Pathology of Metaplastic Breast Carcinoma

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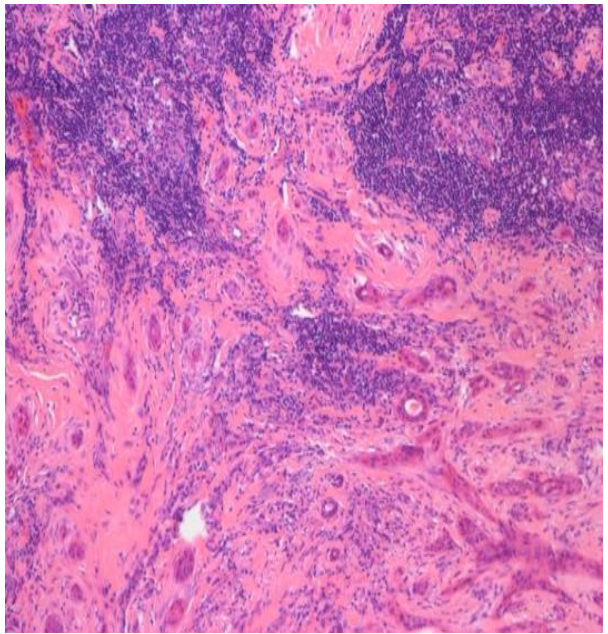
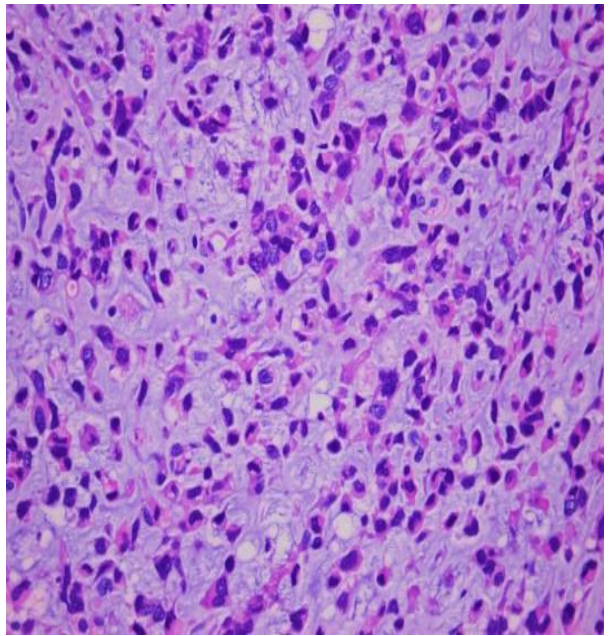
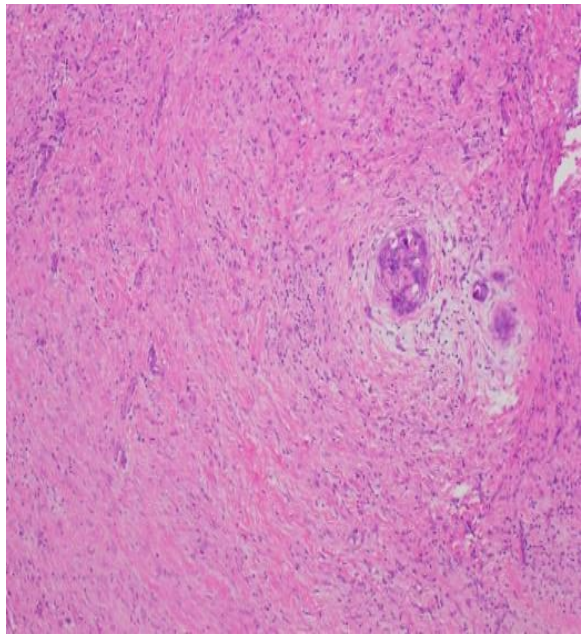
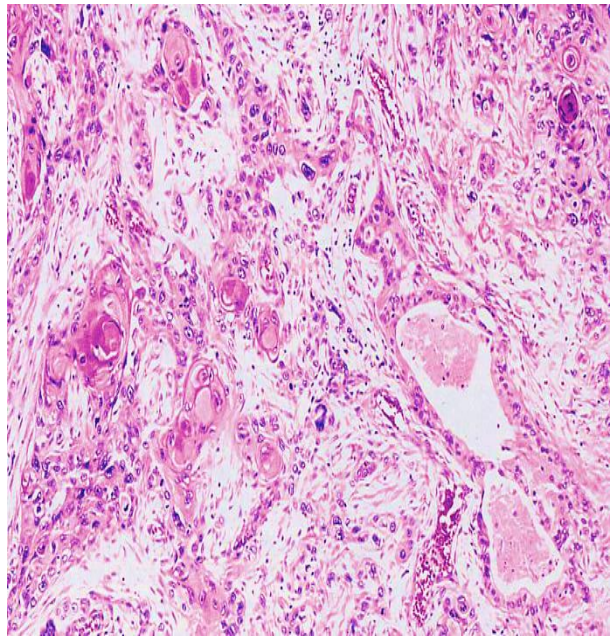
Wentao Yang

Variability in the diagnosis and reporting of metaplastic breast carcinoma: results of an international survey

Ellen Yang,[1] Susan Fineberg,[2] Anas Mohamed,[2] Edi Brogi[3] & Hannah Wen[3]
[1]*Mount Sinai Hospital, Sinai Health, Toronto, Ontario, Canada,* [2]*Montefiore Medical Centre, Bronx and* [3]*Memorial Sloan Kettering Cancer Center, New York, New York, USA*

- **2023.4-2023.7, online survey with 22 multiple-choice questionnaire (with free-text options)**

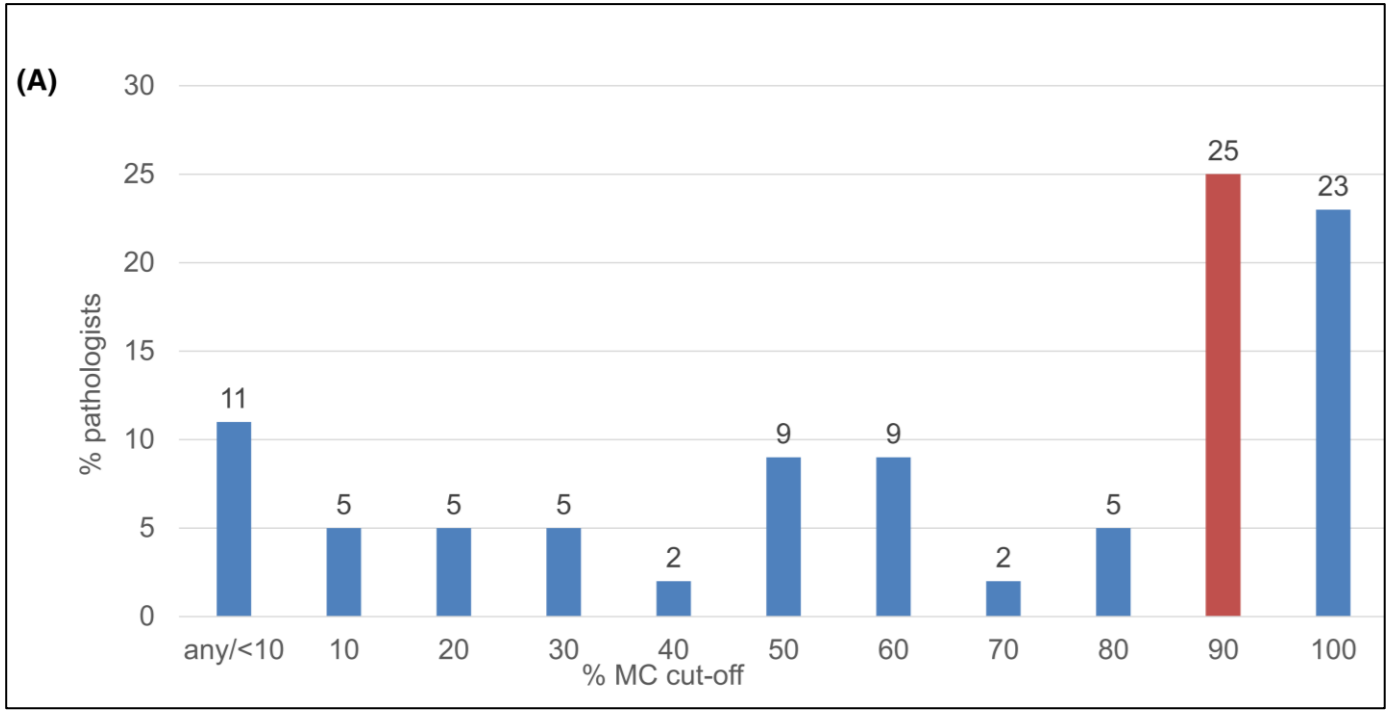
A total of 44 survey responses

- **80% were from academic hospitals**
- **61% specialized in breast pathology (>75% of total practice)**
- **60% had been in practice for more than 10 years**
- **64% had fellowship training in breast pathology**
- **91% attend multidisciplinary breast tumour boards regulaly**
- **80% had weekly tumour boards**

Histopathology. 2025 Apr;86(5):742-749

Table 2. Diagnostic cutoffs used for metaplastic carcinoma (MBC), and most frequent diagnosis with various percentage of metaplastic component (MC)

% MC used for diagnosing MBC	No. (%)
<10/any	5 (11)
10	2 (5)
20	2 (5)
30	2 (5)
40	1 (2)
50	4 (9)
60	4 (9)
70	1 (2)
80	2 (5)
90	11 (25)
100	10 (23)



- **Diagnostic criteria utilized were highly variable, ranging from any amount of MC, including any/<10% to >90% MC.**
- **The most frequently reported percentage cutoff was 90%; however, it was only in 25% of respondents.**

Histopathology. 2025 Apr;86(5):742-749

Table 3. Reporting practices

	No. (%)
Report % of each component	
Yes	40 (90)
No	3 (7)
Other	1 (2)
Report MBC differently on core biopsy versus resection	
Yes	19 (43)
No	16 (36)
Other	9 (21)
Aware of different clinical approaches with MBC	
Yes	29 (66)
If yes, please specify	10 (23)
No	14 (33)
N/A	1 (2)
Diagnose MBC if tumour morphology changed from IBC-NST to MBC predominantly post NAC	
Yes—without comment	23 (52)
Yes—with comment	8 (18)
No—without comment	6 (14)
No—with comment	4 (9)
Other	3 (7)

Table 4. Reported diagnostic challenges

Diagnostic challenges	No. (%)
Reported (most freq.)	34 (77)
Morphology	9 (21)
Lack of % cutoff	8 (18)
Squamous differentiation	8 (18)
Biopsy-related (sampling, *etc.*)	7 (16)
Assessment of matrix	5 (11)
IHC interpretation	4 (9)
Low-grade adenosquamous carcinoma	4 (9)
Tumour heterogeneity	3 (7)
N/A	10 (23)

Histopathology. 2025 Apr;86(5):742-749

Metaplastic Carcinoma (5th WHO Classification)

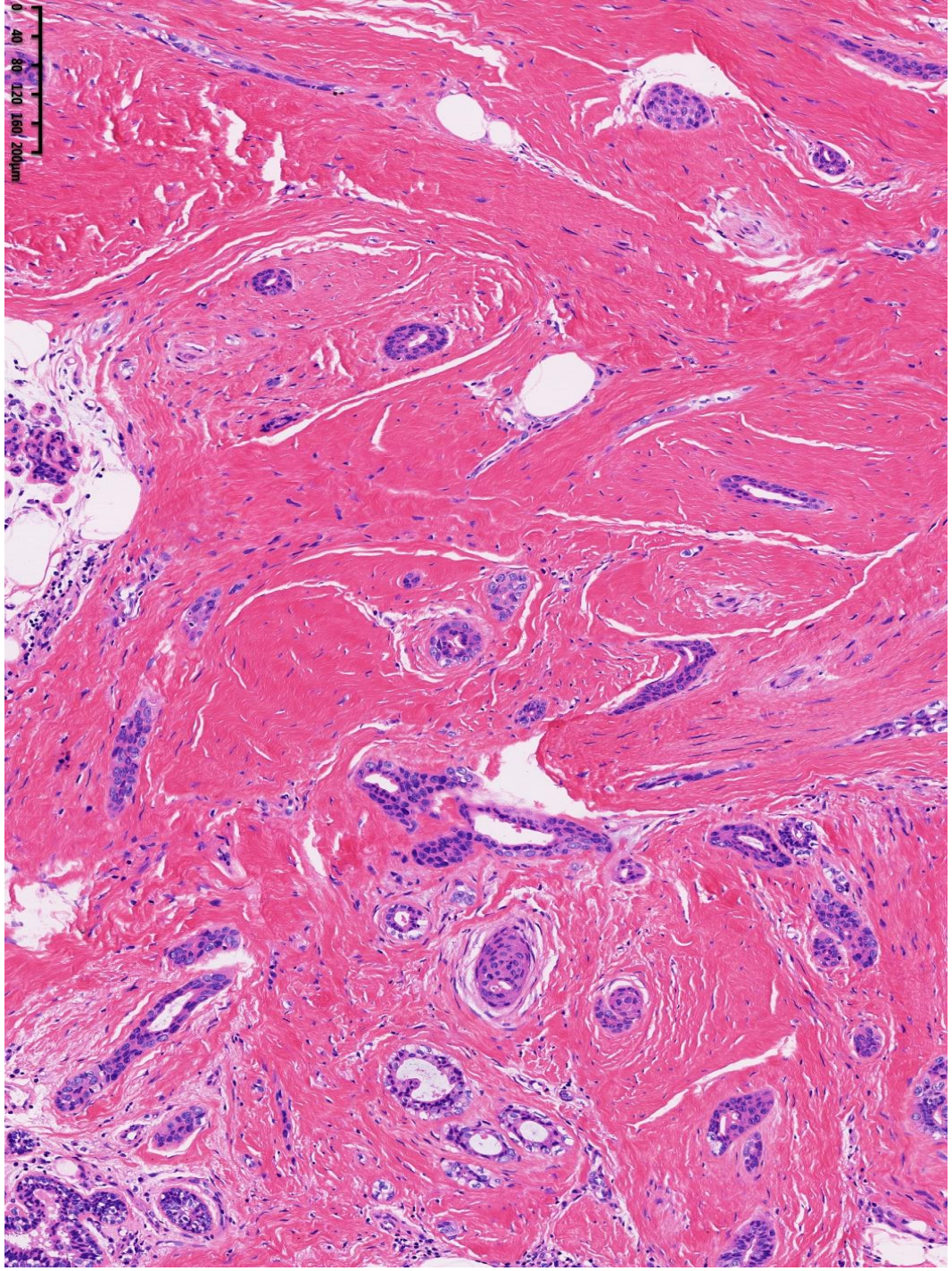
- **Definition:** ***Metaplastic carcinoma is a heterogeneous group of invasive breast carcinomas characterized by differentiation of the neoplastic epithelium towards spindle, squamous cells and/or mesenchymal elements, including but not restricted to chondroid and osseous cells.***

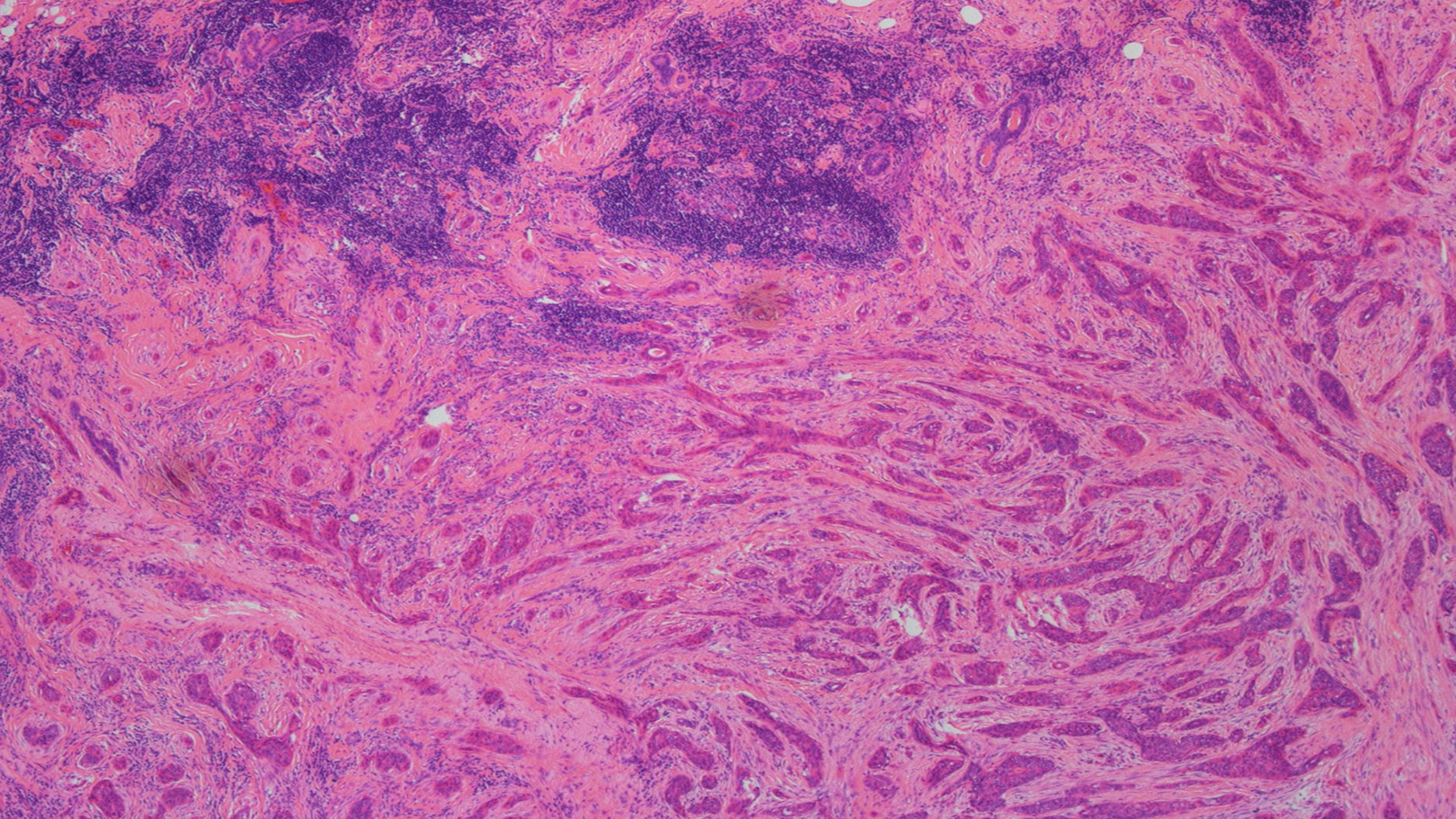
- **Low-grade adenosquamous carcinoma**
- **Fibromatosis-like metaplastic carcinoma**
- **Squamous cell carcinoma**
- **Spindle cell carcinoma**
- **Metaplastic carcinoma with heterologous mesenchymal differentiation/matrix production**
- **Mixed metaplastic carcinoma**

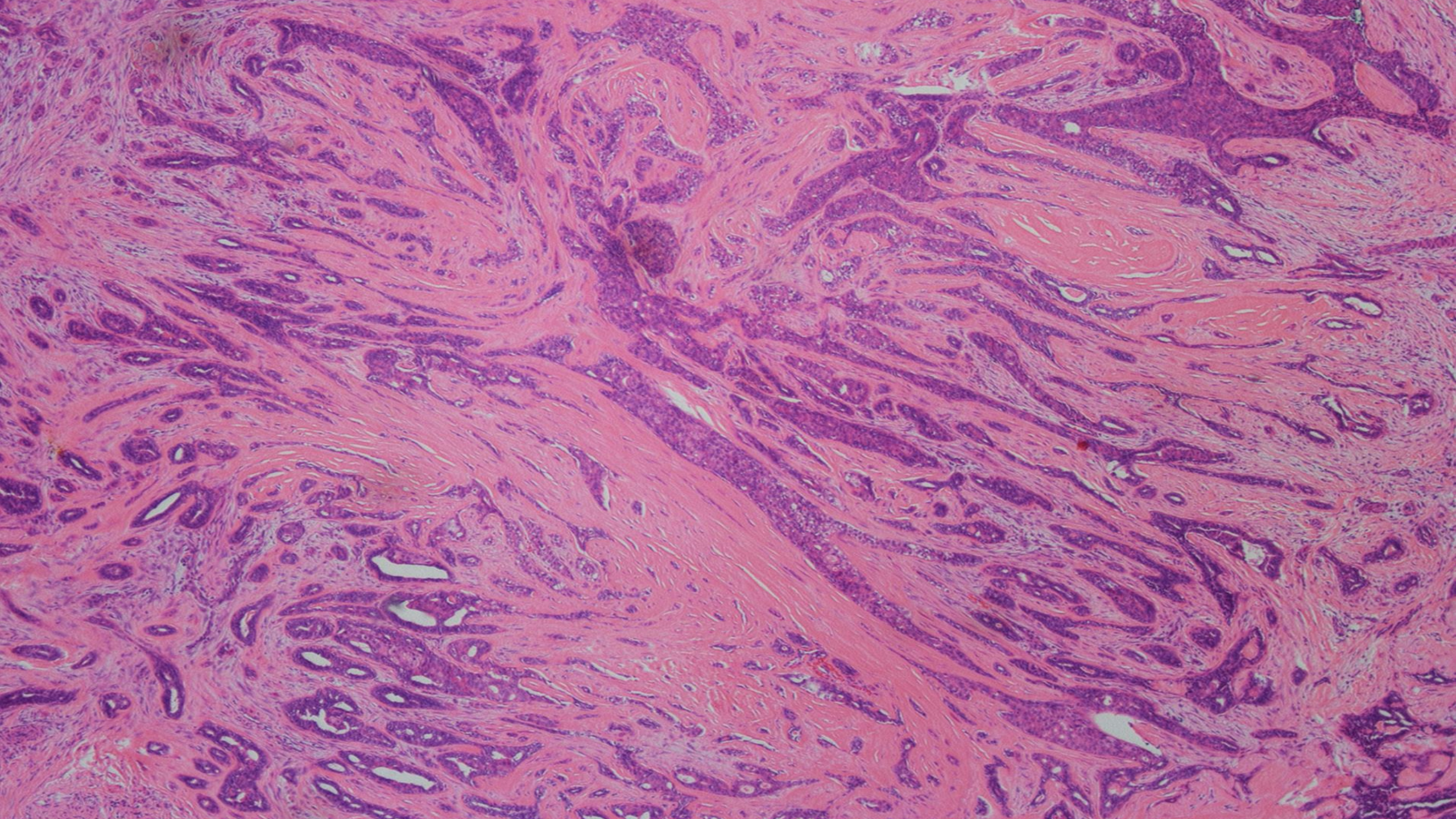
- **0.2-1% of all invasive breast cancers in woman**
- **Most cases are triple-negative**
- **Lymph node metastases are less common**
- **Prognosis varies significantly, some are low-grade with indolent behaviour; some have a high incidence of local recurrence or distant metastasis**
- **Some subtypes are highly aggressive and have poor response to chemotherapy.**

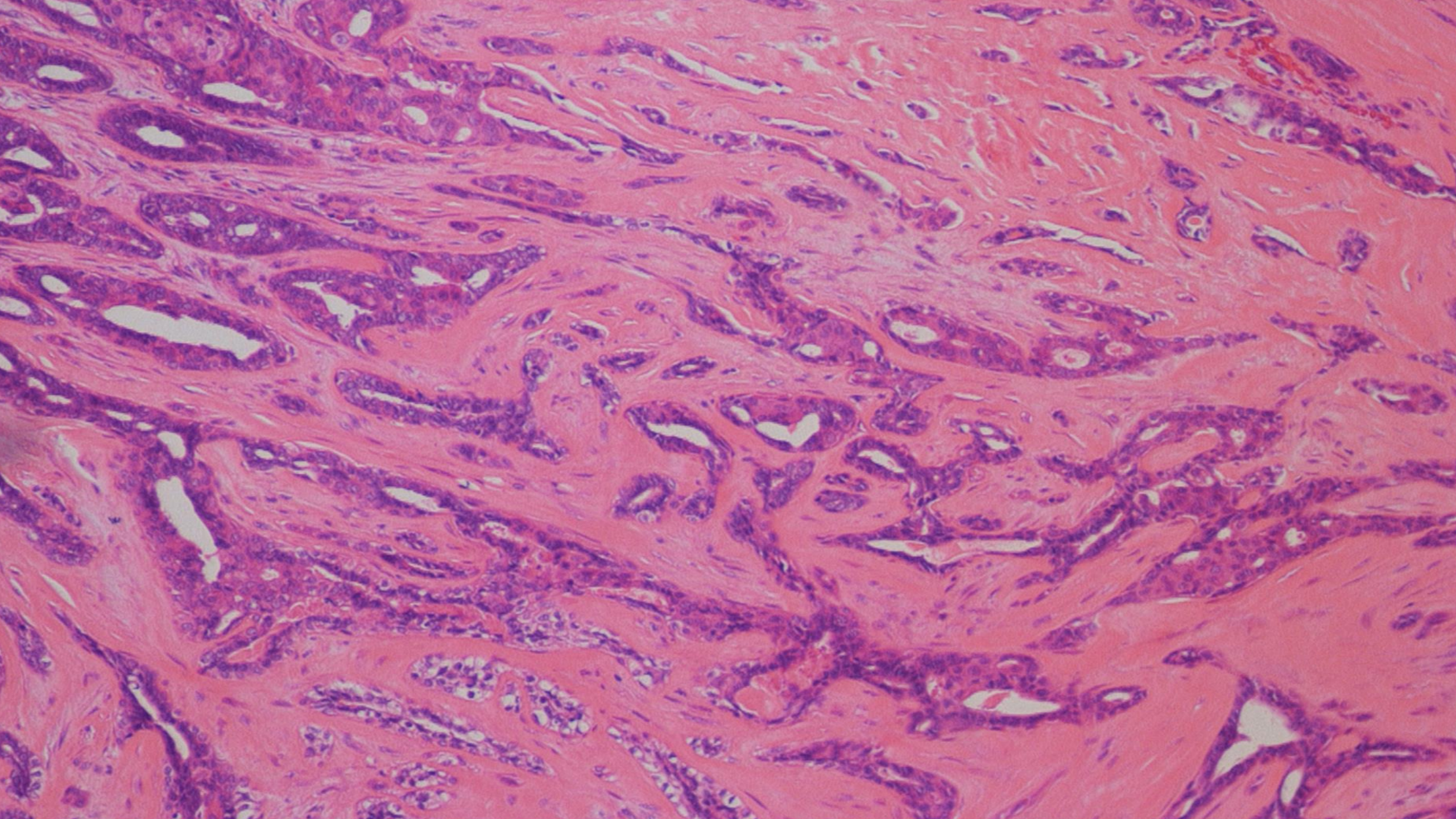
Low-grade adenosquamous carcinoma

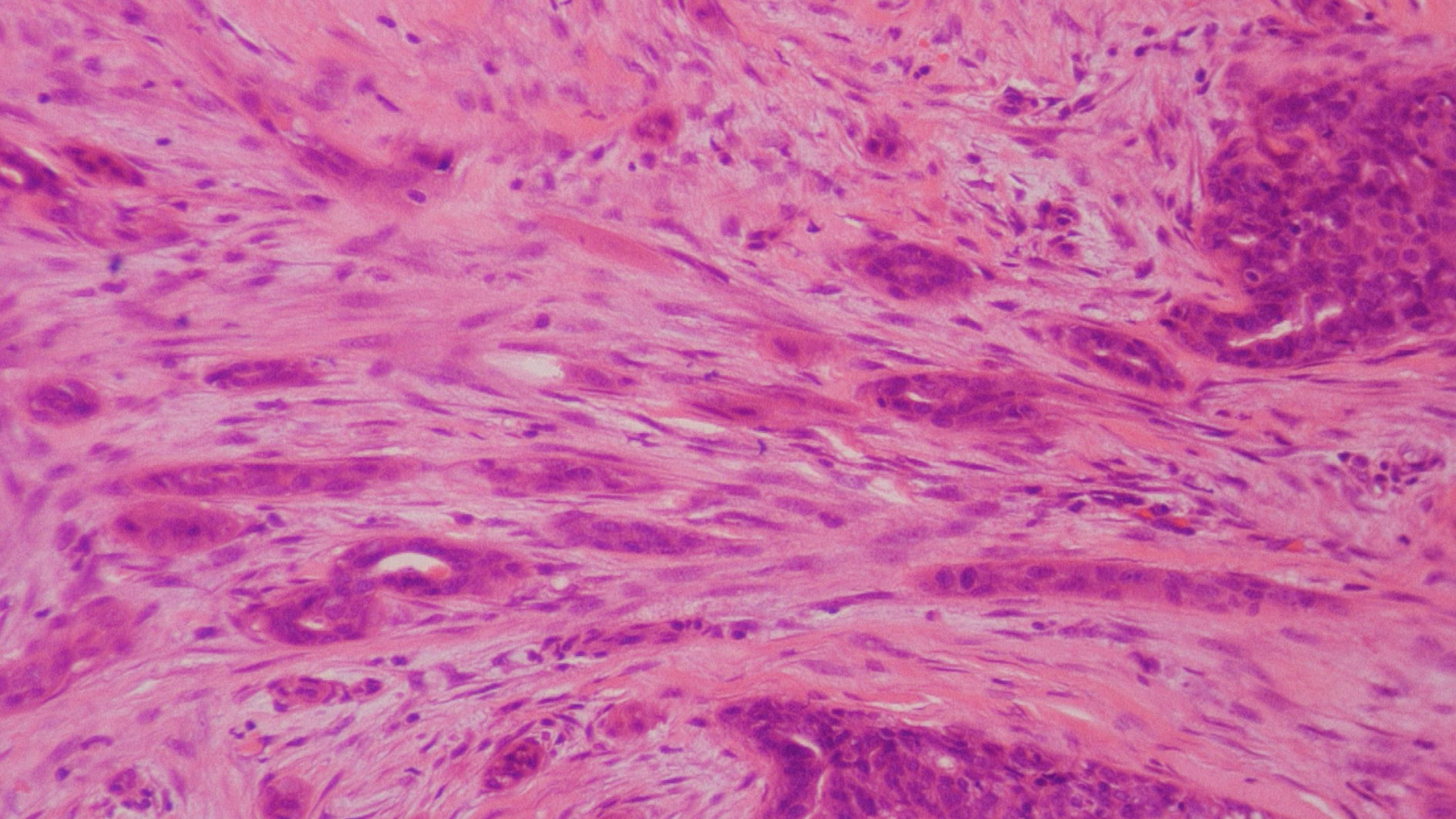
- First reported by Rosen and Ernsberger in 1987.
- **Glandular Component:** lumens of variable shapes (round, elongated, cord-like).
- **Squamous Component:** spectrum of differentiation including epidermoid, syringomatous, solid patterns, and occasional squamous cyst.
- Cytological atypia is **mild and mitotic activity is low**.
- The tumor stroma may be cellular or exhibit varying degrees of collagenization and hyalinization.
- Lymphocytic aggregates are commonly observed.
- It has a similar morphology to syringomatous tumors; the main difference lies in the lesion location—syringomatous tumors occur in the nipple and areolar skin.

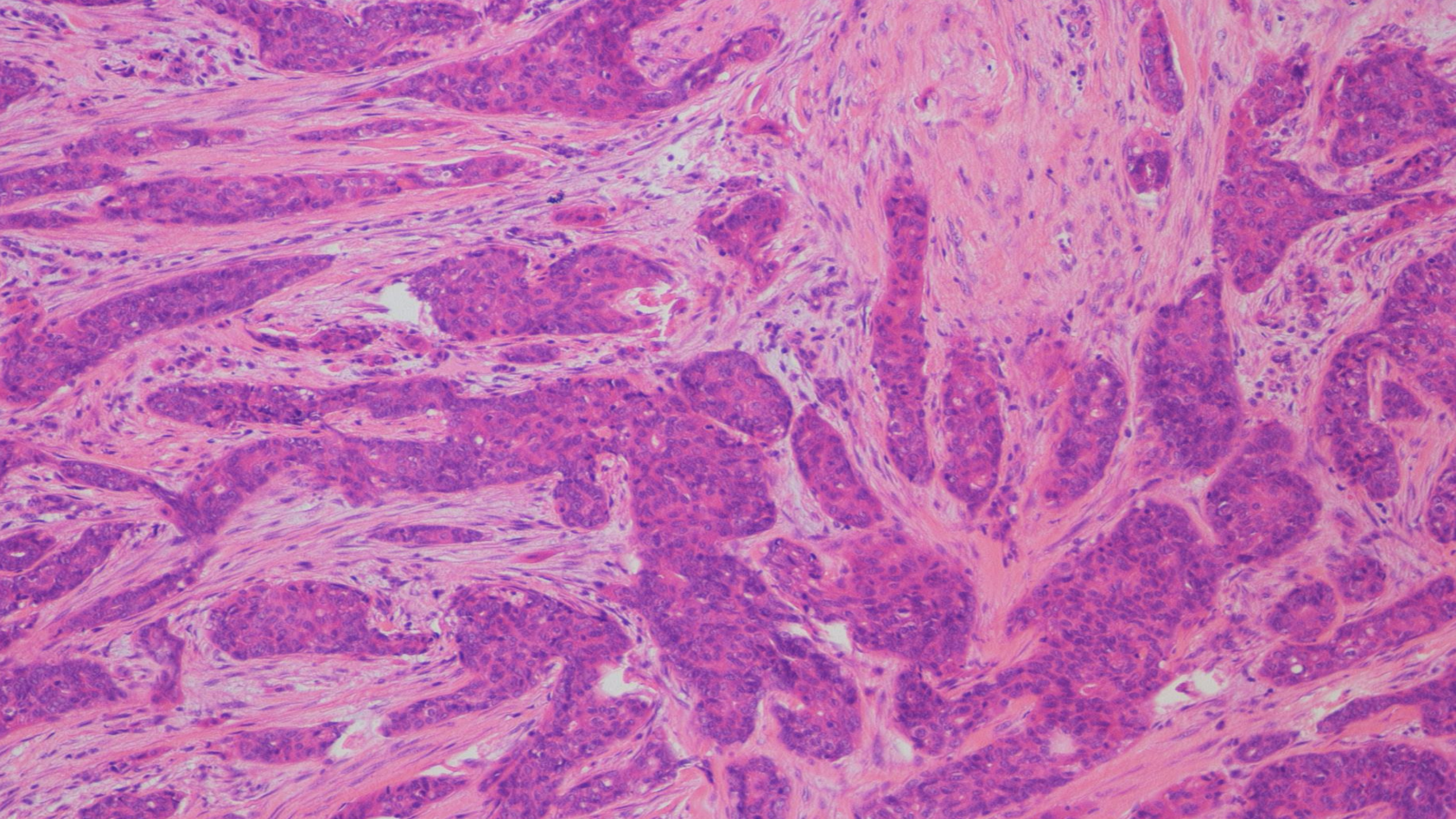


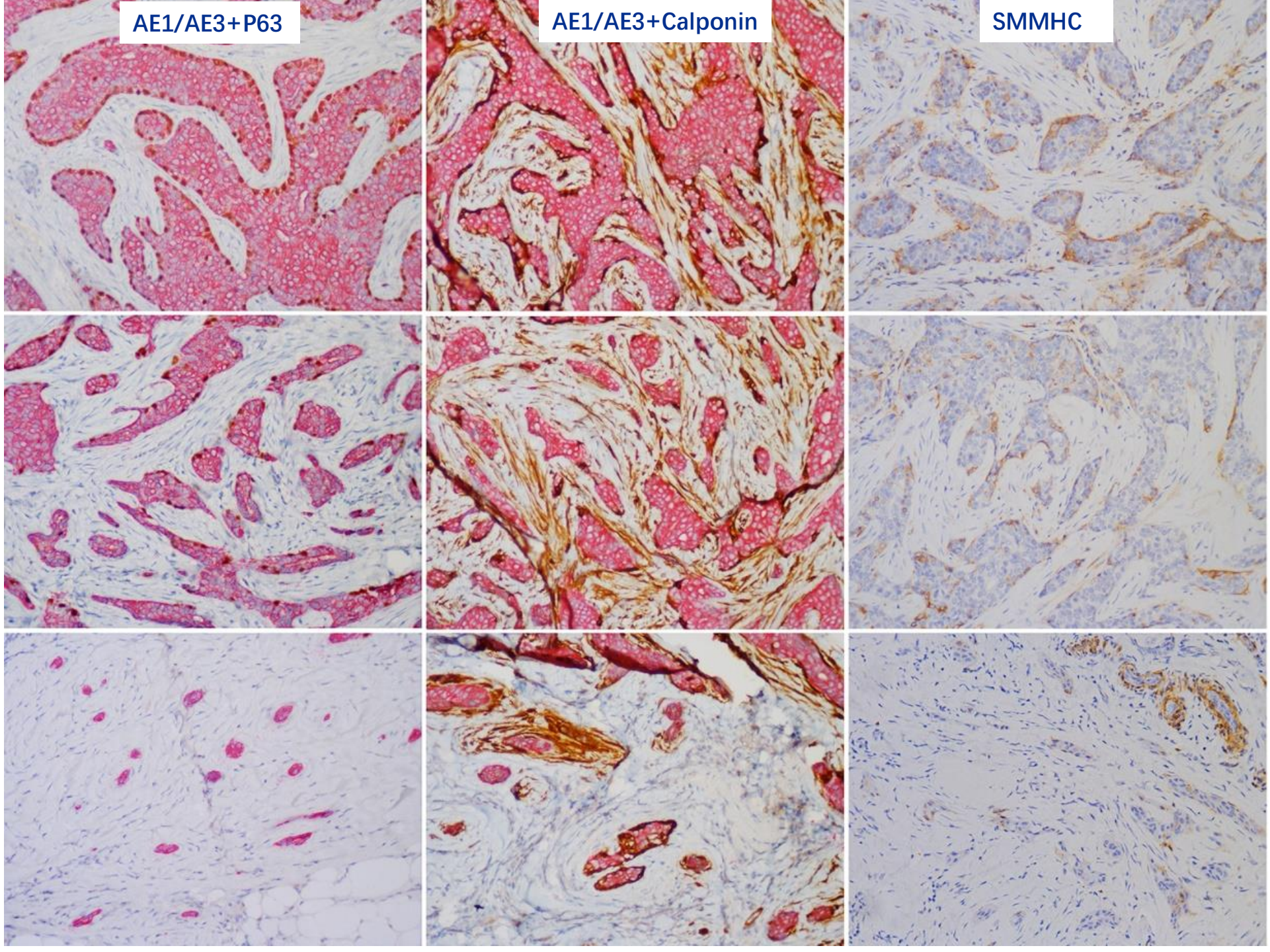








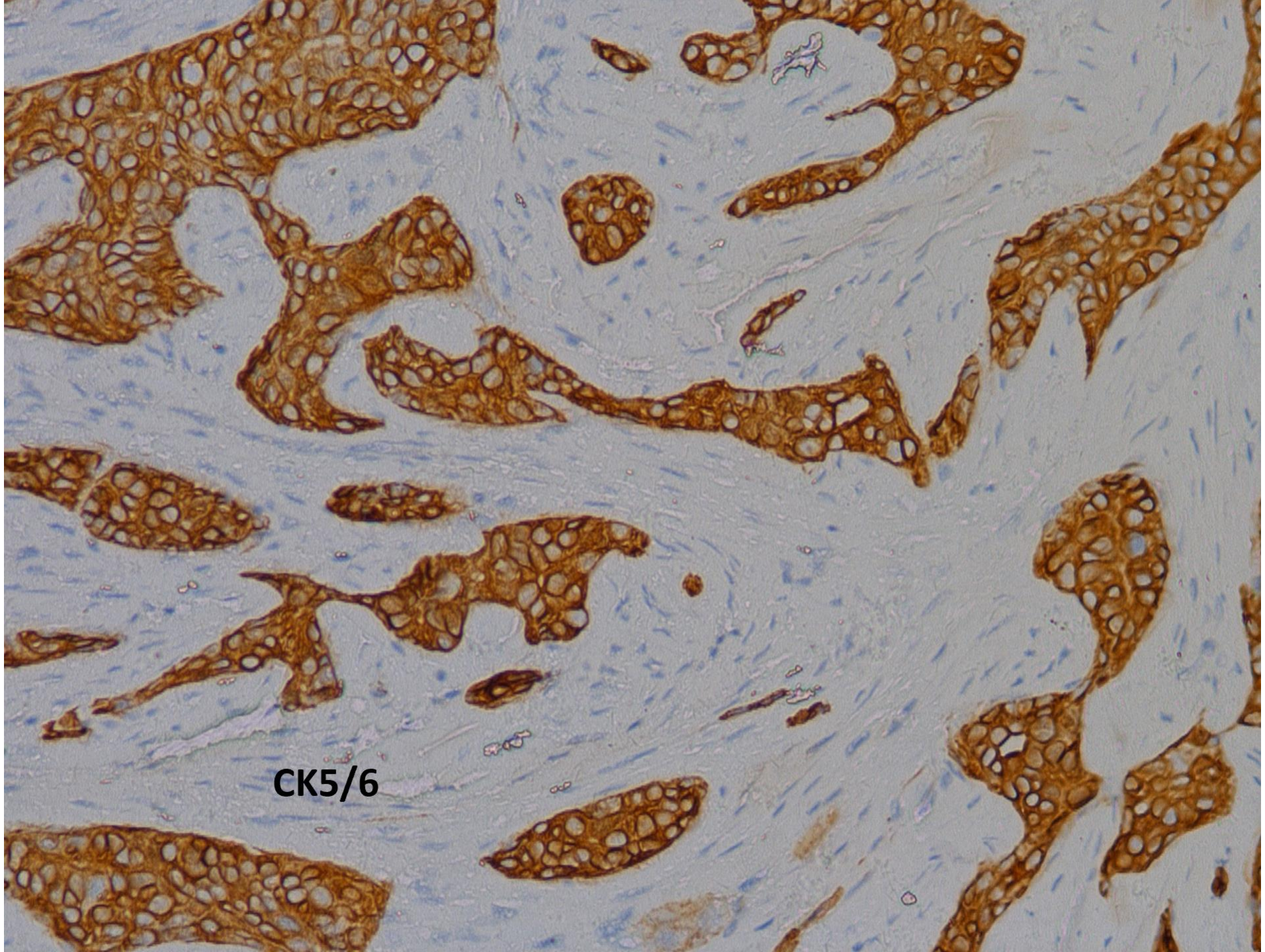


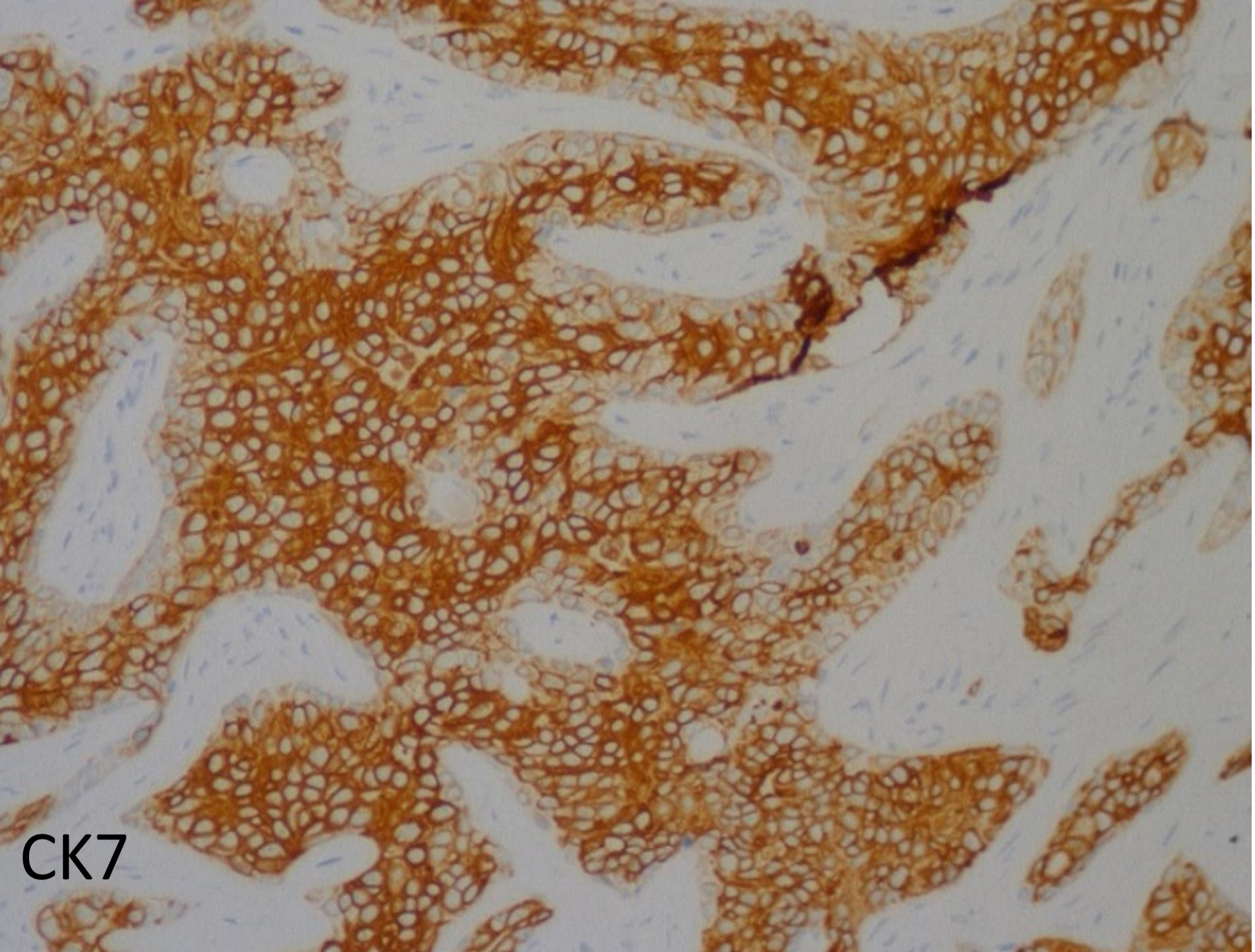


Complete

Discontinuous

Loss


CK5/6



core staining pattern

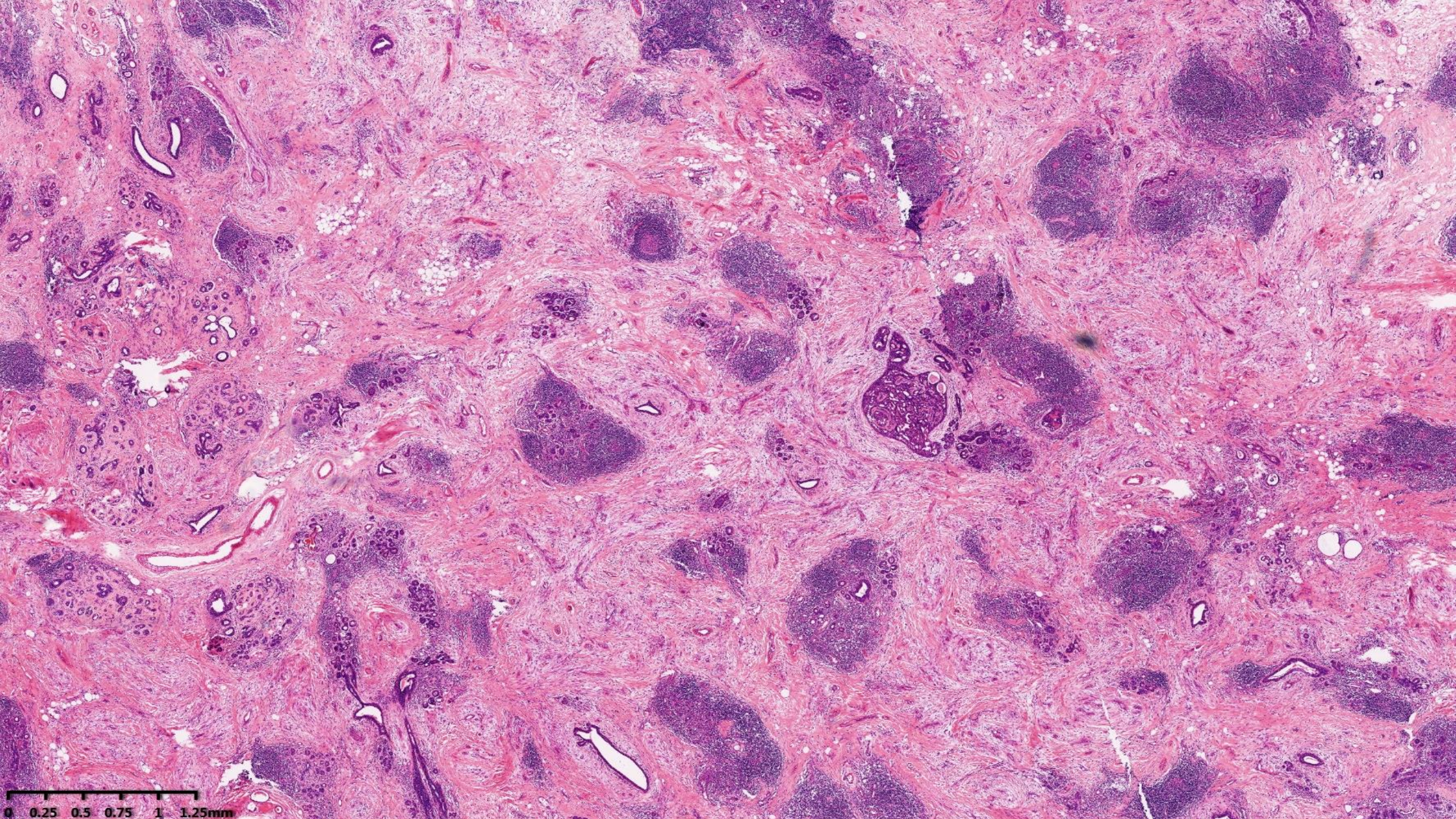
TABLE 2. Morphologic Features of 30 Patients With LGASC

Cases	Squamous Differentiation	Stroma	Lymphoid Aggregates	Other Notable Histologic Findings
1	Mild	Cellular	Yes	None
2	Marked	E/H	Yes	None
3	Mild	E/H	Lymphocytic background	None
4	Mild	Cellular	Yes	Lactational Change
5	Mild	Cellular	Yes	Associated Ca^{++}
6	Mild	Cellular	Lymphocytic background	None
7	Moderate	E/H	Yes	None
8	Mild	E/H	Yes	SCMC
9	Marked	Cellular	Yes	None
10	Mild	Cellular	Yes	Associated RS
11	Moderate	Cellular	No	SCMC
12	Mild	E/H	Lymphocytic background	Separate pap lesion
13	Moderate	E/H	Yes	Associated Ca^{++}, associated RS
14	Marked	E/H	Yes	None
15	Mild	Cellular	Yes	Associated RS
16	Marked	E/H	Yes	None
17	Moderate	Cellular	Yes	SCMC, associated pap lesion
18	Marked	Cellular	Yes	Associated Ca^{++}
19	Marked	Cellular	Yes	Associated Ca^{++}
20	Mild	E/H	Yes	Associated RS
21	Marked	Cellular	Yes	Isolated CK+ cells in 4 SLNs
22	Moderate	E/H	Lymphocytic background	Associated Ca^{++}, associated pap lesion
23	Moderate	E/H	Yes	None
24	Moderate	Cellular	Yes	None
25	Mild	E/H	Yes	None
26	Mild	E/H	Yes	Associated Ca^{++}, separate DCIS
27	Mild	E/H	Yes	None
28	Mild	Cellular	Yes	None
29	Marked	Cellular	Yes	None
30	Mild	E/H	Yes	None

Ca^{++} indicates calcifications; DCIS, ductal carcinoma in situ; E/H, elastotic or hyalinized; pap, papillary; RS, radial scar; SCMC, spindle cell metaplastic carcinoma; SLN, sentinel lymph node.

Most cases contain lymphocytic aggregates.

Am J Surg Pathol. 2012,36(7):1009-20.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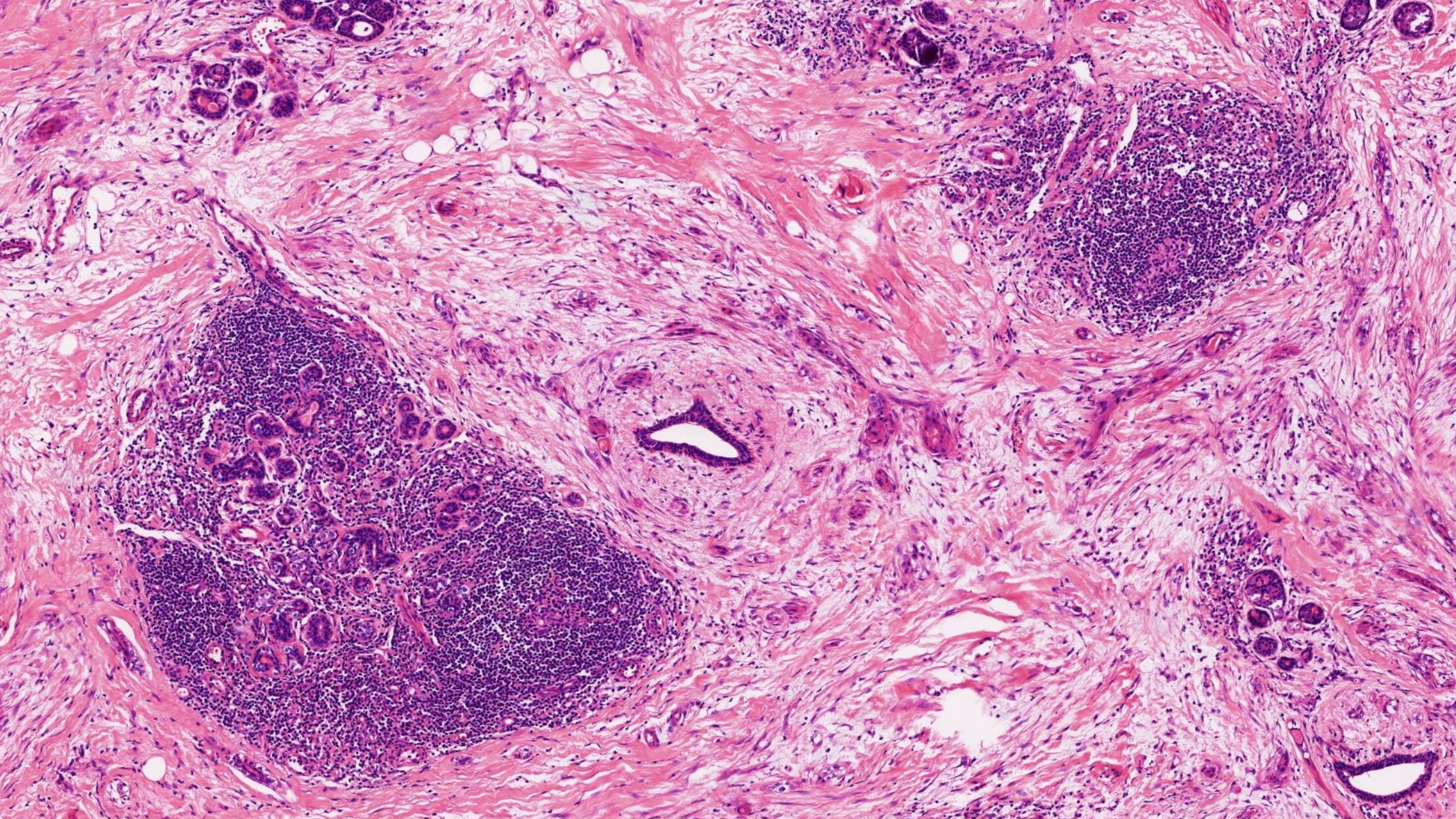


Table 2. Morphological features of 25 patients with LGASC

Patient	Associated lesions	Squamous diff. %	Fibrolamellar stromal change	Lymphocytic aggregates
1	None	30%	Focal	Yes
2	None	40%	Diffuse	Yes
3	Intraductal papilloma	20%	Diffuse	Yes
4	Intraductal papilloma	60%	Diffuse	Yes
5	Intraductal papilloma	60%	Diffuse	Yes
6	Intraductal papilloma, ADH	30%	Diffuse	Yes
7	Intraductal papilloma	NA*	NA*	NA*
8	Nodular sclerosis	40%	Minimal	Yes
9	None	90%	Focal	Yes
10	Nodular sclerosis	40%	Focal	Not present
11	Intraductal papilloma	50%	Diffuse†	Yes
12	None	30%	Diffuse	Yes
13	Intraductal papilloma	70%	Diffuse	Yes
14	None	90%	Diffuse	Not present
15	None	60%	Diffuse	Yes
16	None	60%	Diffuse	Yes
17	Complex sclerosing lesion	15%	Diffuse	Yes
18	Radial scar	50%	Diffuse	Not present
19	None	5%	Focal	Yes
20	None	60%	Focal	Yes
21	None	30%	Diffuse	Yes
22	None	30%	Focal	Yes
23	None	80%	Diffuse	Yes
24	Intraductal papilloma	75%	Diffuse	Yes
25	None	20%	Diffuse	Yes

Histopathology. 2023 Aug;83(2):252-263

- Commonly associated with intraductal papilloma, sclerosing adenosis, and radial scar
- 83% of cases had squamous differentiation in at least 30% of the tumour
- 75% of cases contain desmoplastic (fibrolamellar) stroma
- 87.5% of cases contain lymphocytic aggregates.

Histopathology 2000, **36**, 203–209

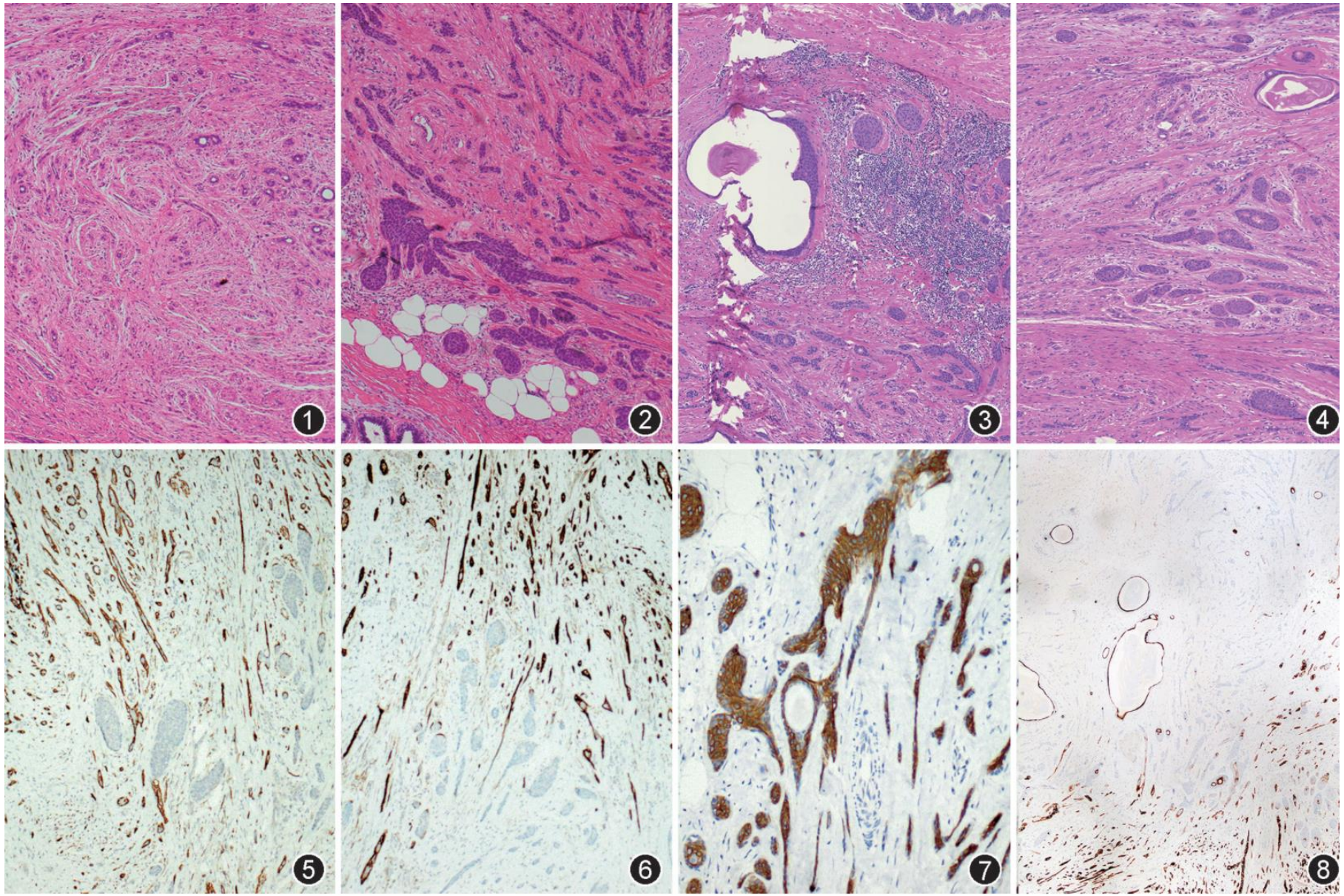
Metaplastic carcinoma of the breast arising within complex sclerosing lesion: a report of five cases

H Denley, S E Pinder, P H Tan, C S Sim, R Brown, T Barker, J Gearty, C W Elston & I O Ellis
Department of Histopathology, Nottingham City Hospital, Nottingham, UK

Table 1. Clinical details and features of sclerosing lesions

Case	Age (years)	Sex	Site of lesion	Presentation	Lymph node status	Configuration	Central sclerosis	Elastosis	Radiating tubules with myoepithelium	Benign papillary areas
1	60	F	Left breast	Mammographic screening	Negative	Stellate	Present	Present	Present	Absent
2	49	F	Left breast	Mammographic screening	Not known	Stellate	Present	Present	Present	Absent
3	64	F	Right breast	Symptomatic	Not known	Stellate	Present	Present	Present	Absent
4	68	F	Right breast	Symptomatic	Not known	Circumscribed	Present	Present	Present	Present
5	68	F	Right breast	Symptomatic	Not known	Stellate	Present	Present	Present	Absent

Low-grade adenosquamous carcinoma arising from sclerosing adenosis



Chinese Journal of Pathology, 2019; 48(5):

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC ADJUVANT TREATMENT: FAVORABLE HISTOLOGIES[r,w]

小管癌
黏液癌
筛状癌
包被性/实性乳头状癌

- Pure tubular
- Pure mucinous
- Pure cribriform
- Encapsulated or solid papillary carcinoma[x]

→ ER-positive and/or PR-positive, HER2-negative[y]

- pT1, pT2, or pT3; and pN0 or pN1mi (≤2 mm axillary node metastasis)
  - <1 cm → Consider adjuvant endocrine therapy[bb] for risk reduction
  - 1–2.9 cm → Consider adjuvant endocrine therapy[bb]
  - ≥3 cm → Adjuvant endocrine therapy[bb,ff]
- pN+ (≥1 ipsilateral metastases >2 mm) → Adjuvant endocrine therapy[bb,ff] ± adjuvant chemotherapy[a,bb,cc]

- Adenoid cystic and other salivary carcinomas
- Secretory carcinoma
- Rare low-grade forms of metaplastic carcinoma[v]

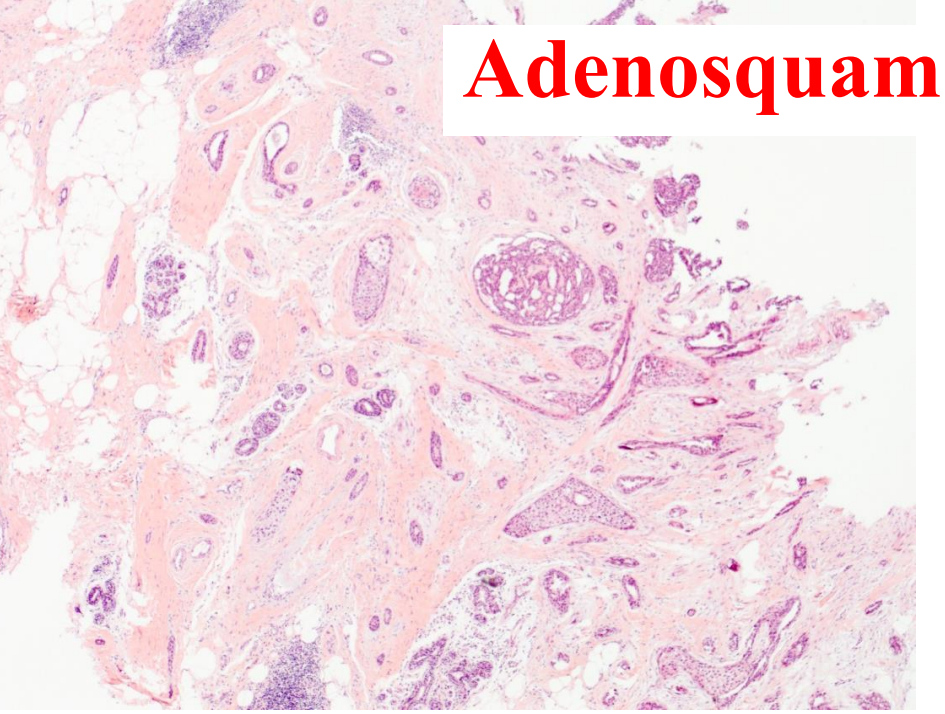
→ ER-negative and PR-negative, HER2-negative[y]

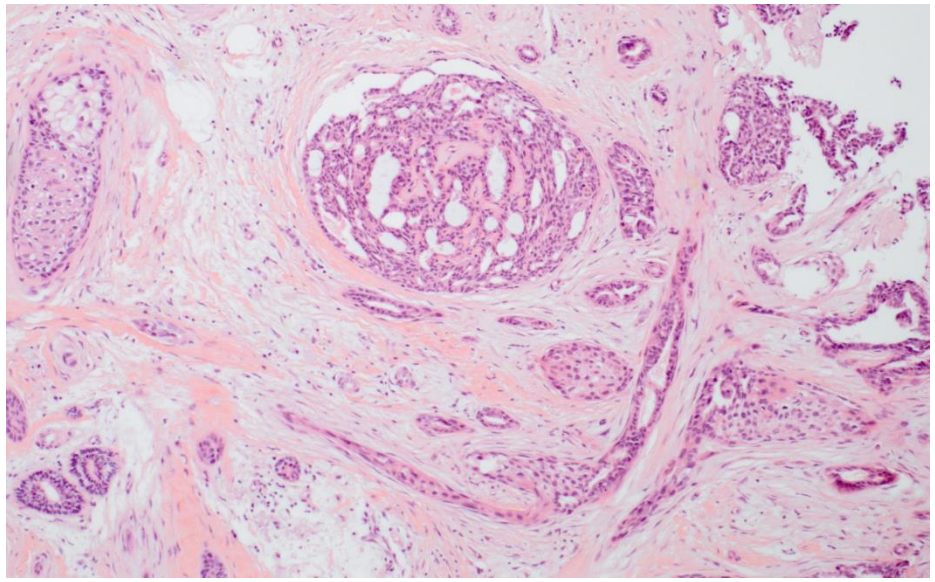
→ Limited available data support local therapy only with consideration for systemic/targeted therapies only in pN+ disease

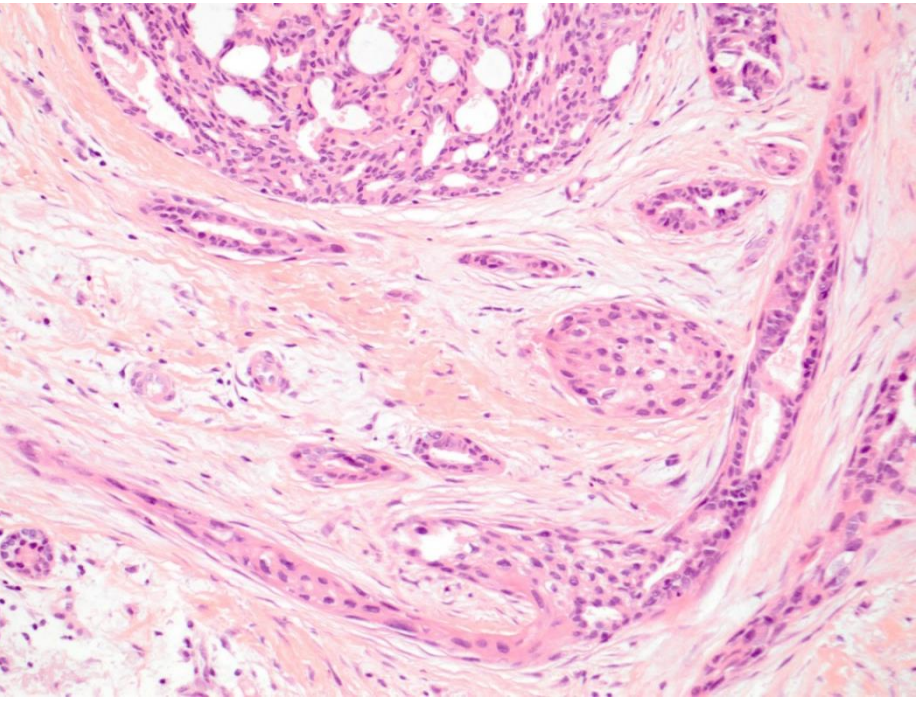
→ See Follow-Up (BINV-17)

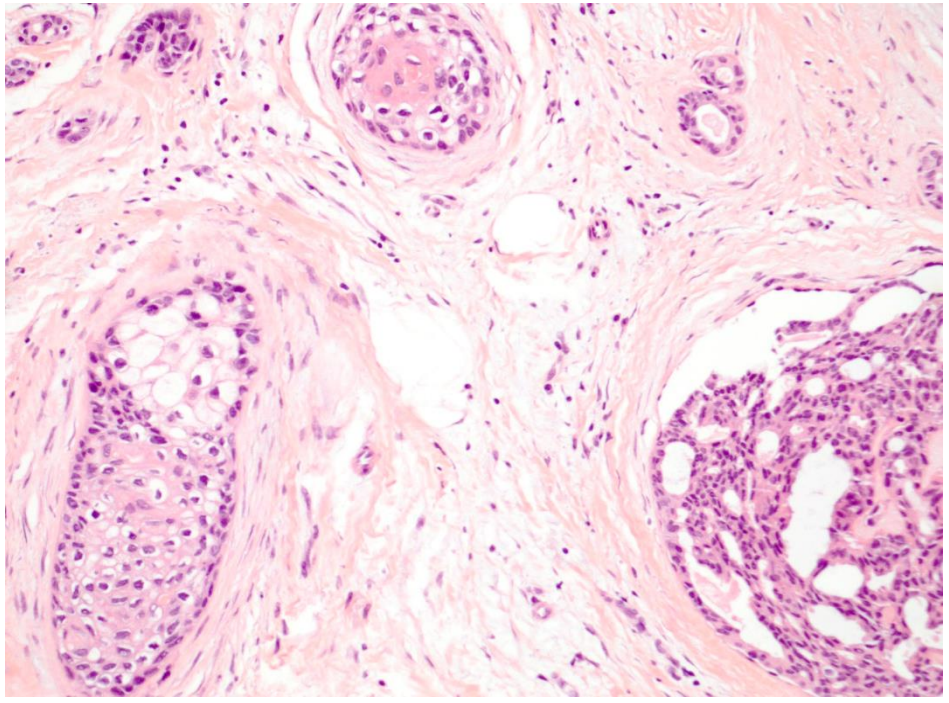
- **Histological types of TNBC with favorable prognosis:** adenoid cystic carcinoma and other salivary gland-type carcinomas, secretory carcinoma, low-grade metaplastic carcinoma **(low-grade adenosquamous carcinoma and low-grade fibromatosis-like carcinoma)**
- **Pure histological types (surgical specimens, not core needle specimens)**

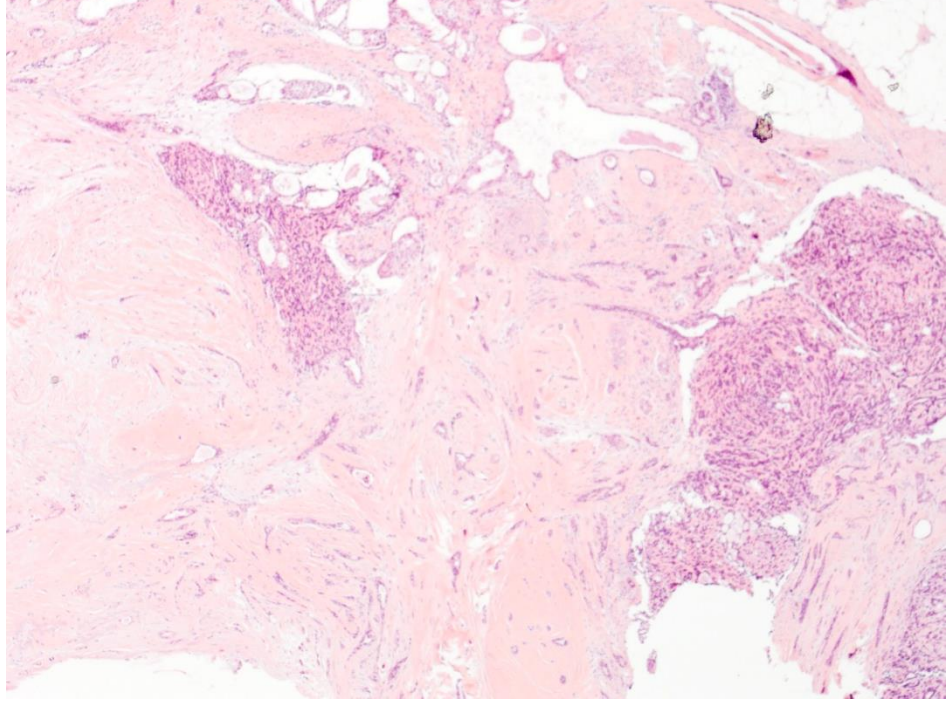
Adenosquamous proliferation (ASP)

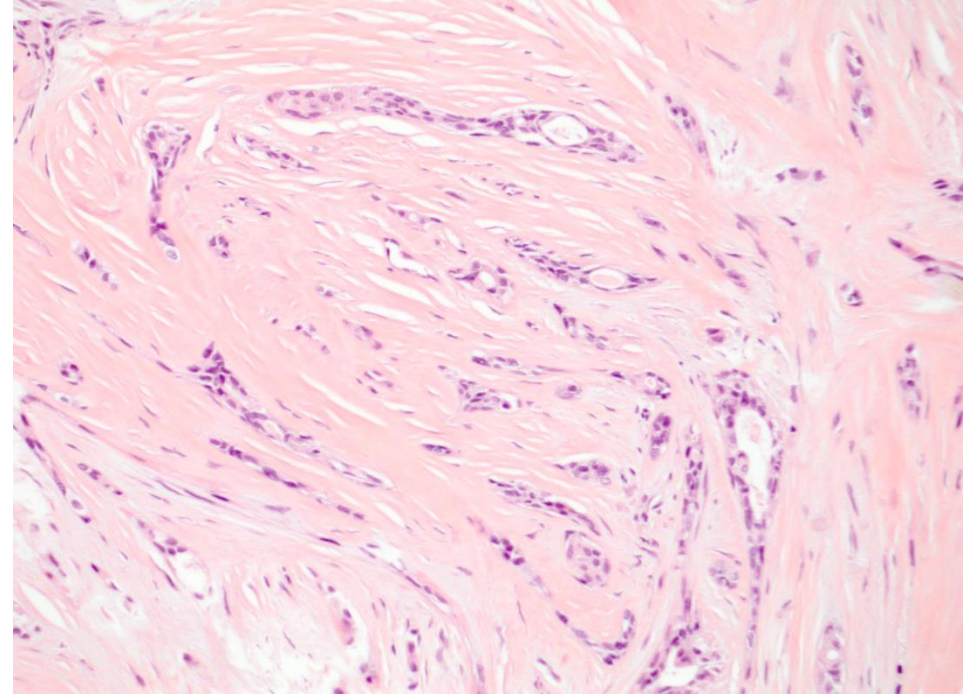


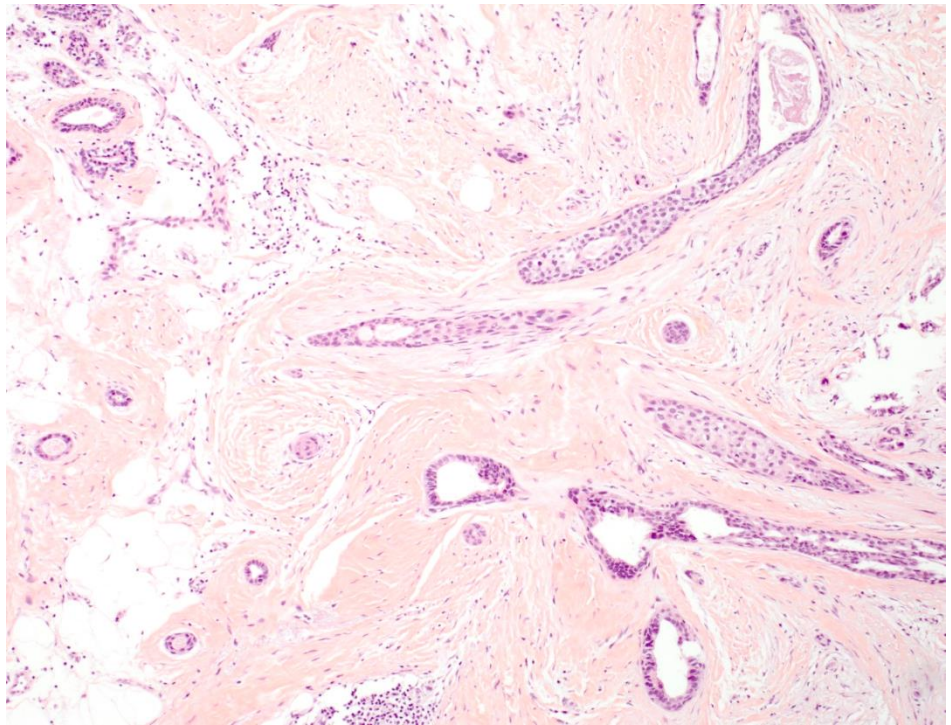


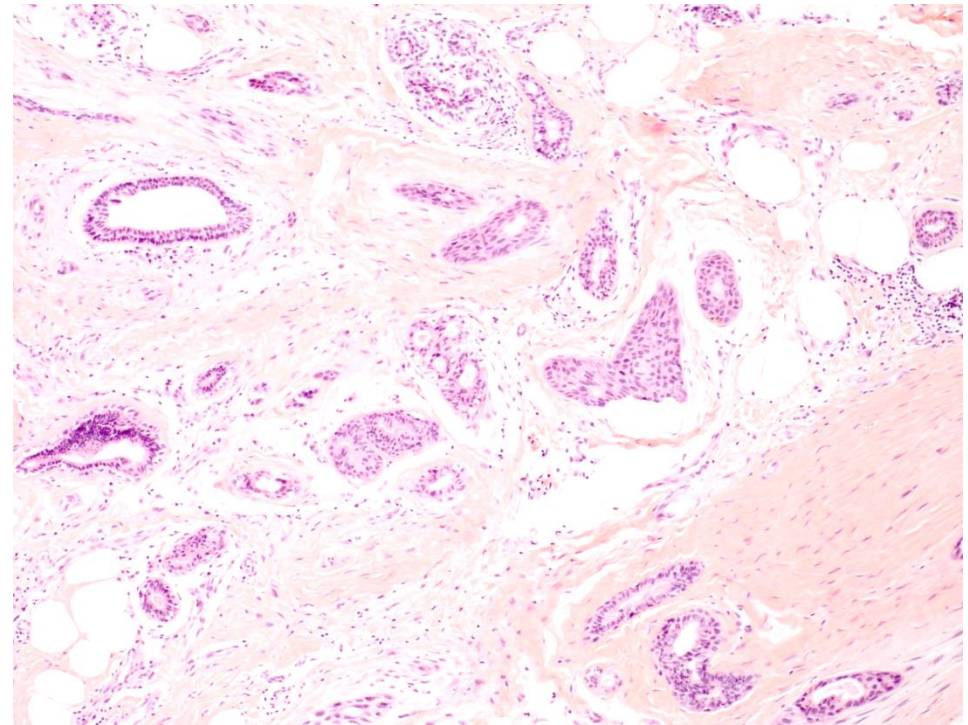












Differential Diagnosis Between ASP and Low-Grade Adenosquamous Carcinoma (LGASC)

- ASP and LGASC share overlapping features in morphology, IHC and molecular profiles
- No clear-cut criteria exist to reliably distinguish them
- LGASC is diagnosed when an obvious mass forms from these lesions, accompanied by reactive stroma and infiltration into adjacent adipose tissue.
- Avoid overdiagnosing ASP as LGASC, which could lead to inappropriate clinical management of ASP as ordinary TNBC.
- When differential diagnosis is challenging, complete surgical excision with clinical follow-up is recommended.

Histopathology

Histopathology 2018 DOI: 10.1111/his.13514

High rate of *PIK3CA* mutations but no *TP53* mutations in low-grade adenosquamous carcinoma of the breast

Guillaume Bataillon,[1] Laetitia Fuhrmann,[1] Elodie Girard,[1] Emanuelle Menet,[2] Marick Laé,[1] Mathieu Capovilla,[3] Isabelle Treilleux,[4] Laurent Arnould,[5] Frederique Penault-Llorca,[6] Roman Rouzier,[7] Caterina Marchiò,[1,8] Ivan Bieche[1] & Anne Vincent-Salomon[1]

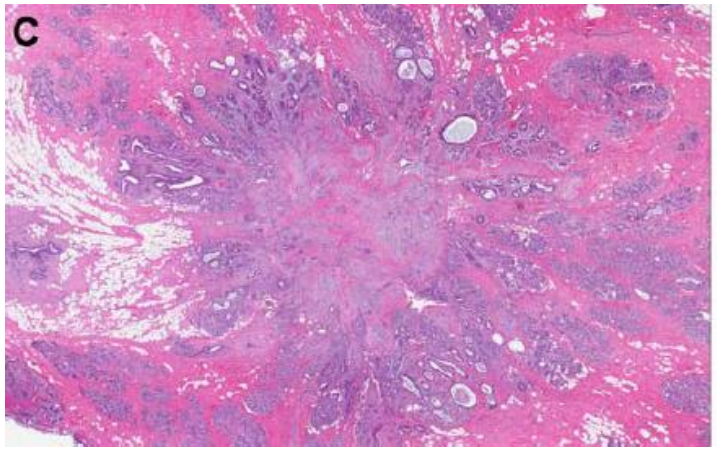
Institut Curie, Paris Sciences Lettres Research University, Pôle de médecine diagnostique et théranostique, Paris, Institut Curie, Versailles Saint Quentin University, Pôle de médecine diagnostique et théranostique, Saint-Cloud, Department of Pathology, Centre François Baclesse, Caen, [4]Department of Pathology, Centre Léon-Bérard, Lyon, Department of Pathology, Centre Georges François Leclerc, Dijon, [6]Department of Pathology, Centre Jean Perrin, Clermont-Ferrand, [7]Institut Curie, Versailles Saint Quentin University, Surgery Department, Saint-Cloud, France, and Department of Medical Sciences, University of Turin, Turin, Italy

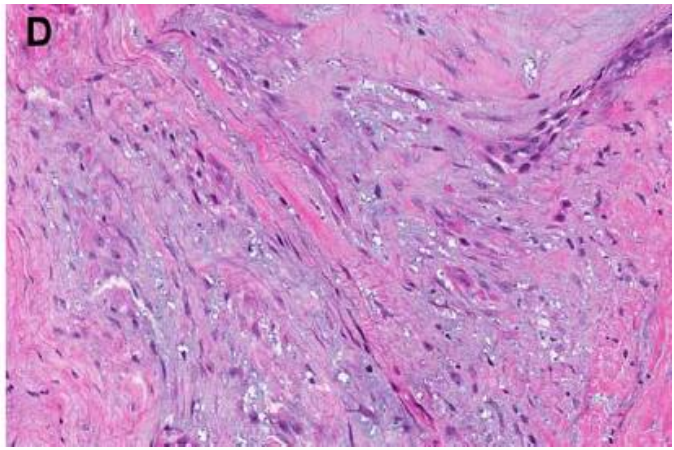
- **10 cases were all triple-negative**
- **7 /10 cases had PIK3CA mutation**
- **No case had TP53 mutation.**

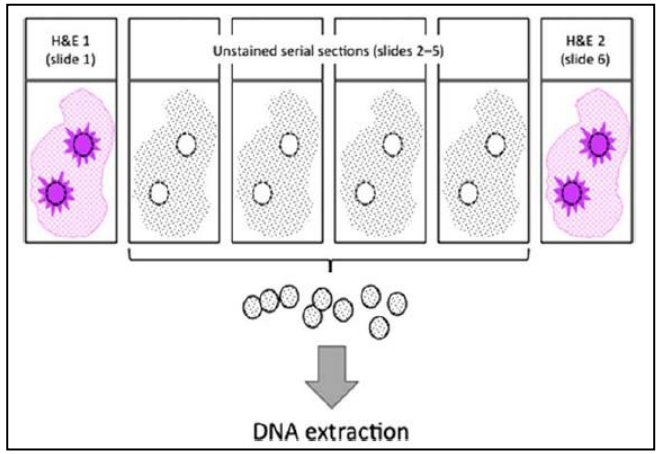
Histopathology. 2018 Aug;73(2):273-283

Next generation sequencing of the nidus of early (adenosquamous proliferation rich) radial sclerosing lesions of the breast reveals evidence for a neoplastic precursor lesion

Mark J Wilsher,[1]* Thomas W Owens[2] and Richard JN Allcock[3,4]







Sample code	Gene	Locus	Type	Ref	Genotype	Variant Allele Frequency	Exon	Protein
A1	*PIK3CA*	chr3:178952085	SNV	A	A/T	0.15	21	p.His1047Leu
A2	*JAK3*	chr19:17945696	SNV	C	C/T	0.54	16	p.Val722Ile
A3	-	-	-	-	-	-	-	-
A4	*PDGFRA*	chr4:55141026	SNV	G	G/A	0.07	7	p.Arg234Gln
	PTEN	chr10:89717676	SNV	C	C/T	0.07	12	p.Arg558Cys
	STK11	chr19:1220394	SNV	G	G/A	0.06	4	p.Gly163Ser
B1	*PIK3CA*	chr3:178952085	SNV	A	A/G	0.06	21	p.His1047Arg
	RET	chr10:43609955	SNV	C	C/T	0.06	11	p.Thr636Met
B2	*PIK3CA*	chr3:178952085	SNV	A	A/G	0.08	21	p.His1047Arg
B3	*ATM*	chr11:108138003	SNV	T	T/C	0.60	17	p.Phe858Leu
	JAK3	chr19:17945696	SNV	C	C/T	0.47	16	p.Val722Ile
	PIK3CA	chr3:178952085	SNV	A	A/G	0.15	21	p.His1047Arg
B4	*PIK3CA*	chr3:178952085	SNV	A	A/G	0.08	21	p.His1047Arg
B5	*PIK3CA*	chr3:178952085	SNV	A	A/G	0.26	21	p.His1047Arg
B6	*ATM*	chr11:108155132	SNV	G	G/A	0.48	26	p.Ala1309Thr
	PIK3CA	chr3:178952085	SNV	A	A/G	0.28	21	p.His1047Arg
B7	-	-	-	-	-	-	-	-
B8	*SMAD4*	chr18:4860475	SNV	A	A/G	0.52	12	p.Ile525Val

75% of radial scars with ASP-rich lesions have somatic PIK3CA mutations.

J Path: Clin Res April 2017; **3:** 115–122

Differential Diagnosis Between Low-Grade Adenosquamous Carcinoma and High-Grade Metaplastic Carcinoma

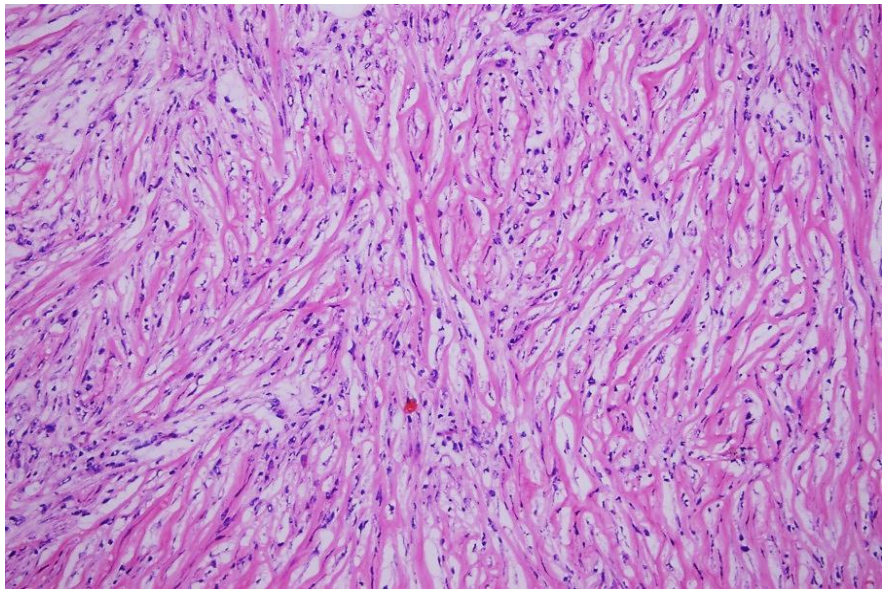
Exclusion Criteria for LGASC

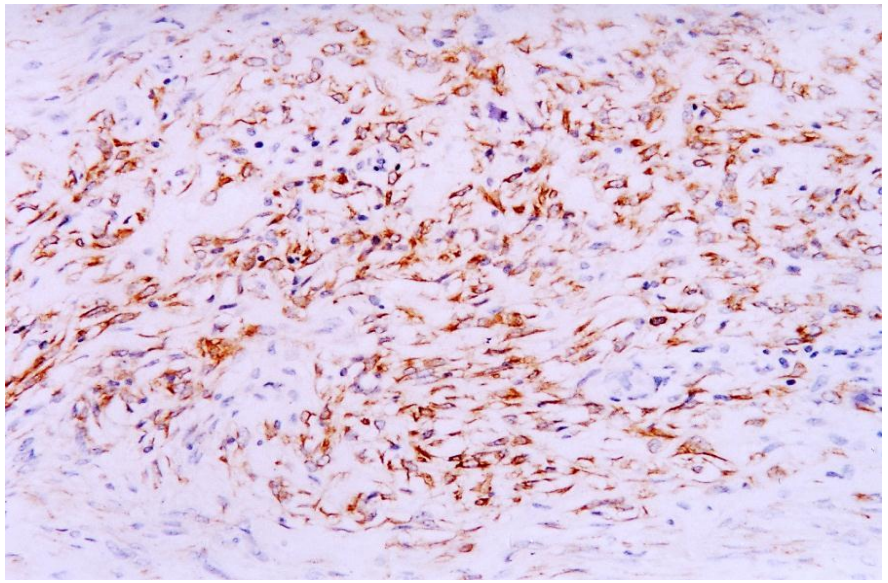
- Significant cellular atypia
- Abundant mitotic figures
- Extensive epithelioid differentiation
- Squamous differentiation
- Heterologous differentiation

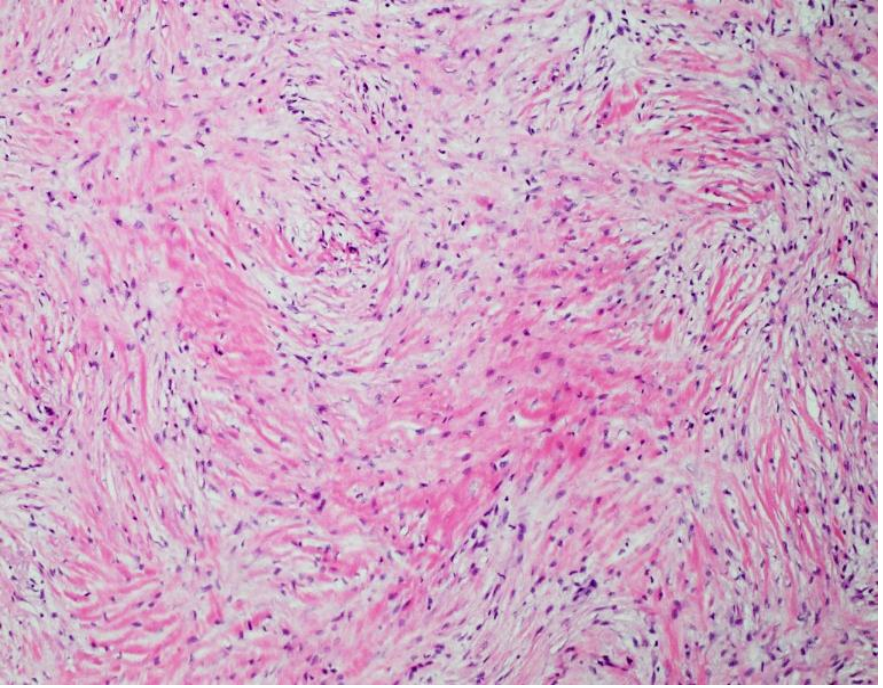
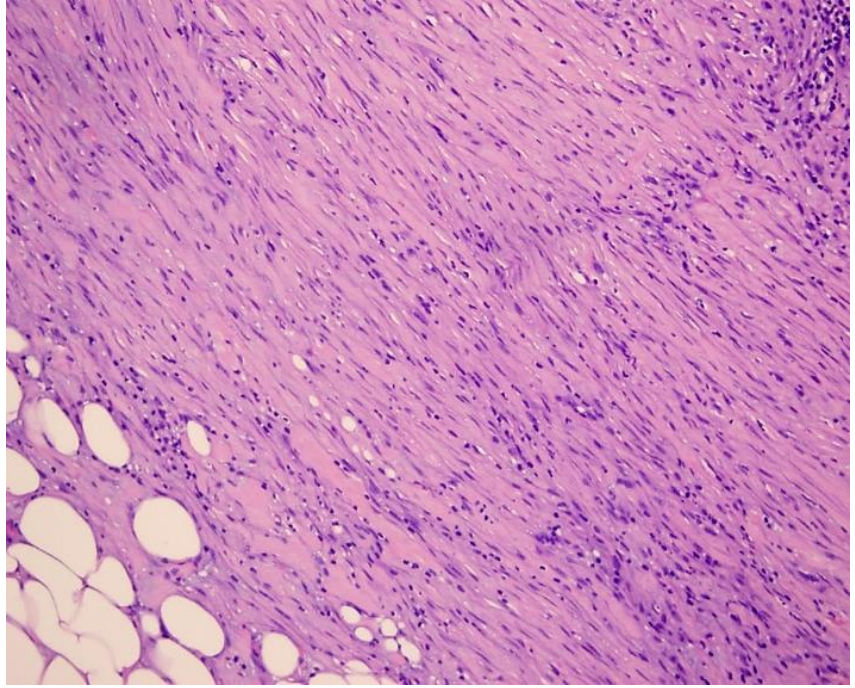
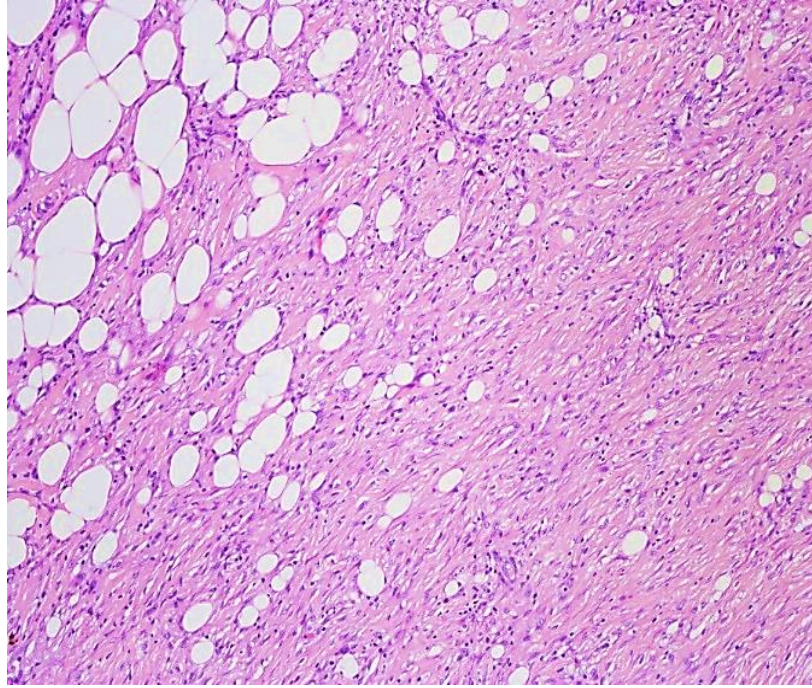
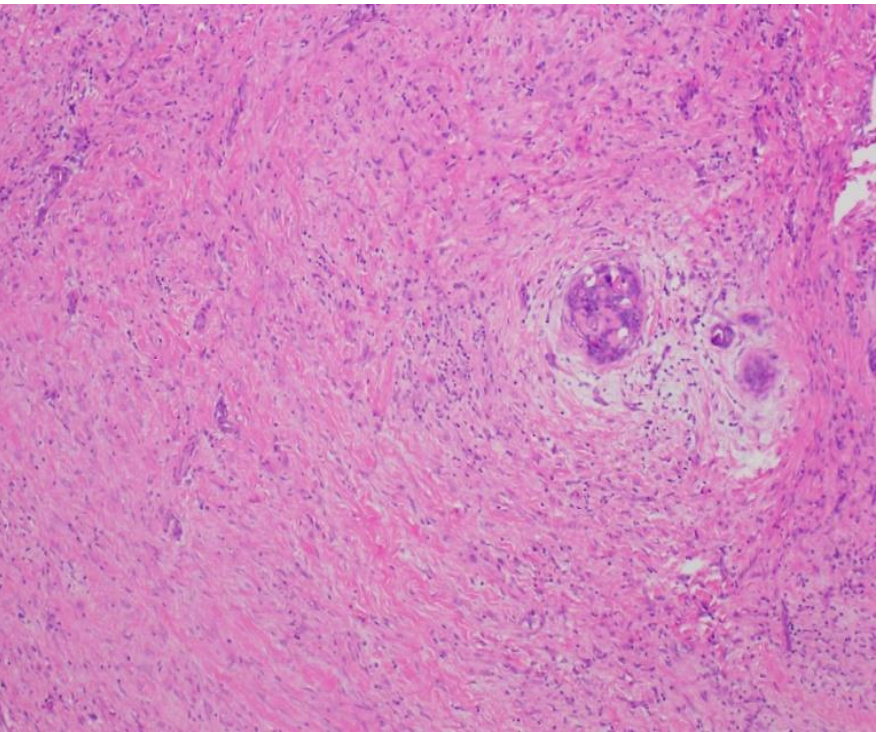
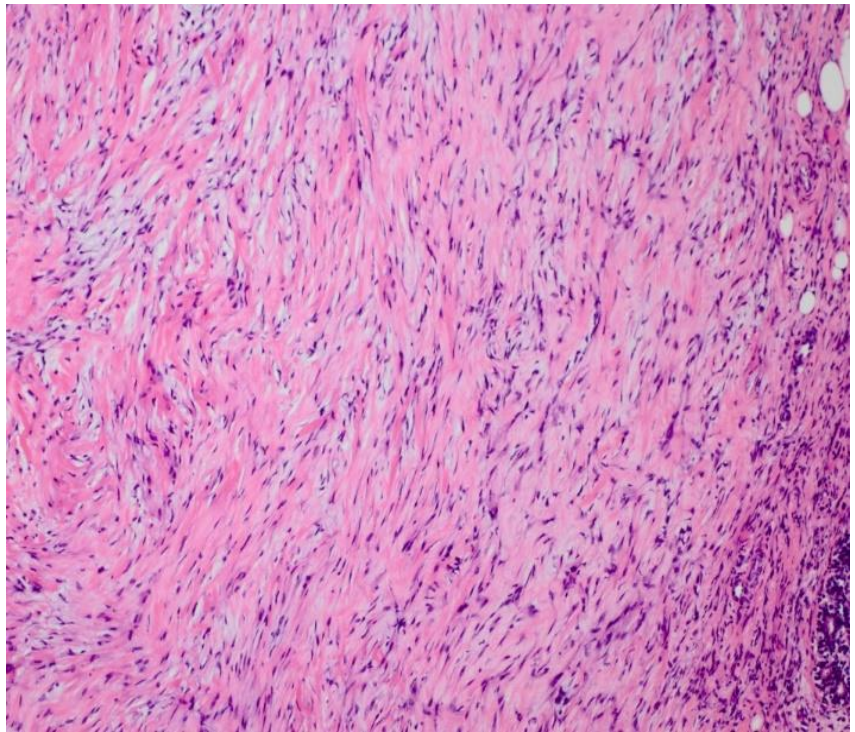
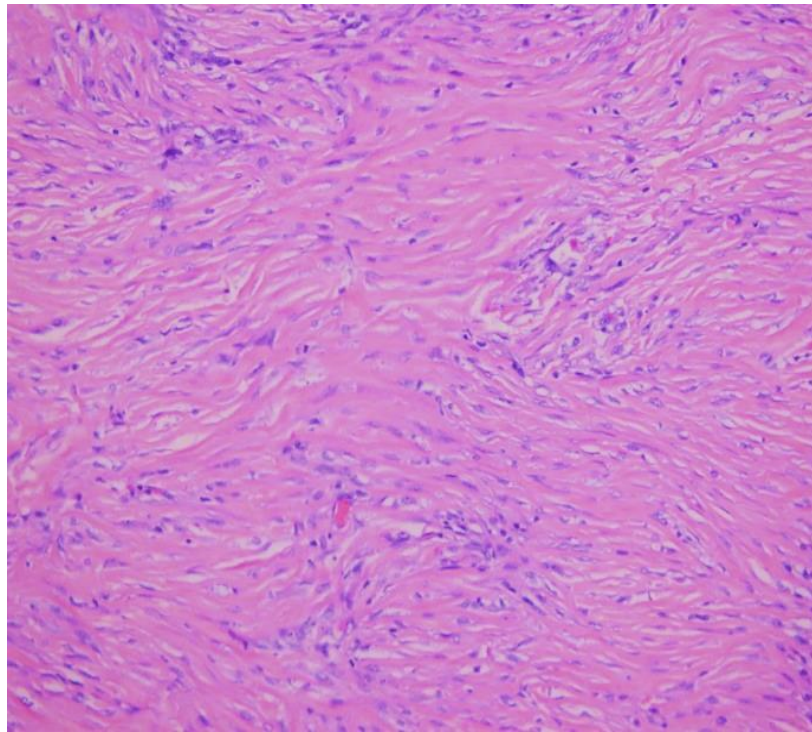
careful observation

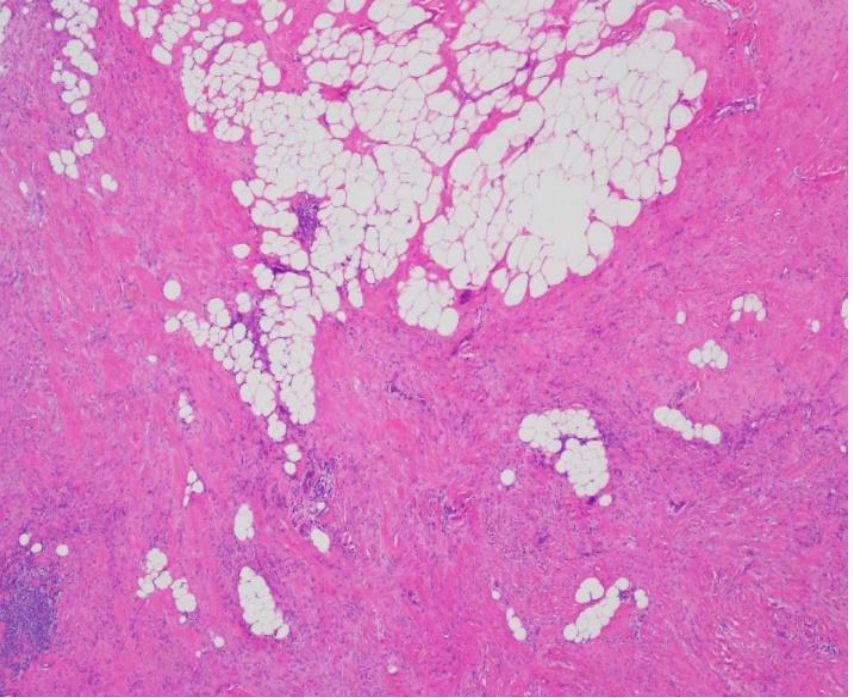
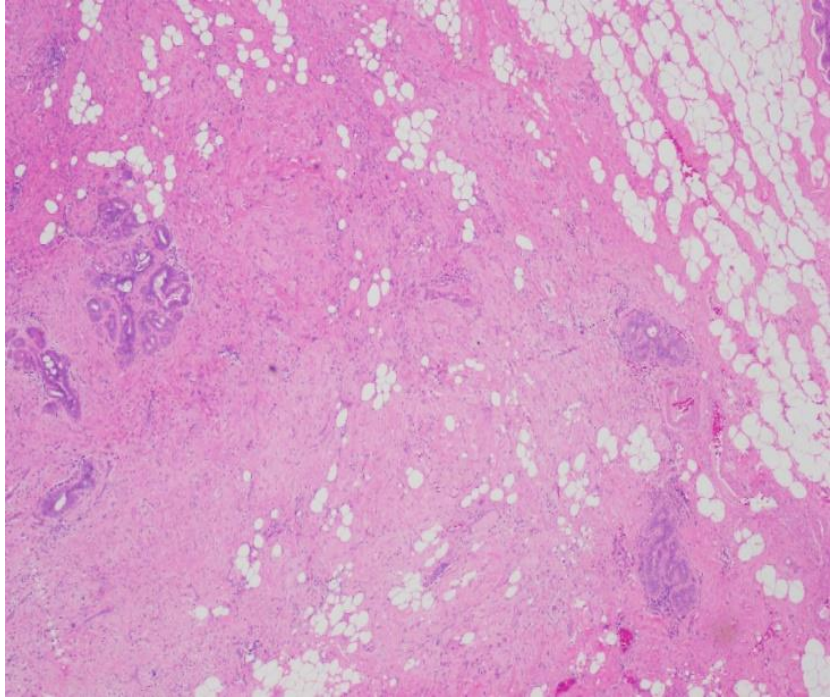
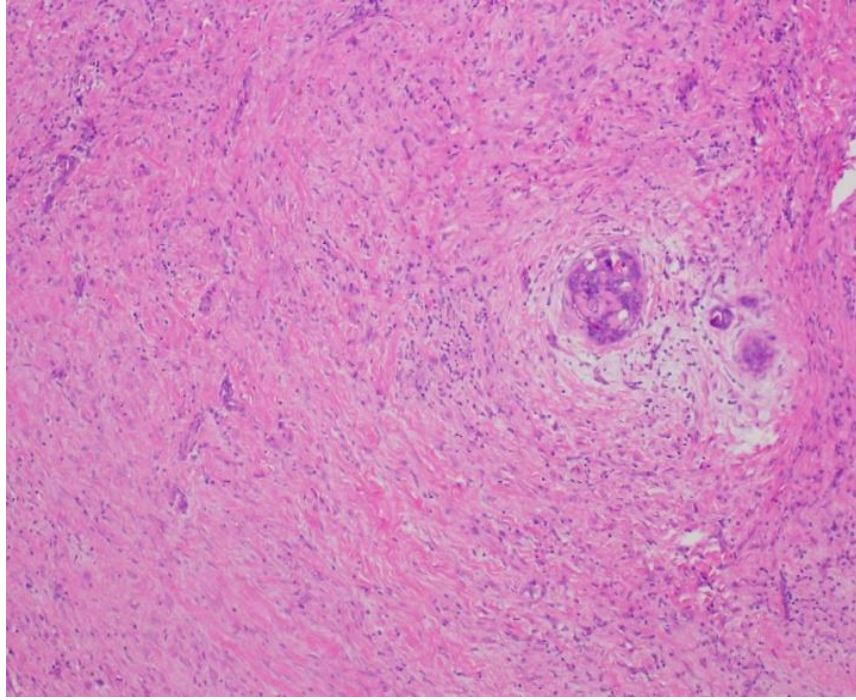
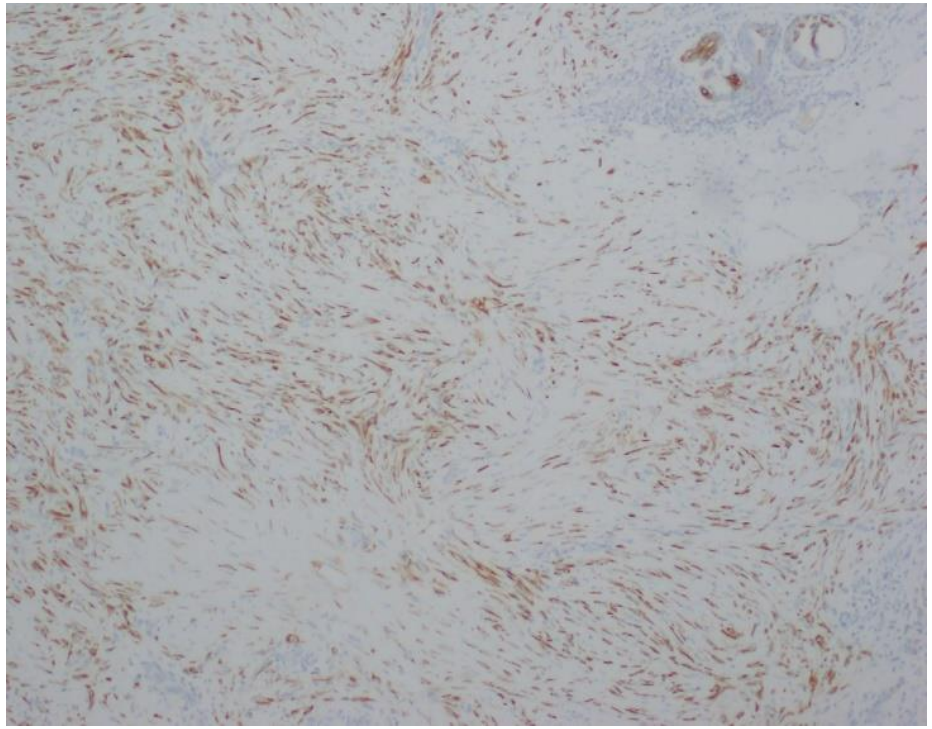
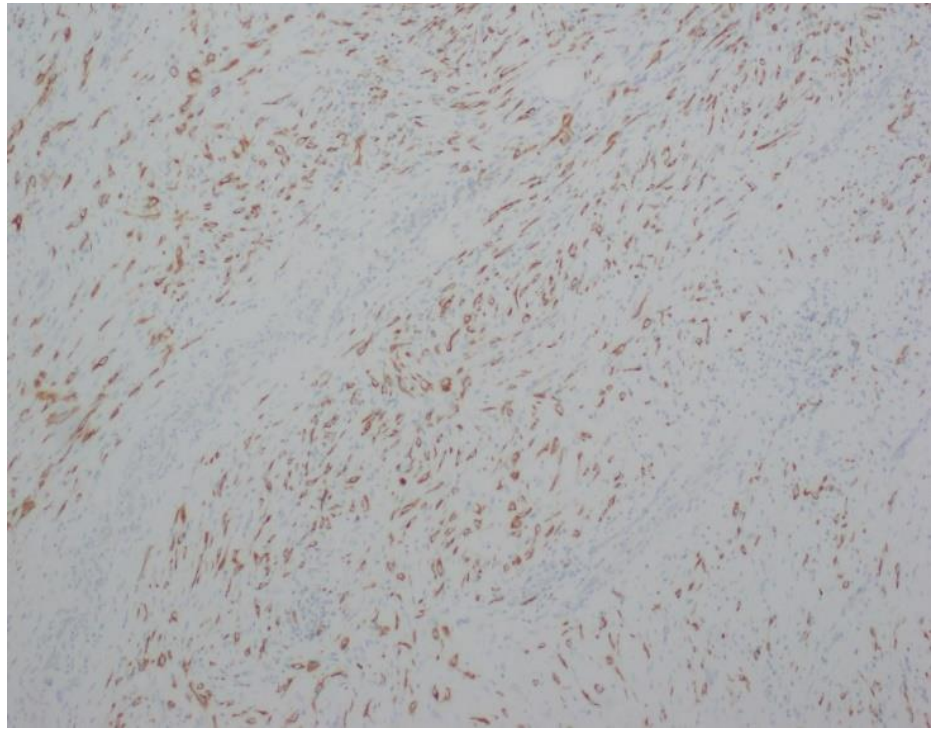
Fibromatosis-Like Metaplastic Carcinoma

- 95% of the area is composed of bland spindle cells, interspersed with varying amounts of collagen
- Tumor cells exhibit minimal nuclear atypia and a low mitotic (<3/10 HPF)
- Tumor cells are arranged in bundles or a storiform pattern and may exhibit infiltration into surrounding breast tissue
- Scattered plump spindle cells are present, with focal (<5%) epithelioid or squamous differentiation
- A variable inflammatory infiltrate of lymphocytes and plasma cells may be observed.
- The Ki67 index is usually <5%.





Avoid Missing Fibromatosis-like Spindle Cell Carcinoma

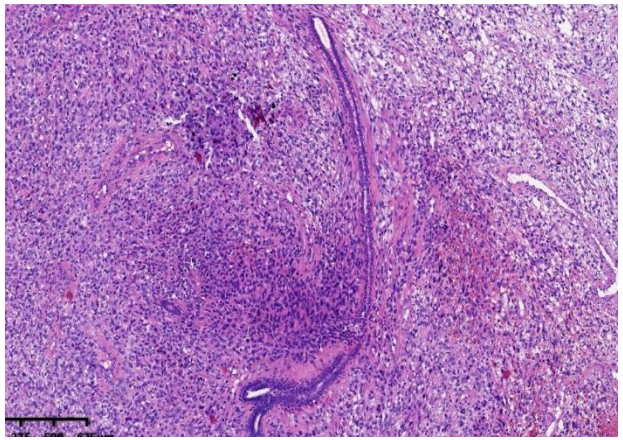
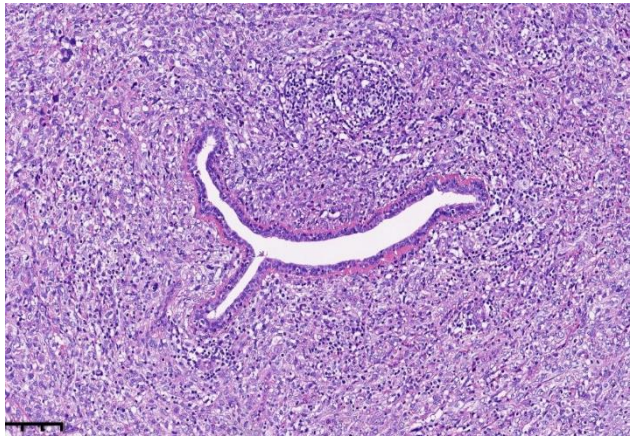
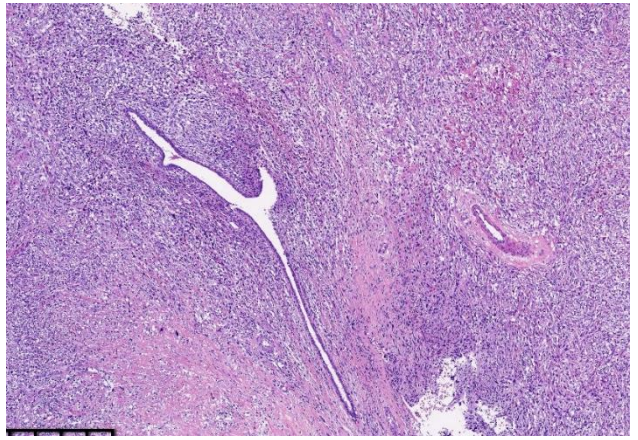
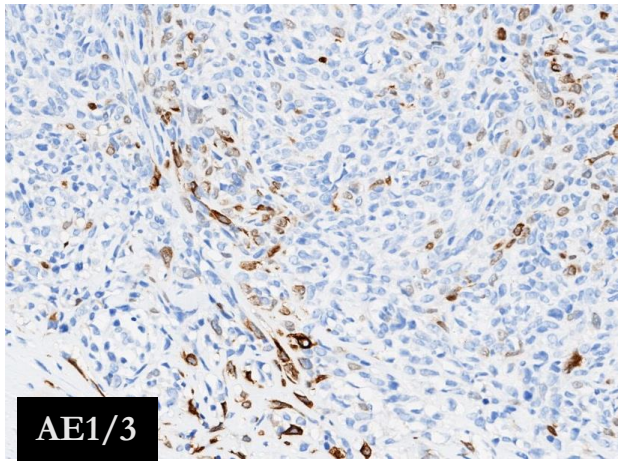
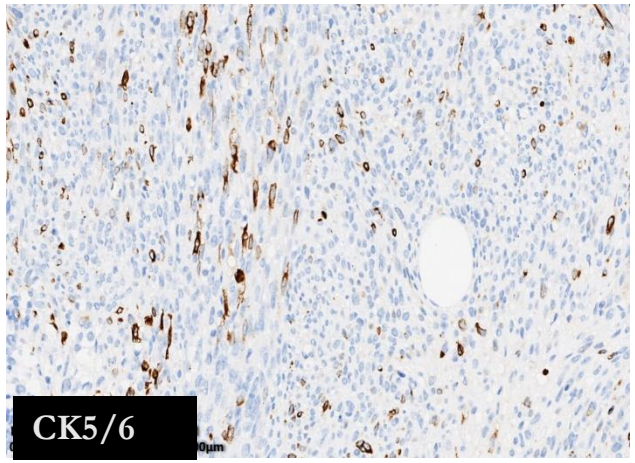
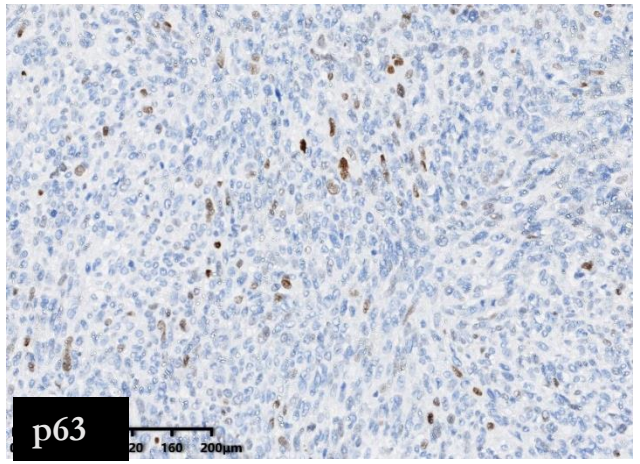
- Nodular fasciitis (subcutaneous nodules, rapid growth, painful)
- Fibrous scar (old hemorrhage, fat necrosis, foreign body giant cell reaction, or relevant medical history)
- Fibromatosis
- Benign/borderline fibroepithelial tumors

Immunohistochemistry

- **Using a panel of epithelial markers**
- **CK (AE1/3, CAM5.2), basal-like CK (34βE12, CK5/6, CK14), and p63.**
- **It often expresses SMA, vimentin, EGFR, S100, and CD10.**
- **~ 20% of cases show nuclear positivity for β-catenin.**

Note:

Focal positivity for CK and p63 can also be observed in malignant phyllodes tumors.





AE1/3

CK5/6

p63
160
200µm

249 Pitfalls of Keratin and P63 Expression and Utility of Targeted DNA Sequencing and HMGA2 in Malignant Phyllodes Tumors of the Breast

Julia Ye[1], Talent Theparee[2], Gregory Bean[3], Christopher Schwartz[1], Poonam Vohra[1], Guofeng (George) Gao[4], Grace Allard[5], Megan Troxell[6], Yunn-Yi Chen[1], Gregor Krings[1]

[1]University of California, San Francisco, San Francisco, CA, [2]UCSF Medical Center, San Francisco, CA, [3]Stanford Medicine/Stanford University, Stanford, CA, [4]Stanford University School of Medicine, Stanford, CA, [5]Feinberg School of Medicine/Northwestern University, Chicago, IL, [6]Stanford University Medical Center, Stanford, CA

	Malignant Phyllodes Tumor	Metaplastic Carcinoma
TRPS1	68% positive (21/31); 42% focal, 53% patchy, 5% diffuse 3/3 cases with heterologous chondrosarcoma, 4/4 cases with osteosarcoma, and 3/4 cases with liposarcoma were TRPS1+.	57% positive (20/35)
GATA3	16% positive (5/31); <5% of cells show weak to moderate positivity	54% positive (25/46).
β-catenin	58% nuclear positive (22/38); 67% focal, 19% patchy, 14% diffuse.	53% nuclear positive (20/38)
CK	38% positive (21/56); all focal positivity.	
p63	67% positive (32/48); 85% focal, 15% patchy.	
HMGA2	85% of cases have ≥10% positive tumor cells 62% have ≥50% positive tumor cells.	8% of cases have ≥10% positive tumor cells; 3% have ≥50% positive tumor cells.

CK/p63 Co-expression: Malignant Phyllodes Tumors: 38%; • Metaplastic Carcinomas: 96%

Expression of TRPS1 in phyllodes tumor and sarcoma of the breast☆,☆☆

- 66 cases of breast phyllodes tumors (malignant, borderline, benign), 21 cases of primary breast sarcomas, 12 cases of breast radiation-induced angiosarcomas, 9 cases of breast metastatic sarcomas, and 478 cases of soft tissue sarcomas from other sites.
- TRPS1 was highly expressed in malignant phyllodes tumors (95%), primary breast osteosarcomas (100%), and chondrosarcomas (100%).
- Expressed in extra-mammary osteosarcomas (56%) and conventional chondrosarcomas (28%).

Phyllodes tumor		Negative n (%)	Positive, n (%)			Total
			Low	Intermediate	High	
		2(3)	9(14)	27(41)	28(42)	66
Benign		0	2(20)	6(60)	2(20)	10
Borderline		0	0	6(50)	6(50)	12
Primary malignant	Spindle	1(3)	6(20)	10(33)	13(44)	30
	Chondro/osteo-sarcoma	0	0	0	4(100)	4
	Liposarcomatous	1(16)	1(17)	3(50)	1(17)	6
Metastatic (to lung)		0	0	2(50)	2(50)	4

- **95% of malignant phyllodes tumors express TRPS1; the positive rate of TRPS1 in benign and borderline phyllodes tumors is 100%.**
- **Spindle cell sarcoma, osteosarcoma/chondrosarcoma, and liposarcoma components in malignant phyllodes tumors highly express TRPS1.**
- **TRPS1 cannot distinguish between metaplastic carcinoma and malignant phyllodes tumor.**

Hum Pathol 2022;121:73–80

β-catenin nuclear positivity

	Clone 14	Clone 17C2
Fibromatosis (n=8)	8 (100%)	8 (100%)
Phyllodes Tumor (n=23)		
Benign (n=16)	15 (93.7%)	15(93.7%)
Borderline/malignant (n=7)	4 (57.1%)	5(71.4%)
Metaplastic Carcinoma (n=52)		
Squamous metaplasia (n=17)	3 (17.6%)	3 (17.6%)
Heterologous components (n=13)	2 (15.4%)	1 (7.7%)
Spindle cell components (n=22)	4 (18.2%)	4 (18.2%)

* Both metaplastic carcinoma and phyllodes tumors in the breast can be β-catenin positive.

Modern Pathology (2010) 23, 1438–1448

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Invasive Breast Cancer

NCCN Guidelines Index
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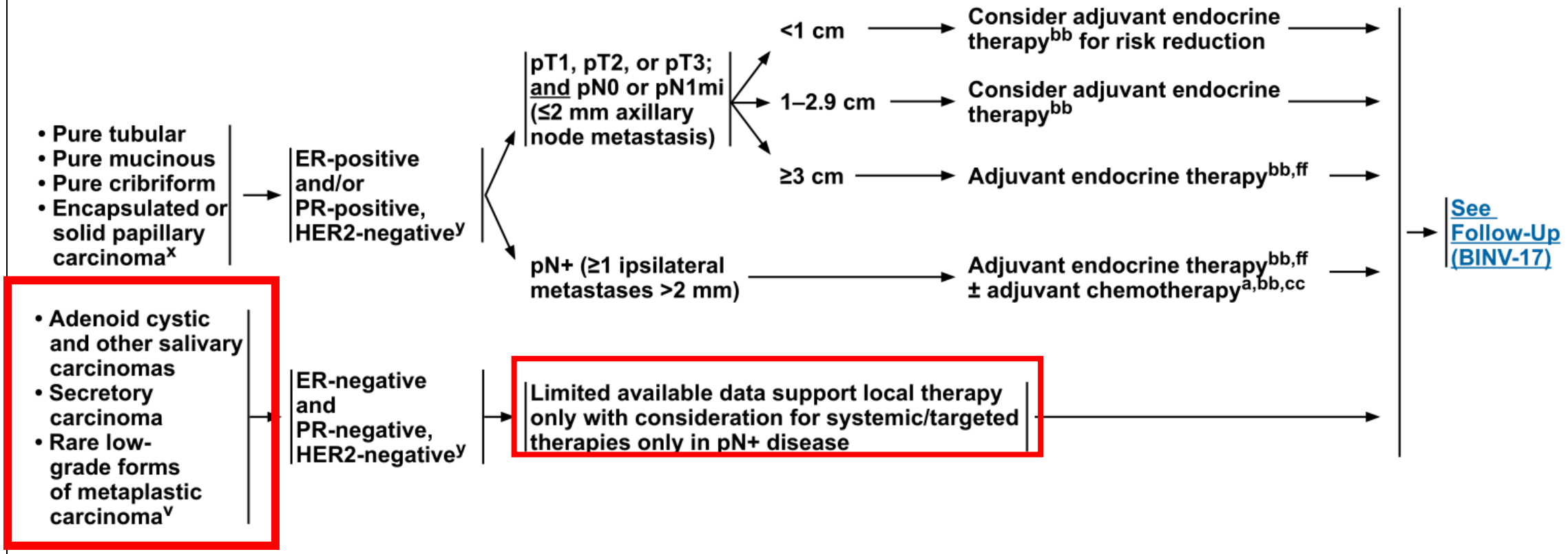
Discussion

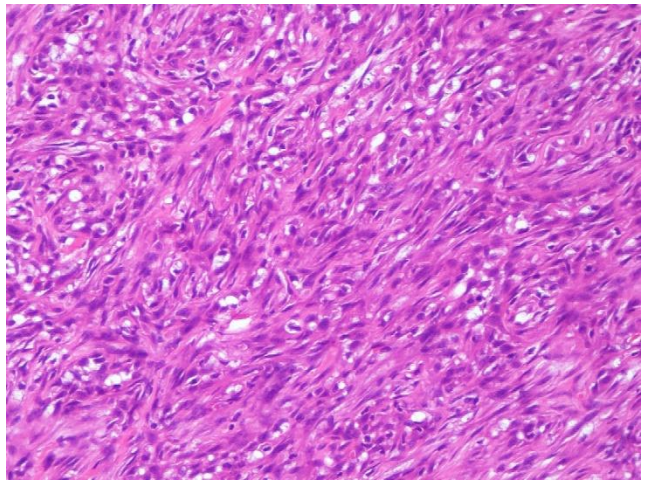
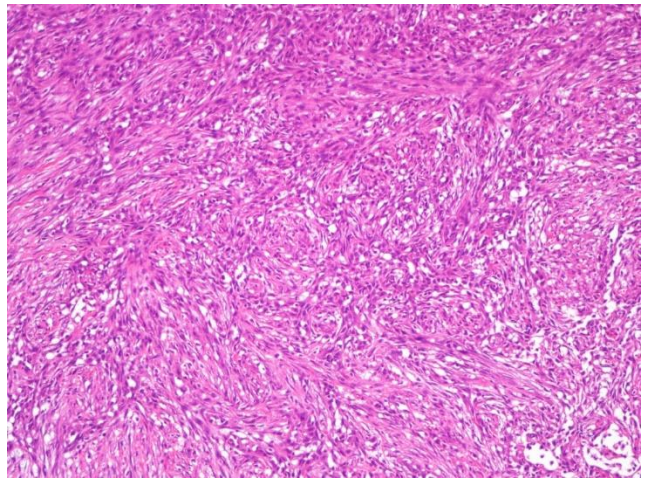
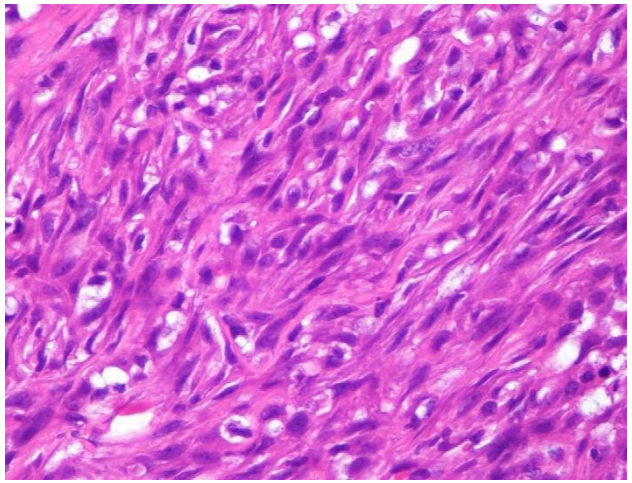
SYSTEMIC ADJUVANT TREATMENT: FAVORABLE HISTOLOGIES[r,w]



- **Histological types of TNBC with favorable prognosis:** adenoid cystic carcinoma and other salivary gland-type carcinomas, secretory carcinoma, low-grade metaplastic carcinoma **(low-grade adenosquamous carcinoma and low-grade fibromatosis-like carcinoma)**
- **Pure histological types (surgical specimens, not core needle specimens)**

Spindle Cell Carcinoma

- **Atypical spindle cells are arranged in long bundles, interlacing patterns, or short bundles.**
- **Cells show moderate to severe atypia, with frequent mitotic figures.**

Spindle Cell Metaplastic Tumor

Fibromatosis-like metaplastic carcinoma

Spindle cell carcinoma

moderate to severe nuclear atypia, with easily visible or numerous mitotic figures

Do not underdiagnose moderate to high-grade spindle cell carcinoma as fibromatosis-like metaplastic carcinoma.

Exclusion criteria:

- **Significant cellular atypia**
- **Abundant mitotic figures**
- **High density of spindle cells**
- **Extensive epithelioid differentiation,**

squamous differentiation, or heterologous differentiation

Adequate sampling and comprehensive observation

Emad Rakha : In our practice, we have observed, on review, that many large-sized spindle cell MBCs diagnosed as fibromatosis-like MBC contained foci of moderate cytological atypia, which may explain the reported metastases in some series.

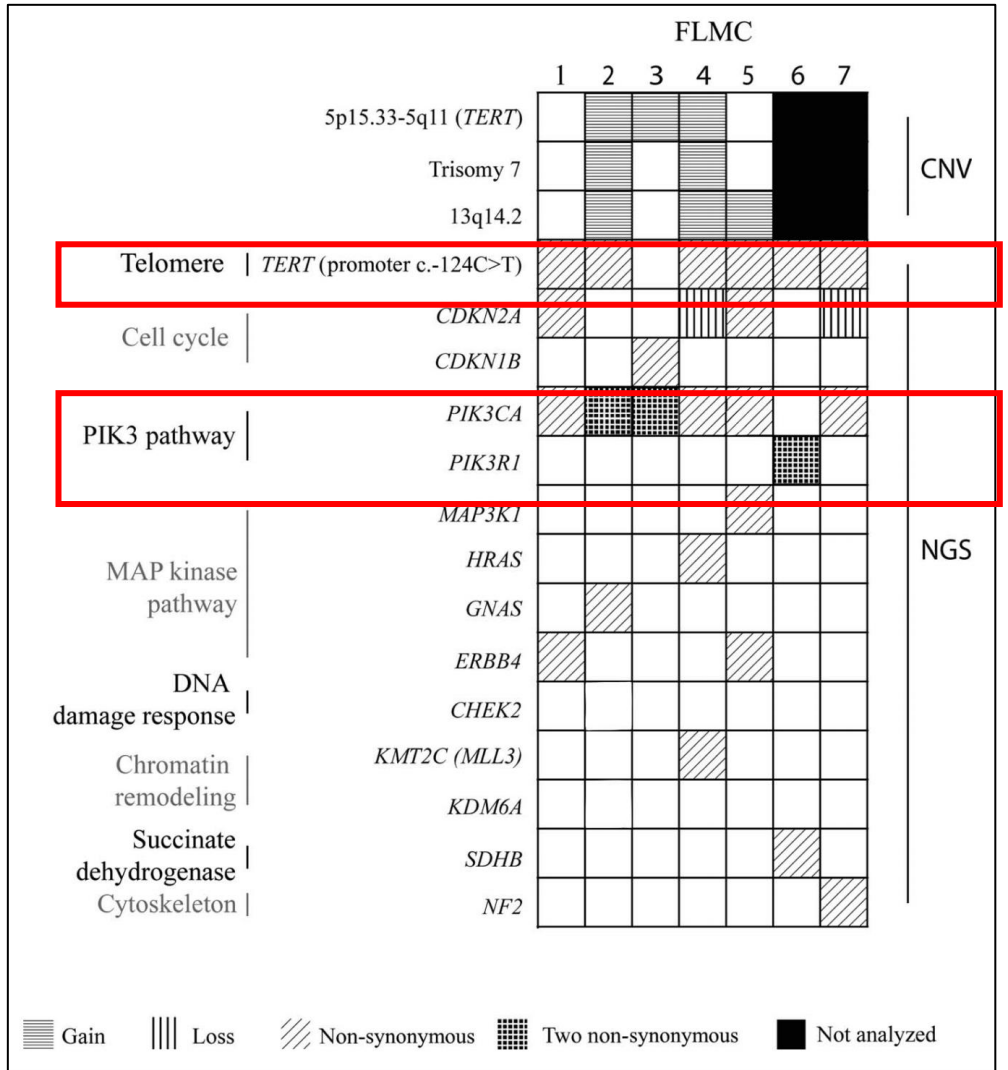
Some cases could pose a challenge for the pathologist to classify. The degree of nuclear atypia, the mitotic count, and percentage of spindle cell component seem to help subclassify these tumors. In the author's opinion, when in doubt, the case should be discussed in a multidisciplinary approach

Virchows Arch. 2022 Jan;480(1):127-145

Clin Lab Med. 2023 Jun;43(2):221-243

TERT Promoter Mutation c.-124C>T Commonly Occurs in Low-Grade Fibromatosis-like Metaplastic Breast Carcinoma

Gerald Webersinke, PhD; Jonathan Burghofer, PhD; Theodora Malli, PhD; Melanie Rammer, PhD; Stephan Wenzel Jahn, MD; Axel Niendorf, MD; Fattaneh A. Tavassoli, MD; Farid Moinfar, MD



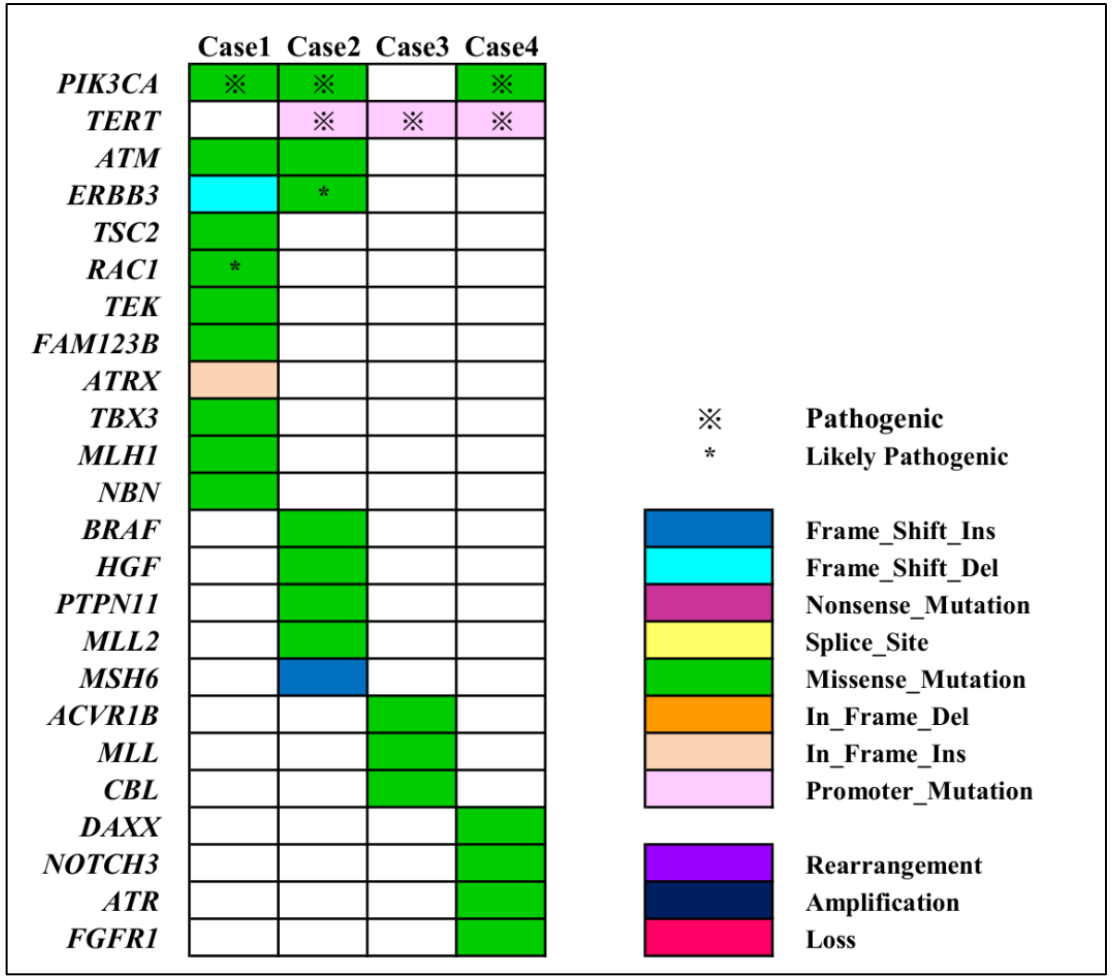
Low-Grade Fibromatosis-Like Metaplastic Carcinoma

- **TERT promoter mutation**
- **Activation of the PI3K/AKT/mTOR pathway**
- **Relatively stable genome**
- **Lack of TP53 gene mutation**

Arch Pathol Lab Med. 2023;147(12):1451-7

High frequency of *PIK3CA* and *TERT* promoter mutations in fibromatosis-like spindle cell carcinomas

Siyuan Zhong , Shuling Zhou, Anqi Li, Hong Lv, Ming Li, Shaoxian Tang, Xiaoli Xu , Ruohong Shui, Wentao Yang

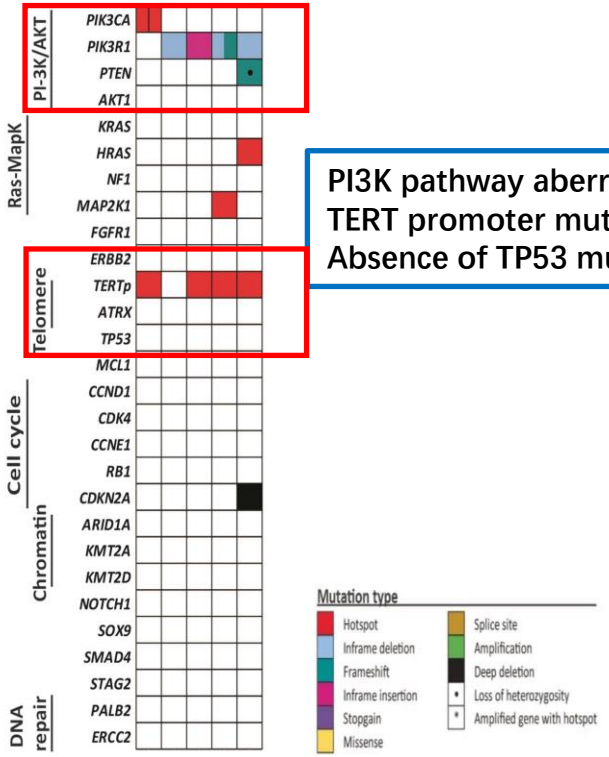


- PIK3CA (75%)
- TERT promoter mutation (75%)
- Absence of TP53 mutation

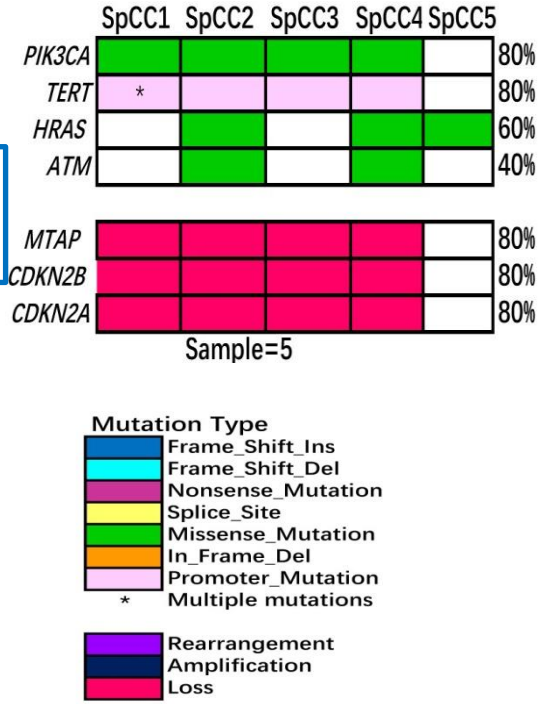
Compared with intermediate-high grade spindle cell carcinoma

- Absence of mutations or abnormalities in HRAS, ATM, MTAP, CDKN2B, and CDKN2A

J Clin Pathol . 2022 Jul;75(7):477-482



PI3K pathway aberration
TERT promoter mutation
Absence of TP53 mutation



Krings and Chen: *Mod Pathol* 2018;31:1661-74

Sample=5

PIK3CA (80%)
TERT promoter mutation (80%)
Absence of TP53 mutation

HRAS (60%)
ATM (40%)
MTAP deletion (80%)
CDKN2B deletion (80%)
CDKN2A deletion (80%)

Unpublished Data from the Department of Pathology, Fudan University Shanghai Cancer Center

Differential Diagnosis of Spindle Cell Lesions of the Breast

Spindle cells with bland morphology

- Fibromatosis
- Myofibroblastoma
- PASH (Pseudangiomatous Stromal Hyperplasia)
- Low-grade spindle cell metaplastic carcinoma
- Low-grade spindle cell sarcoma (dermatofibrosarcoma protuberans, leiomyosarcoma)
- Nodular fasciitis
- Phyllodes tumor

Spindle cells with significant atypia

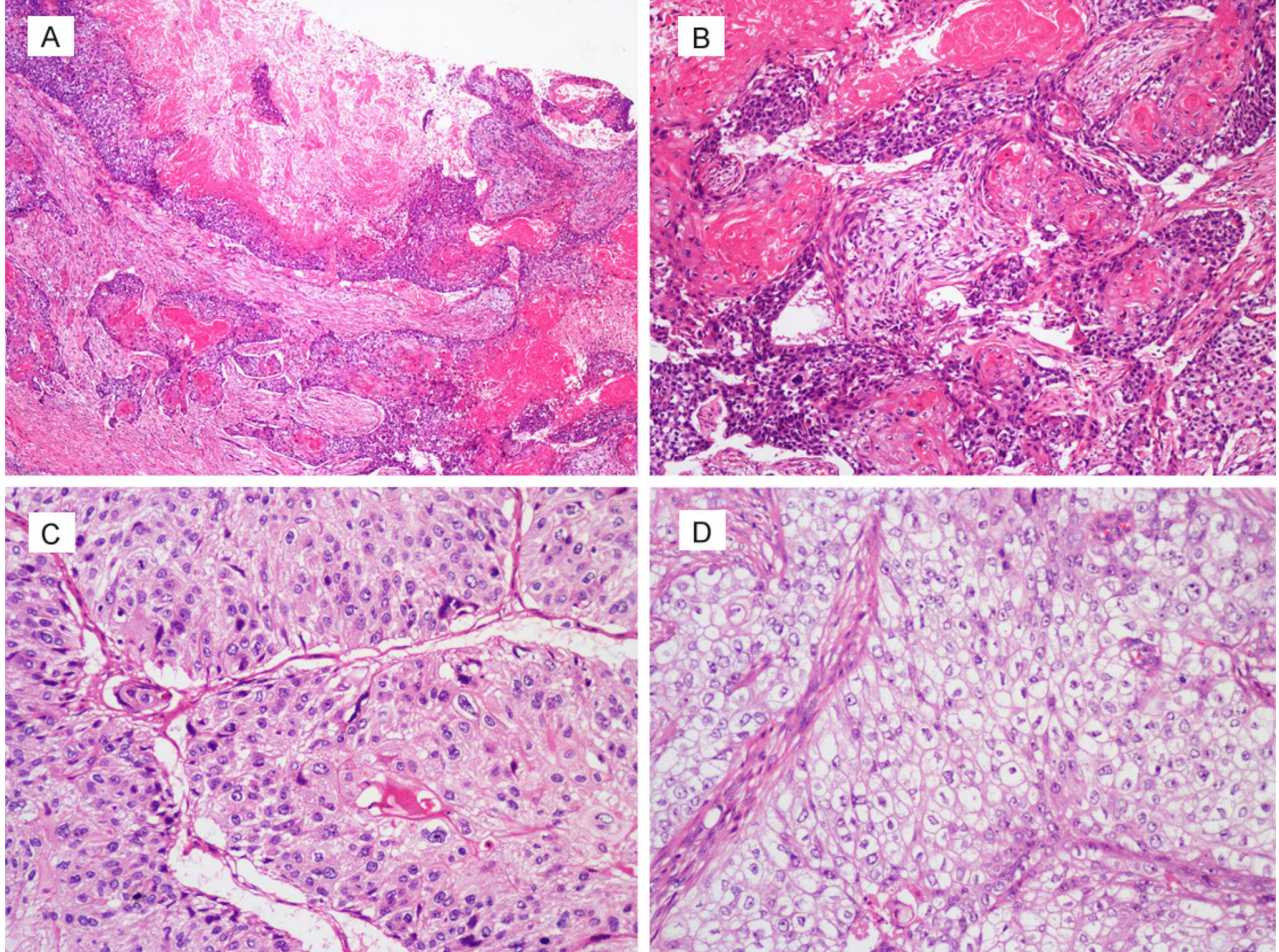
- Spindle cell metaplastic carcinoma
- Malignant phyllodes tumor
- Primary sarcoma
- Metastatic sarcoma
- Metastatic spindle cell carcinoma
- Metastatic malignant melanoma

How to distinguish metaplastic carcinoma from malignant phyllodes tumor in spindle cell malignant tumors with overlapping immunohistochemical results

- **Medical history is crucial**
  History of fibroepithelial tumor surgery, history of breast cancer (review slides), history of breast cancer radiotherapy

- **Adequate sampling and careful morphological observation are essential**
  Presence of leaf-like structures/periductal stromal hyperplasia/slit-like epithelium (phyllodes tumor)
  ADH/DCIS, squamous differentiation, classic invasive carcinoma morphology (metaplastic carcinoma)

- **Molecular testing:**
- Fibroepithelial tumors: MED12 mutations (40% of malignant phyllodes tumors) PIK3CA, RARA, FLNA, SETD2, KMT2D, TP53, RB1, EGFR, NF1
- TERT promoter mutations increase the malignancy of fibroepithelial tumors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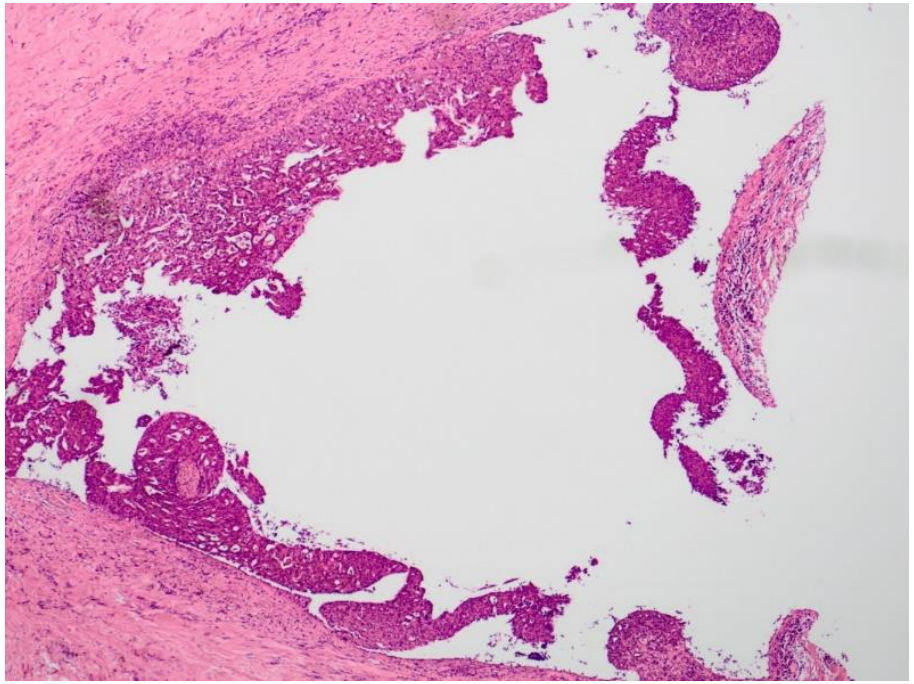
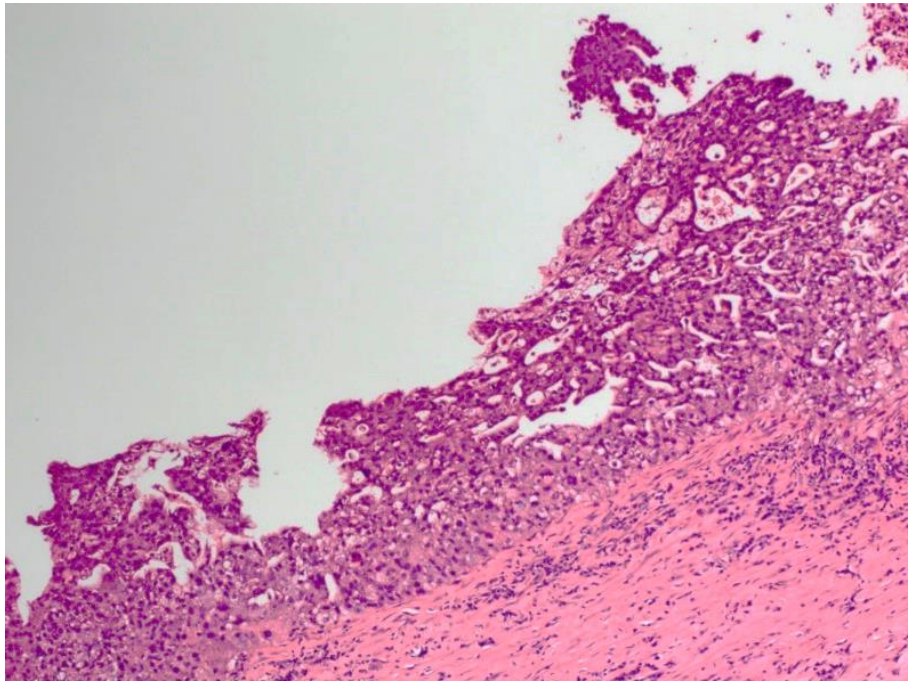
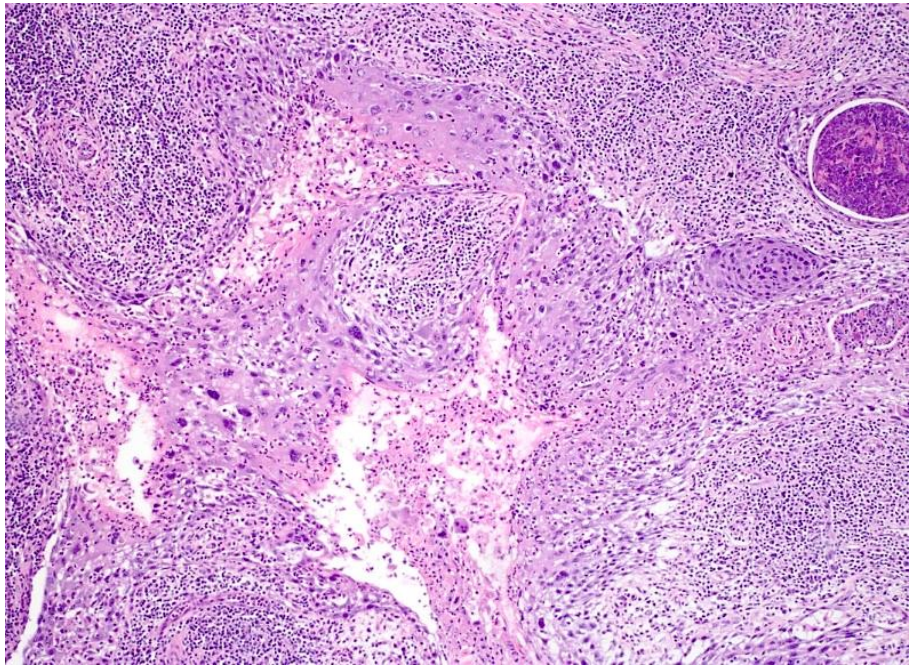
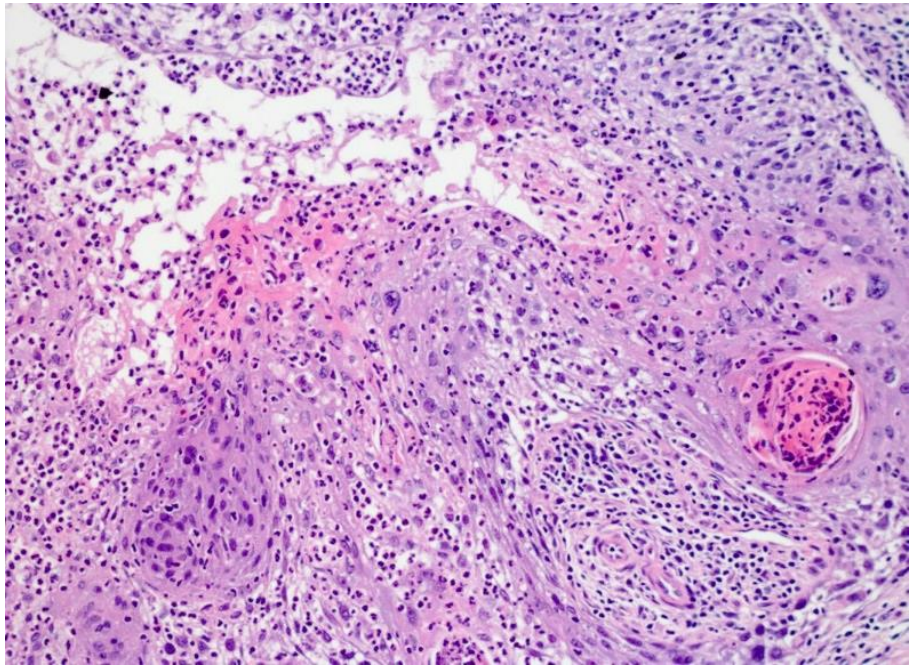








- Squamous cell carcinoma of the breast often presents with significant cystic change.
- The cyst wall is lined by neoplastic squamous epithelium, which sometimes can mimic an epidermal cyst

129 Sox10 and p16 are Co-expressed by Immunohistochemistry in Triple Negative Breast Cancer (TNBC)

Kimberly Cole[1], Parker Wilson[2], Esther Yoon[1], Lina Irshaid[3], Marguerite Pinto[4], Malini Harigopal[1]
[1]Yale University School of Medicine, New Haven, CT, [2]Washington University, St. Louis, MO, [3]Yale New Haven Hospital, New Haven, CT, [4]Yale University, Westport, CT

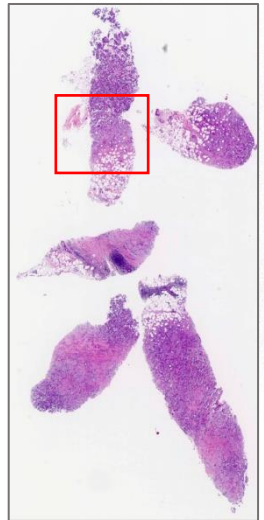
	Score	TNBC	Non-TNBC
Sox10 p<0.0001	Positive	117 (80%)	202 (44%)
	Negative	30 (20%)	262 (56%)
	Total	147	464
p16 p<0.0001	Positive	91 (56%)	77 (16%)
	Negative	72 (44%)	408 (84%)
	Total	163	485

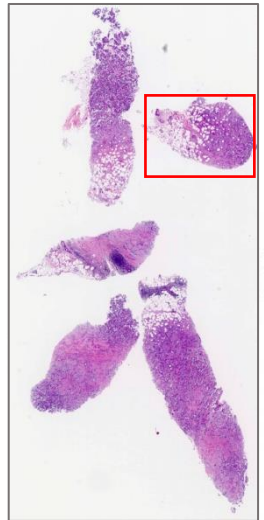
284 P16 Expression is correlated with Androgen Receptor (AR) expression in Triple-Negative Breast Cancers (TNBC)

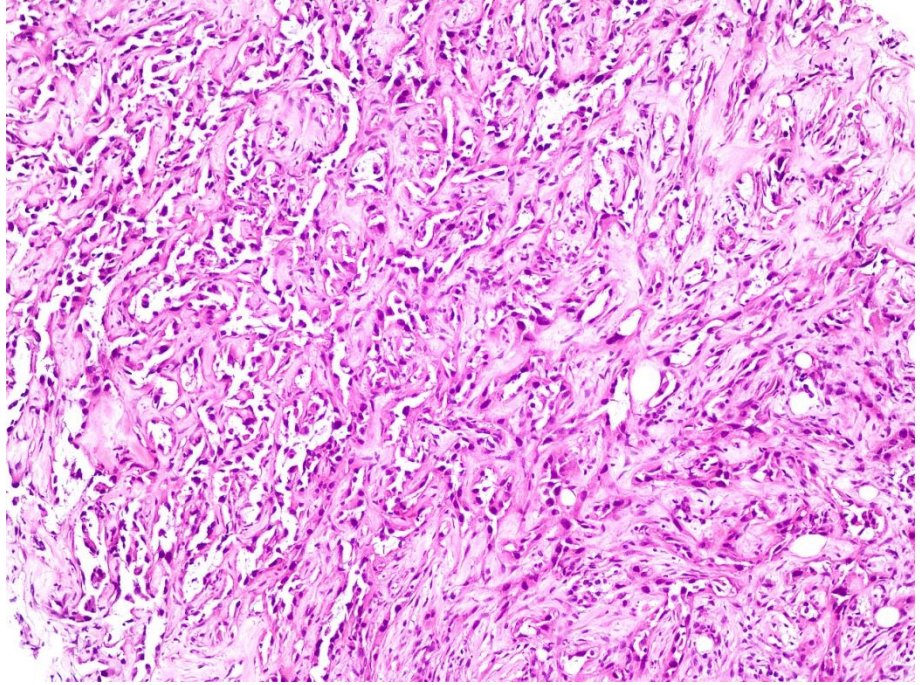
Esther Yoon[1], Parker Wilson[2], Lina Irshaid[3], Tao Zuo[4], Marguerite Pinto[5], Kimberly Cole[1], Malini Harigopal[1]
[1]Yale University School of Medicine, New Haven, CT, [2]Washington University, St. Louis, MO, [3]Yale New Haven Hospital, New Haven, CT, [4]Newton Center, MA, [5]Yale University, Westport, CT

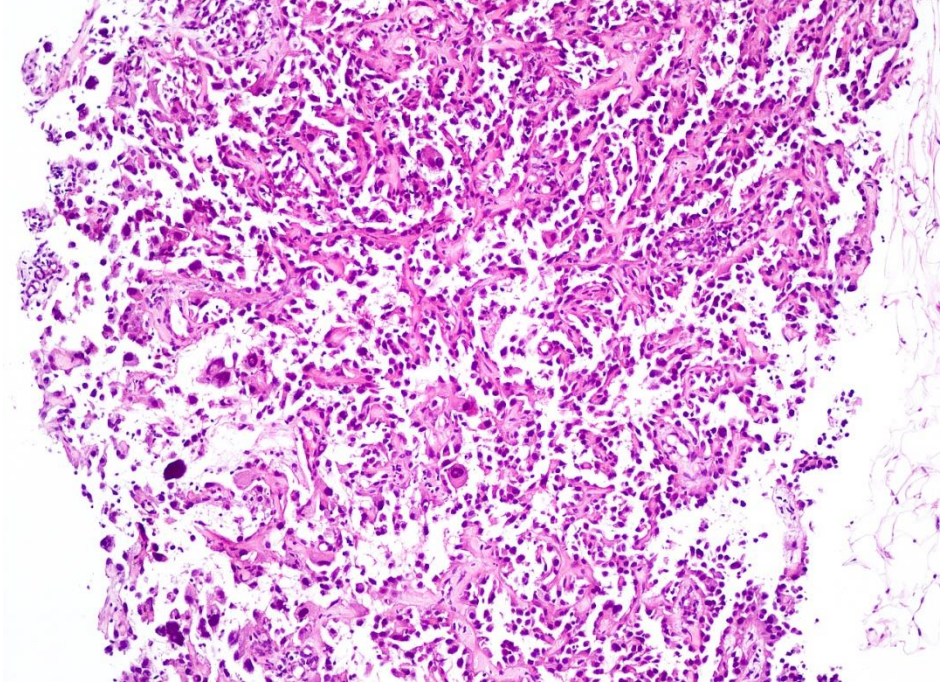
n = 75 (%)	P16 intensity in TBNCs			
0	1	2	3	Positive (1-3)
12 (16.0)	15 (20.0)	10 (13.3)	38 (50.7)	42 (56)

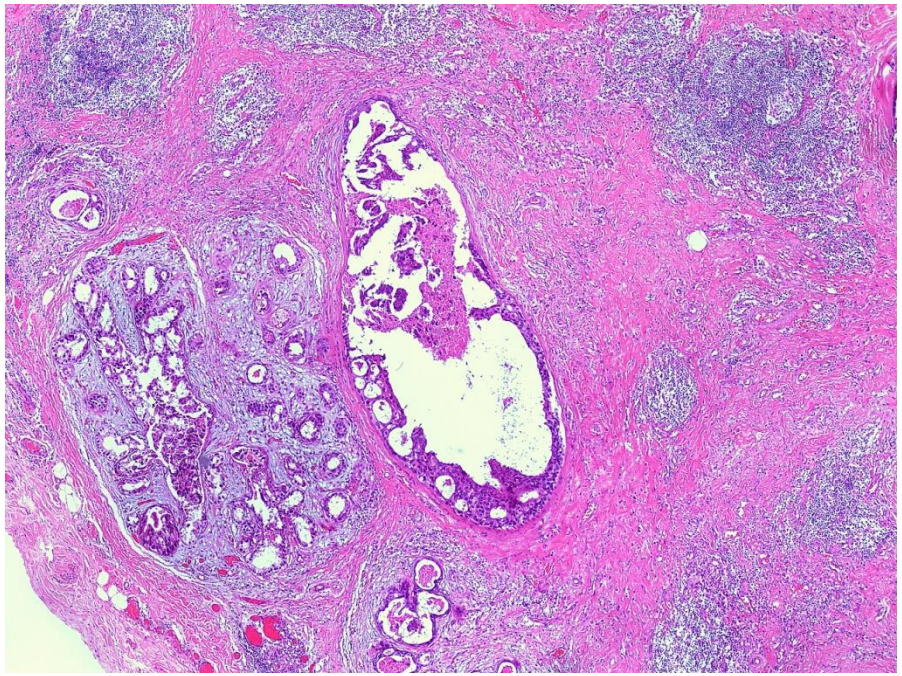
- **p16 positivity is common in TNBC (~50%) . In the differential diagnosis with metastatic cervical squamous cell carcinoma, HPV testing provides more reliable discrimination**

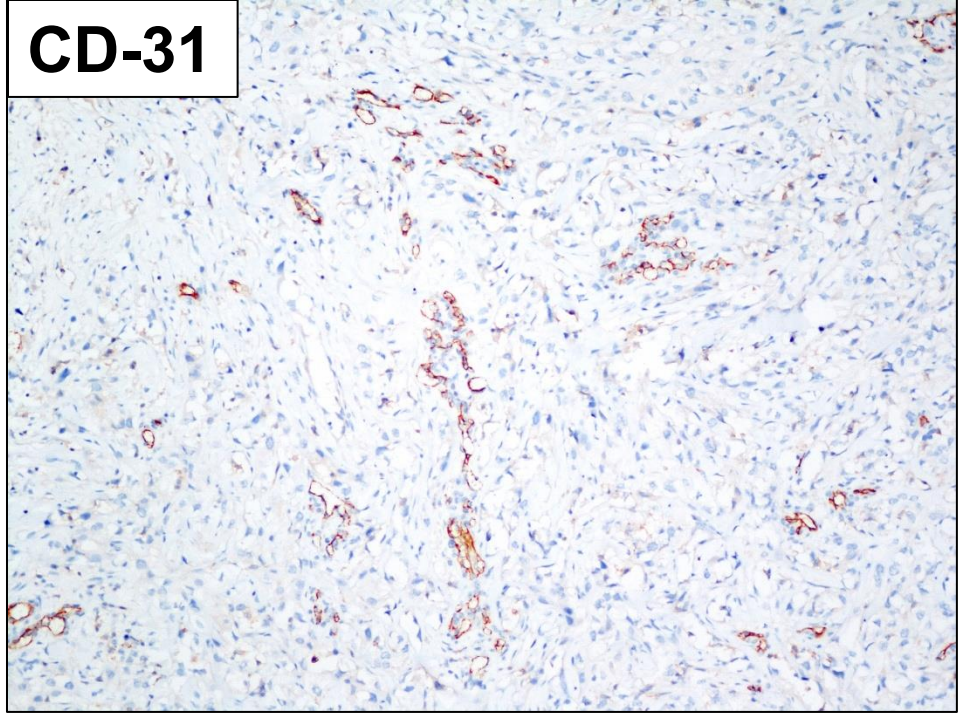


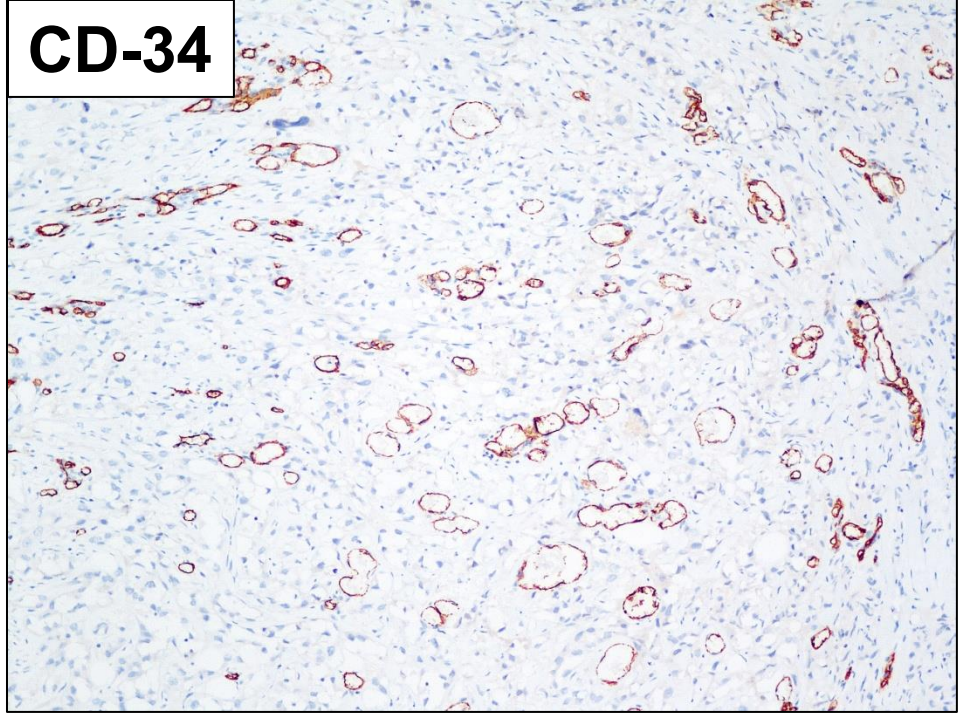









CD-31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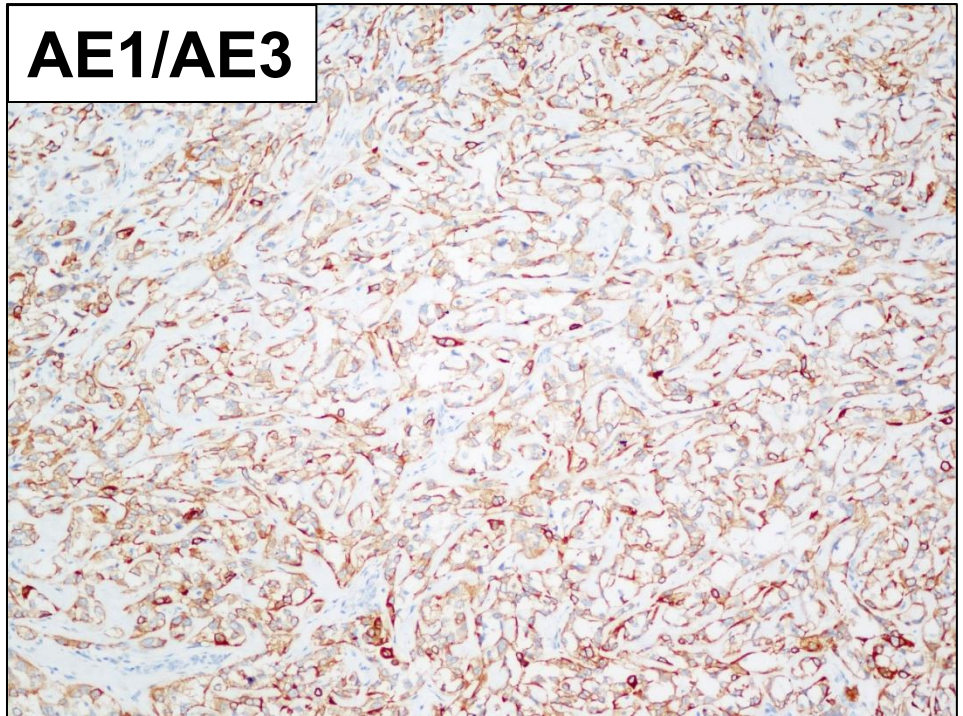
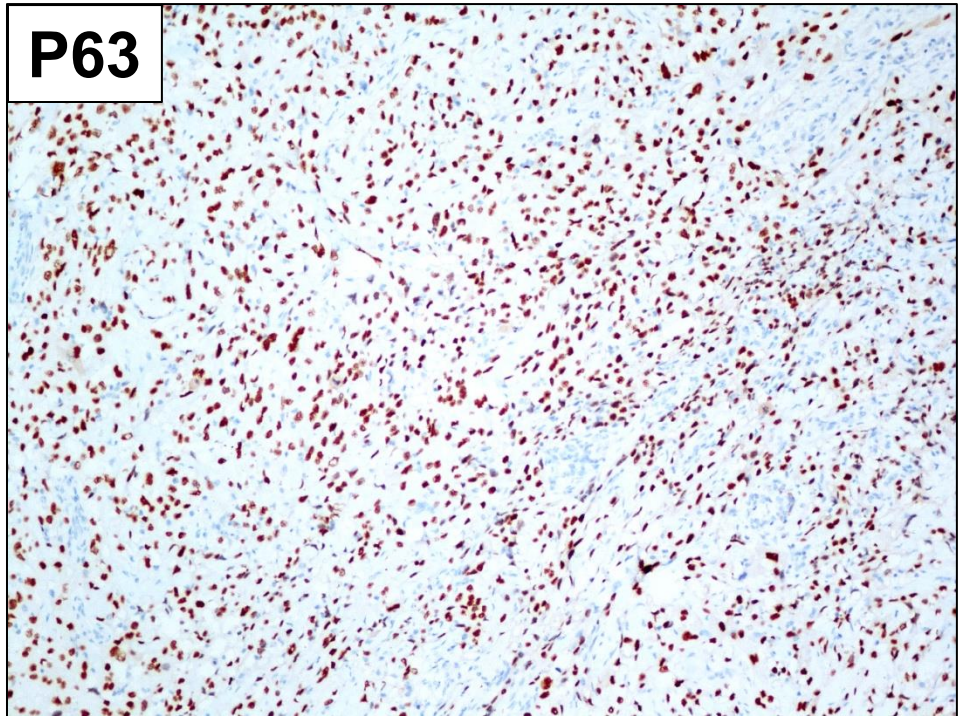
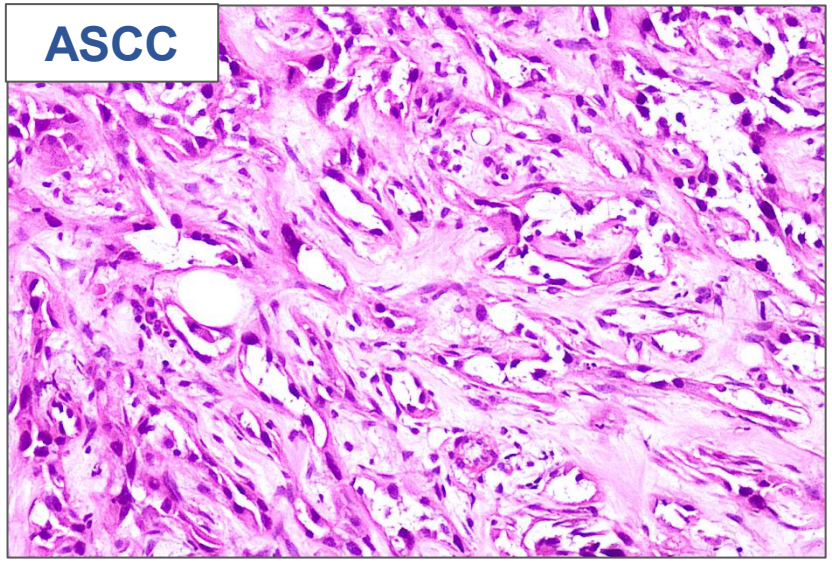
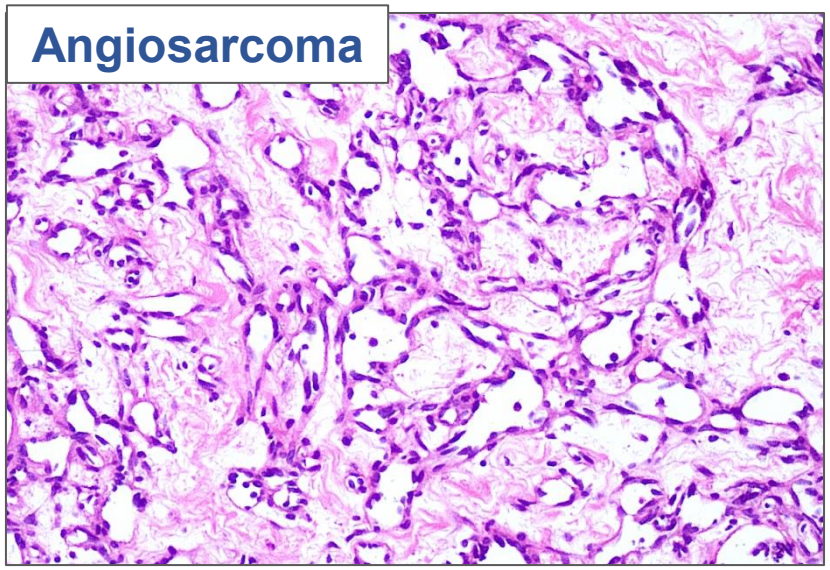

AE1/AE3

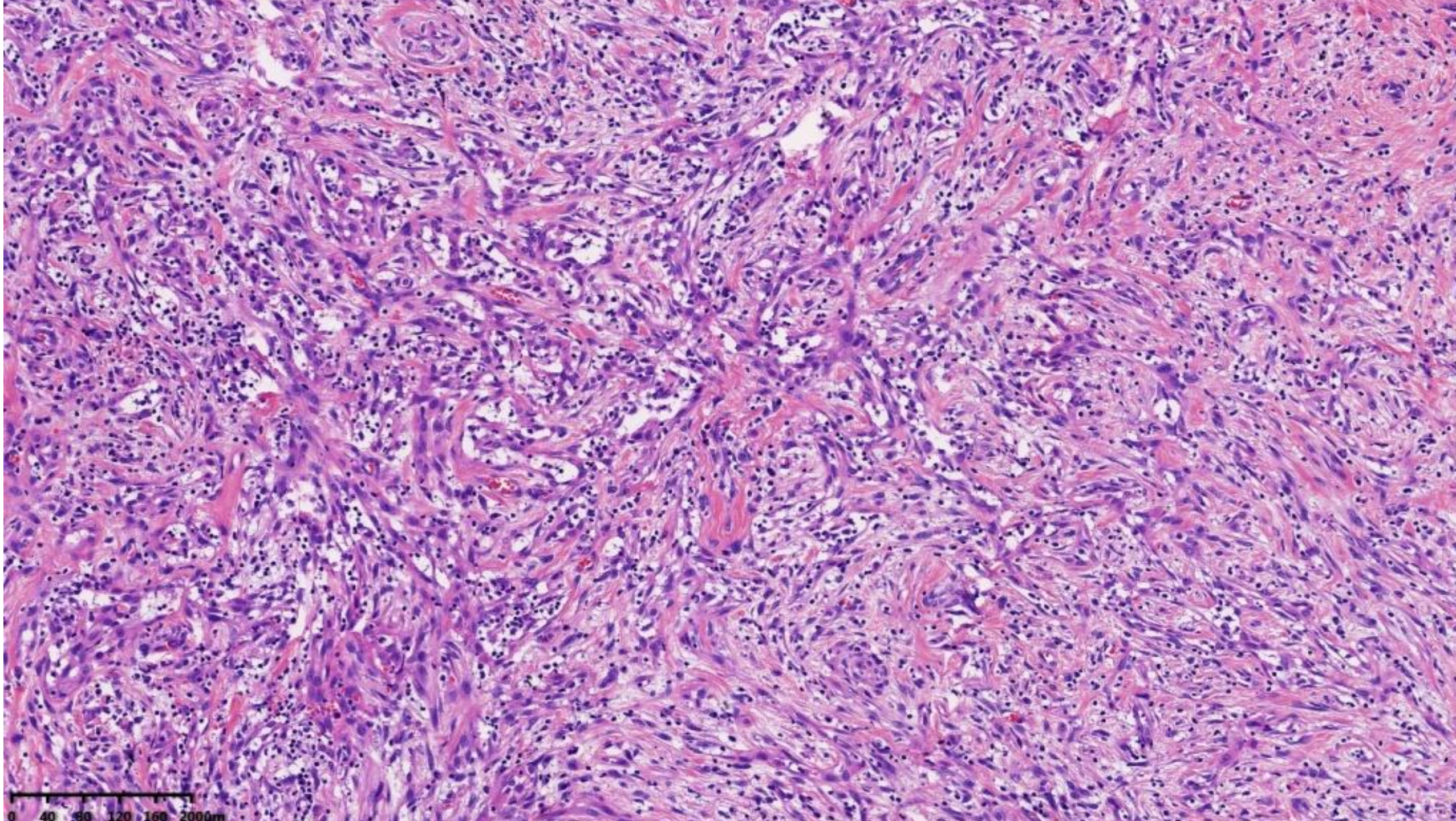

P63

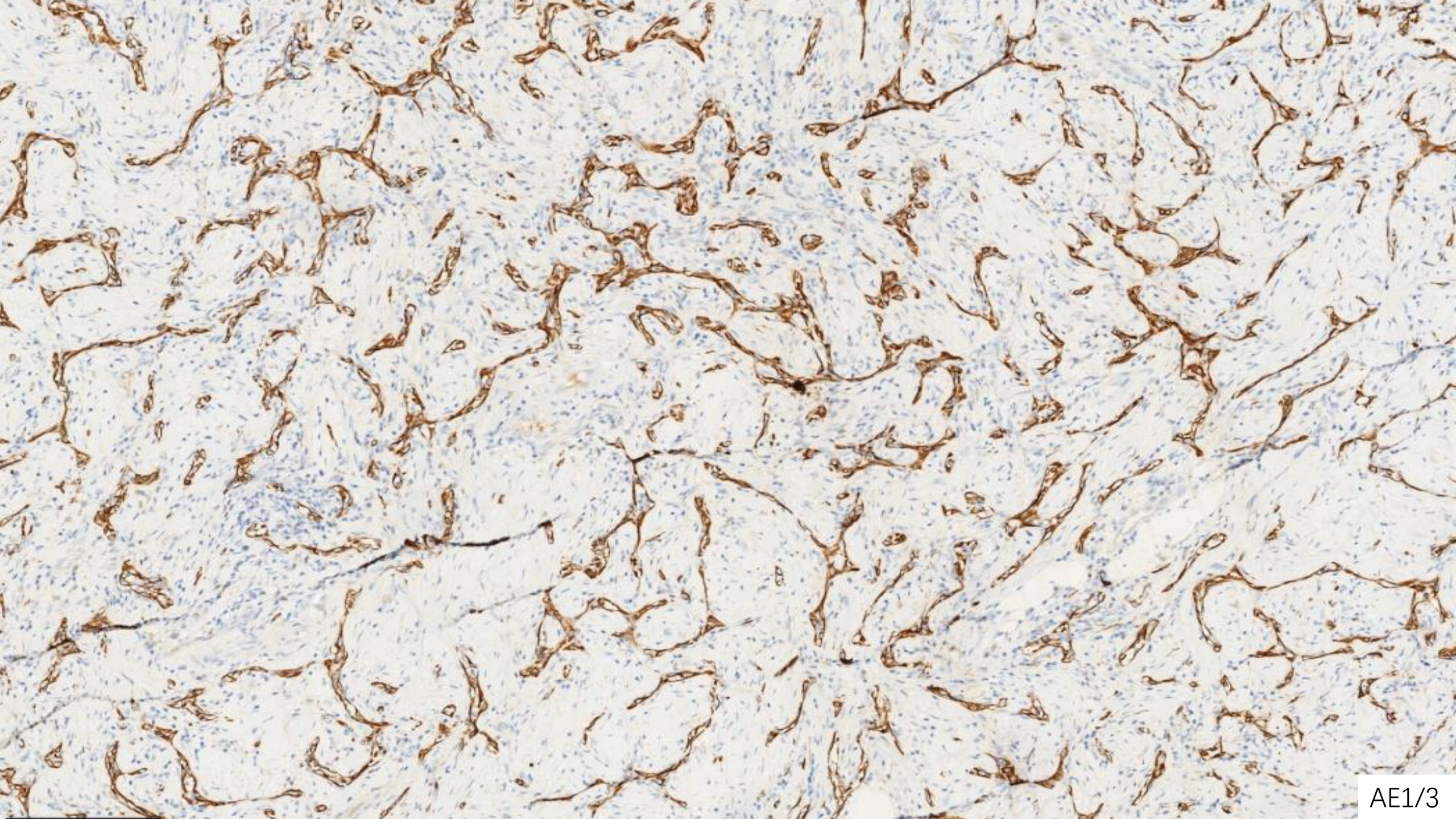
Acantholytic Squamous Cell Carcinoma

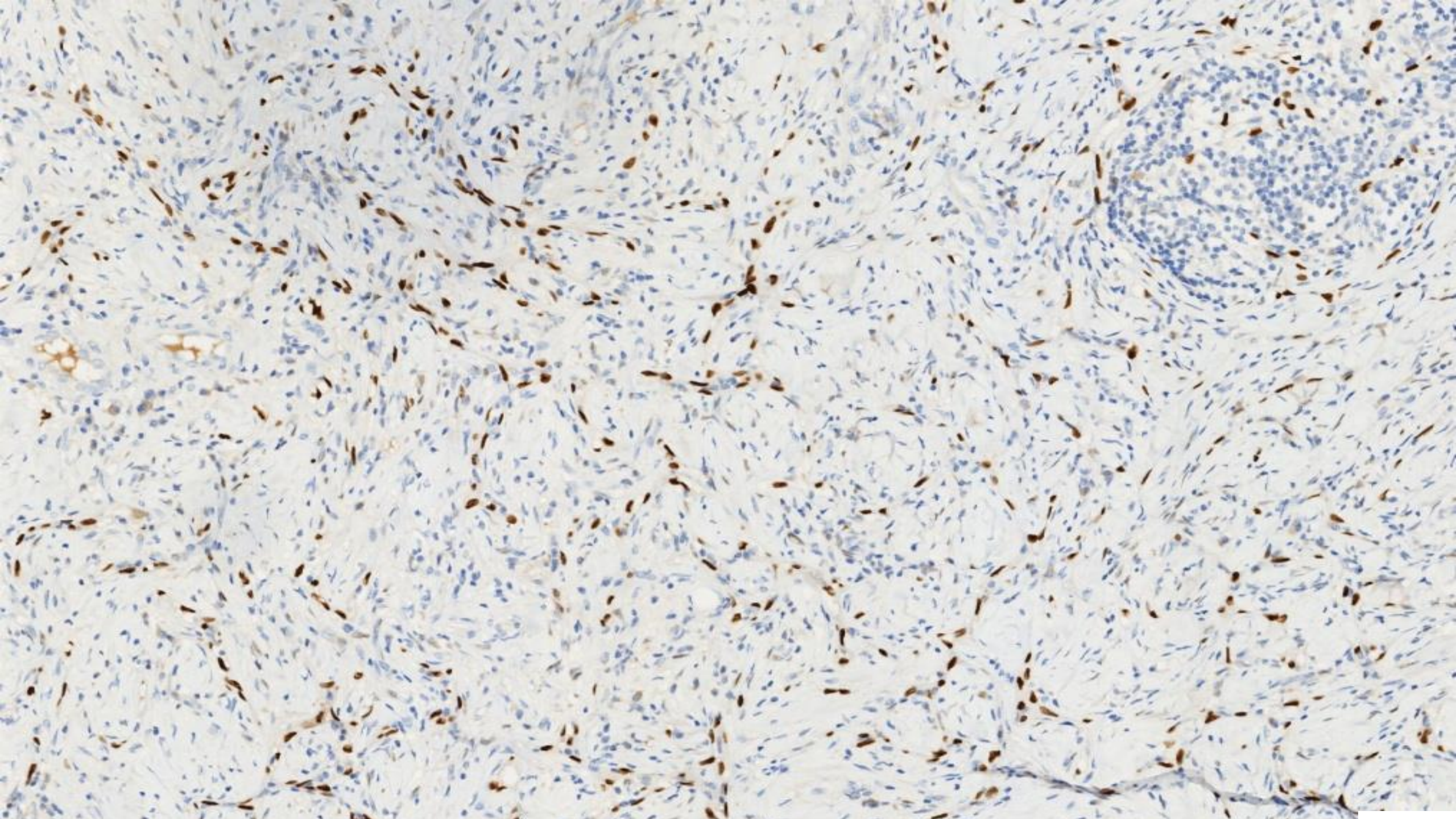
- **Histology: Acantholysis, dyskeratosis, atypical mitotic figures**
- **Decreased intercellular adhesion gives rise to pseudovascular or pseudo-glandular morphology.**
- **Pseudovascular pattern must be distinguished from angiosarcoma.**

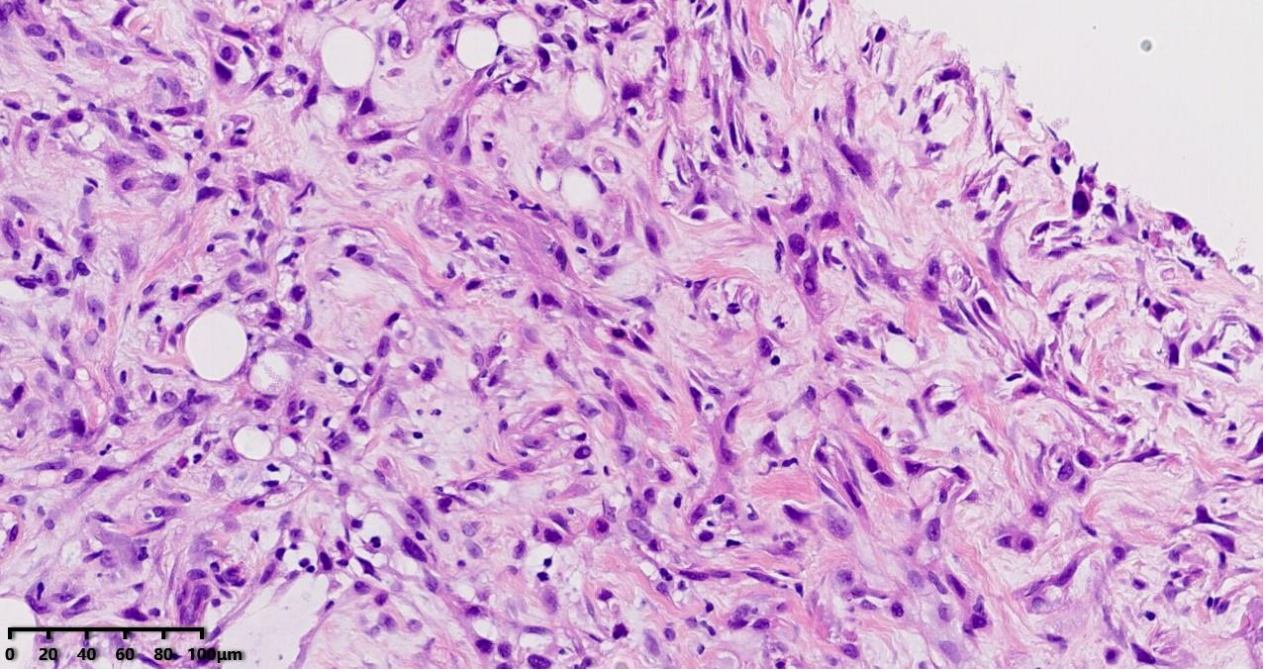


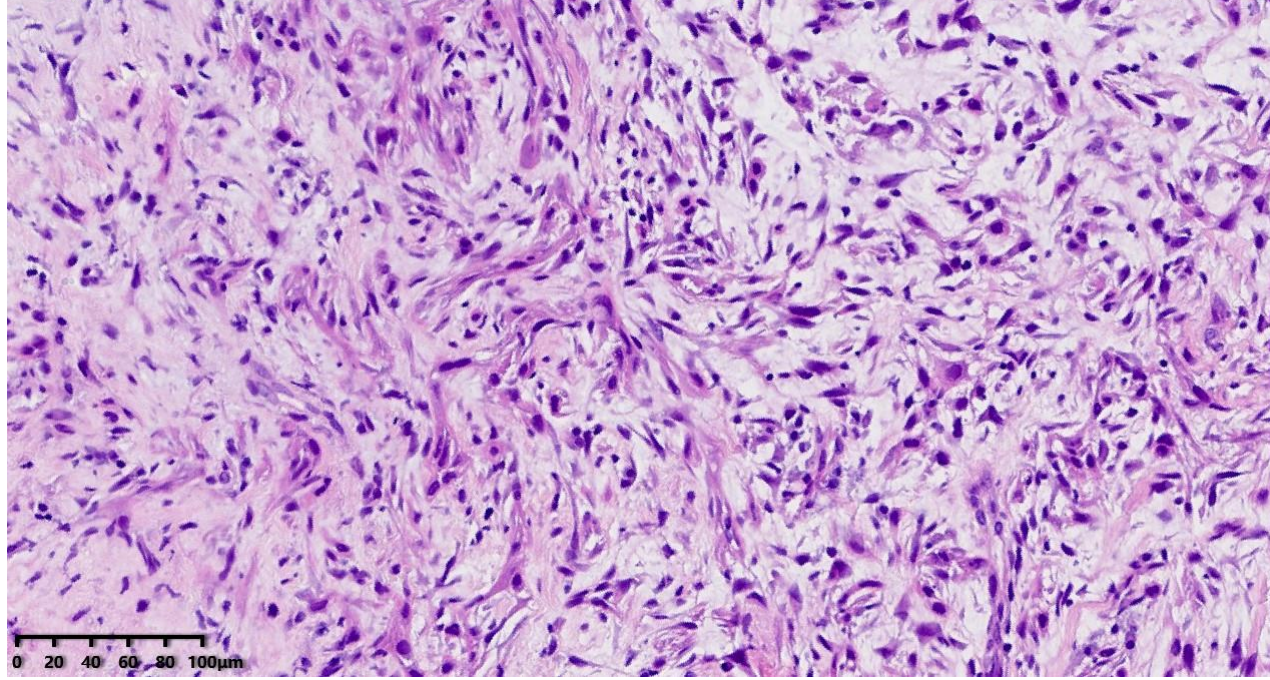



0 40 80 120 160 200µm


AE1/3




0 20 40 60 80 100µm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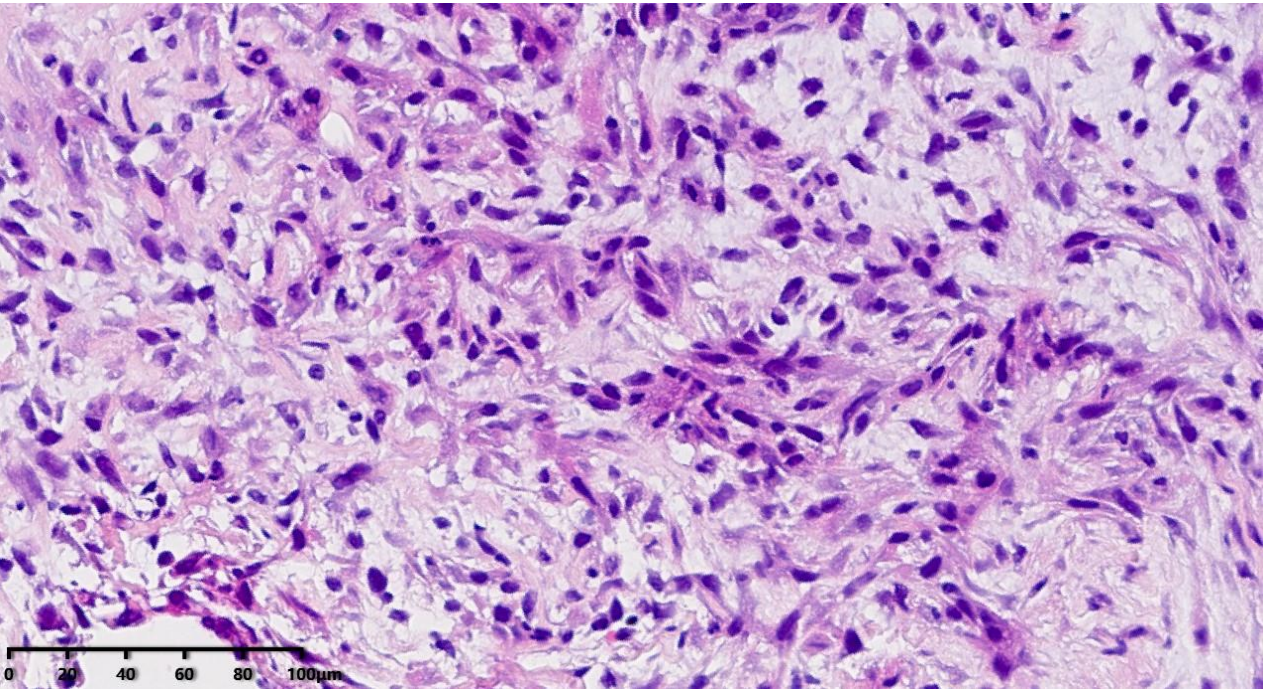
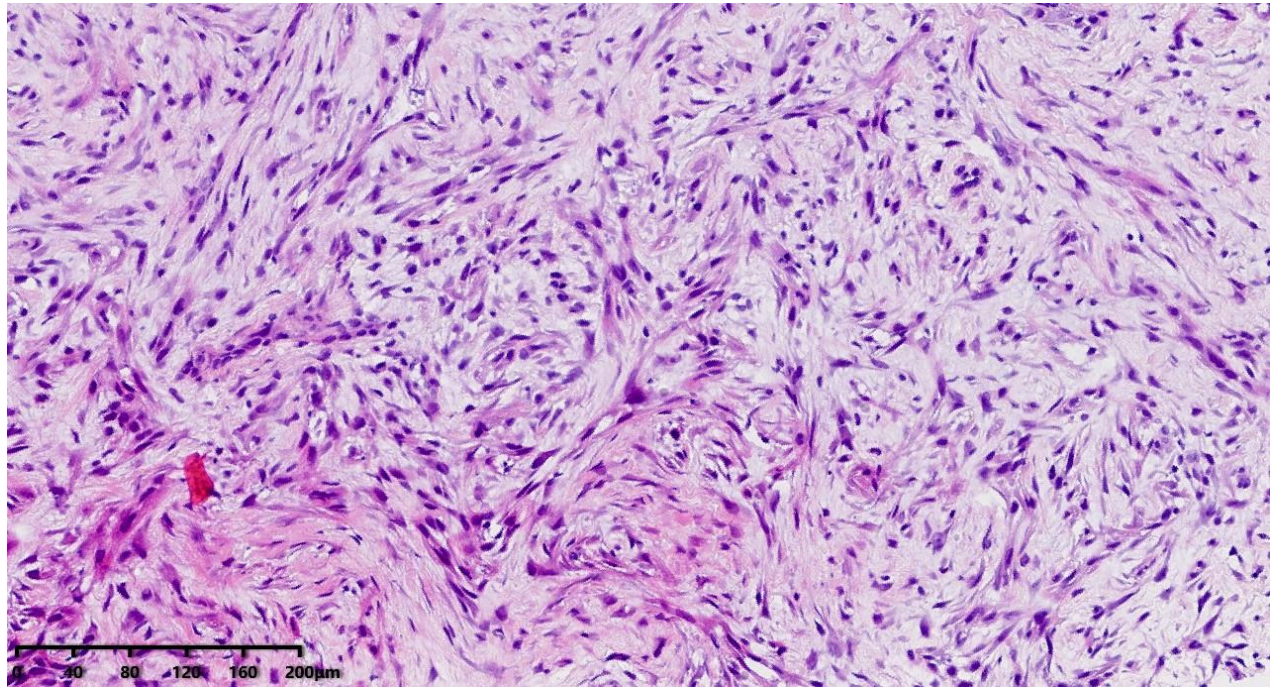
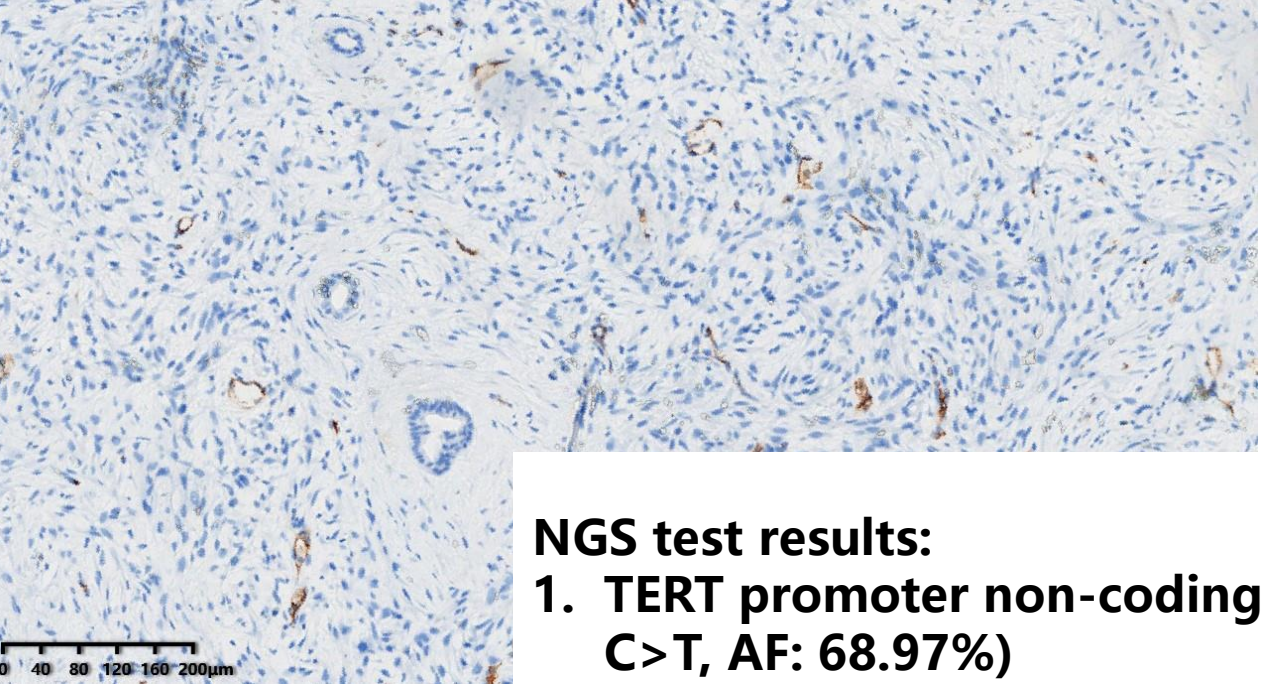
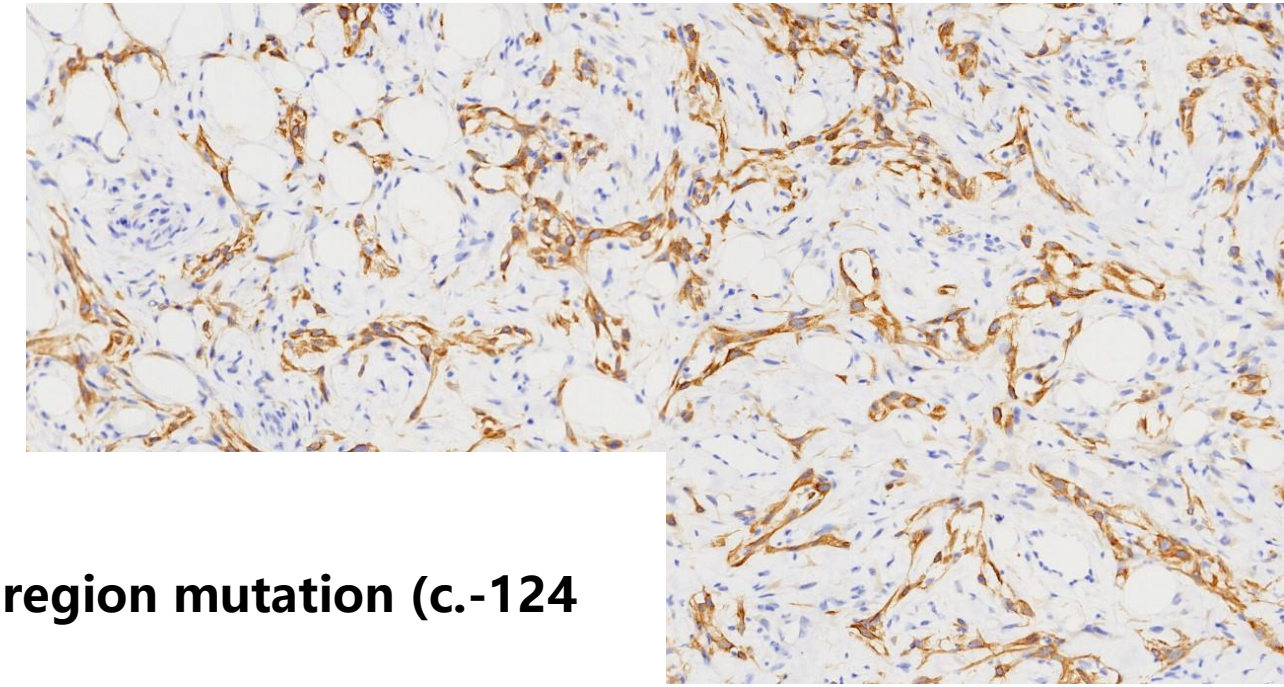

0 20 40 60 80 100µm

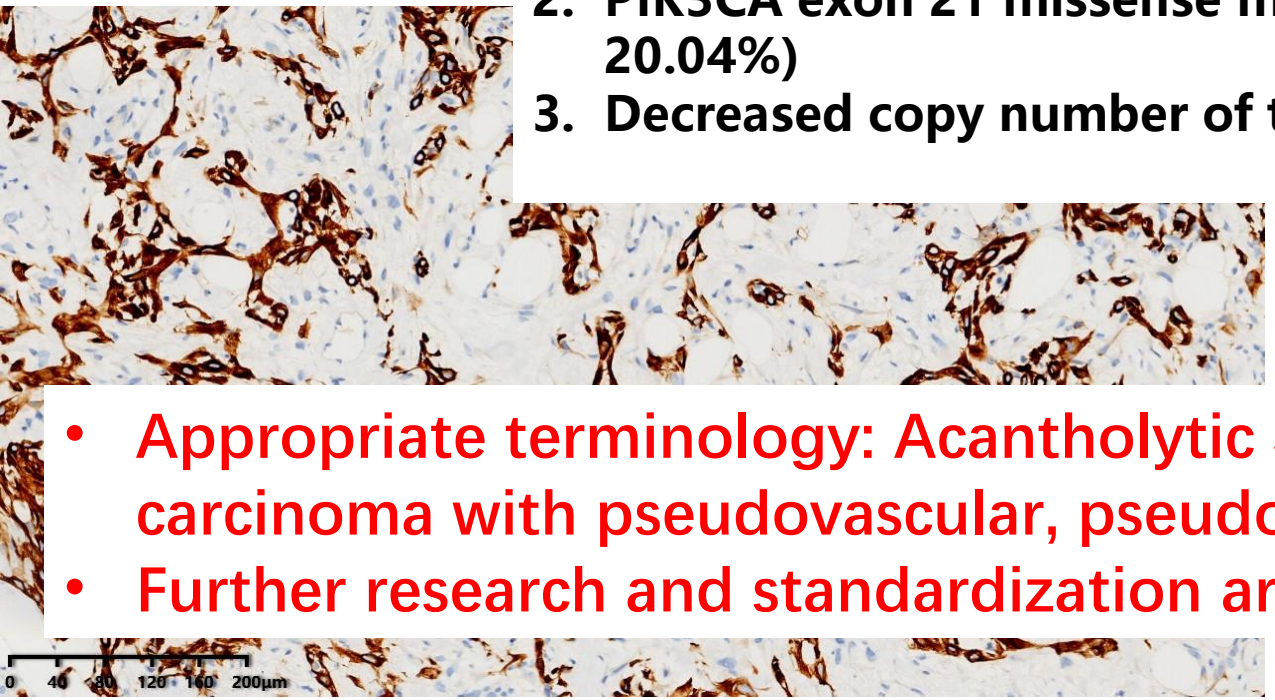

0 40 80 120 160 200µm

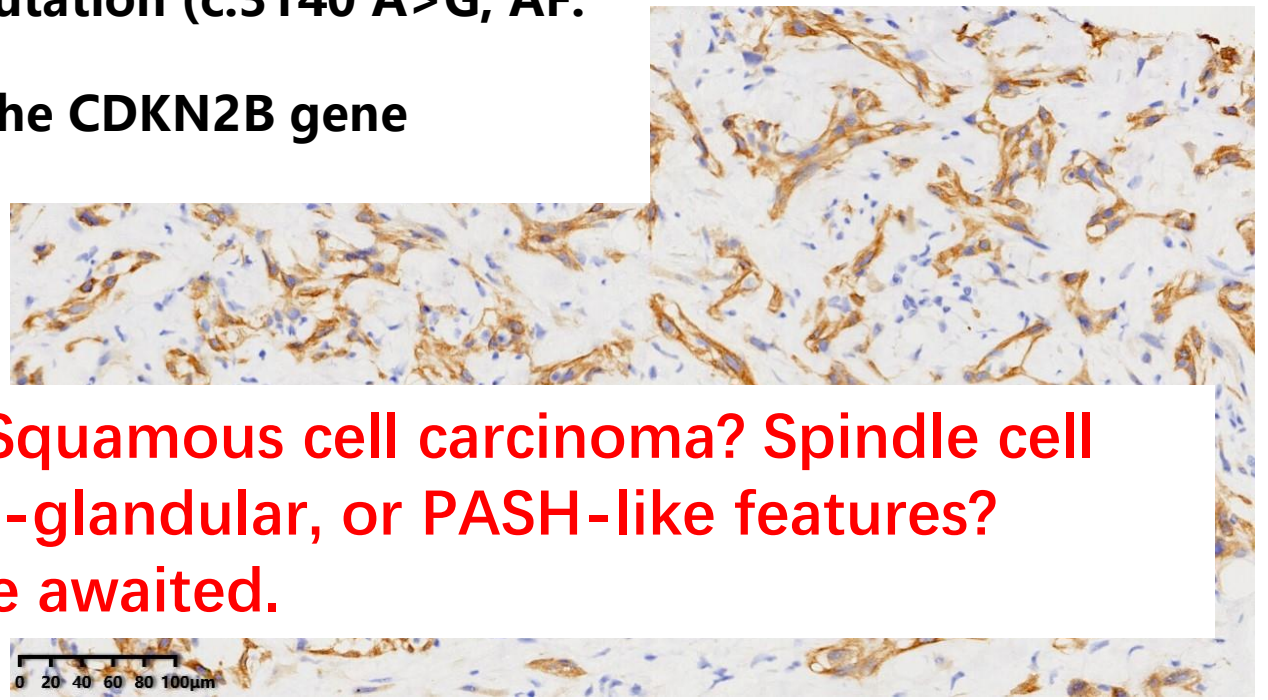




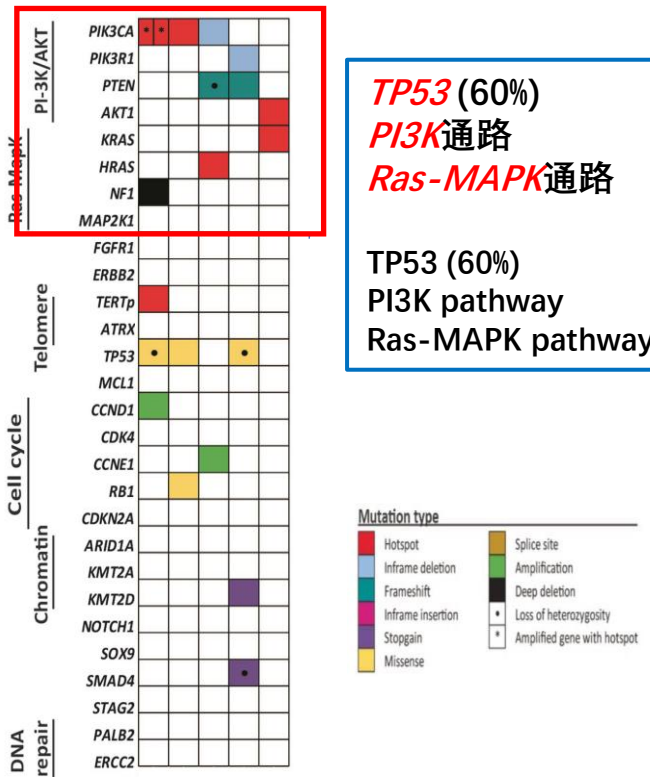
NGS test results:

1. **TERT promoter non-coding region mutation (c.-124 C>T, AF: 68.97%)**
2. **PIK3CA exon 21 missense mutation (c.3140 A>G, AF: 20.04%)**
3. **Decreased copy number of the CDKN2B gene**





- Appropriate terminology: Acantholytic Squamous cell carcinoma? Spindle cell carcinoma with pseudovascular, pseudo-glandular, or PASH-like features?
- Further research and standardization are awaited.

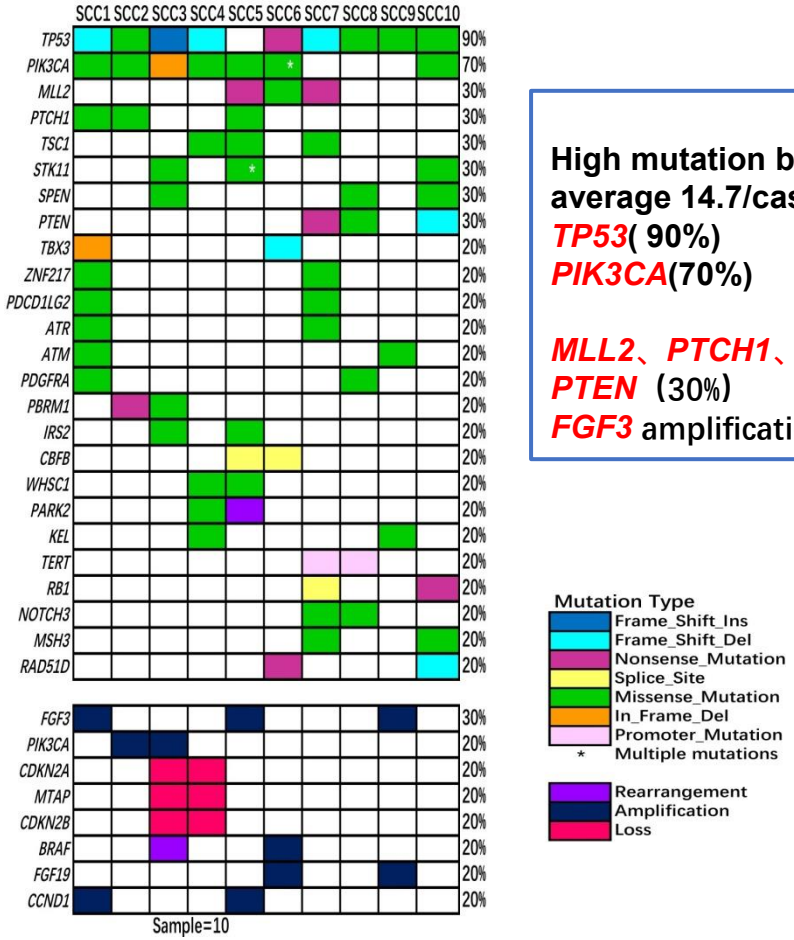


TP53 (60%)
*PI3K*通路
*Ras-MAPK*通路

TP53 (60%)
PI3K pathway
Ras-MAPK pathway

Sample=5

Krings and Chen: *Mod Pathol* 2018;31:1661-74



High mutation burden: 9-29 mutations/case, average 14.7/case
***TP53*(90%)**
***PIK3CA*(70%)**

MLL2*、*PTCH1*、*TSC1*、*STK11*、*SPEN*、*PTEN (30%)
FGF3 amplification**(30%)**

Unpublished Data from the Department of Pathology, Fudan University Shanghai Cancer Center

Int J Clin Exp Pathol 2014;7(8):5203-5209
www.ijcep.com /ISSN:1936-2625/IJCEP0001032

Case Report

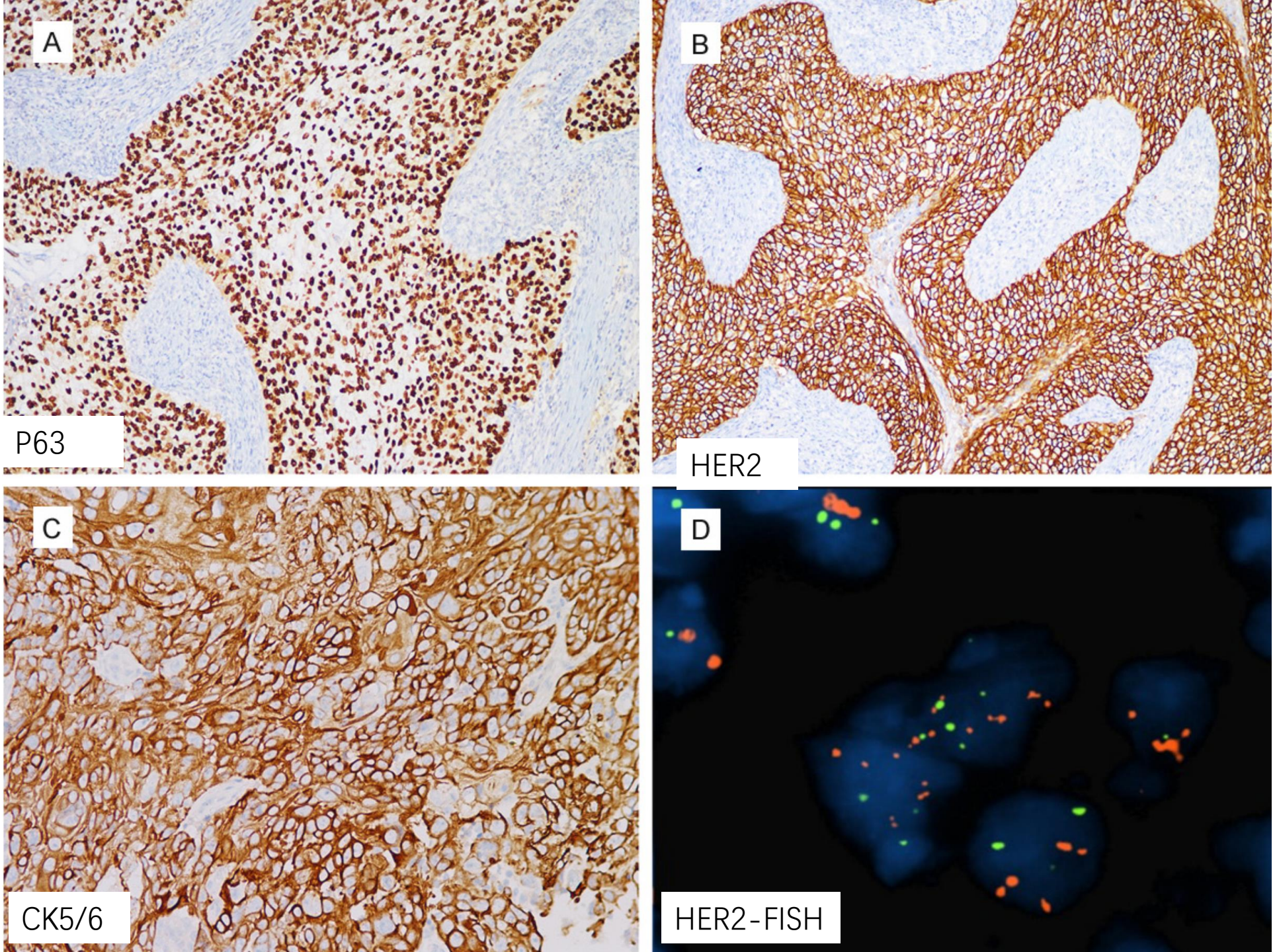
Primary squamous cell carcinoma of the breast with unusual basal-HER2 phenotype

Ruohong Shui*, Anqi Li*, Fei Yang, Xiaoyan Zhou, Baohua Yu, Xiaoli Xu, Wentao Yang

- Between 2009 and 2013
- In totally 25232 cases of invasive breast carcinoma
- 3 cases of 30 pure squamous cell carcinoma
- All 3 cases: ER-, PR-, HER2 amplification

Not all squamous cell carcinomas are triple-negative; approximately 10% are HER2-positive.

Int J Clin Exp Pathol . 2014 Jul 15;7(8):5203-9.

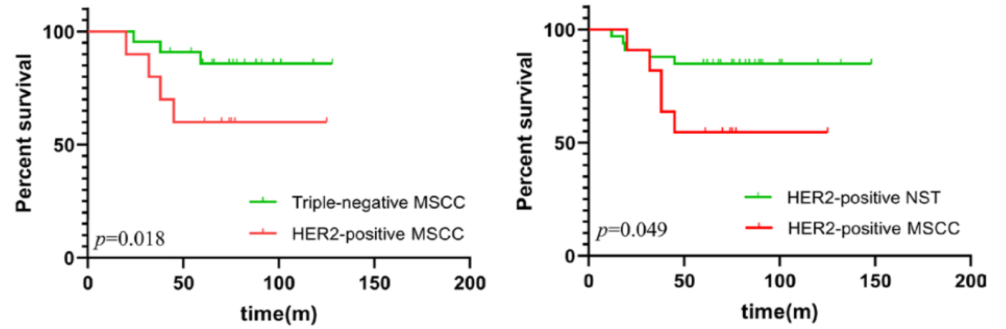

A
P63
B
HER2
C
CK5/6
D
HER2-FISH

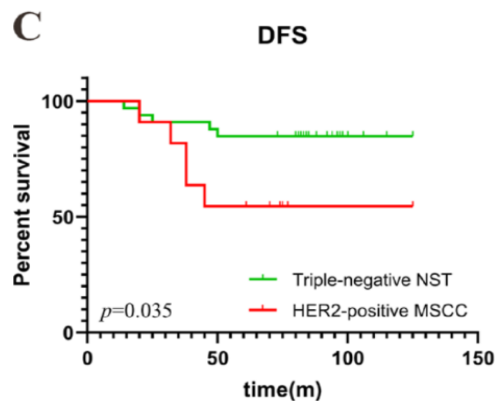
Clinicopathologic characteristics of HER2-positive metaplastic squamous cell carcinoma of the breast

Ting Lei ,[1,2] Tianjie Pu,[1,2] Bing Wei,[1] Yingying Fan,[1] Libo Yang,[1,2] Mengjia Shen,[1,2] Min Chen,[1] Jieliang Yang,[1] Yu Zhang,[1] Zhang Zhang ,[1] Hong Bu[1,2]

Table 2 Patients' demographics and clinicopathologic characteristics of HER2-positive MSCC versus triple-negative MSCC

	HER2-positve MSCC n=13	%	Triple-negative MSCC n=45	%	P value
Age at diagnosis					
Median	55		47		
Range	39–77		30–75		0.277
<50	5	38.5	25	55.6	
≥50	8	61.5	20	44.4	
Position					0.862
Left	7	53.8	23	51.1	
Right	6	46.2	22	47.9	
Tumour size (cm)					0.213
≤5	12	92.3	41	91.1	
>5	1	7.7	4	8.9	
Lymph node involvement					0.675
N	8	61.5	29	64.4	
Y	5	38.5	16	35.6	
Ki-67					0.032*
Ki-67<20%	3	23.1	1	2.2	
Ki-67≥20%	10	76.9	44	97.8	
Menopausal status					0.119
Premenopausal	4	30.8	26	57.8	
Postmenopausal	9	69.2	19	32.2	

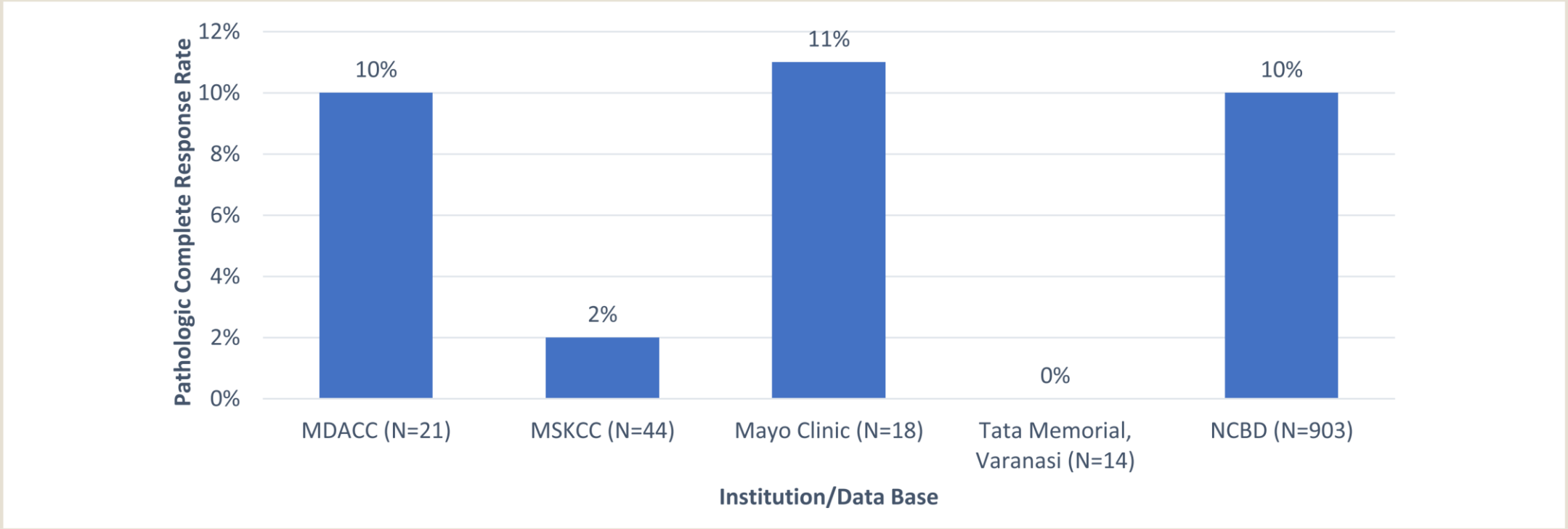




- Only 1 patient received anti-HER2 targeted therapy.
- The prognosis of HER2-positive metaplastic squamous cell carcinoma is worse than that of triple-negative metaplastic squamous cell carcinoma and TNBC-NST.

J Clin Pathol. 2022;75(1):18-23

Figure 3 Pathologic complete response rates to neoadjuvant therapy in single institution and database series.



Abbreviations: MDACC = MD Anderson Cancer Center, MSKCC = Memorial Sloan Kettering Cancer Center NCDB = National Cancer Database.

Metaplastic carcinoma has poor response to traditional adjuvant and neoadjuvant chemotherapy.

Clin Breast Cancer. 2023 Dec;23(8):775-783

Table 2 Reports of Exceptional Responses in Metaplastic Breast Cancer

Class	Novel Agent(s)	MBC Subtypes Described	Responses Described
Immunotherapy and immunotherapy combinations	Durvalumab, pembrolizumab, nivolumab, ipilimumab	Spindle cell (N = 2), Chondromyxoid (N = 1)[53]; Mesenchymal components and osseous differentiation[55] Squamous cell subtype[56]	Prolonged disease control in metastatic disease
PARP Inhibition with deleterious germline BRCA mutations	Talazoparib	Metaplastic chondrosarcomatous carcinoma[57]	Pathologic complete response with single agent neoadjuvant therapy
Anti-angiogenesis	Apatinib	Spindle cell breast carcinoma[58]	Prolonged disease control in metastatic disease
Pathway Inhibition	Buparlisib	Osteoid metaplastic breast cancer[59]	Prolonged disease control in metastatic disease
BRAF inhibition/MEK inhibition combination	Dabrafenib and Trametinib	Metaplastic carcinoma with melanocytic differentiation; BRAF mutation present[60]	Partial response and symptom control for one cycle in advanced disease

Abbreviations: MBC = metaplastic breast cancer; PARP = poly-ADP ribose polymerase.

Clin Breast Cancer. 2023 Dec;23(8):775-783

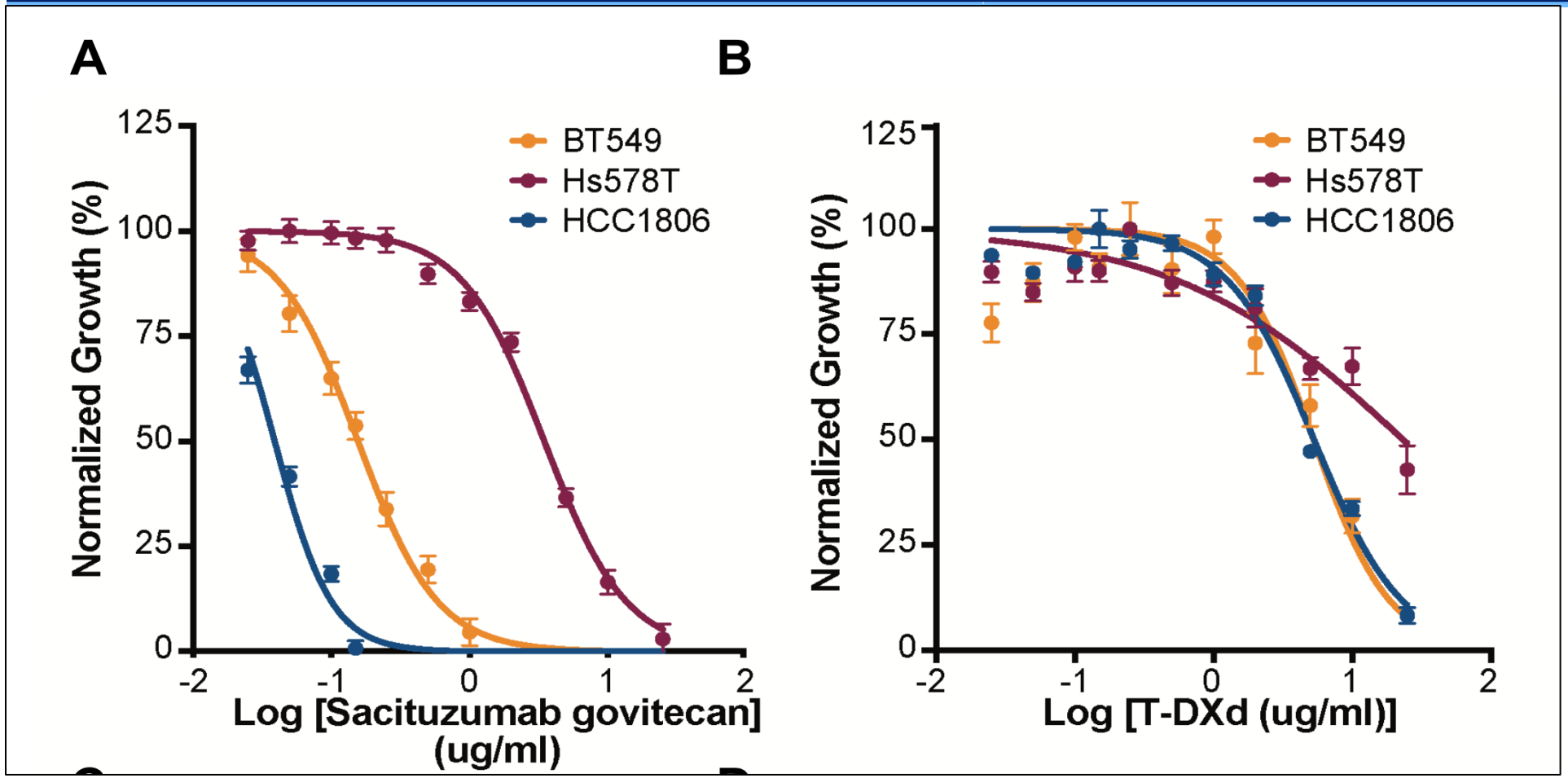
Memorial Sloan Kettering Cancer Center

Metaplastic Breast Cancer: Whole Genome Sequencing Analysis and Emerging Therapeutic Targets

Fresia Pareja[1], Andrea Gazzo[1], Higinio Dopeso[1], David N. Brown[1], Pier Selenica[1], Yingjie Zhu[1], Juan Blanco[1], Laxmi Gusain[1], Xin Pei[2], Giacomo Montagna[3], Nour Abuhadra[4], Hannah Wen[1], Edi Brogi[1], Nadeem Riaz[2], Sarat Chandarlapaty[4], Maurizio Scaltriti[1], Larry Norton[4], Simon Powell[2], Jorge S. Reis-Filho[1*], Britta Weigelt[1]

[1]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY USA. [2]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY USA. [3]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY USA. [4]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY USA *Current affiliation: AstraZeneca

San Antonio Breast Cancer Symposium®- December 5-9, 2023



Therapeutic Targets: Metaplastic carcinoma expresses HER2 and TROP2.
Preclinical Efficacy: Cell line studies demonstrate tumor sensitivity to the respective antibody-drug conjugates, trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan.

Metaplastic Carcinoma: Histological Subtypes and Clinical Prognosis

Favorable Prognosis

- Low-grade adenosquamous carcinoma
- Fibromatosis-like spindle cell carcinoma

Poor Prognosis

- Squamous cell carcinoma
- Spindle cell carcinoma
- Metaplastic carcinoma with mesenchymal differentiation
- Mixed metaplastic carcinoma

Metaplastic carcinomas represent a heterogeneous group of tumors characterized by distinct morphological patterns and diverse clinical outcomes.

- **MBC is characterized by frequent mutations in PIK3CA, TP53, and TERT promoter.**
- **Each histological subtype possesses distinct genetic alterations.**

Squamous Cell Carcinoma	Spindle Cell Carcinoma	Fibromatosis-like Spindle Cell Carcinoma	Matrix producing carcinoma
High Frequency of TP53 Mutations（90%）	Lack of TP53 mutation		High Frequency of TP53 Mutations（100%）
High Frequency of PIK3CA Mutations（SCC 70%，SpCC80%，FLSCC75%）			Lack of PI3K pathway variation
Low TERT promoter mutation	High Frequency of TERT promoter Mutations（SpCC80%，FLSCC75%）		Lack of TERT promoter mutation
High mutation burden	HRAS mutation（60%） ATM mutation（40%） MTAP deletion（80%） CDKN2A deletion（80%） CDKN2B deletion（80%）	Lack of all other mutations in spindle cell carcinoma	BRCA1(67%) CDKN2A deletion（67%） RAD21 amplification（67%）

Conclusion

- **Highly Heterogeneous**: Metaplastic carcinoma encompasses a diverse group of tumors with varying morphology, pathogenesis, and outcomes.
- **Accurate Subtyping is Crucial**: Precise histological diagnosis is essential for guiding management.
- **Low-Grade Disease**: A conservative treatment approach is often appropriate.
- **High-Grade Disease**: Poor response to conventional chemotherapy; warrants exploration of targeted and immunotherapy.


Thank you