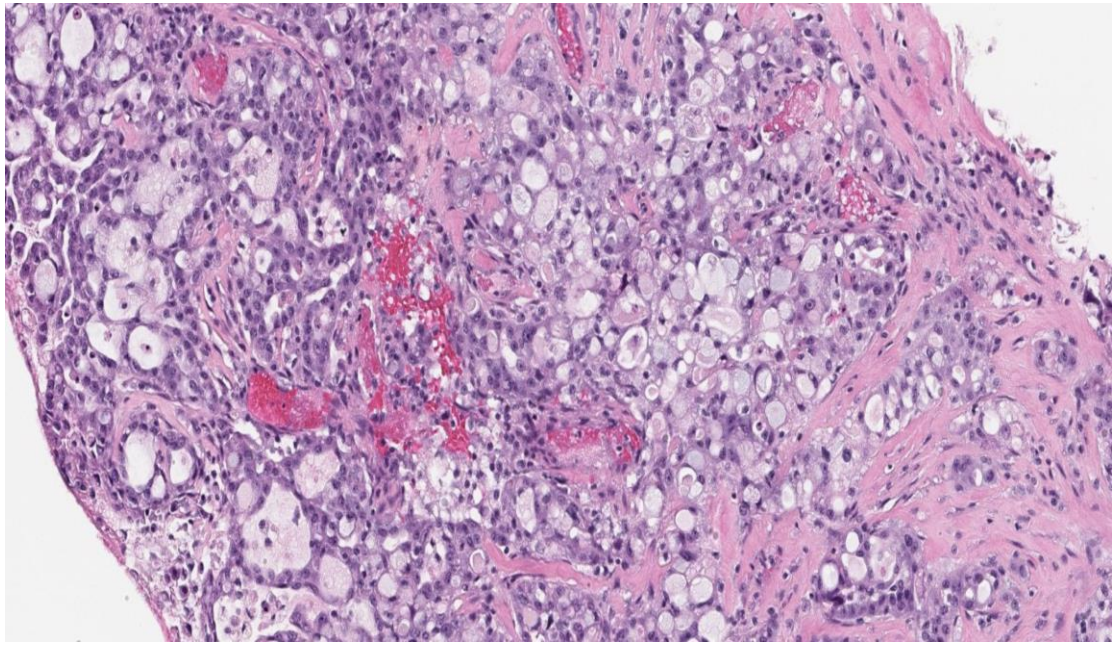


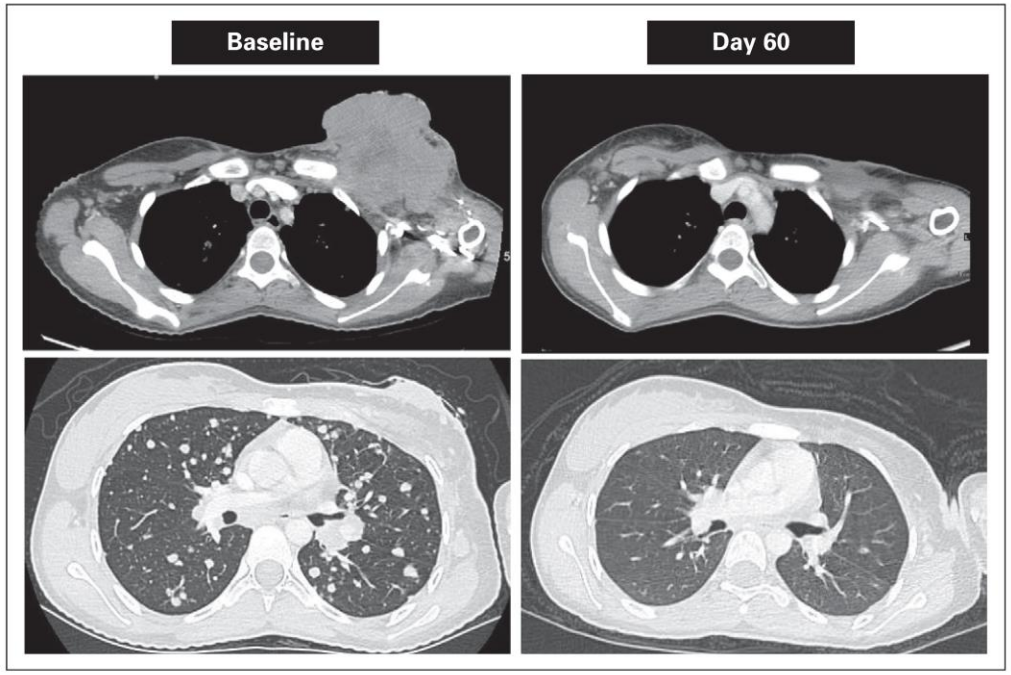
2019: Remoue reported 1 case with NTRK1 rearrangement

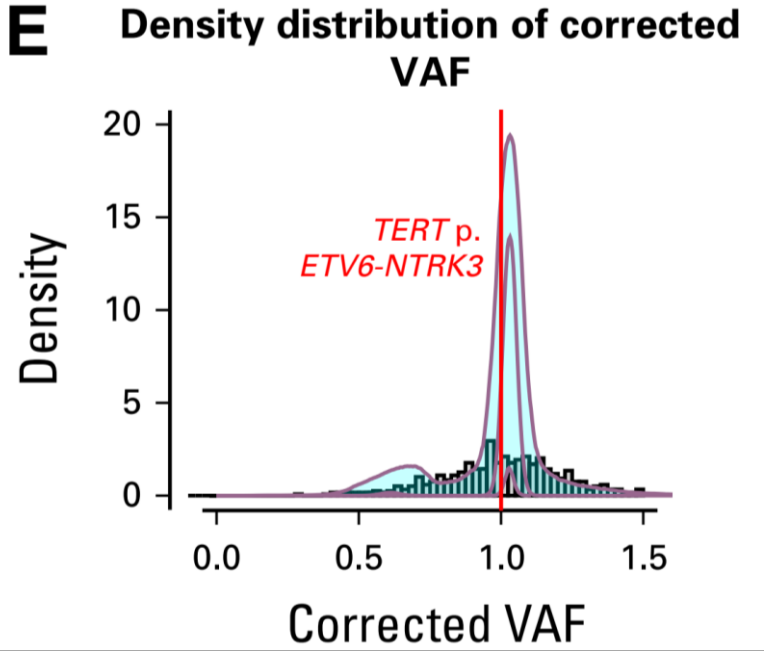
2022: Maund reported 4 cases of breast secretory carcinoma with NTRK1 rearrangement

Pathol Int. 2019 ;69(2):94-96.

Pathol Int 2022;72(3):187-192







TERT (NM_198253) promoter variant (g. 1295228C>T) may account of the aggressive behavior of this tumor

Salivary Gland Secretory Carcinoma

Clinicopathologic and Genetic Characteristics of 215 Cases and Proposal for a Grading System

TABLE 1. Histopathologic Parameters in the Proposed Grading System of SC

Parameters	Grade 1	Grade 2	Grade 3*
Morphology and architecture	Predominantly microcystic and tubular with ample secretory material	Solid-cribriform (< 50%), microcystic-cystic, and/or tubulopapillary	• Predominantly solid with minimal or abortive microcystic spaces • Limited secretory material and/or intracytoplasmic vacuoles • Disintegration of tumor cell nests with the production of small tumor buds
Septa, fibrosis, and hyalinization	Lobulated architecture with thin fibrous septa	Abundant fibrous septa with limited/focal hyalinization	• Irregular fibrous septa and/or highly sclerotic
Nucleus and nucleoli	• Regular vesicular nuclei • Fine chromatin • One centrally located nucleolus	• Mild-moderate pleomorphism • Convoluted/wrinkled nuclei often with grooves • One or more small and distinct nucleoli	• Severe pleomorphism • Convoluted/wrinkled hyperchromatic nuclei with occasional nuclear clearing • Multiple nucleoli
Mitoses/2 mm^2	< 3/2 mm^2	3-10/2 mm^2 (nonquantitatively: present, but limited)	≥ 10/2 mm^2 (nonquantitatively: increased) Atypical mitoses
Ki-67 proliferation index	< 15%	15%-31%	≥ 31%
Necrosis	None	Variably present	Present
PNI/LVI	No or limited PNI No LVI	Present PNI and/or LVI (but not common)	Present
Infiltration	Circumscribed, focally encapsulated	Circumscribed, not encapsulated, with invasion	Destructively invasive

*High-grade transformation is part of the grade 3 category, but with more sheet-like growth and comedonecrosis.

Am J Surg Pathol. 2023 Jun 1;47(6):661-677.

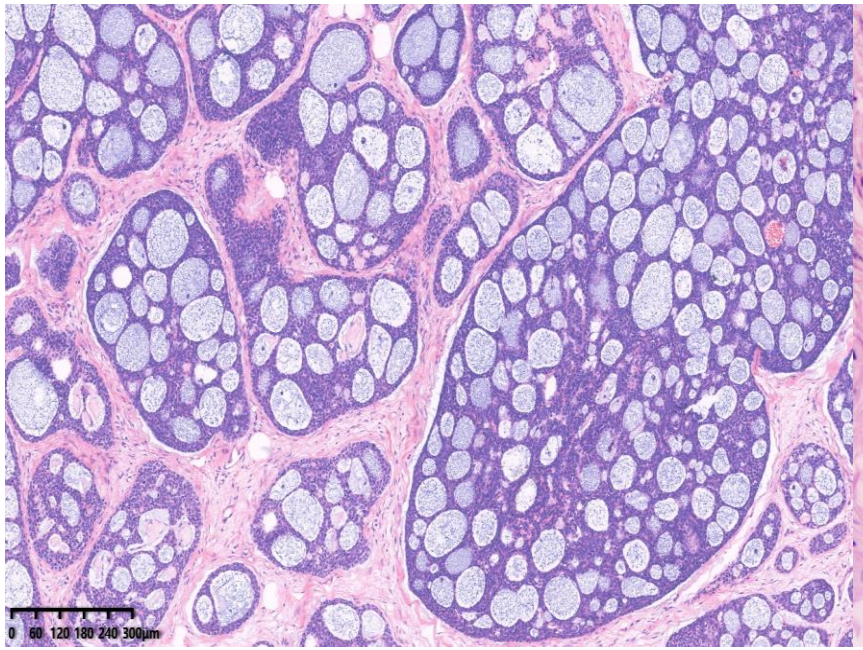
Adenoid Cystic Carcinoma

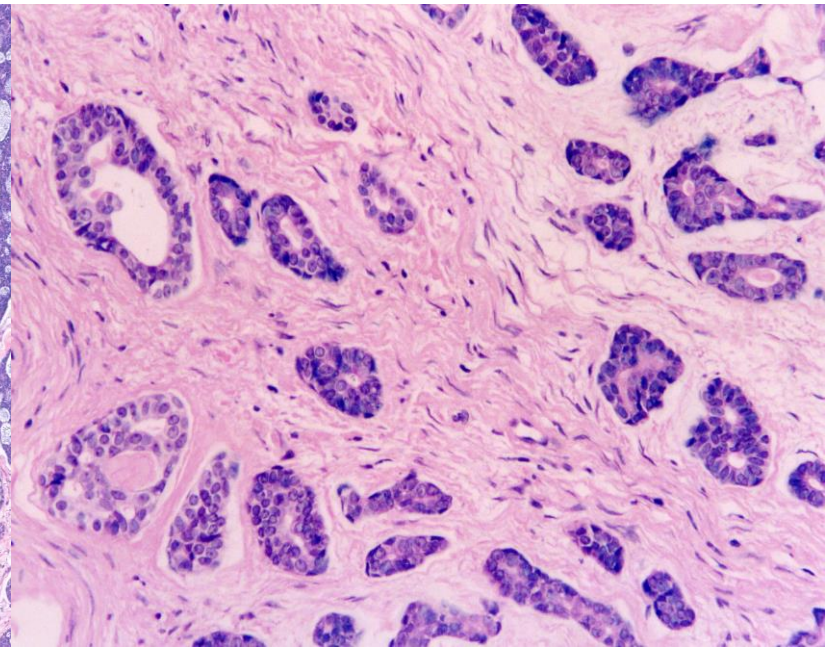
- **Classic adenoid cystic carcinoma**
  Constitutes the vast majority of breast Adcc.
  Usually shows favorable behavior. Local and distance metastases are rare.
  Radical surgical excision is usually curative.

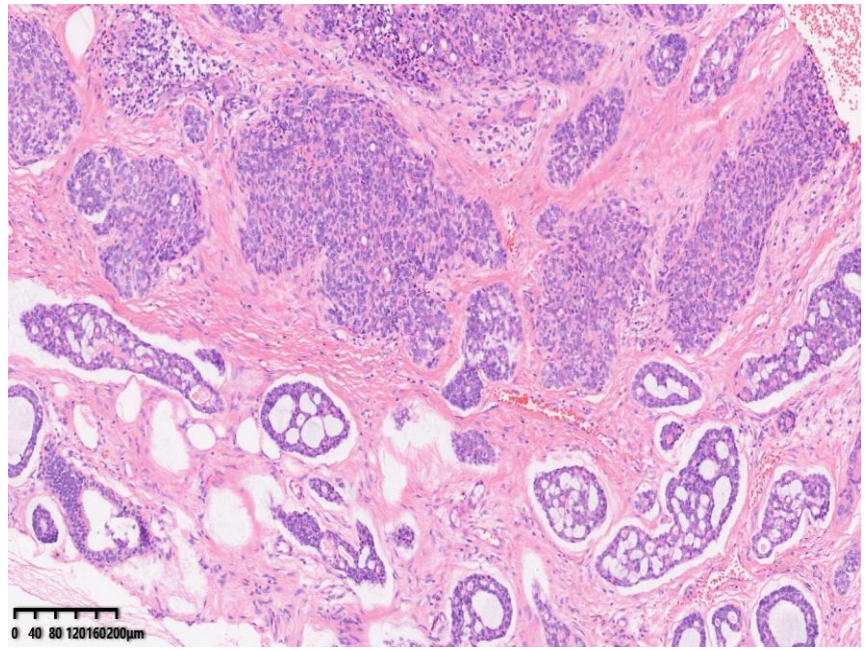
- **Solid basaloid adenoid cystic carcinoma**
  Lymph node metastases and perineural invasion can frequently be observed. Local recurrences and distant metastases to lung, bone, skin have been reported.

- **Adenoid cystic carcinoma with high-grade transformation**
  Very rare, most of which lead to the patient's death.

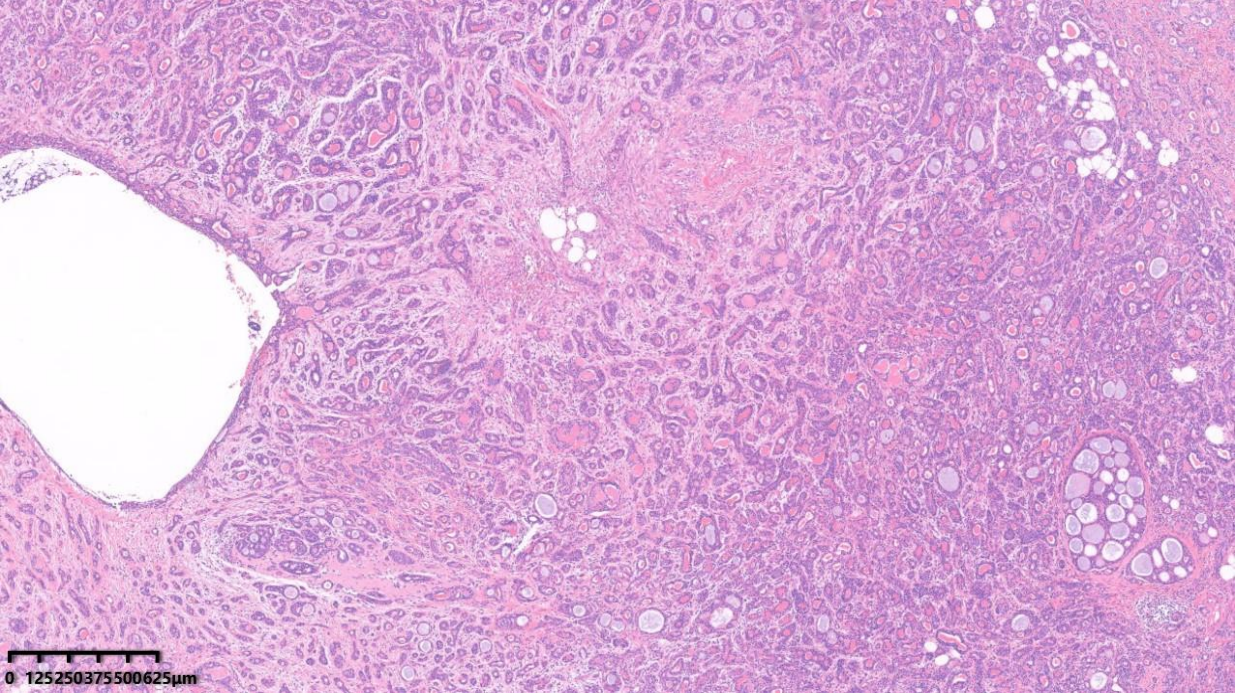
Classic subtype







- Cribriform architecture, true/pseudolumina, tubular and trabecular structures; focal solid areas may also be present.
- Intraluminal myxoid or basement-membrane-like material is common.
- Variable proportions of epithelial and myoepithelial cells; some cells can appear basaloid.
- Necrosis is usually absent.
- Mitotic figures are rare.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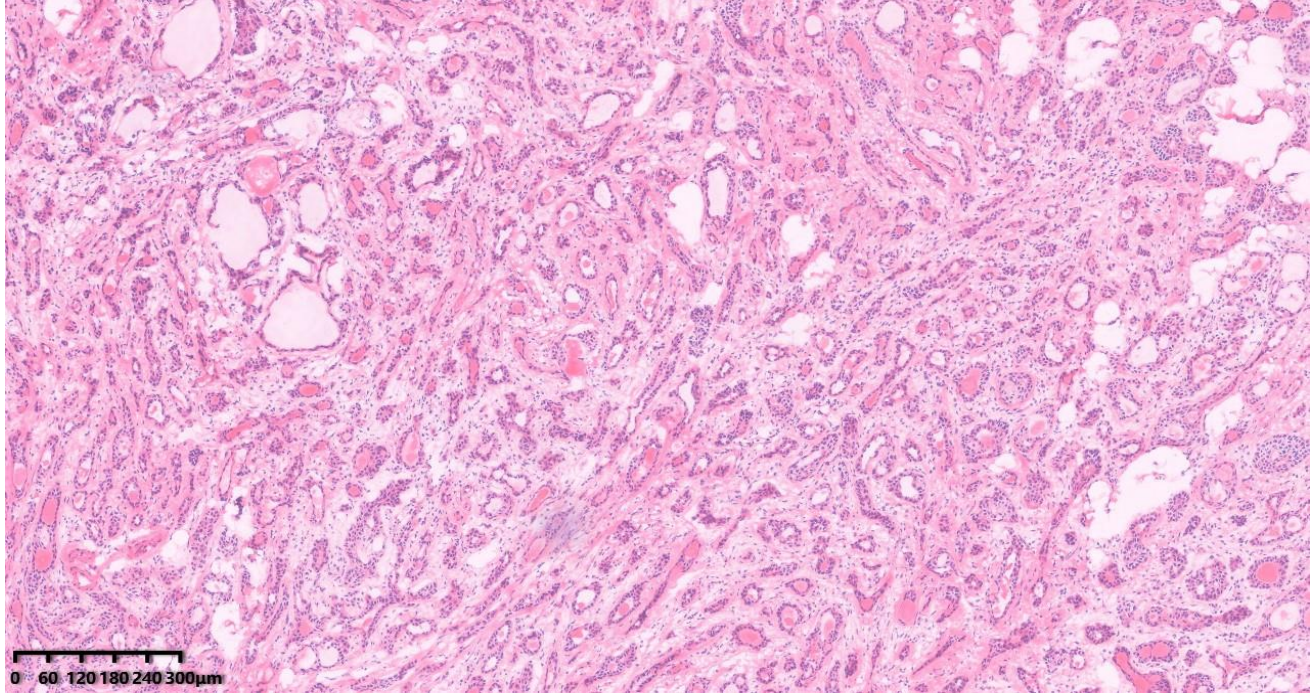
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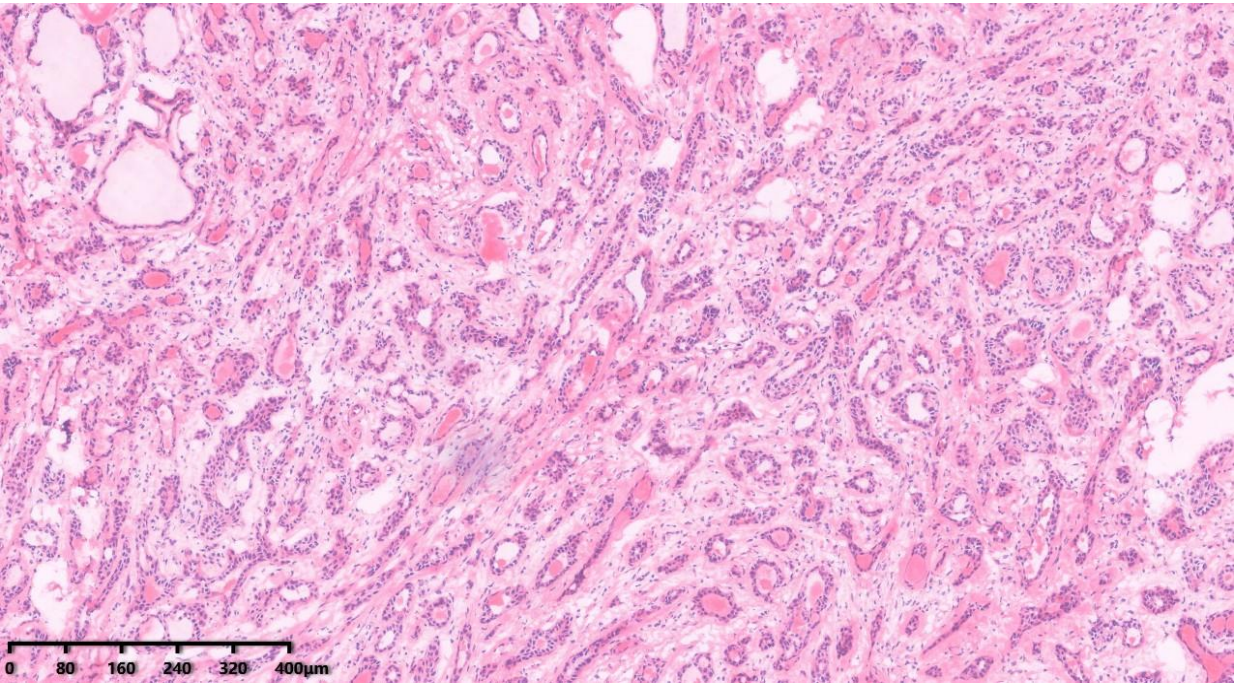
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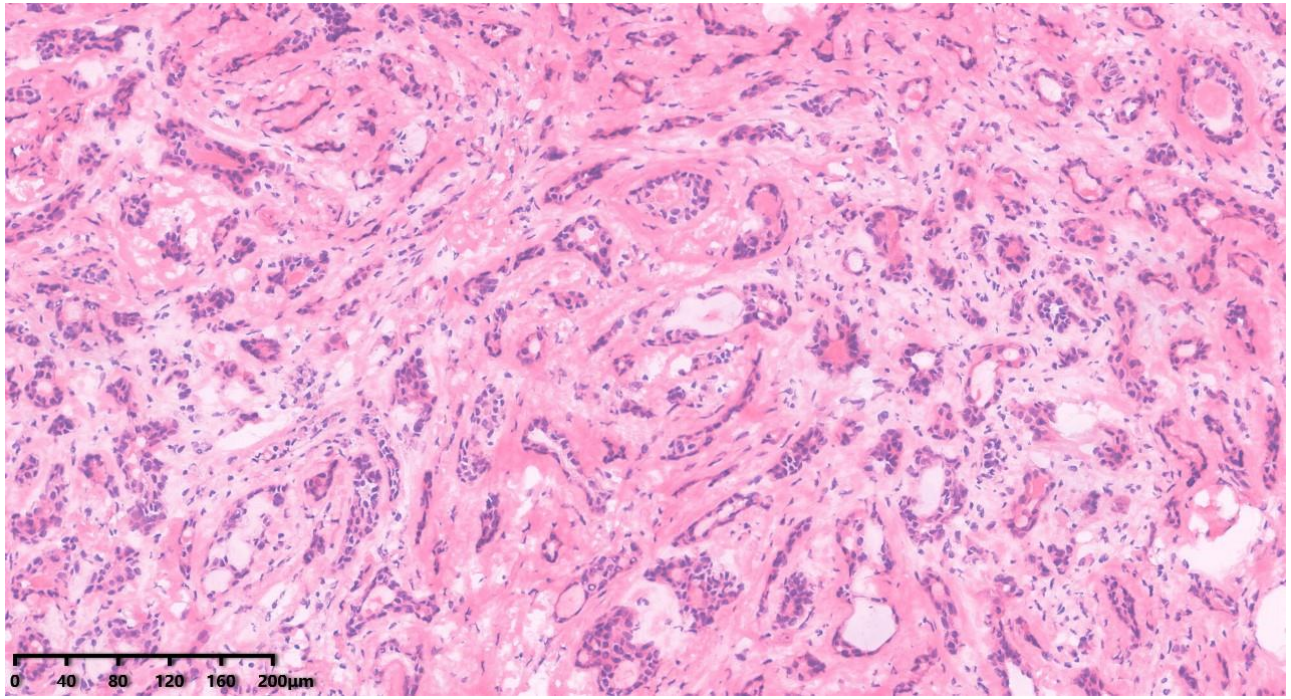
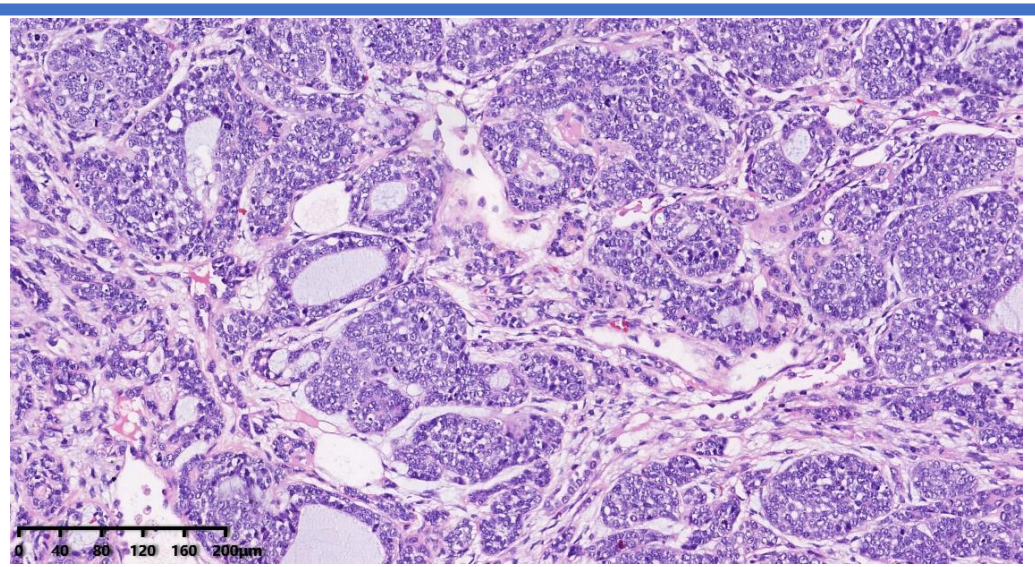
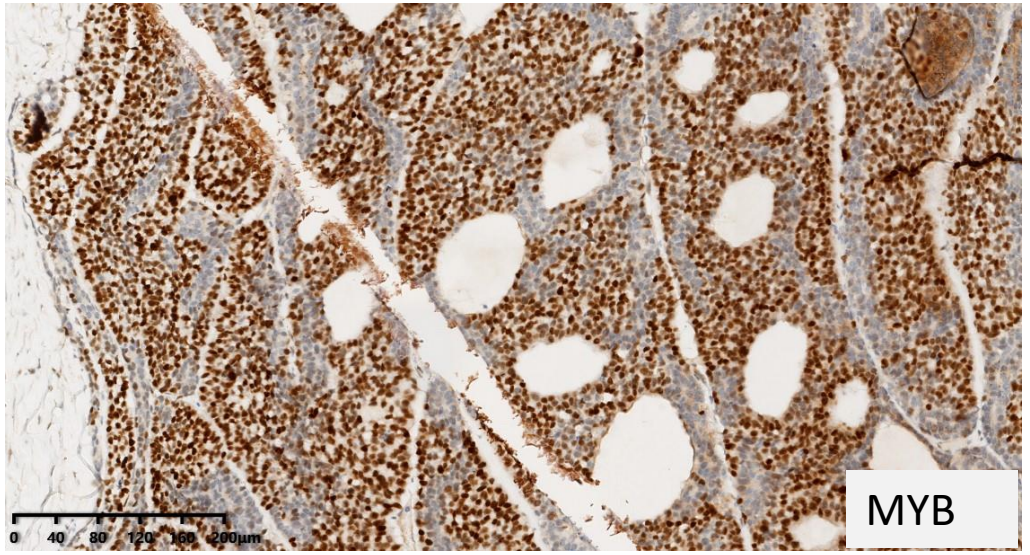

0 40 80 120 160 200µm

Immunoprofile of Classic Adenoid Cystic Carcinoma

- **Epithelial cells:** low molecular weight keratins (CK7, CK8/18) and CD117 positive
- **Myoepithelial cells :** p63, SMMHC, calponin and high molecular weight keratins (CK5/6, CK14, CK17)
- MYB diffuse positive
- Triple-negative





MYB Labeling by Immunohistochemistry is More Sensitive and Specific for Breast Adenoid Cystic Carcinoma than *MYB* Labeling by FISH

TABLE 1. Clinicopathologic Features and MYB Status of Breast ACC and Non-ACC Basaloid and Cribriform Proliferations

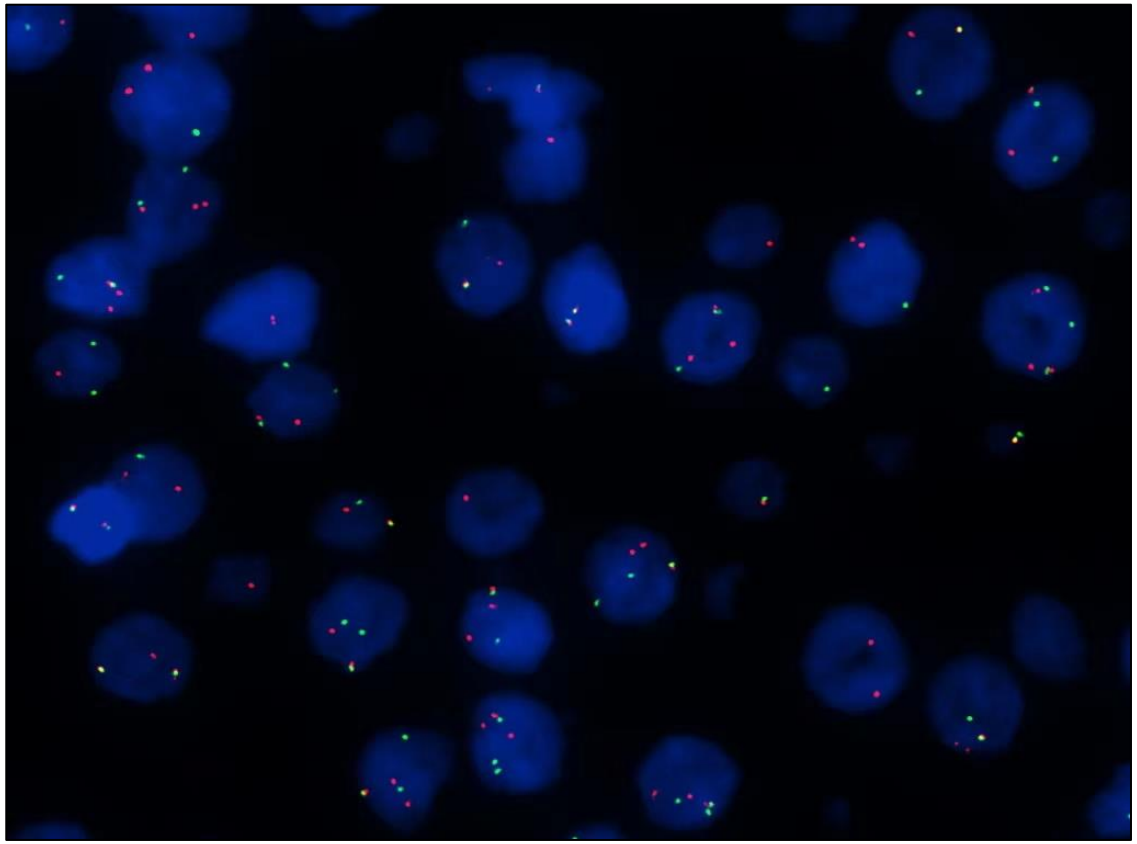
	n (%)			
	Breast Adenoid Cystic Carcinoma	**Basal-like, Triple-negative Ductal Carcinoma**	**MGA/AMGA**	**Collagenous Spherulosis**
Number	11	16	5	7
Average age (range) (y)	54 (36-69)	49 (35-65)	61 (36-89)	56 (33-75)
Sex				
Female	10 (91)	16 (100)	5 (100)	7 (100)
Male	1 (9)	0	0	0
Race				
White	6 (55)	8 (50)	2 (40)	5 (71)
Black	2 (18)	8 (50)	3 (60)	2 (29)
Unknown	3 (27)	0	0	0
MYB IHC positivity (n/N [%])				
Any degree of nuclear labeling	11/11 (100)	10/16 (63)	0/5 (0)	5/7 (71)
Moderate-strong diffuse labeling	11/11 (100)	0	0	0
MYB rearrangement by FISH (n/N [%])	8/9 (89)	1/15 (7)	0/4 (0)	0/7 (0)

- Strong diffuse MyB expression: high sensitivity and specificity for adenoid cystic carcinoma
- weak and focal staining should be interpreted with caution as it can be seen in other lesions (e.g., basal-like TNBC, collagenous spherulosis)

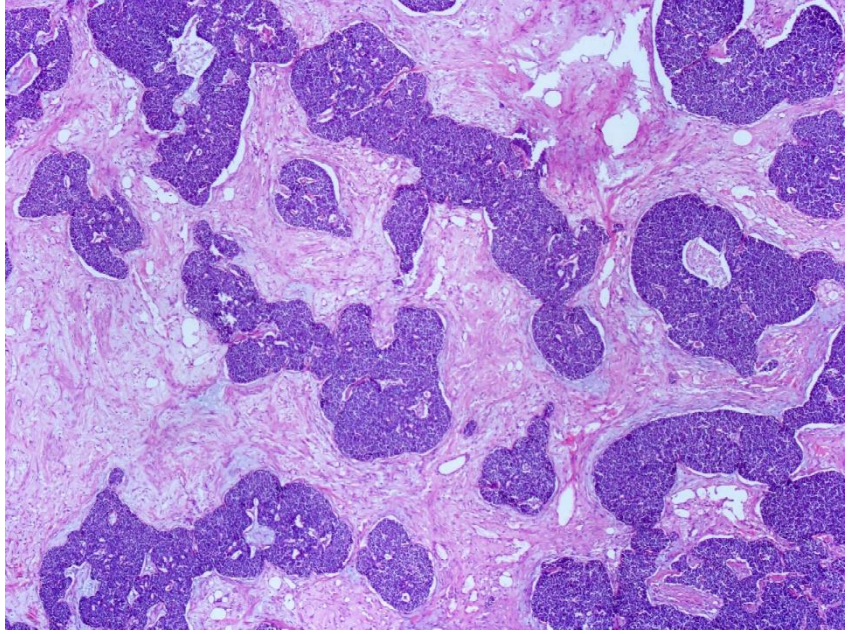
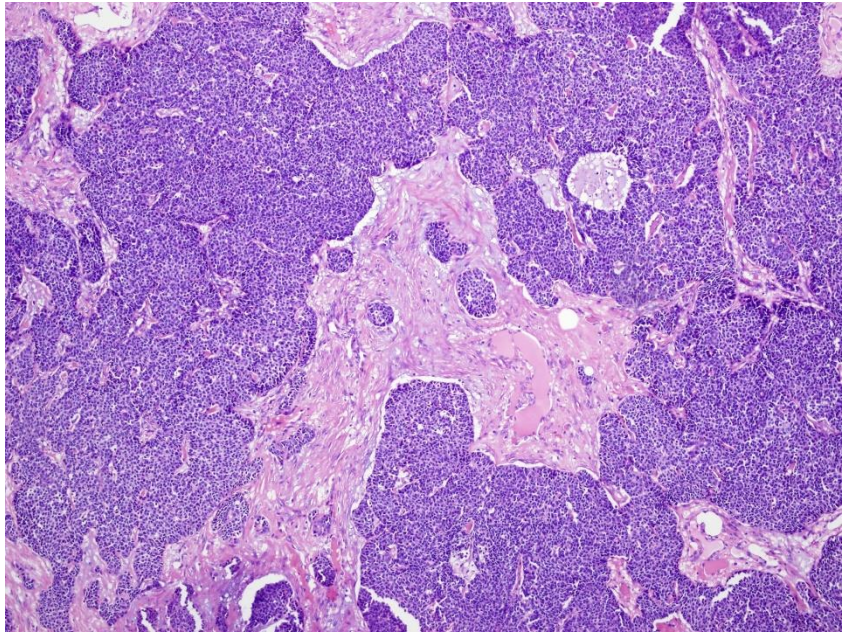
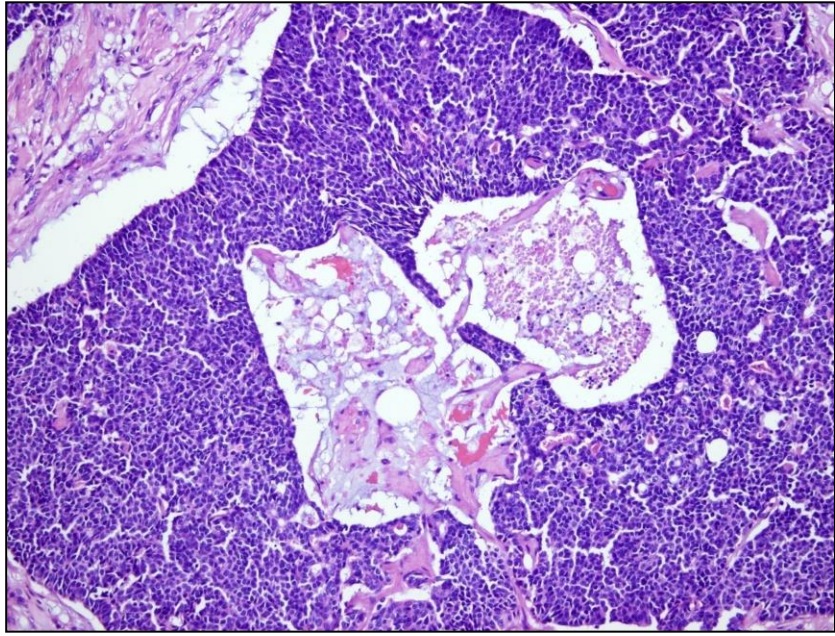
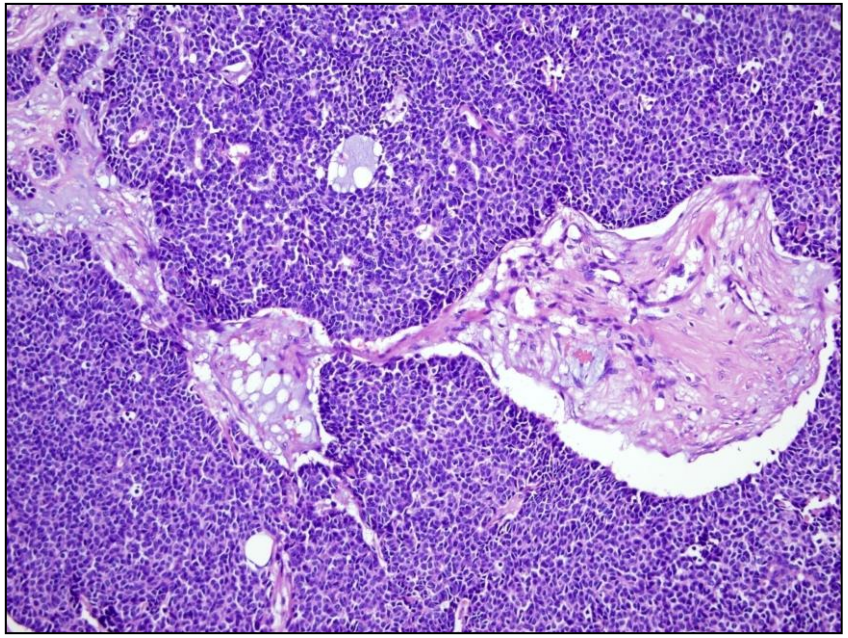
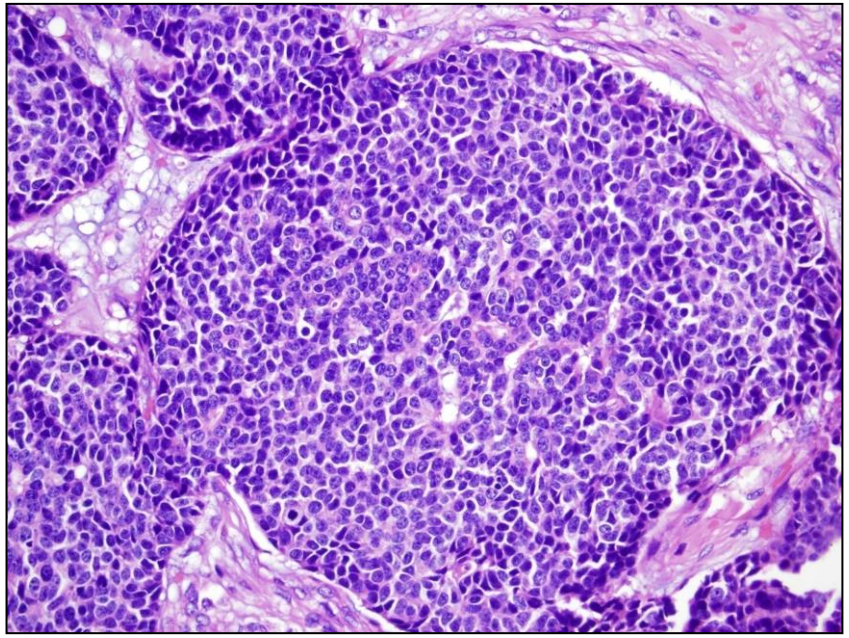
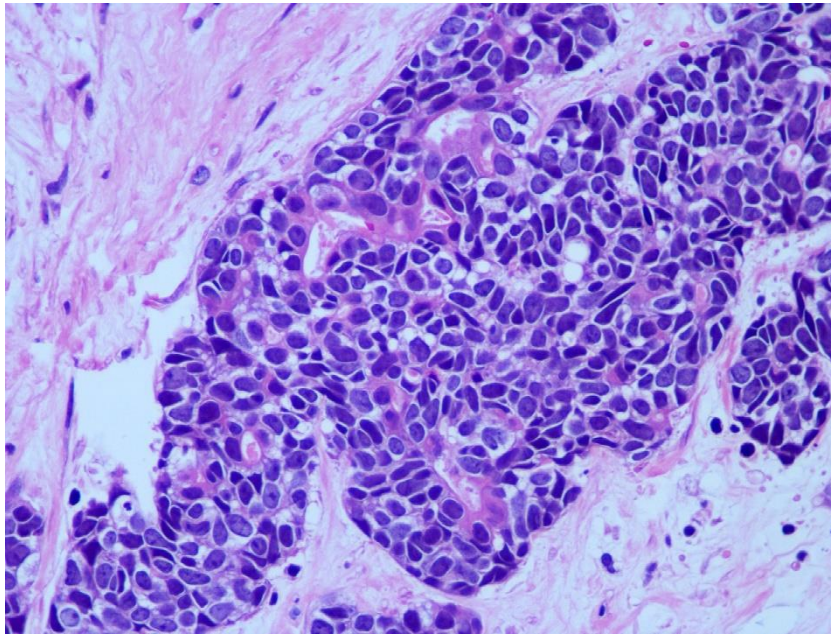
Am J Surg Pathol 2017;41(7):973-979

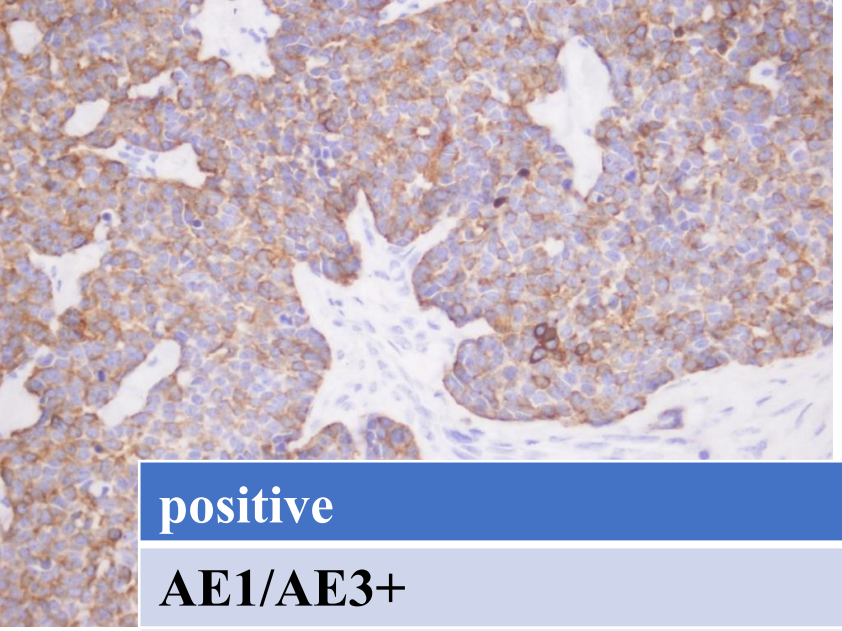
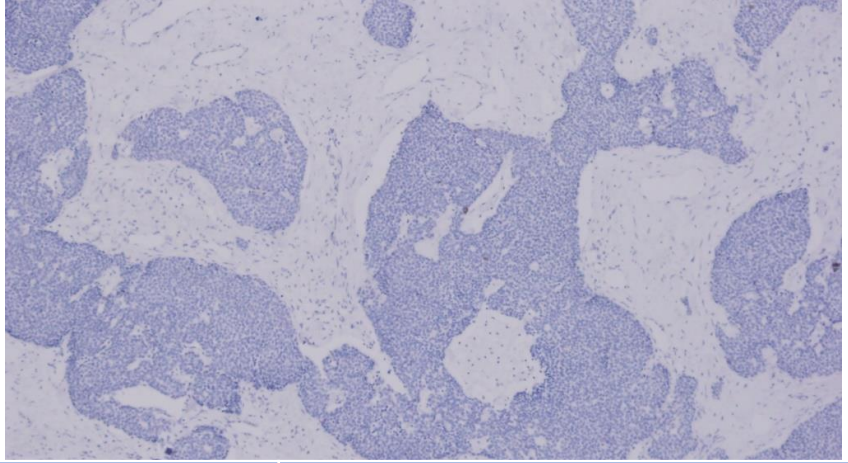
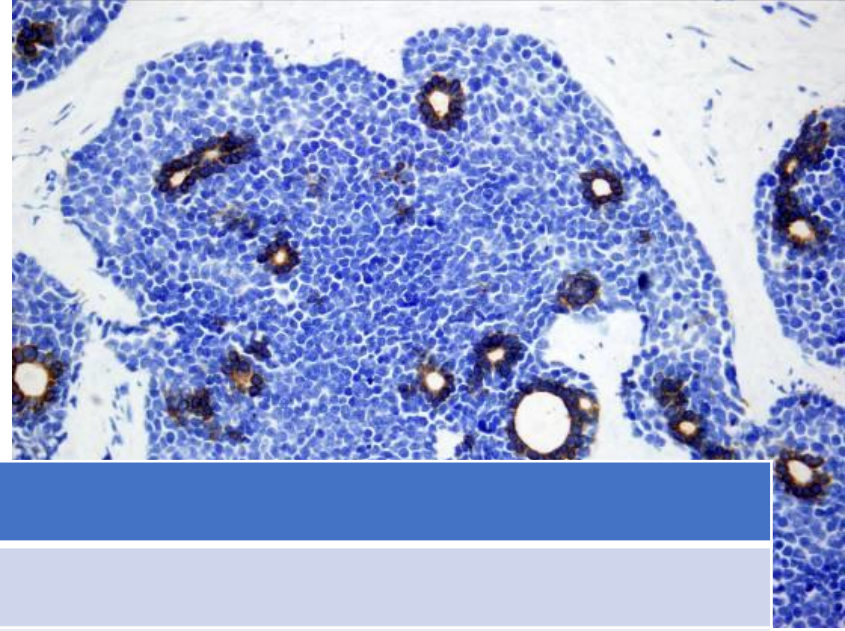
Molecular features of classic AdCC

- *Similar to AdCC at other anatomic sites, most breast C-AdCC harbor a characteristic t(6:9)(q22–23:p23–24) chromosomal translocation that creates a MYB::NFIB fusion gene*
- *In AdCC lacking MYB::NFIB* fusion, MYB overexpression may be due to *MYB* amplification or rearrangement of the related *MYBL1* gene
- C-AdCC generally have simple genomes with low mutation burden and absence of *TP53* mutations, in contrast to TNBC–NST.

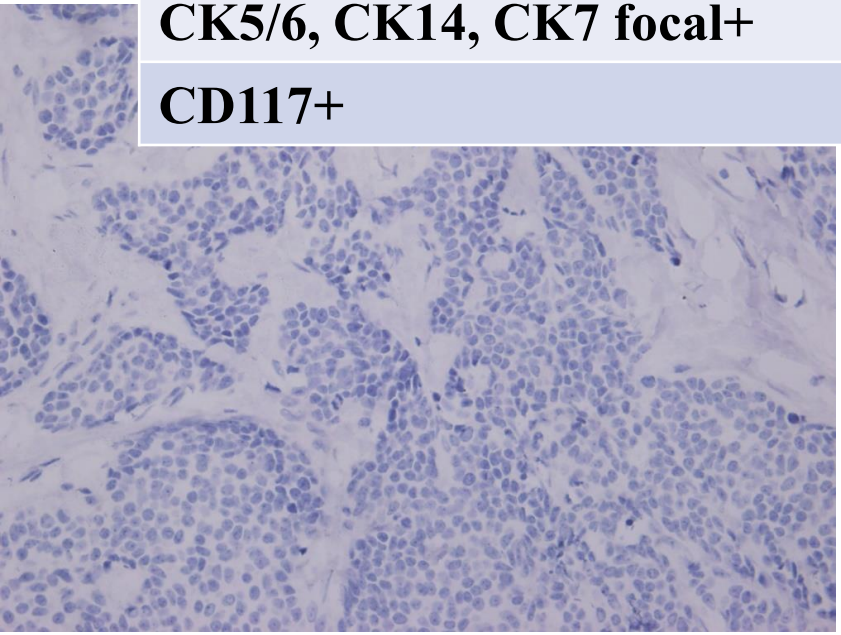
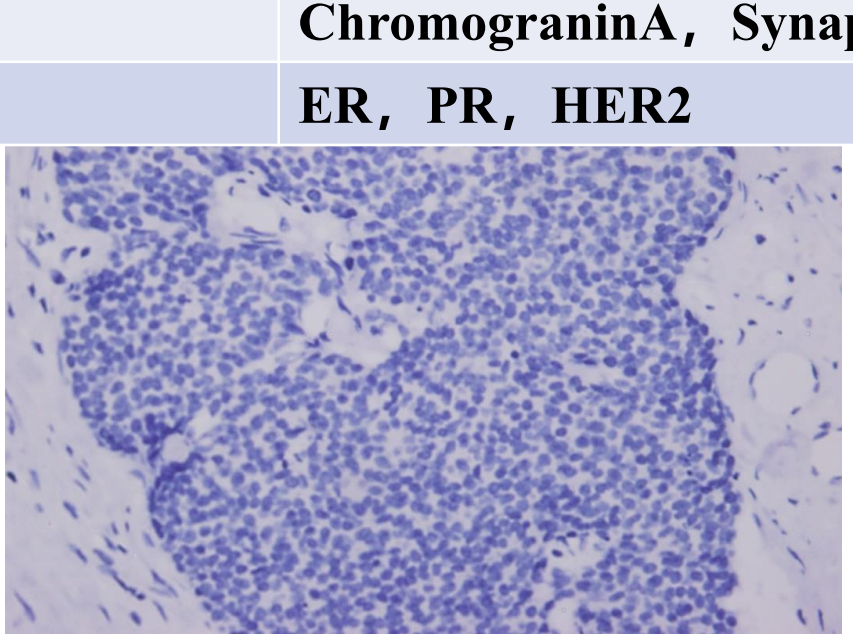
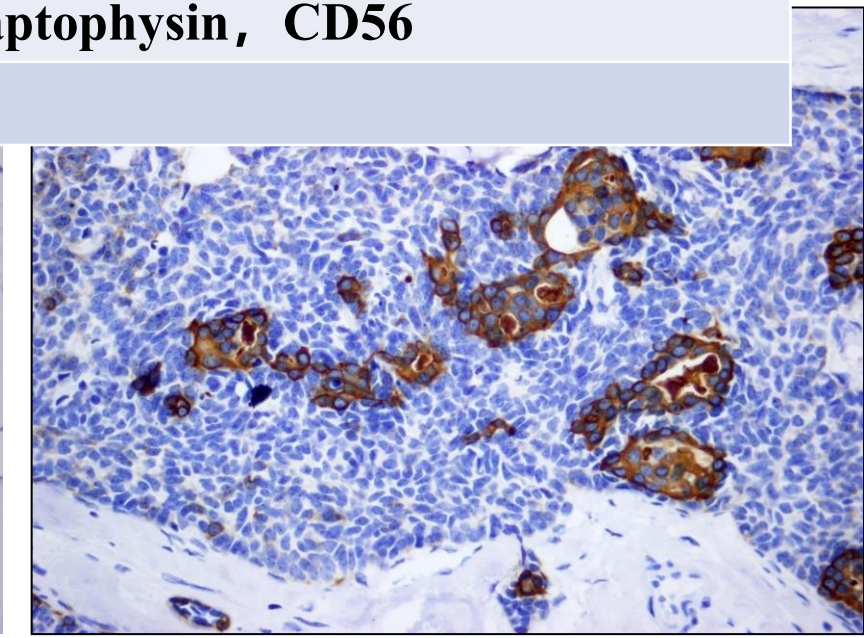


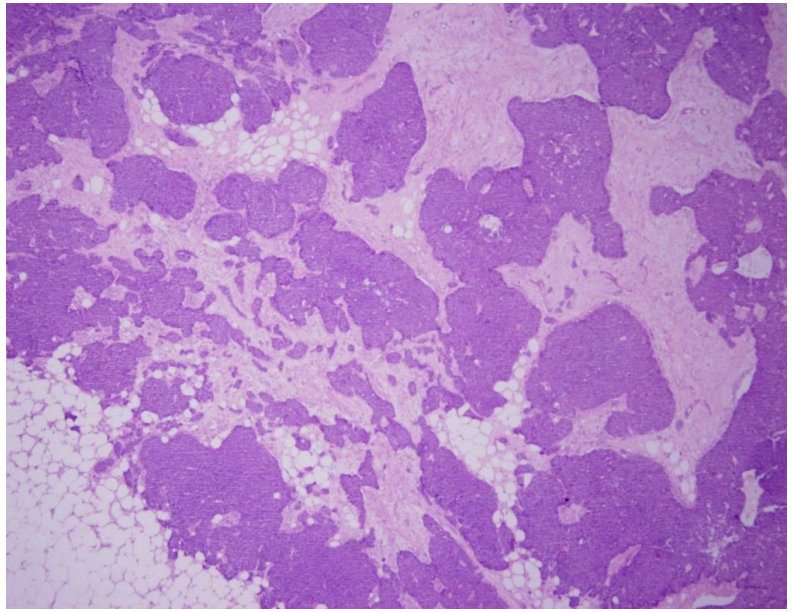
MYB FISH (break-apart probe)

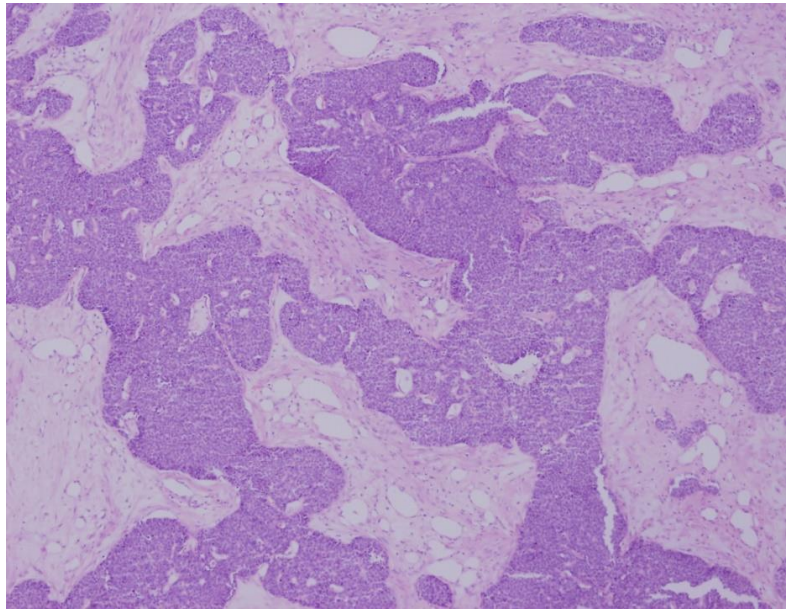







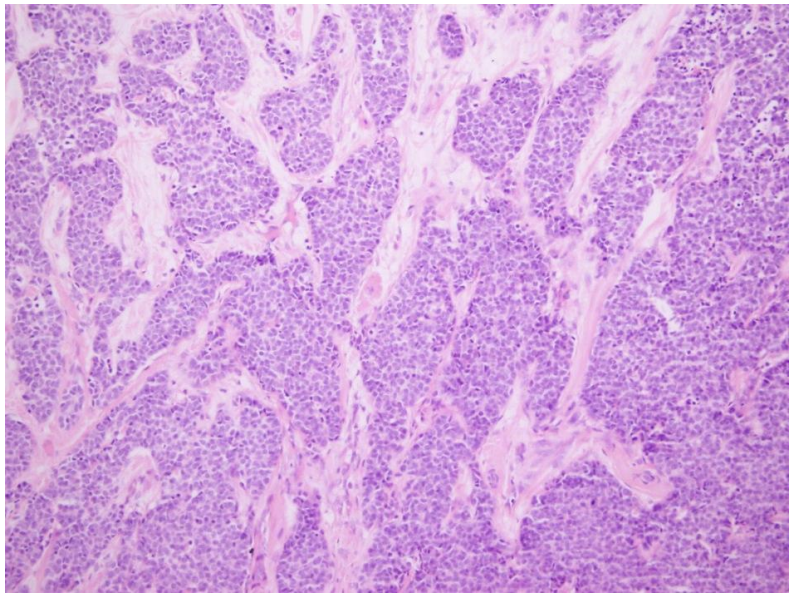




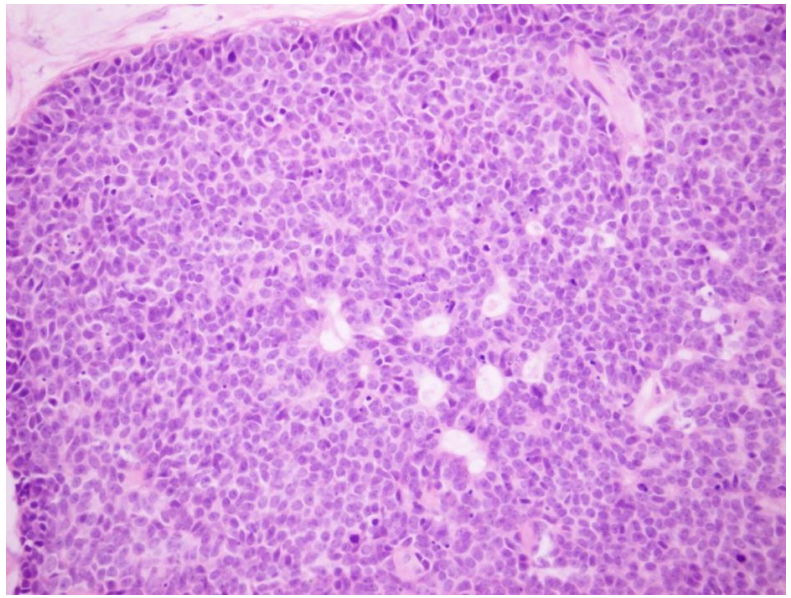
positive	negative
AE1/AE3+	SMA，calponin，p63
CK5/6, CK14, CK7 focal+	ChromograninA，Synaptophysin，CD56
CD117+	ER，PR，HER2









Solid-basaloid subtype

- **90% of the tumor shows a solid growth pattern.**
- **The neoplastic cells are basaloid.**
- **They are larger and exhibit more pronounced pleomorphism.**
- **Mitotic figures are more frequent, sometimes ≥5 /10 HPF**
- **Tumor cell necrosis is common**
- **More aggressive than classical adenoid cystic carcinoma.**

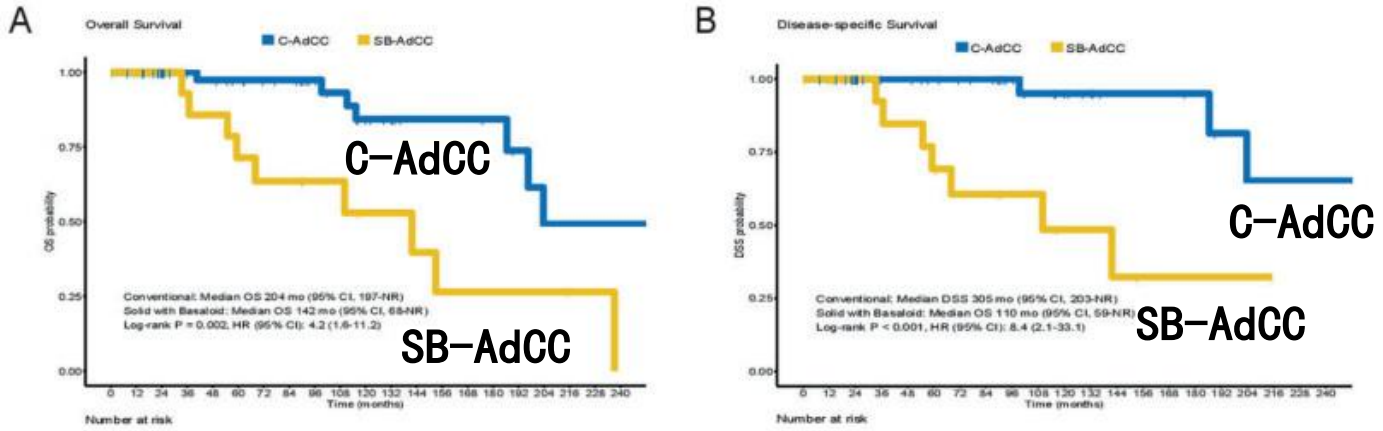
(lymph-node metastasis, distant metastasis, disease-specific death) .

- **poor response to neoadjuvant therapy, low pathological complete response (pCR) rate.**

Mod Pathol 2023;36(12):100324

(SB-AdCC) vs (C-AdCC)

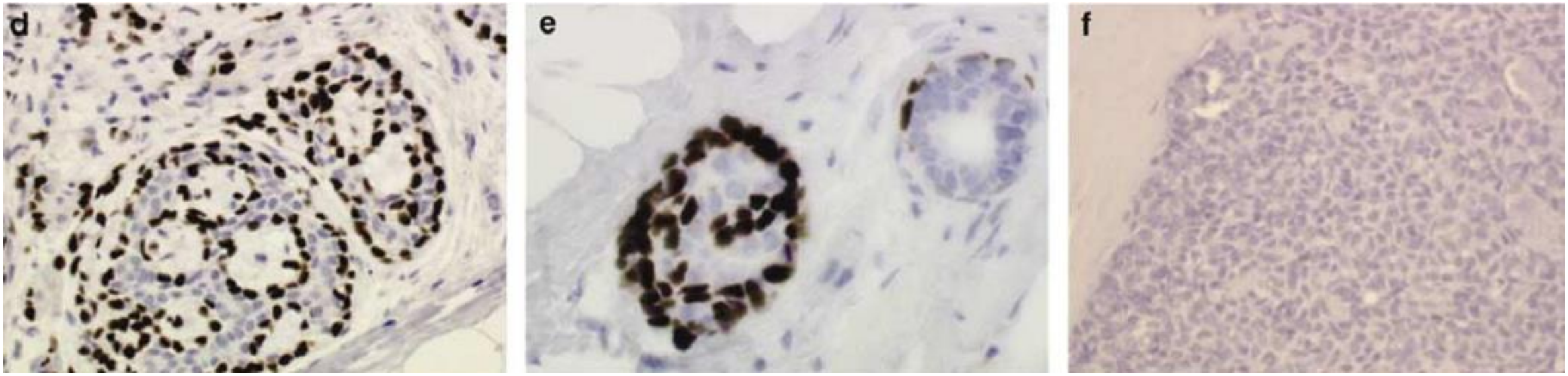
	C-AdCC N = 75	SB-AdCC N = 29	P value
Age at diagnosis			<0.05
Range	36.0–78.0	44.0–88.0	
Median	55.5	63.0	
Q1, Q3	51.0, 64.5	55.5, 75.3	
Nottingham Grade			<0.05
1	25/63 (40%)	0/29 (0%)	
2	38/63 (60%)	6/29 (21%)	
3	0/63 (0%)	23/29 (79%)	
LVI	2/63 (3%)	8/29 (28%)	<0.05
PNI	6/63 (10%)	6/29 (21%)	0.10
Nodal metastasis	0/56 (0%)	3/21 (14%)	<0.05
N stage			0.07
X	4/52 (7.7%)	4/20 (25.0%)	
0	48/52 (92%)	14/20 (70.0%)	
1A	0/52 (0)	3/20 (15%)	
Triple negative	46/54 (85%)	23/24 (96%)	0.27
ER positive (1–10%)	8/54 (15%)	1/24 (4%)	0.27
p63 positive	20/20 (100%)	5/14 (35%)	<0.05
Clinical follow-up	52/75 (69%)	20/29 (76%)	1.00
Local recurrence	2/52 (4%)	6/20 (30%)	
Distant metastasis	10/52 (19%)	20 (/20 (65%)	
DoD	3/52 (6%)	8/20 (40%)	



- ✓ Older age at diagnosis
- ✓ Higher histologic grade
- ✓ More frequent lymphovascular invasion
- ✓ Higher incidence of lymph node metastasis
- ✓ Reduced or absent expression of myoepithelial markers (e.g., P63)
- ✓ Worse prognosis compared to classic type

Mod Pathol 2022;35(2):193-201.

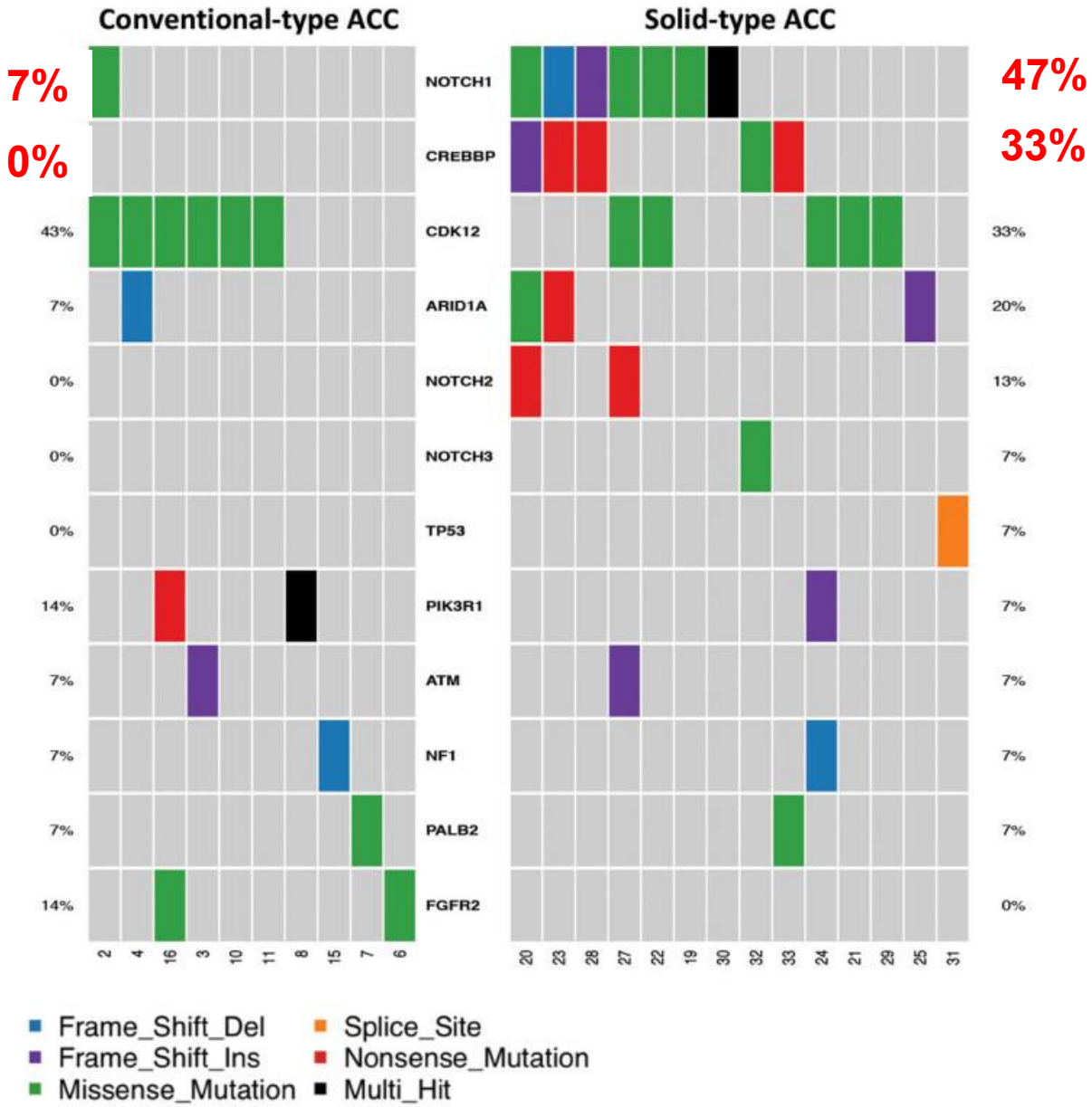
IHC



- **Expression of S100, p63, SMMHC, and SMA is rare in solid-type adenoid cystic carcinoma with basaloid features.**
- **Basaloid cells are primitive precursor cells that lack significant myoepithelial differentiation.**
- **However, they possess multipotential differentiation capabilities and can further differentiate into ductal epithelial cells or myoepithelial cells.**

Mod Pathol 2015;18:1277-1282
Am J Surg Pathol 2002;26: 413-420

Molecular features of SB-Adcc



MYB::NFIB **fusion is infrequently identified in SB-AdCC (0-21%)**

Novel or uncharacterized MYB rearrangements and MYB or MYBL1 amplifications/copy gains

Harbor frequent aberrations in NOTCH pathway and chromatin modifier genes (including CREBBP)

TP53 mutations are less common.

Mod Pathol . 2020;33(6):1041-1055.
Mod Pathol . 2022;35(2):193-201.

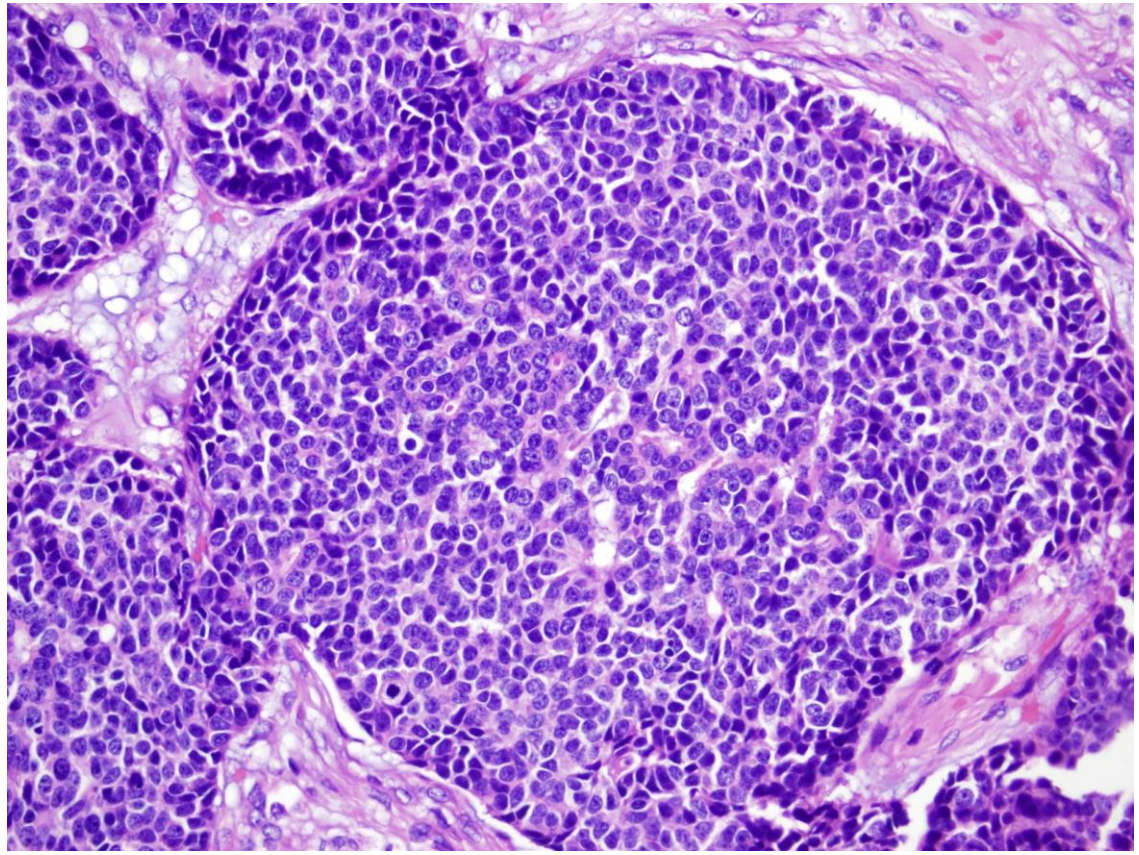
Grading of adenoid cystic carcinoma

Method 1:
Tumors are graded into three levels based on the extent of solid areas:

- ✓ **Grade I: No solid component**
- ✓ **Grade II: Solid component <30%**
- ✓ **Grade III: Solid component ≥30%**

*** Should cytologic atypia and mitotic activity be included?**

Method 2:
Nottingham histologic grading system
Strong predictor of biological behavior



A refined prognostic stratification system with evidence-based treatment recommendations is still awaited.

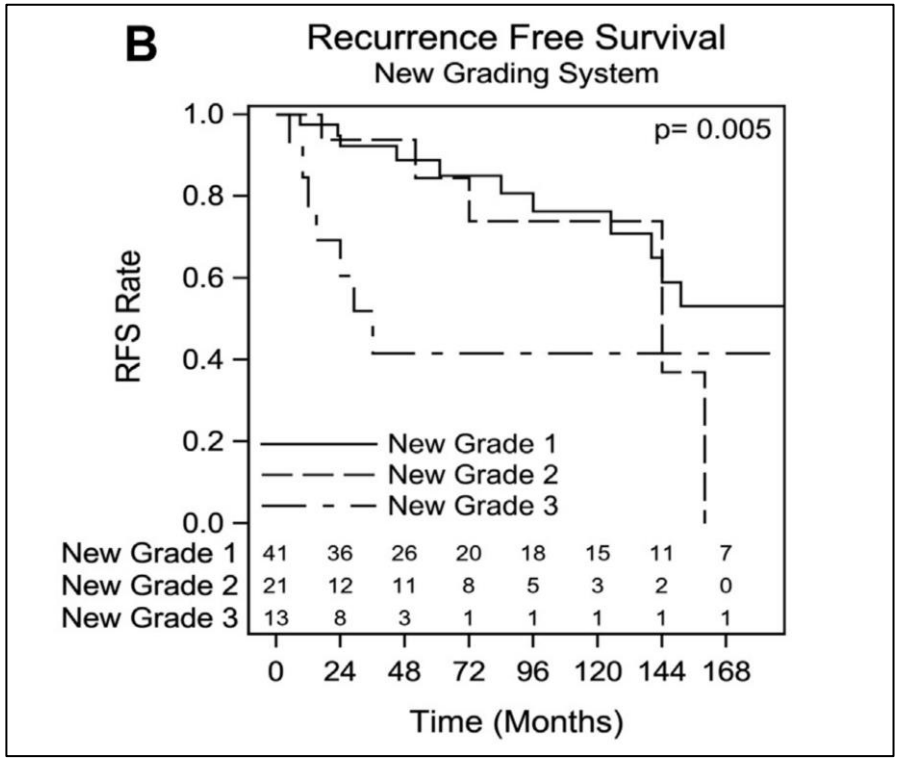
Am J Surg Pathol 1998;22:569-75
Am J Surg Pathol 2020;44:214-223

Clinicopathologic Predictors of Clinical Outcomes in Mammary Adenoid Cystic Carcinoma: A Multi-institutional Study

Table 1
Assignment of points to the histologic variables

Histologic feature	Level	Points
Cribriform and solid type	Cribriform ≥65%	1
	Cribriform <65% and solid <60%	2
	Solid ≥ 60%	3
Basaloid type	<25%	1
	≥25%	2
Mitotic count	<5 per 10 HPF[a]	1
	≥5 per 10 HPF	2

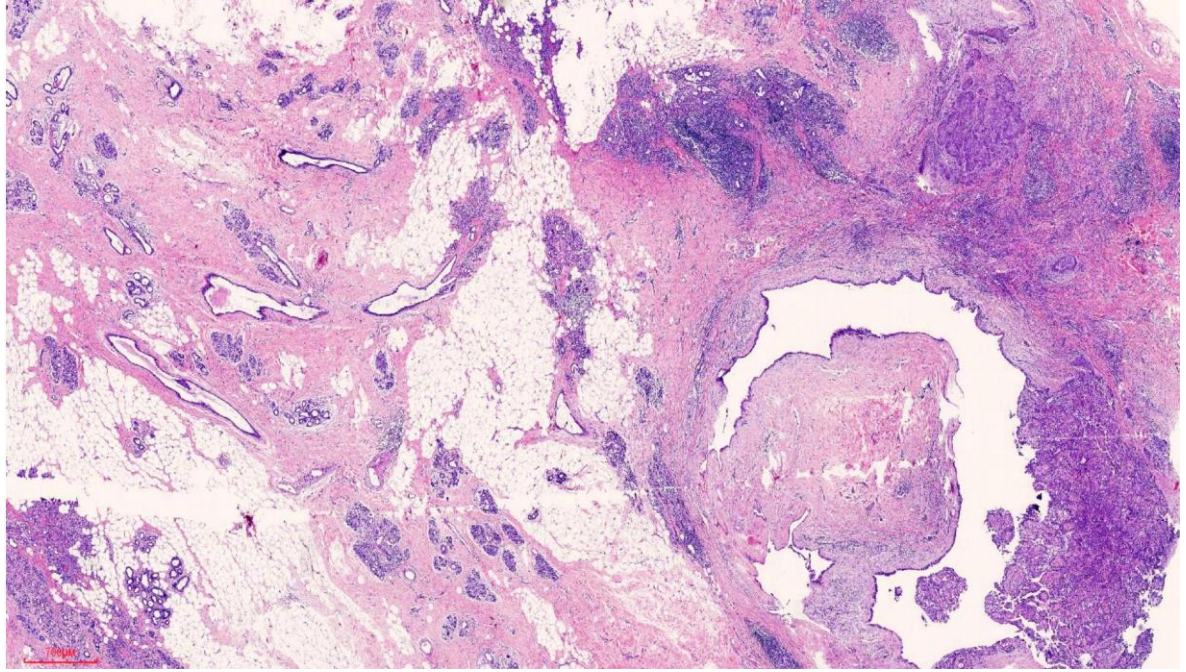
[a] High power field = 0.55 mm

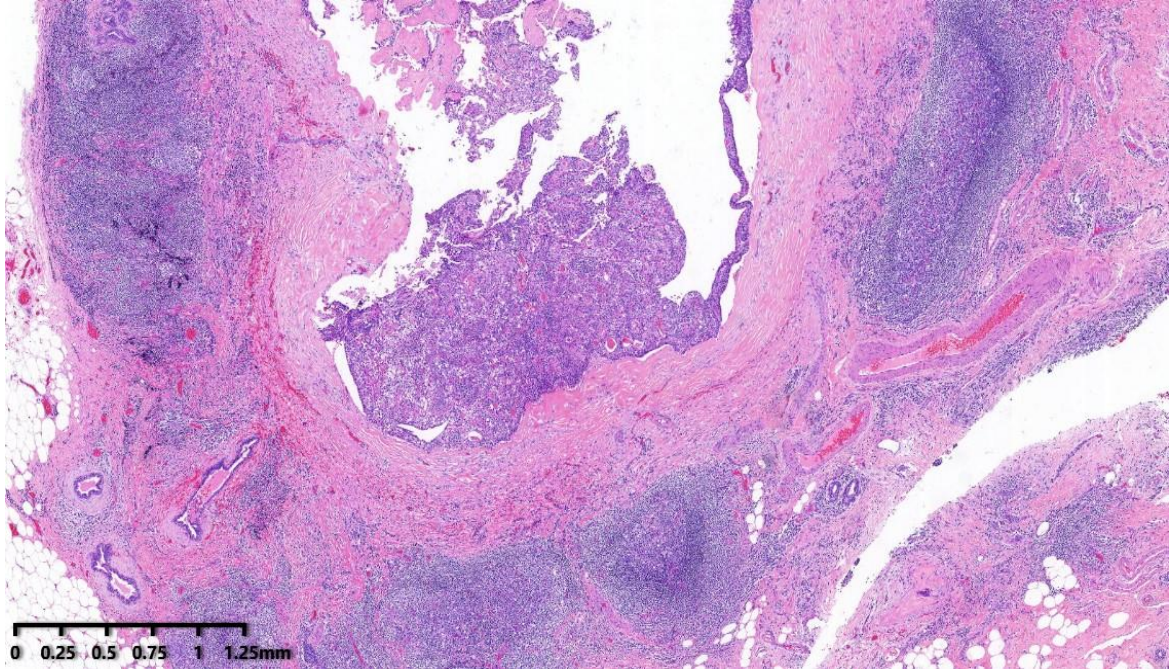


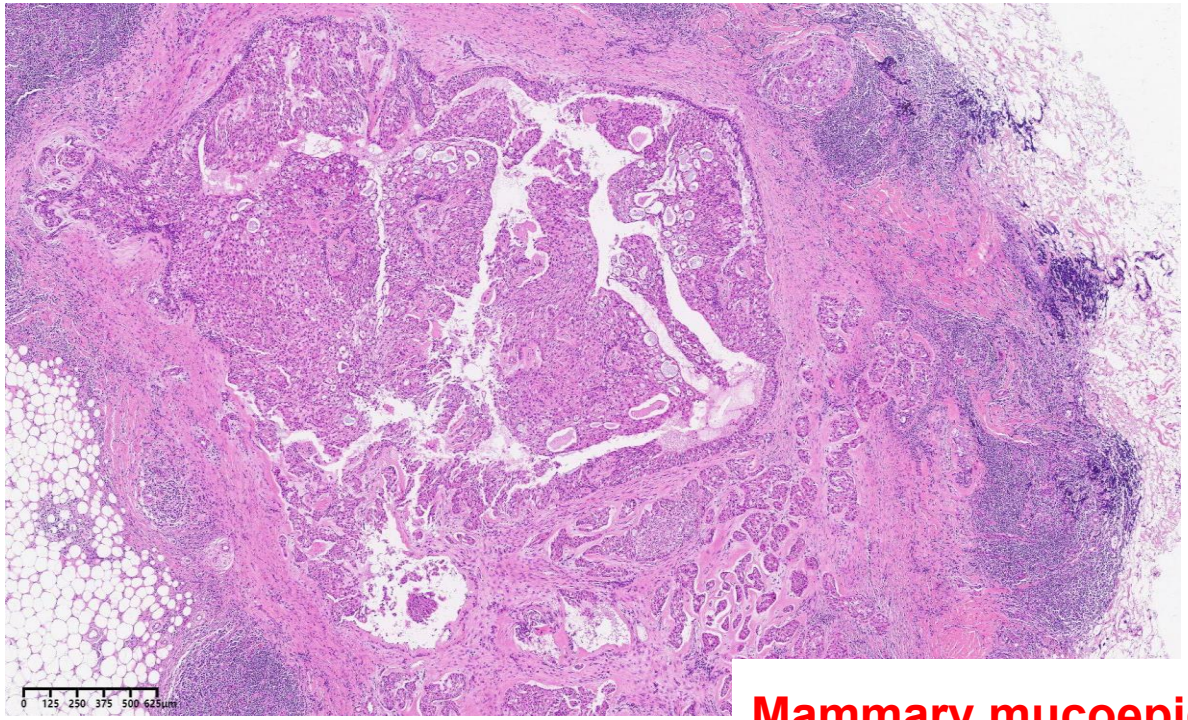
Grade I: 3–4 points ; Grade II: 5–6 points ; Grade III: 7 points
***Basaloid type: Medium to large cells with round or oval nuclei, hyperchromatic, inconspicuous nucleoli, and scant cytoplasm.**

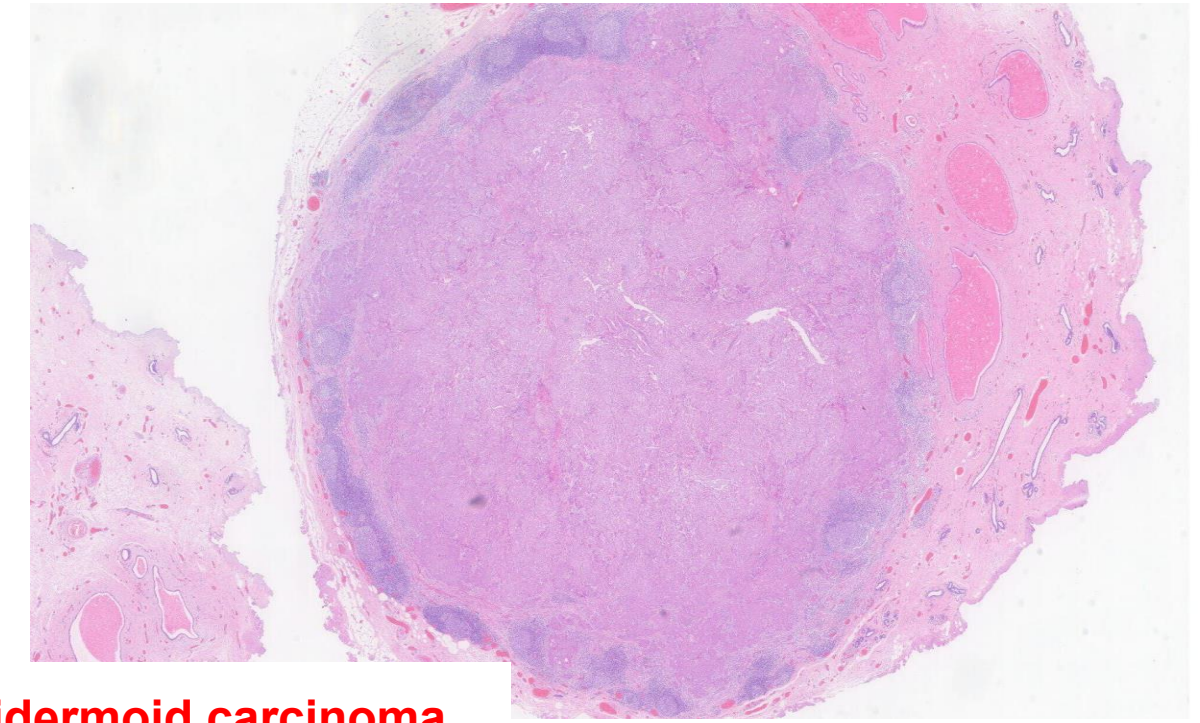
- **The novel grading system showed a significant association with RFS;**
- A higher proportion of solid and basaloid areas is associated with an increased likelihood of recurrence or metastasis.

Mod Pathol 2023;36(2):100006

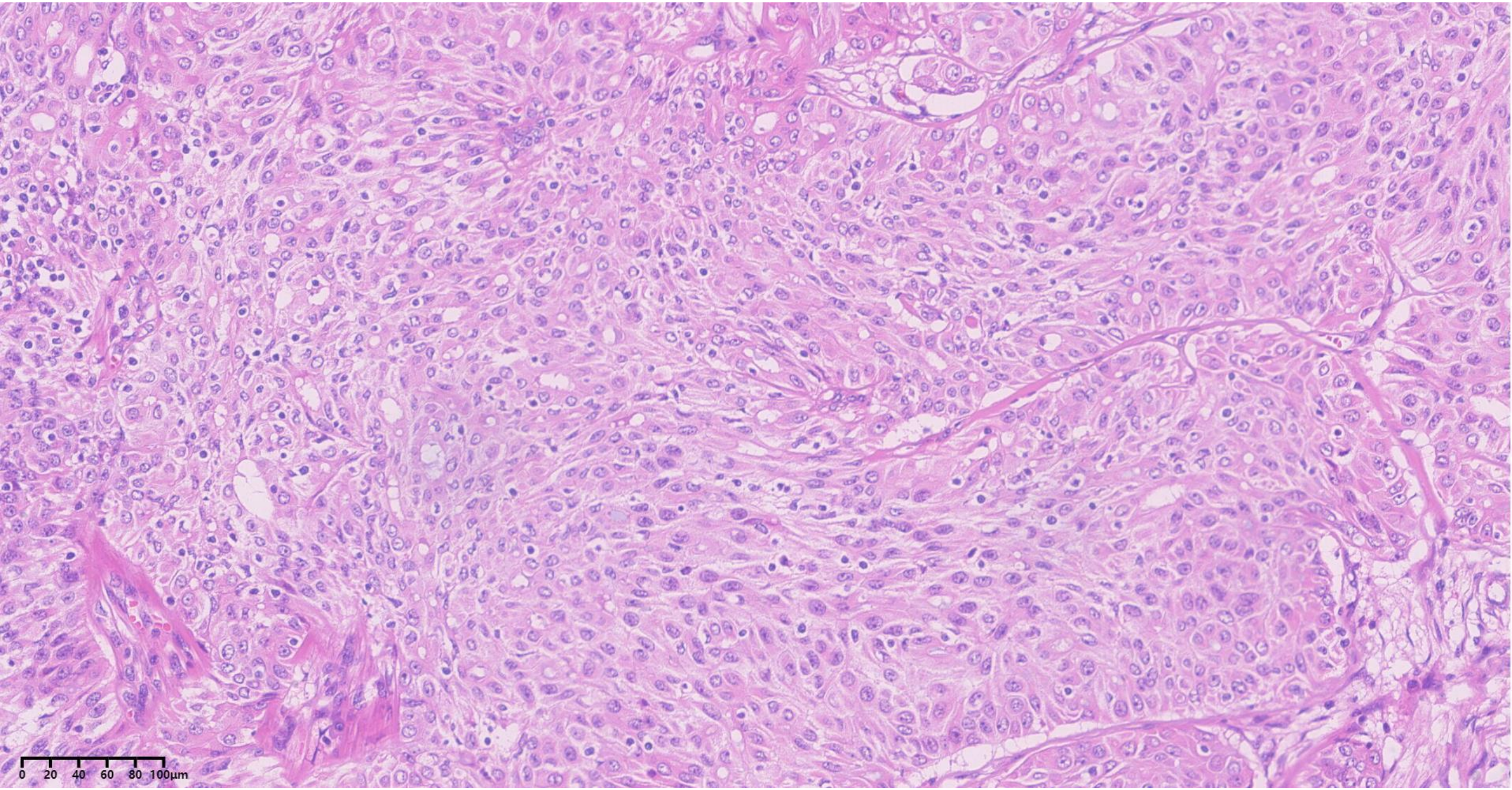


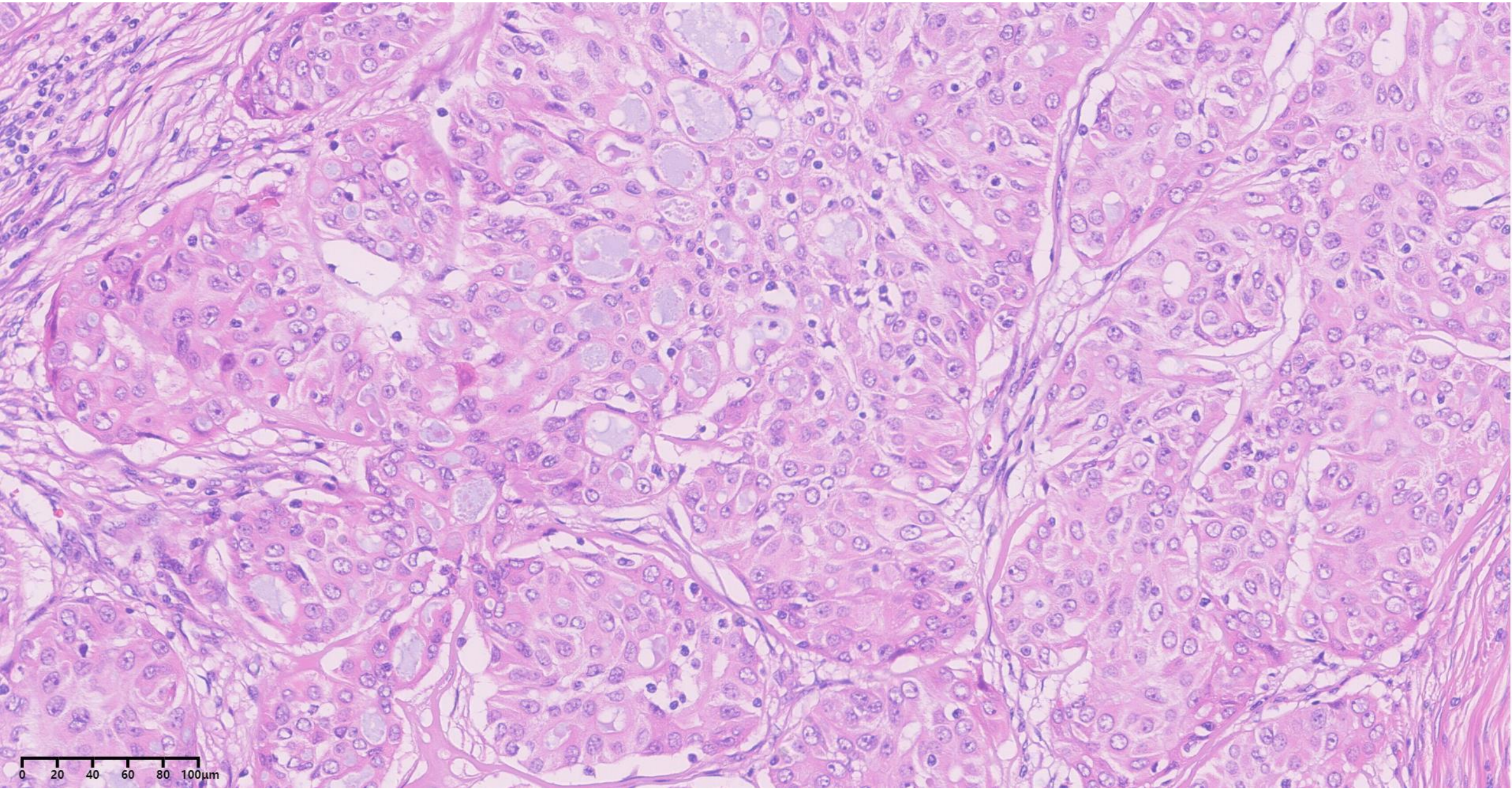


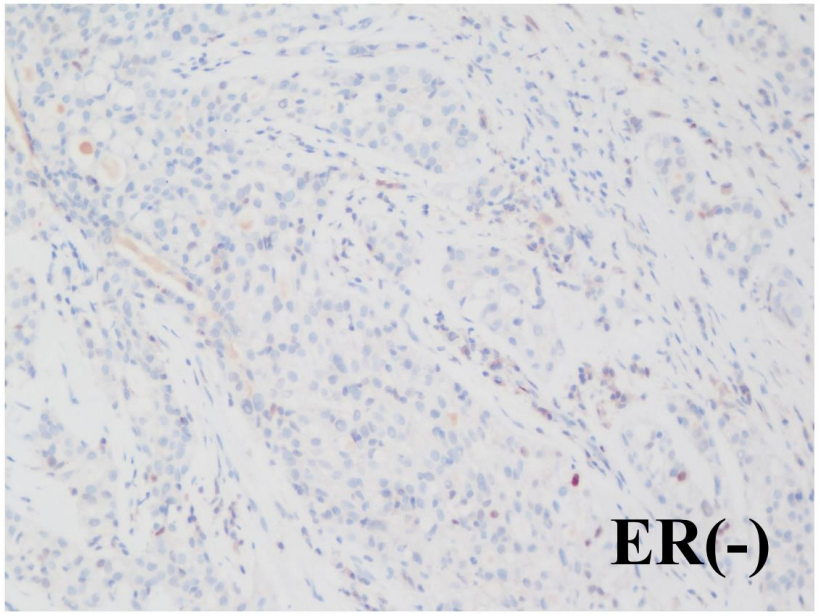


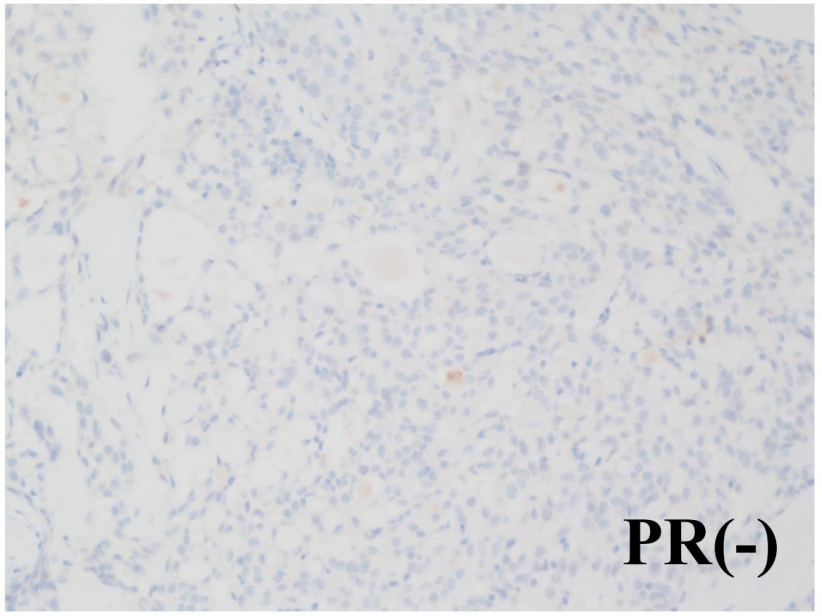


Mammary mucoepidermoid carcinoma


0 20 40 60 80 100µm


0 20 40 60 80 100µm


ER(-)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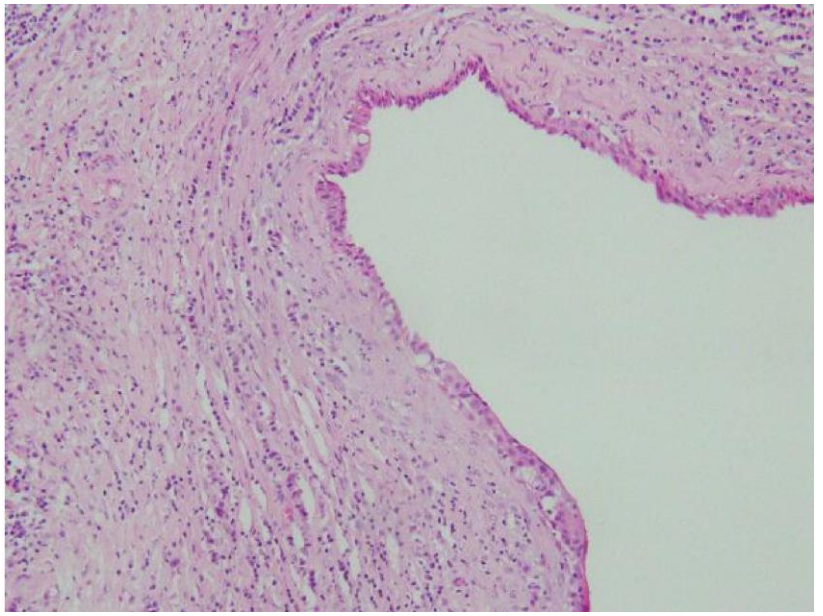
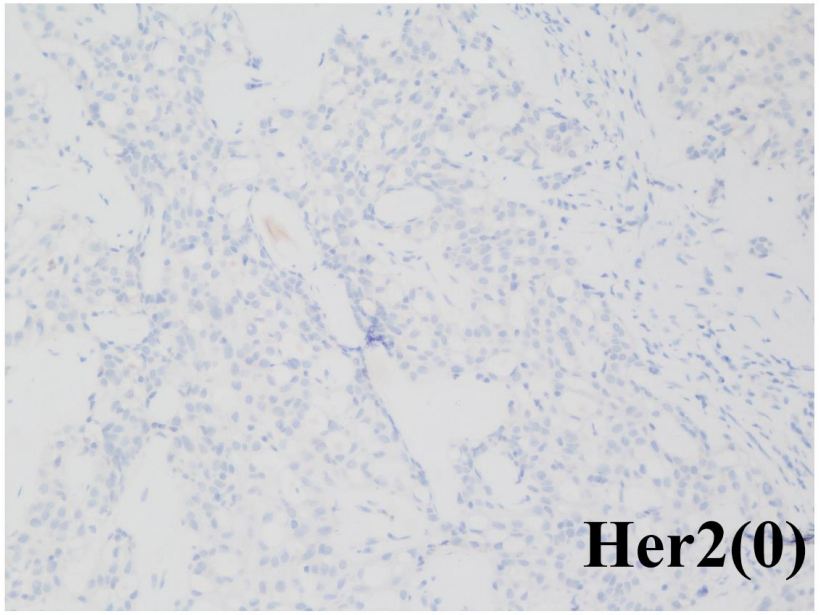
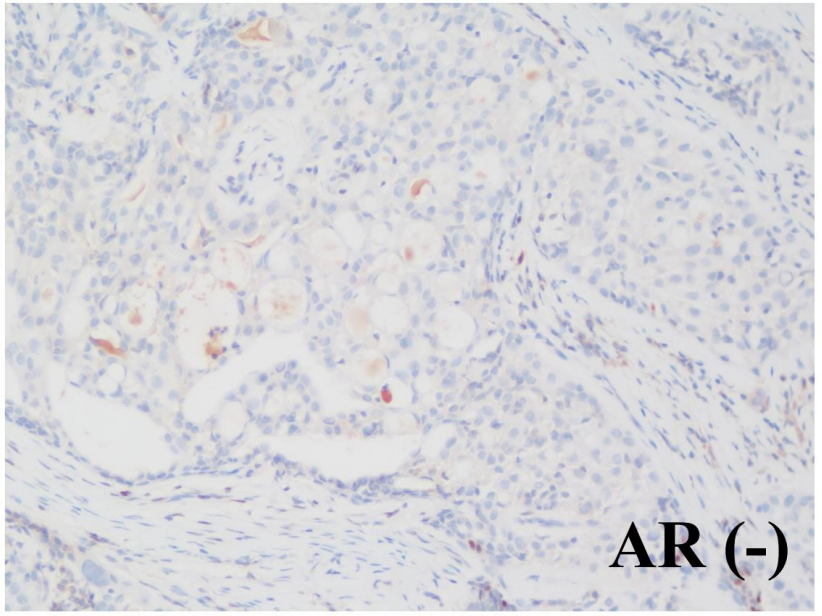
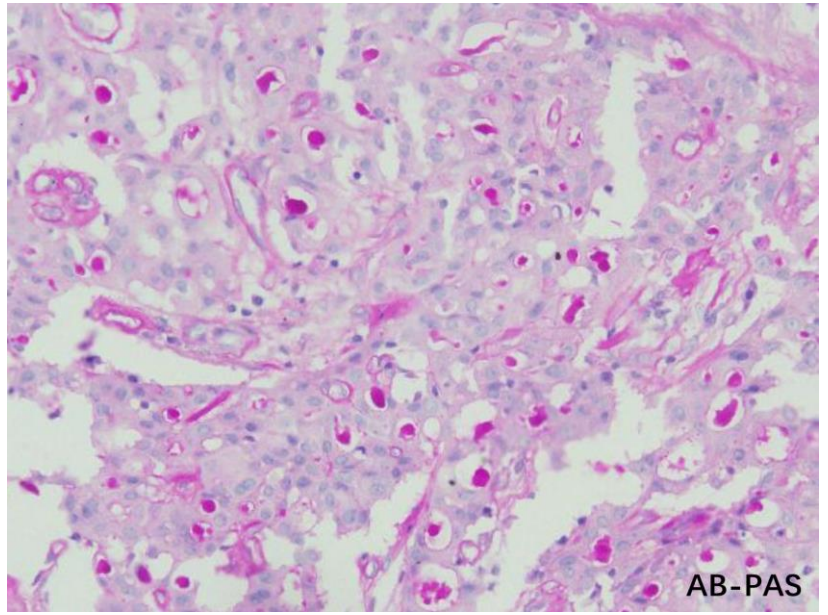
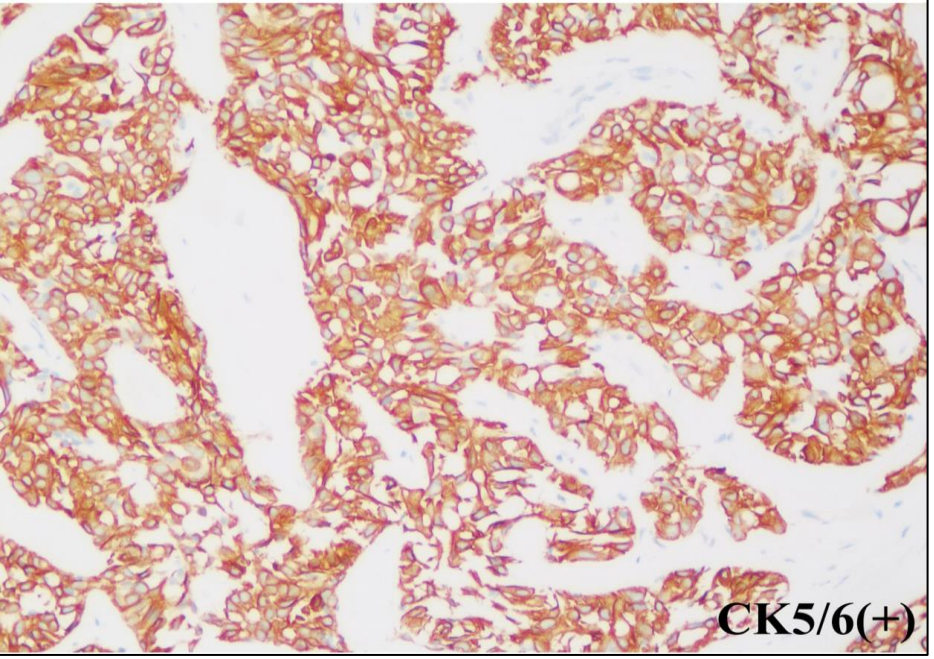
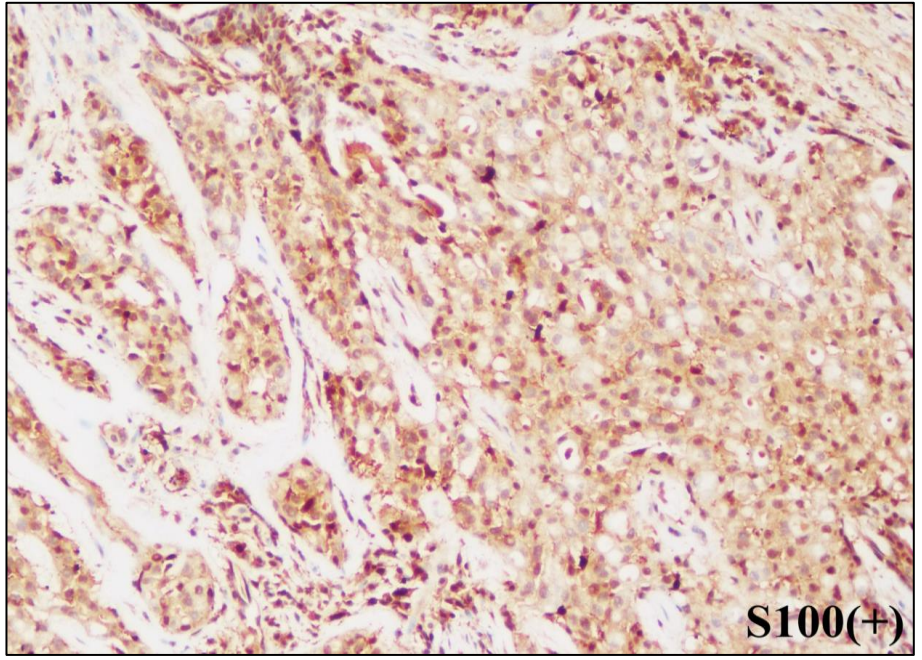


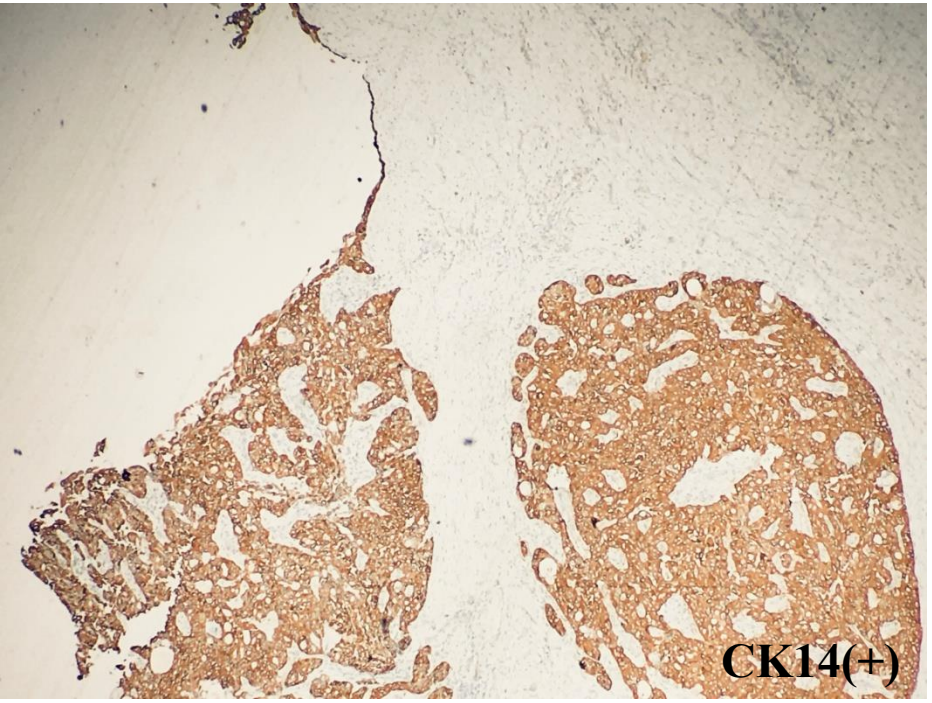

Her2(0)

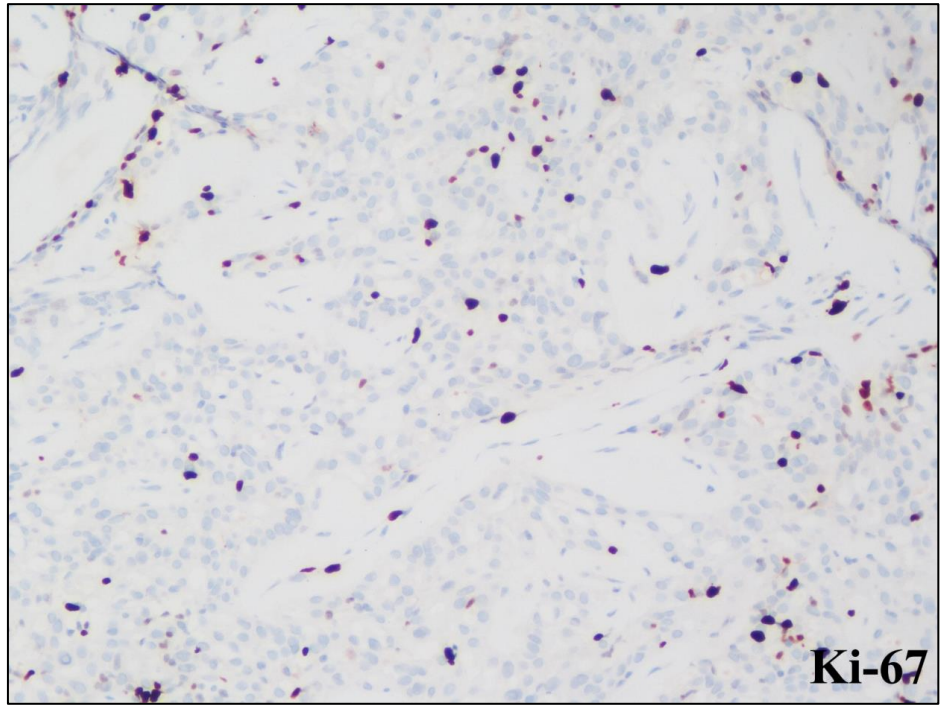

AR (-)


AB-PAS







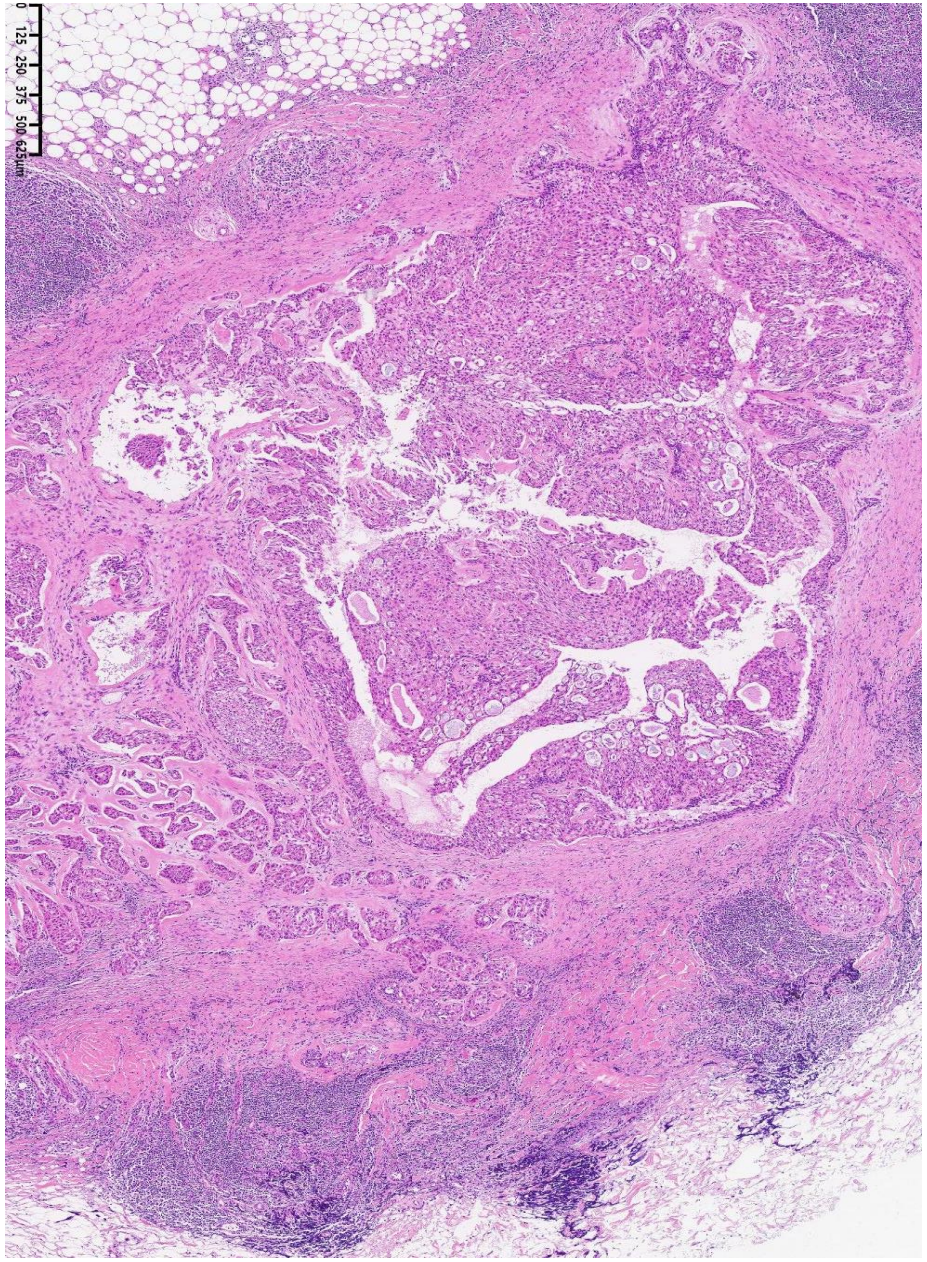


RNA-seq NGS revealed the CRTC1–MAML2 fusion transcript.

Final diagnosis: mammary mucoepidermoid carcinoma.

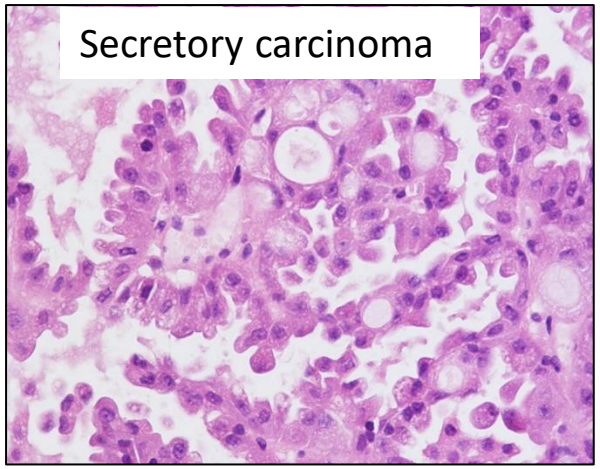
Mammary mucoepidermoid carcinoma

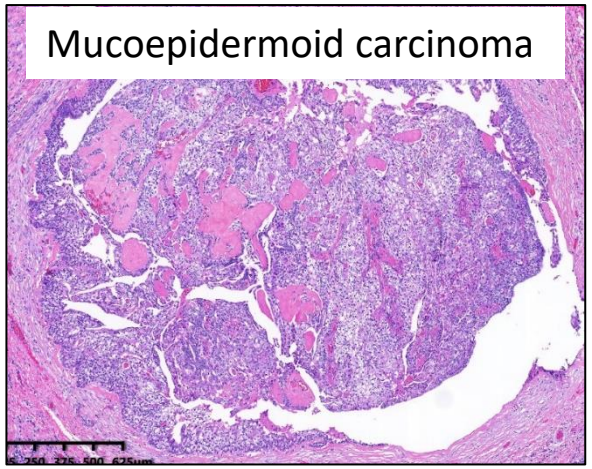
- Extremely rare (0.2–0.3% of all breast tumors) with triple-negative immunophenotype
- Histologically similar to salivary gland mucoepidermoid carcinoma
- Prominent lymphoplasmacytic infiltrate and sclerotic stroma
- Variable-sized cystic or solid nodules; central large, irregular cysts surrounded by smaller, irregular peripheral nodules
- Macrocystic or microcystic spaces containing basophilic and/or eosinophilic secretions
- Diverse cell types: intermediate/basaloid cells, epidermoid cells, and mucinous cells
- Absence of keratin pearls or single-cell keratinization, if present, metaplastic carcinoma must first be excluded.
- Intraductal carcinoma component may be present
- High-grade MEC: more solid architecture, marked nuclear atypia, frequent mitotic figures

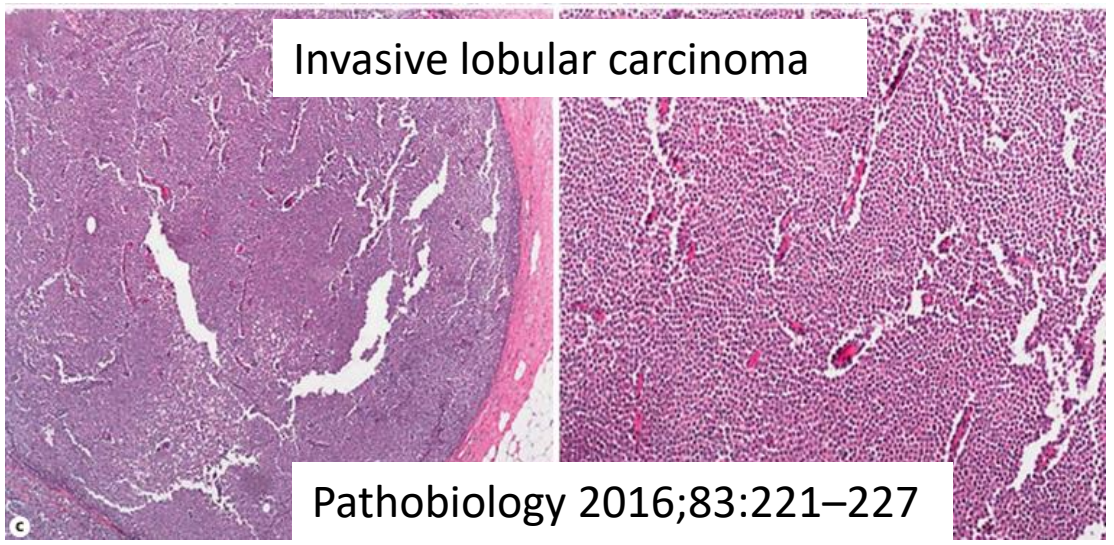


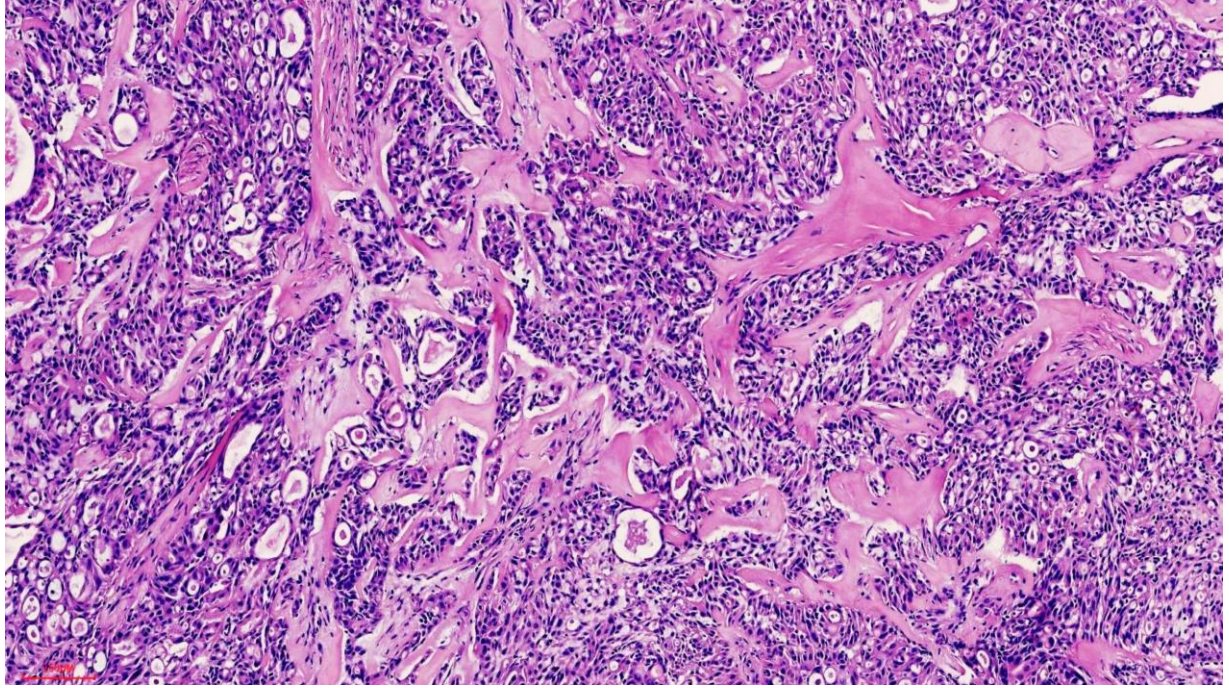
Tumors with papillary growth pattern

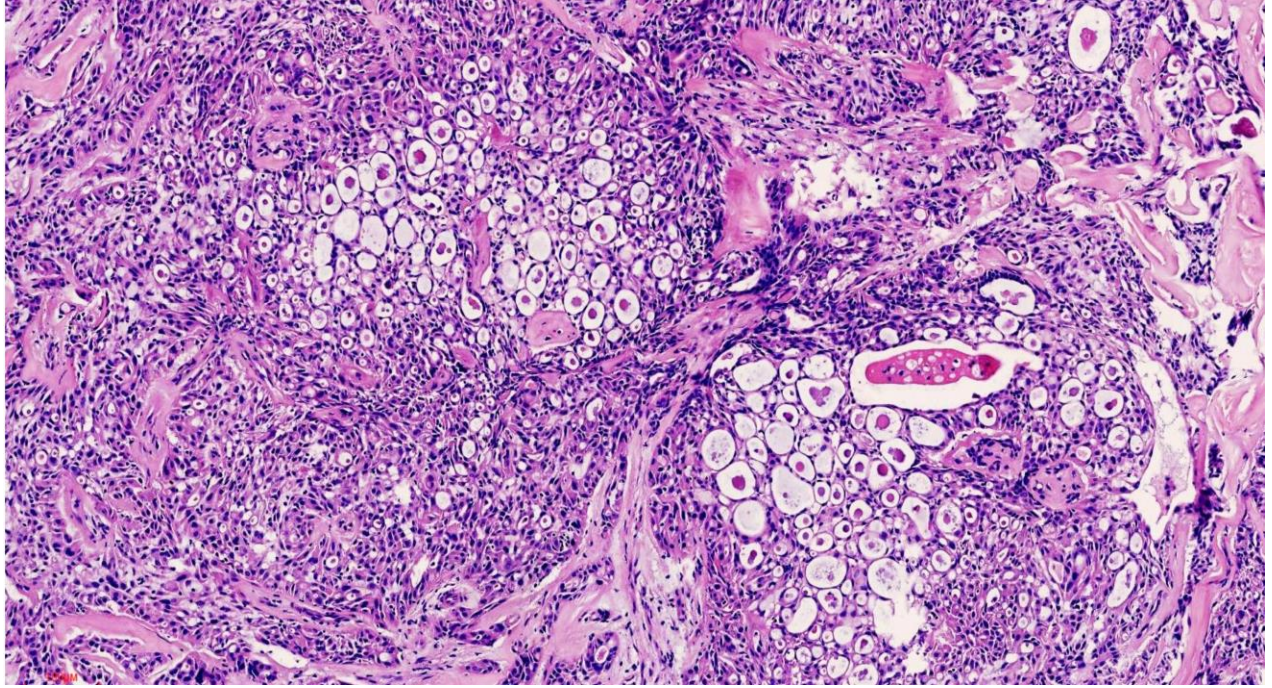
- **Benign, borderline, malignant (solid papillary carcinoma, intraductal papillary carcinoma, encapsulated papillary carcinoma, invasive papillary carcinoma)**
- **Secretory carcinoma**
- **Mucoepidermoid carcinoma**
- **Adenomyoepithelial tumors**
- **Tall-cell carcinoma with reversed polarity**
- **Invasive lobular carcinoma (solid-papillary-like growth pattern)**

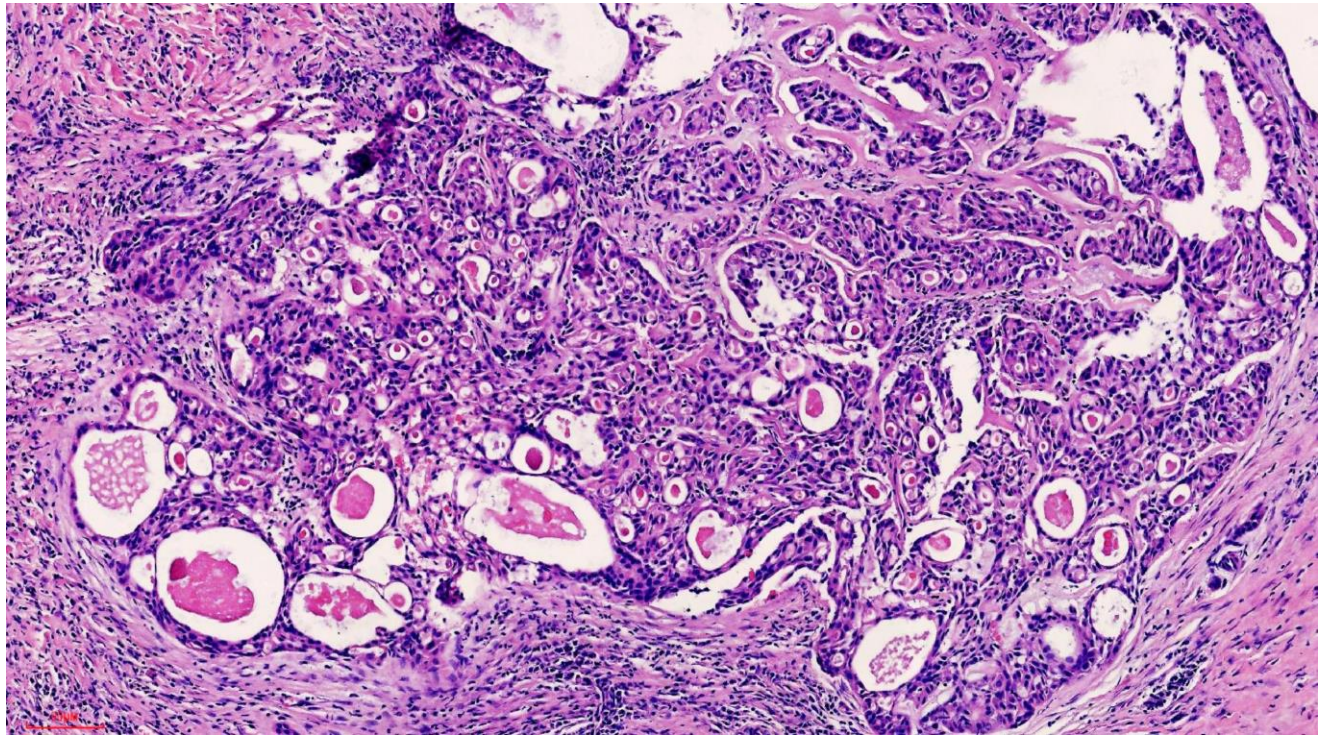






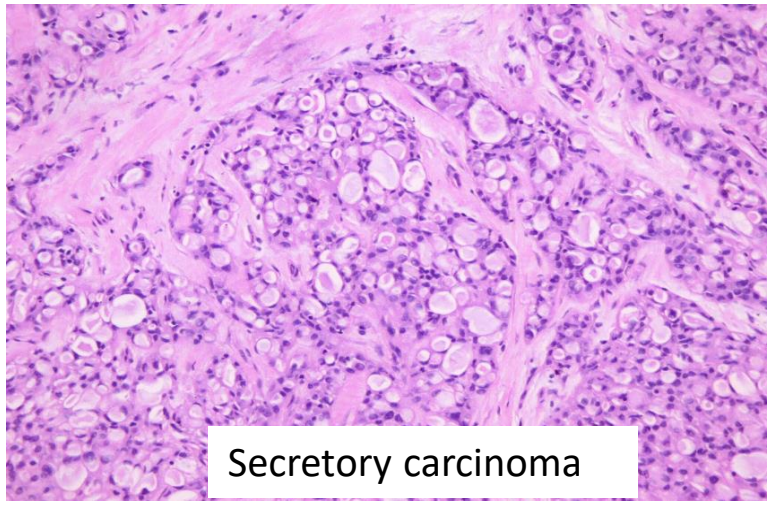




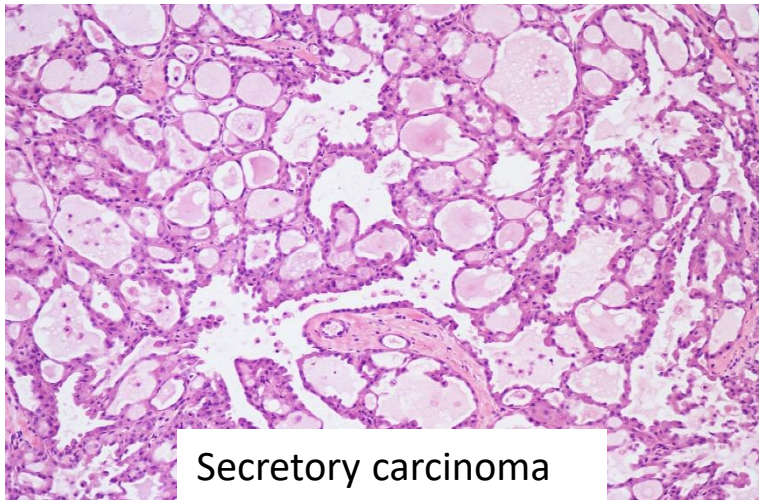


Not all low-grade TNBCs with microcystic and honeycomb-like architecture are secretory carcinomas.

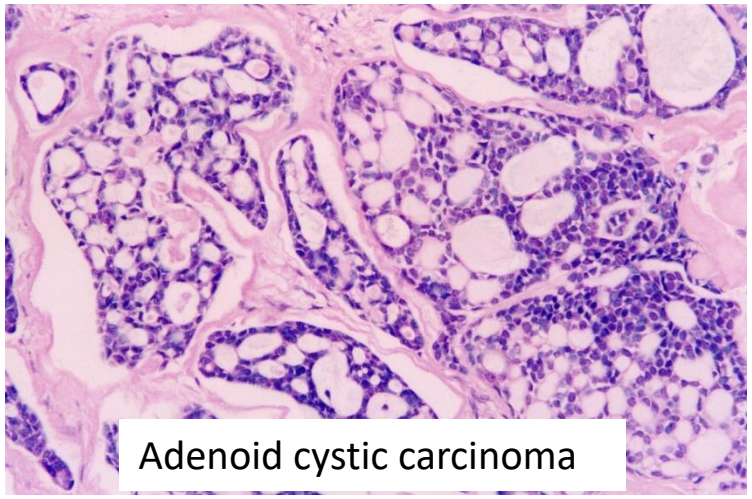
Secretory carcinoma



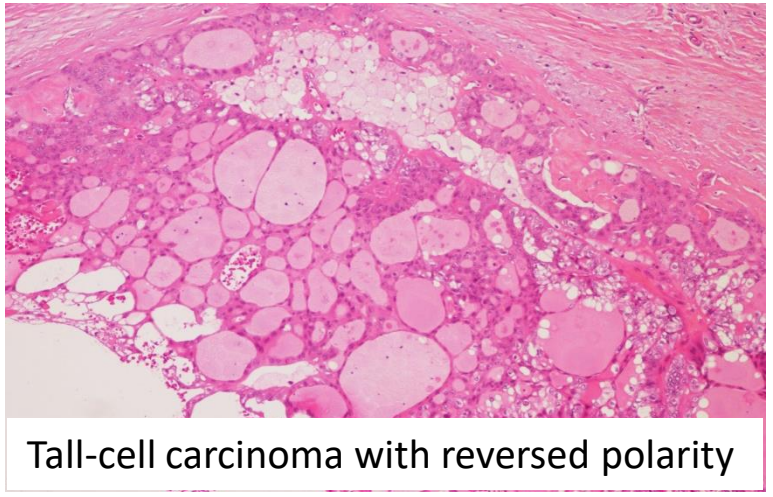
Secretory carcinoma



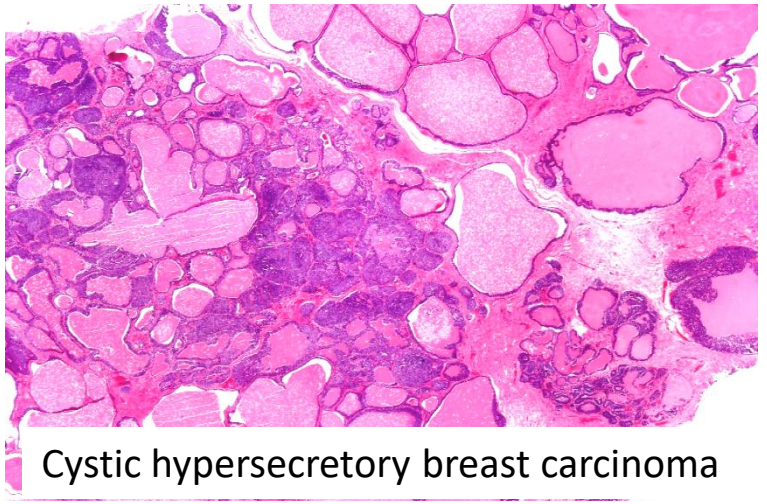
Secretory carcinoma



Adenoid cystic carcinoma



Tall-cell carcinoma with reversed polarity



Cystic hypersecretory breast carcinoma

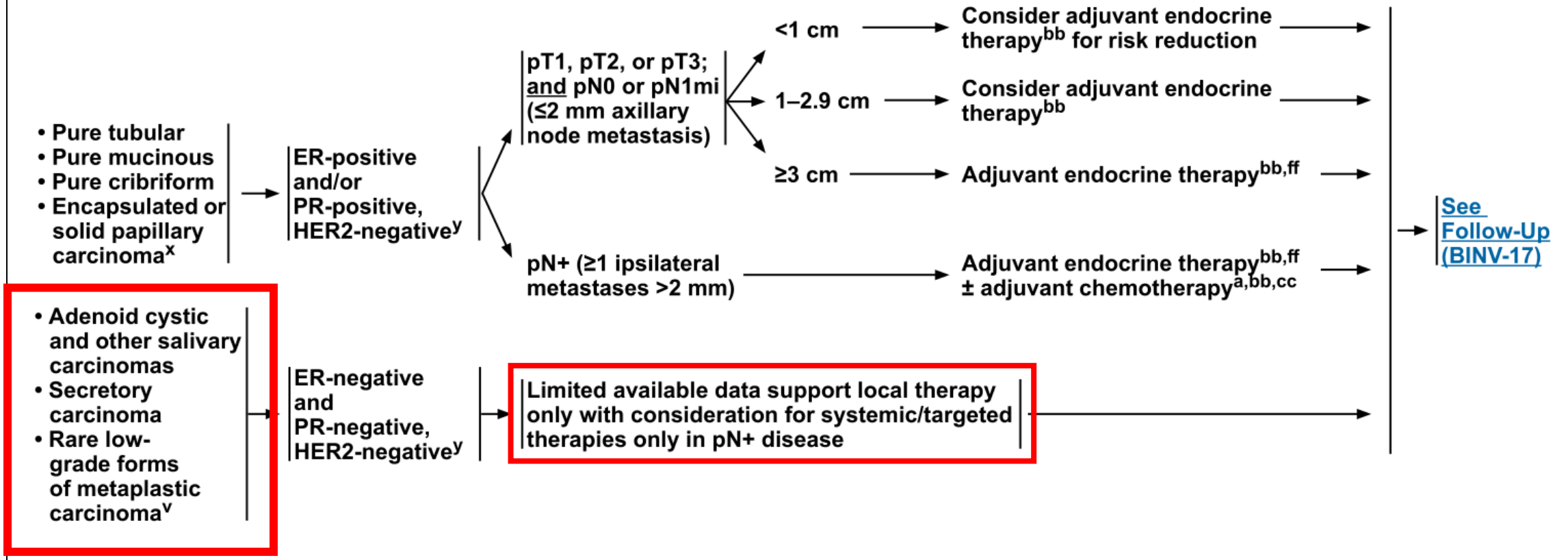
Grading of mucoepidermoid carcinoma is crucial for prognosis and treatment

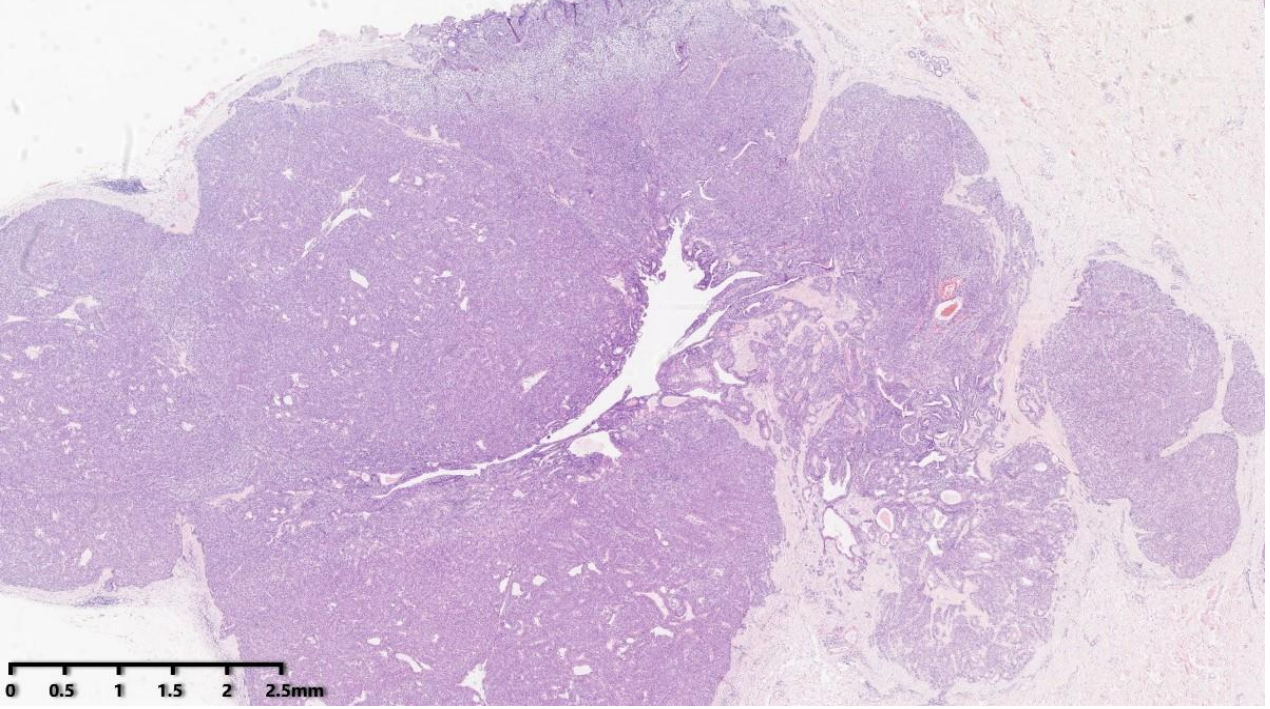
- Prognosis is significantly better than that of conventional TNBC.
- Low-grade MEC: Excellent long-term survival, even in patients who did not receive chemotherapy.
- Low- and intermediate-grade cases: No distant metastases or disease-related deaths; adjuvant chemotherapy is not justified.
- High-grade MEC: Disease-specific death occurred in 5 patients.
- Grading is essential; either the breast-specific or the salivary mucoepidermoid carcinoma grading system can be used, both providing equivalent prognostic value.

- Commonly used grading systems for salivary mucoepidermoid carcinoma:
  - Brandwein system
  - AFIP system
  - Modified Healey system
  - Katabi system
  - MSK system
- Nottingham grading system for breast carcinoma
- Both of grading systems provide comparable prognostic value.

Virchows Arch. 2022 ;480(1):5-19
Virchows Arch. 2022 ;480(1):109-126
Cancers (Basel). 2021;13(22):5694

SYSTEMIC ADJUVANT TREATMENT: FAVORABLE HISTOLOGIES[r,w]

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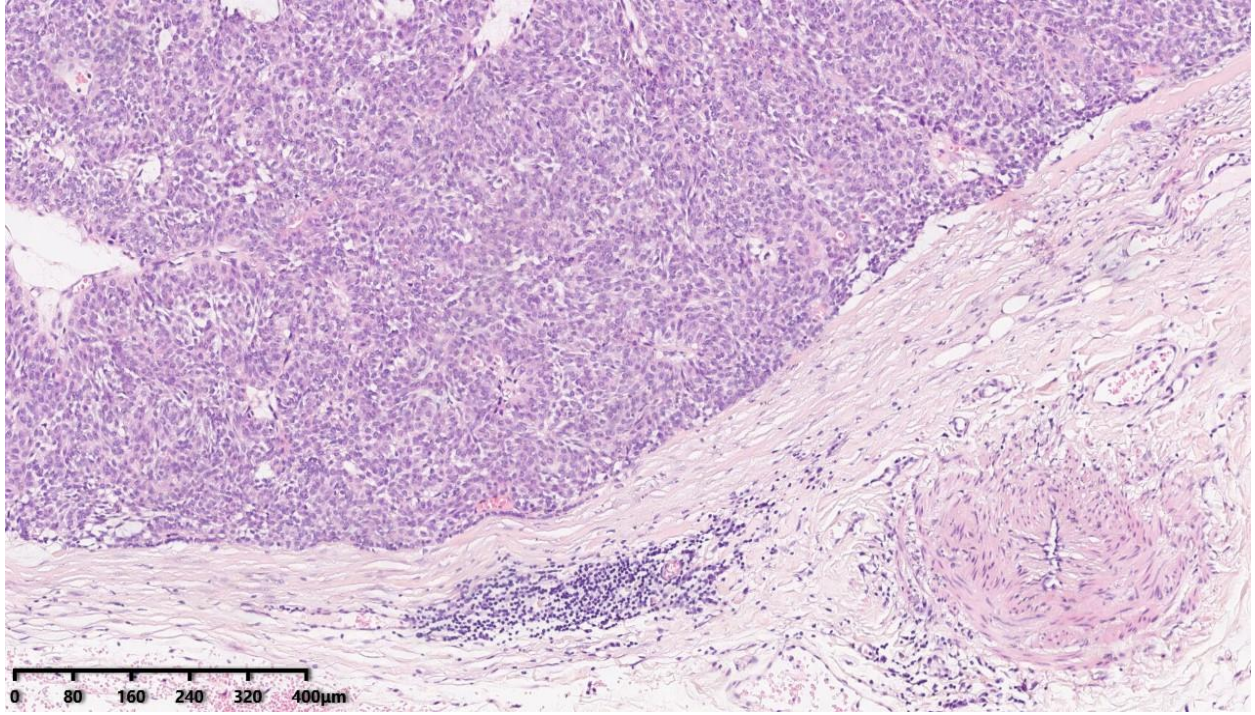
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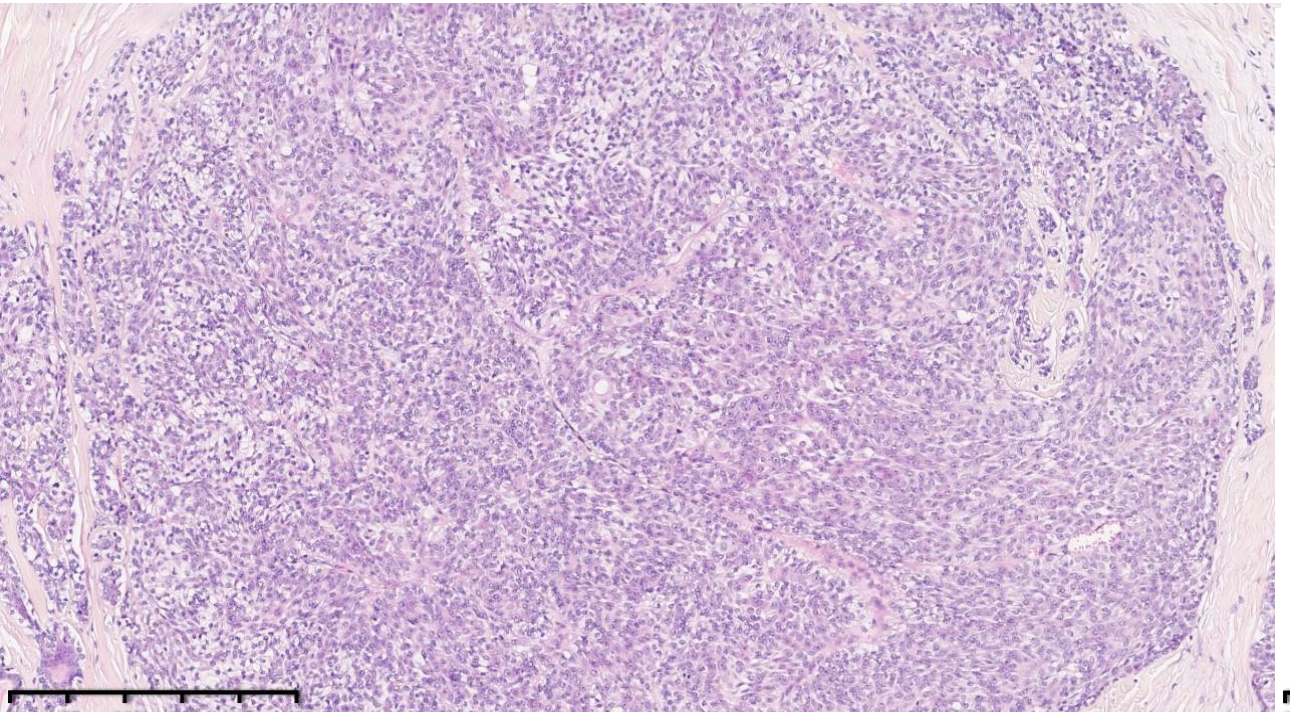
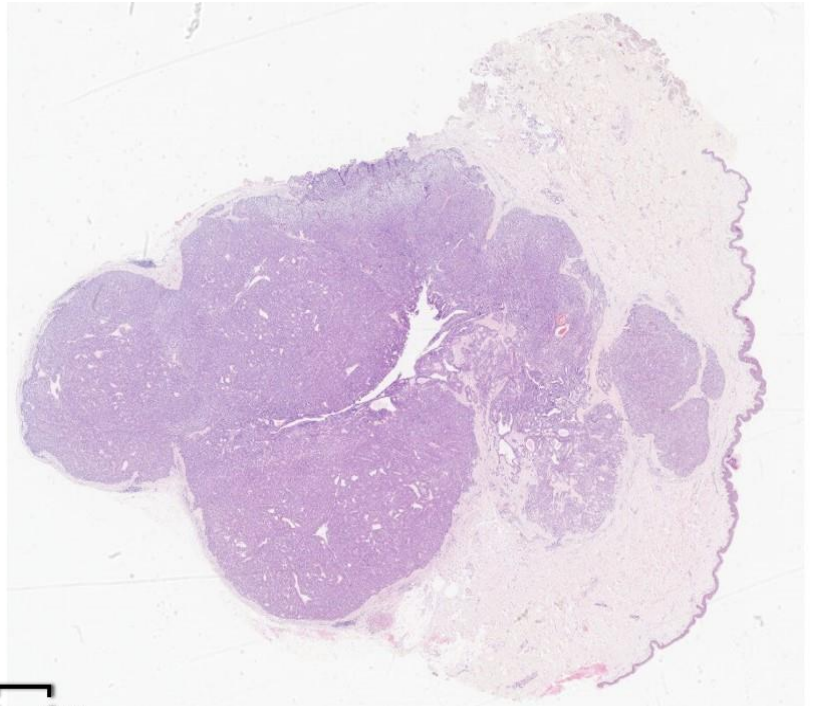




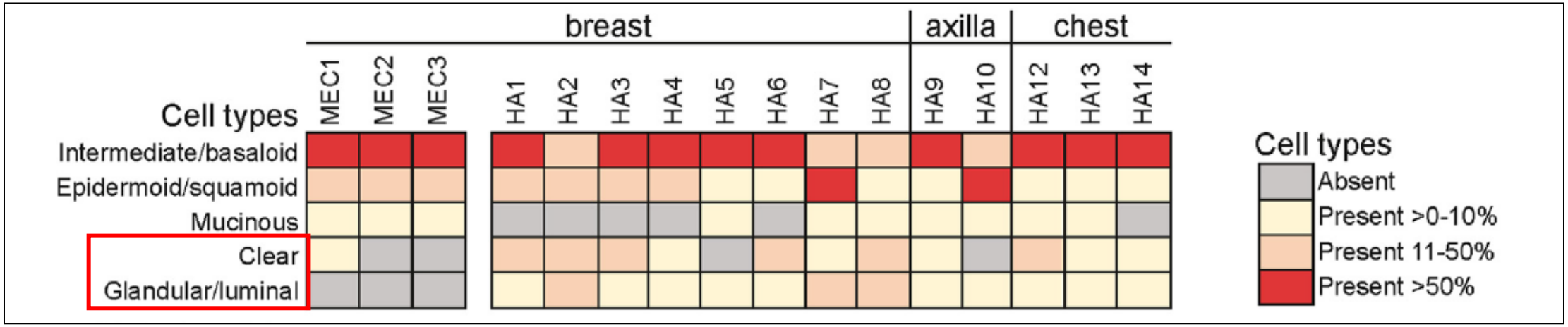
Clear-cell papillary hidradenoma

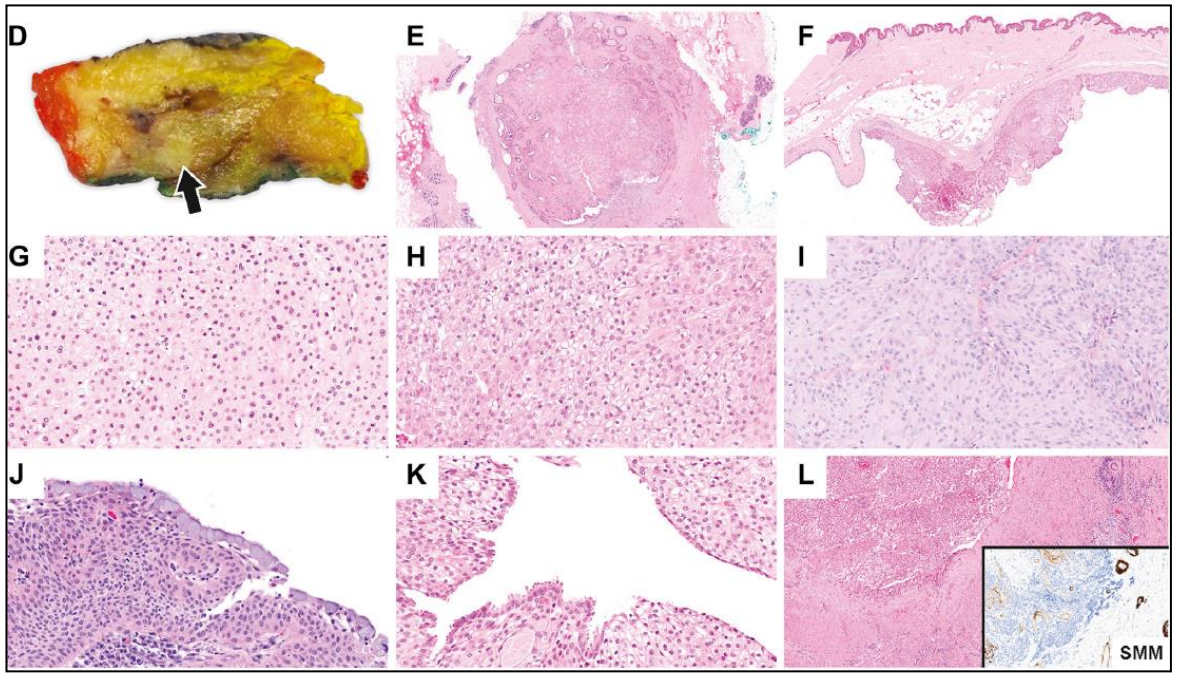
- **Clear-cell hidradenoma and low-grade mucoepidermoid carcinoma show overlapping histomorphology, immunophenotype, and molecular features.**
- **A heterogeneous cell population: clear cells, polygonal cells, mucous cells, squamous cells, oncocytes, and epidermoid cells.**
- **Fewer than 30 cases of mammary clear-cell hidradenoma that are not connected to the skin have been reported; half of these occurred in the nipple or areolar region, while others arose within the breast parenchyma.**

Tumor	Genetic alteration	Frequency
Hidradenoma	CRTC1–MAML2 fusion	50-75%
	CRTC3–MAML2 fusion	Rare
Mucoepidermoid carcinoma	Salivary gland CRTC1-MAML2 fusion CRTC3-MAML2 fusion	 34-70% Rare

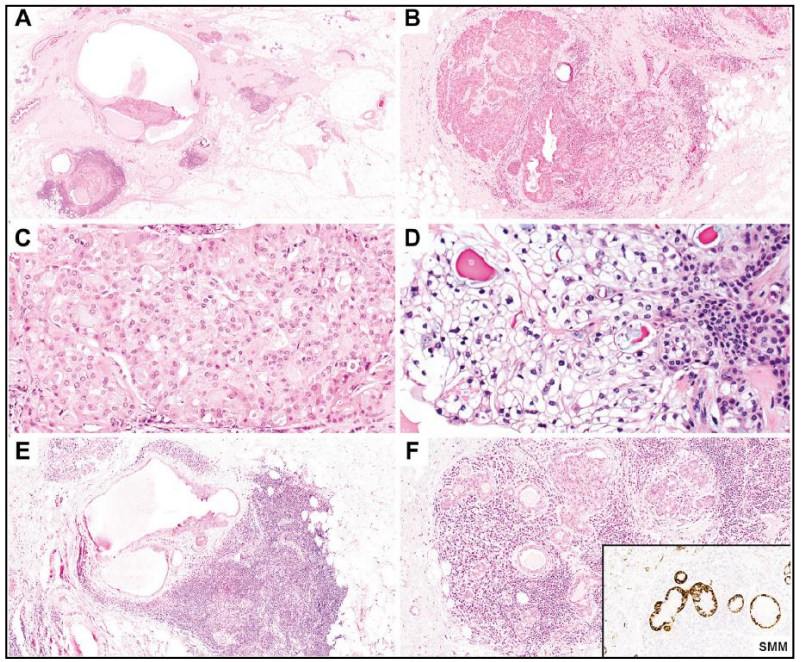
MEC

hidradenoma





hidradenoma



mucoepidermoid carcinoma

Clear cells are more frequently encountered in hidradenoma.
Glandular/luminal cell morphology is seen exclusively in hidradenoma.

Mod Pathol. 2023;36(10):100270

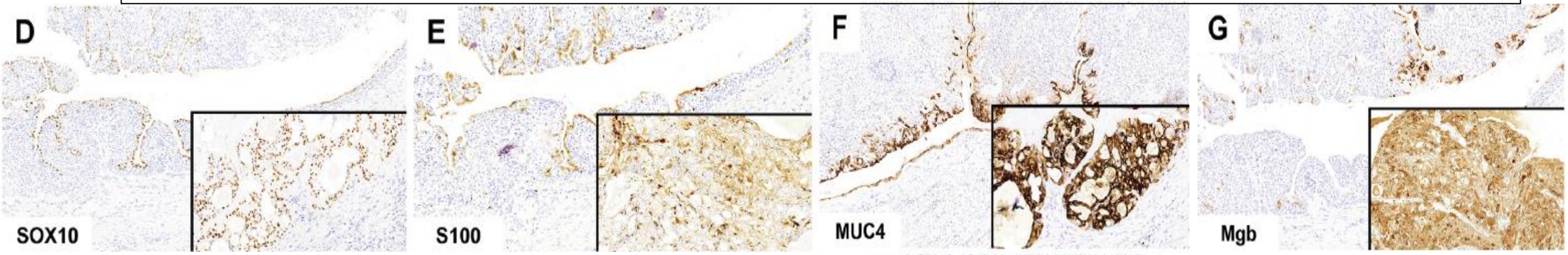
Cell types	breast										axilla		chest		
	MEC1	MEC2	MEC3	HA1	HA2	HA3	HA4	HA5	HA6	HA7	HA8	HA9	HA10	HA12	HA13	HA14
Immunohistochemistry																
Keratin Cam5.2	em	em	iem	eg	ig	eg	ieg	emg	ieg	emg	imc	i	img	g	g	g
Keratin 5/6	iec	ie	ie	iecg	iecg	iec	iecg	ie	iec	iecg	iec	iec	ie	iec	iec	iec
p63	iec	ie	ie	iec	iec	iec	iec	ie	iec	iec	iec	iec	ie	iec	iec	iec
S100 protein	em	iem	im			g	ic		ig	ie	ig		ie		ic	
SOX10	iemc	iem	iem	g	g	g				g						g
MUC4	em	em	iem	g	g	g	g	g	g	mg	g	g	emg		g	g
ER			im	eg	g	e	eg	eg			g		e	g	g	
GATA3	iemc	iem	iem	icg	eicg	eicg	g	emg	icg	img	g		eg	ig	g	g
Mammaglobin	iemc	iem	iem	ecg	eg	eg	ieg	e		ie	iemcg			ig		g
GCDFP15			iem	g	g		eg	eg								
TRPS1	iem		iem	iecg	ieg		ig	emg	icg	eg	iemcg		eg	iemcg	icg	icg
AR	e	e		g	g		g	eg								

Immunohistochemistry

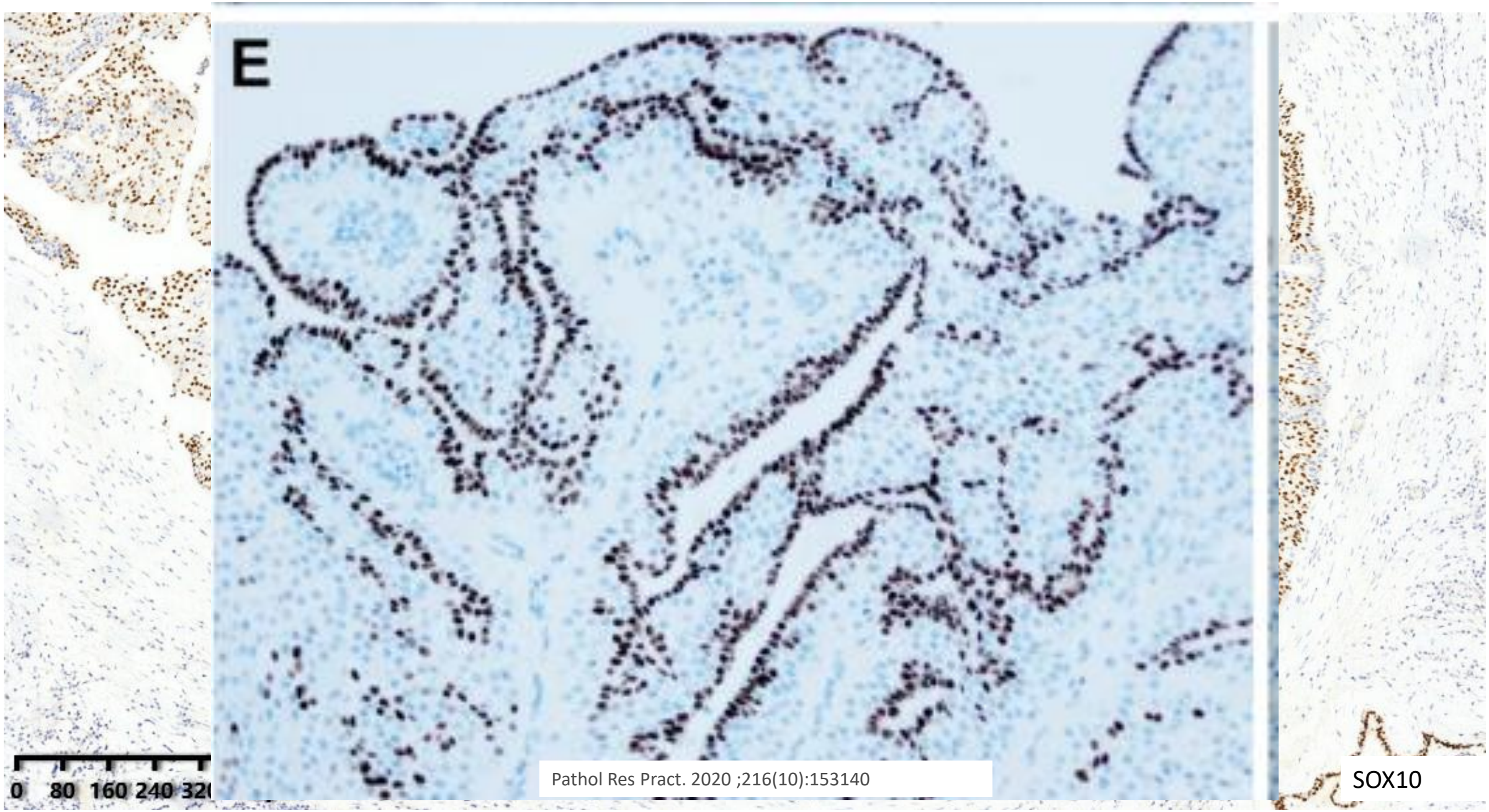
- Negative (<1%)
- Low postitive (1-10%)
- Moderate positive (11-90%)
- Diffuse positive (>90%)
- Not performed

i: intermediate/basaloid
e: epidermoid/squamoid
m: mucinous
c: clear
g: glandular/luminal

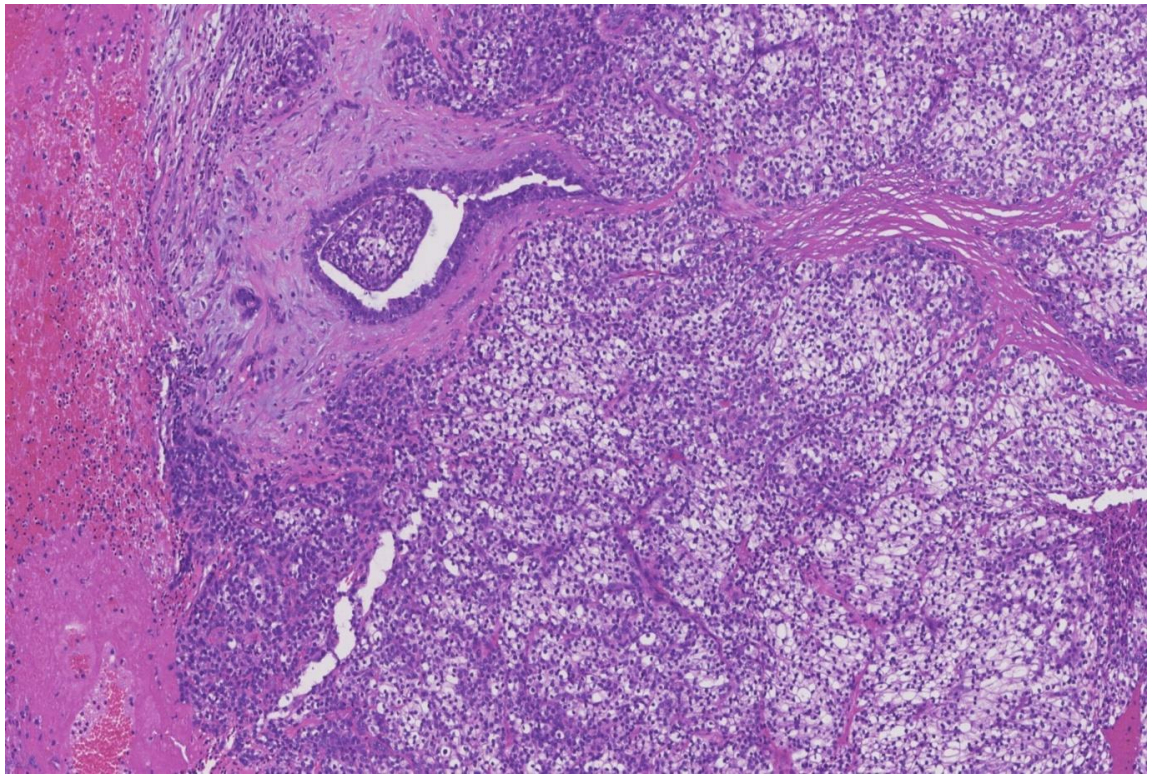
Mucoepidermoid carcinoma：SOX10, S100, MUC4, and mammaglobin show more diffuse staining.
Hidradenoma： SOX10 staining is restricted to the glandular luminal epithelium.



Mod Pathol. 2023 Oct;36(10):100270


E
0 80 160 240 32
Pathol Res Pract. 2020 ;216(10):153140
SOX10

Another case

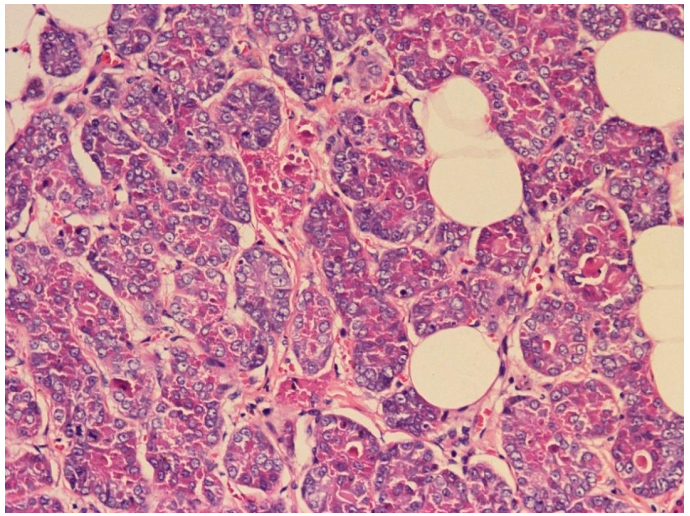


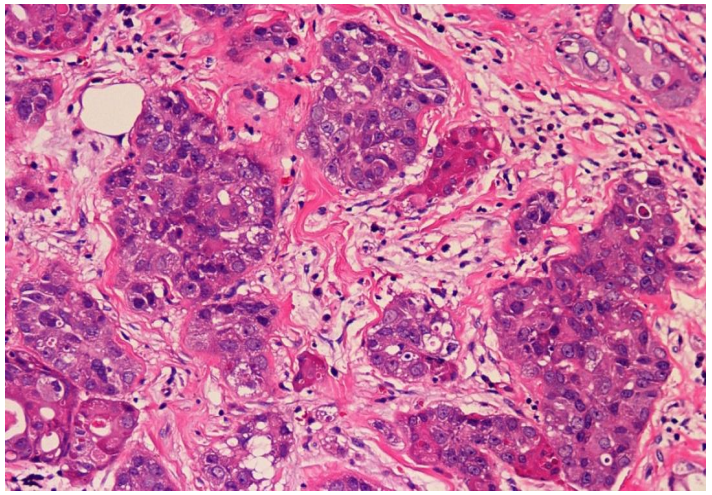
A group of tumors for differential diagnosis:
Clear-cell hidradenoma
Adenomyoepithelioma
Intraductal papilloma
Nipple adenoma (with ductal epithelial hyperplasia, squamous metaplasia, and apocrine metaplasia)
Secretory carcinoma
Metaplastic carcinoma
Solid papillary carcinoma
Primary and metastatic mucoepidermoid carcinoma

2017: Left breast mass – mucoepidermoid carcinoma, MAML2-FISH positive.
2015: Mucoepidermoid carcinoma of the left parotid gland.

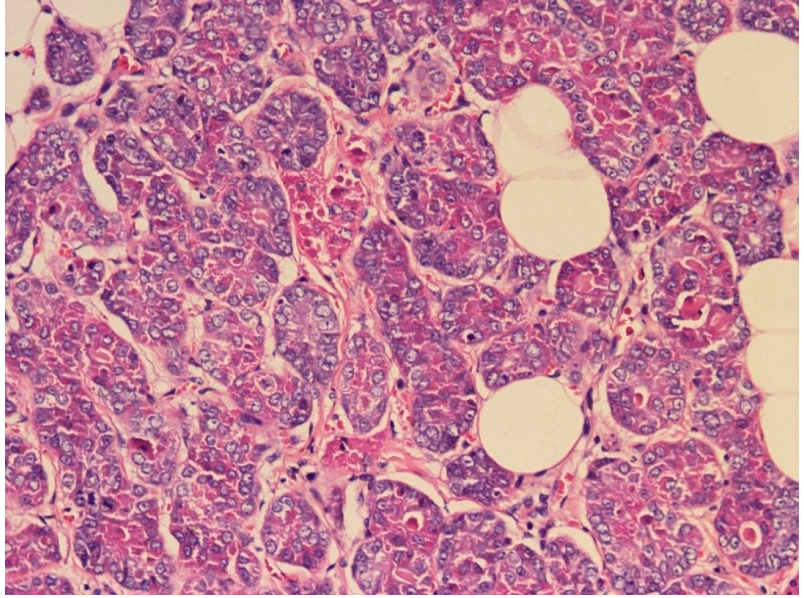
Diagnosis: Metastatic mucoepidermoid carcinoma from the parotid gland to the breast.

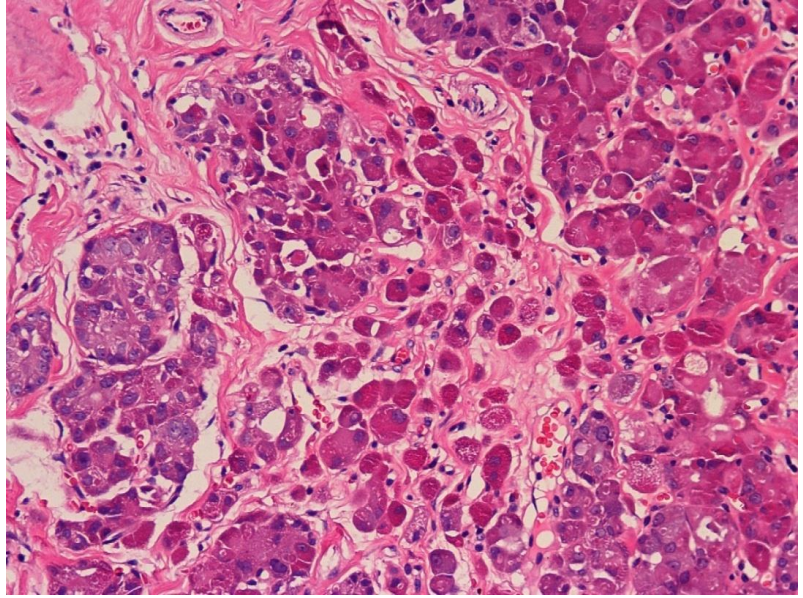
Acinic cell carcinoma of the breast

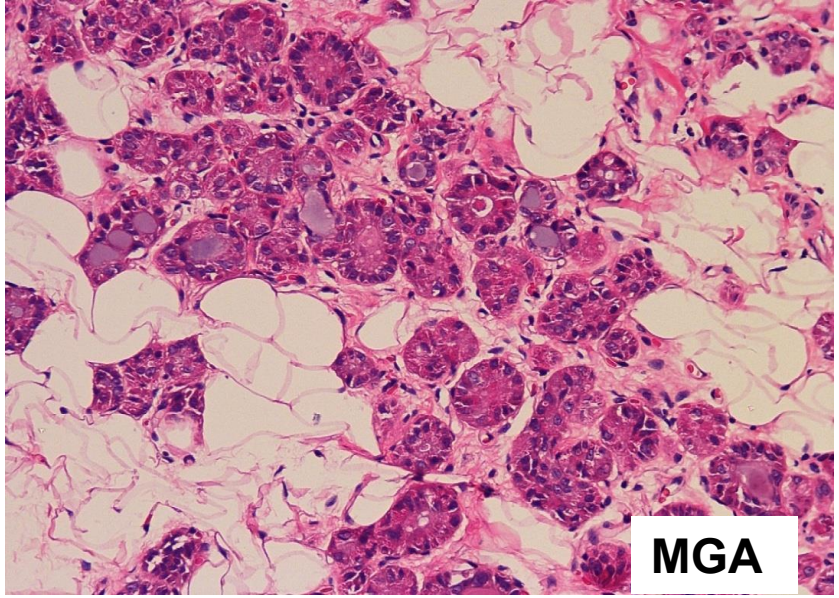


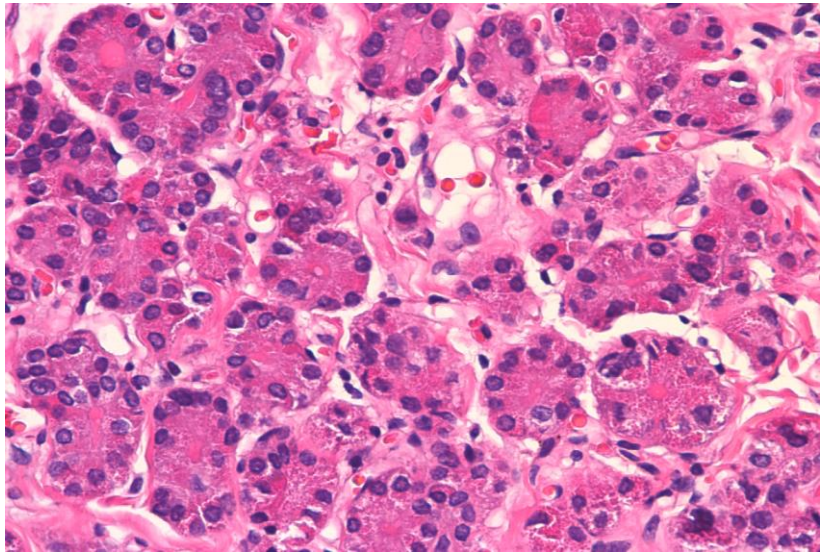


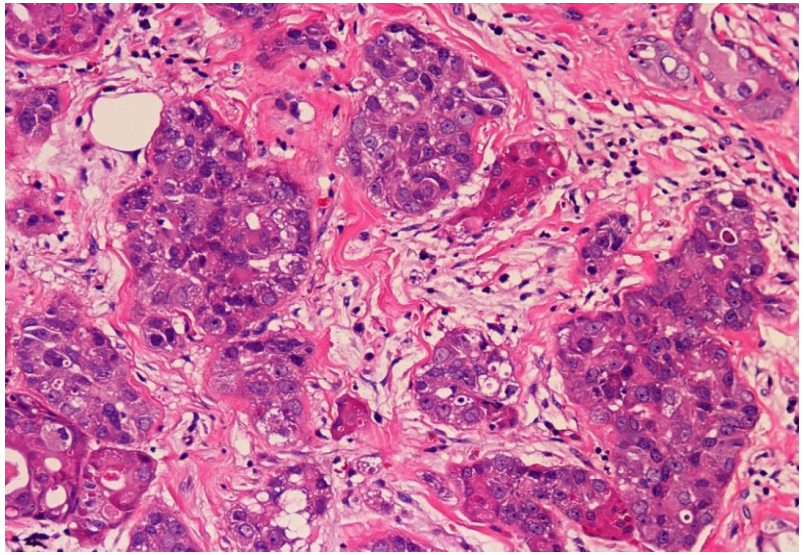
- A great variety of growth patterns, ranging from microglandular proliferation to solid areas
- Variable degrees of cytologic atypia and mitotic figures
- Diagnosis based on cytological features, including abundant, variably eosinophilic and basophilic granular cytoplasm
- Tumor cells are triple negative, positive for serous differentiation markers: lysozyme, anti-trypsin, anti-chymotrypsin. Positive for S-100, SOX10, EMA.
- DNA copy-number and mutation landscape similar to that of TNBC of conventional histology or in association with microglandular adenosis
- The mutation profiles of breast acinic cell carcinomas differ from those of acinic cell carcinomas of the salivary glands, suggesting that these are not related entities

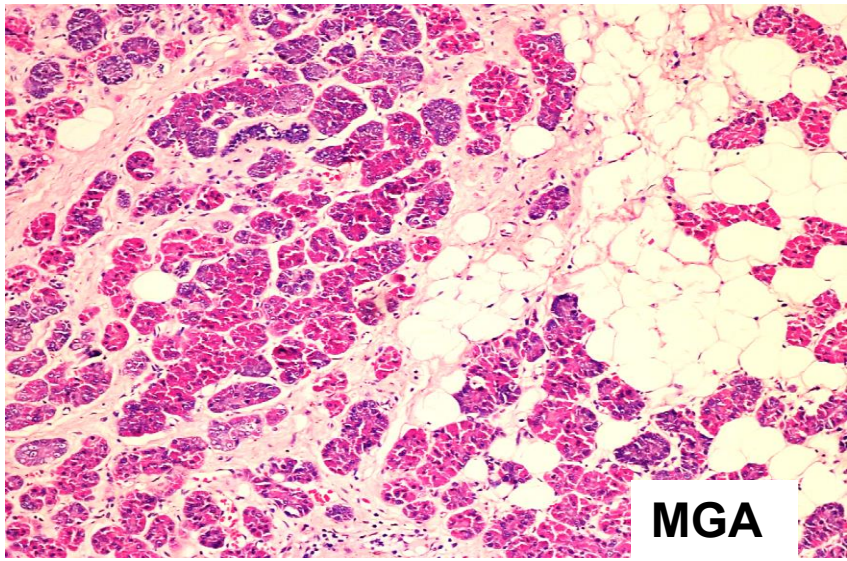





MGA






MGA

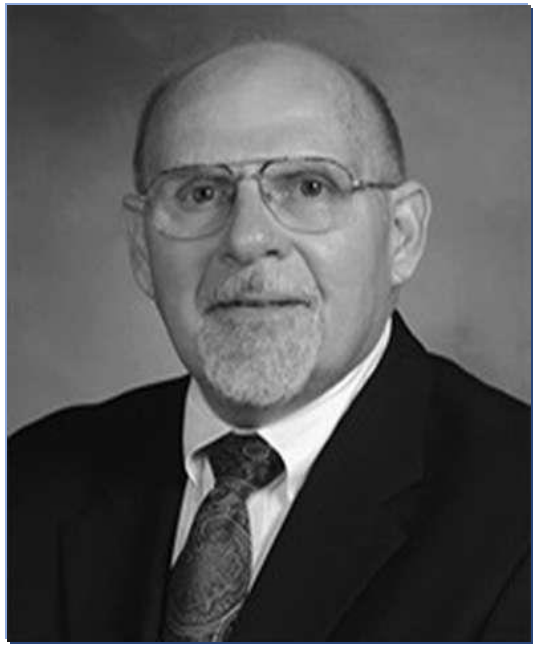
Genetic analysis of microglandular adenosis and acinic cell carcinomas of the breast provides evidence for the existence of a low-grade triple-negative breast neoplasia family

Felipe C Geyer[1,2], Samuel H Berman[1], Caterina Marchiò[1,3], Kathleen A Burke[1], Elena Guerini-Rocco[1,4], Salvatore Piscuoglio[1], Charlotte KY Ng[1], Fresia Pareja[1], Hannah Y Wen[1], Zoltan Hodi[5], Stuart J Schnitt[6], Emad A Rakha[5], Ian O Ellis[5], Larry Norton[1], Britta Weigelt[1] and Jorge S Reis-Filho[1]

Letter to the Editor

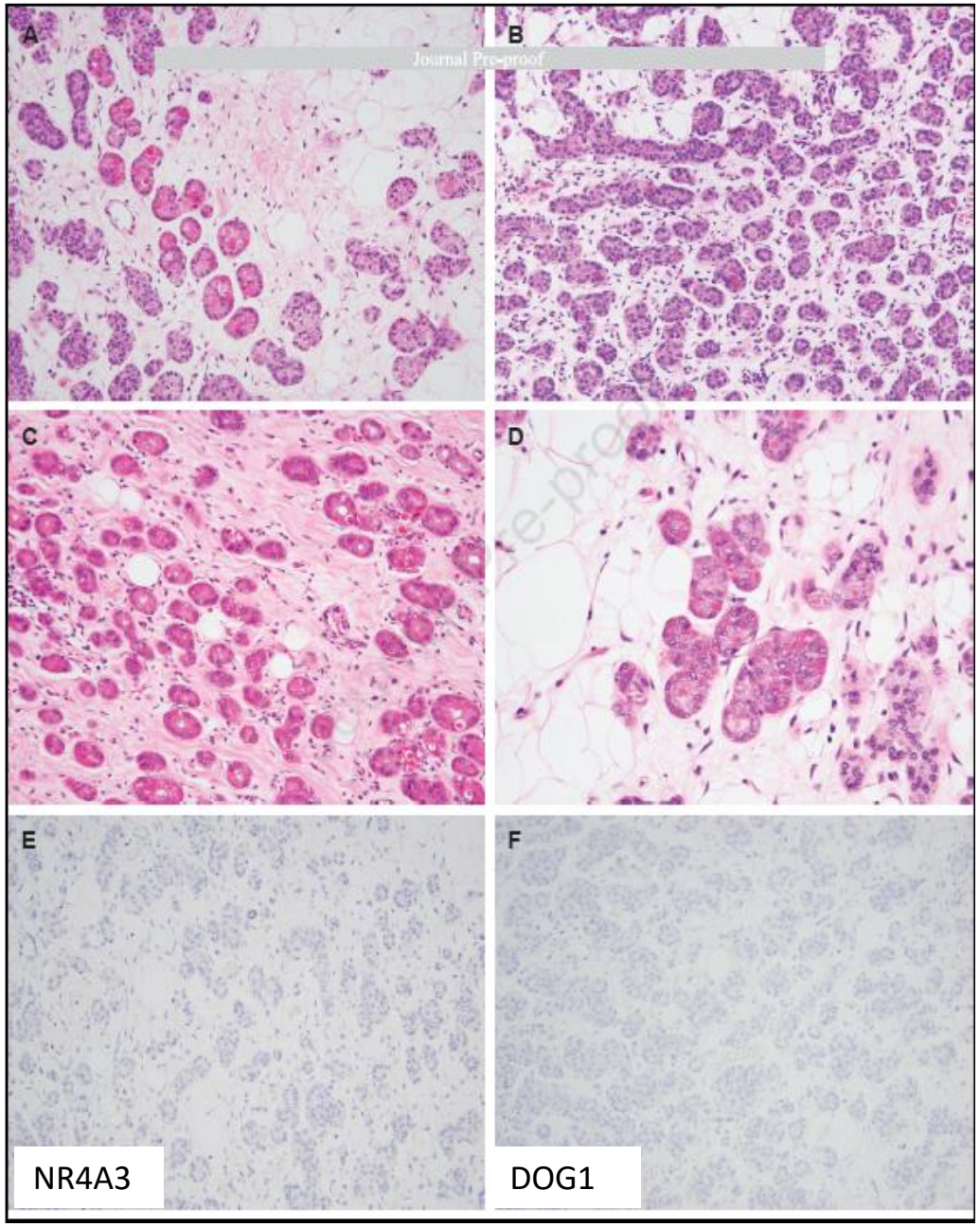
So-called acinic cell carcinoma of the breast arises from microgladular adenosis and is not a distinct entity

Modern Pathology (2017) **30,** 1504; doi:10.1038/modpathol.2017.57



Prof. Rosen

THE CONCLUSION I DRAW FROM YOUR STUDY IS THAT SO-CALLED MAMMARY ACINIC CELL CARCINOMA IS IN FACT INVASIVE CARCINOMA WITH ACINIC CELL DIFFERENTIATION ARISING IN MICROGLANDULAR ADENOSIS, a conclusion I have stated repeatedly for more than a decade.



NR4A3 Expression is Consistently Absent in Acinic Cell Carcinomas of the Breast: A Potential Nosologic Shift

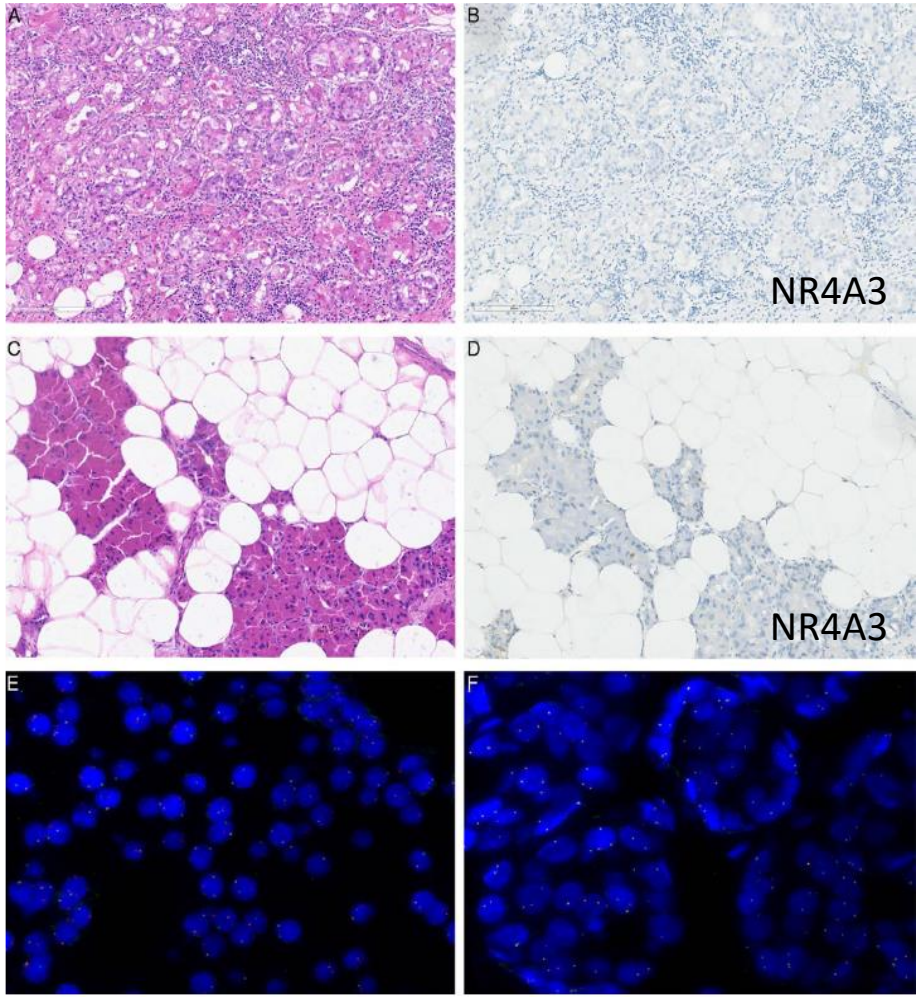
NR4A3 is a specific and sensitive marker for acinic cell carcinoma of the salivary gland

- 16 acinic cell carcinomas of the breast
- breast AciCC consistently lack NR4A3 rearrangement or overexpression, unlike the vast majority of salivary AciCC,
- breast AciCC is associated with genomic alterations more similar to those seen in triple-negative breast carcinomas (TNBC) than salivary gland AciCC
- the molecular underpinnings of salivary gland and breast AciCC are different and that salivary gland and breast AciCC likely represent distinct entities.

Mod Pathol. 2023;36(6):100144.
Am J Surg Pathol 2019;43:1264-1272

Breast Carcinomas Resembling Acinic Cell Carcinoma

Comprehensive Analysis of 14 Cases and Review of the Literature

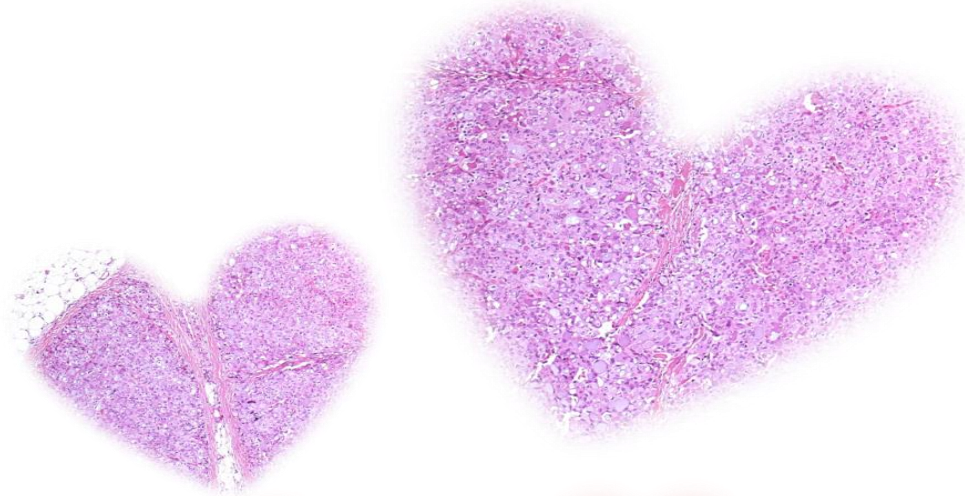


- N=14 cases
- All negative for NR4A3 IHC
- All negative for NR4A3-FISH
- Acinic cell carcinoma of the breast and salivary glands appear to be unrelated entities, despite sharing a similar histologic appearance.

Am J Surg Pathol. 2025 May 1;49(5):448-457

Waiting for updates in the 6th edition of WHO

salivary gland-type tumors
Acinic cell carcinoma ---more appropriate terminology
Adenoid cystic carcinoma
Secretory carcinoma
Mucoepidermoid carcinoma
Polymorphous adenocarcinoma----exceedingly rare
Pleomorphic adenoma
Adenomyoepithelioma and malignant adenomyoepithelioma



Thank you