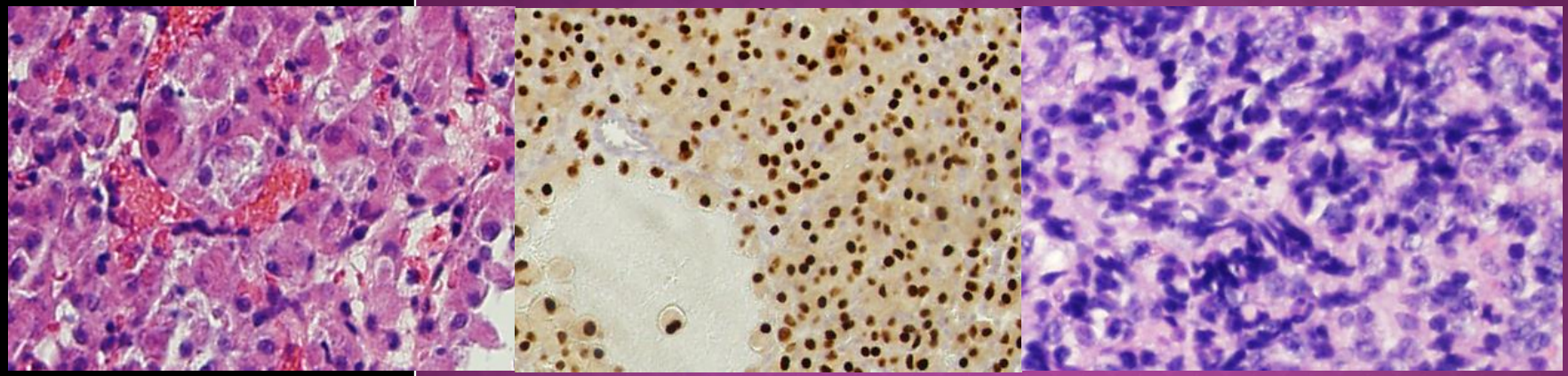
SURPRISE!

BREAST TUMORS WITH UNEXPECTED FINAL PATHOLOGY



Rachel Factor, MD

28th Annual Park City Pathology Update

Tuesday, Feb 10th, 2015

OBJECTIVES

- **Part I**
  - Review Lobular carcinoma and variants
  - Mimics of lobular carcinoma
  - W/u of primary vs metastatic disease

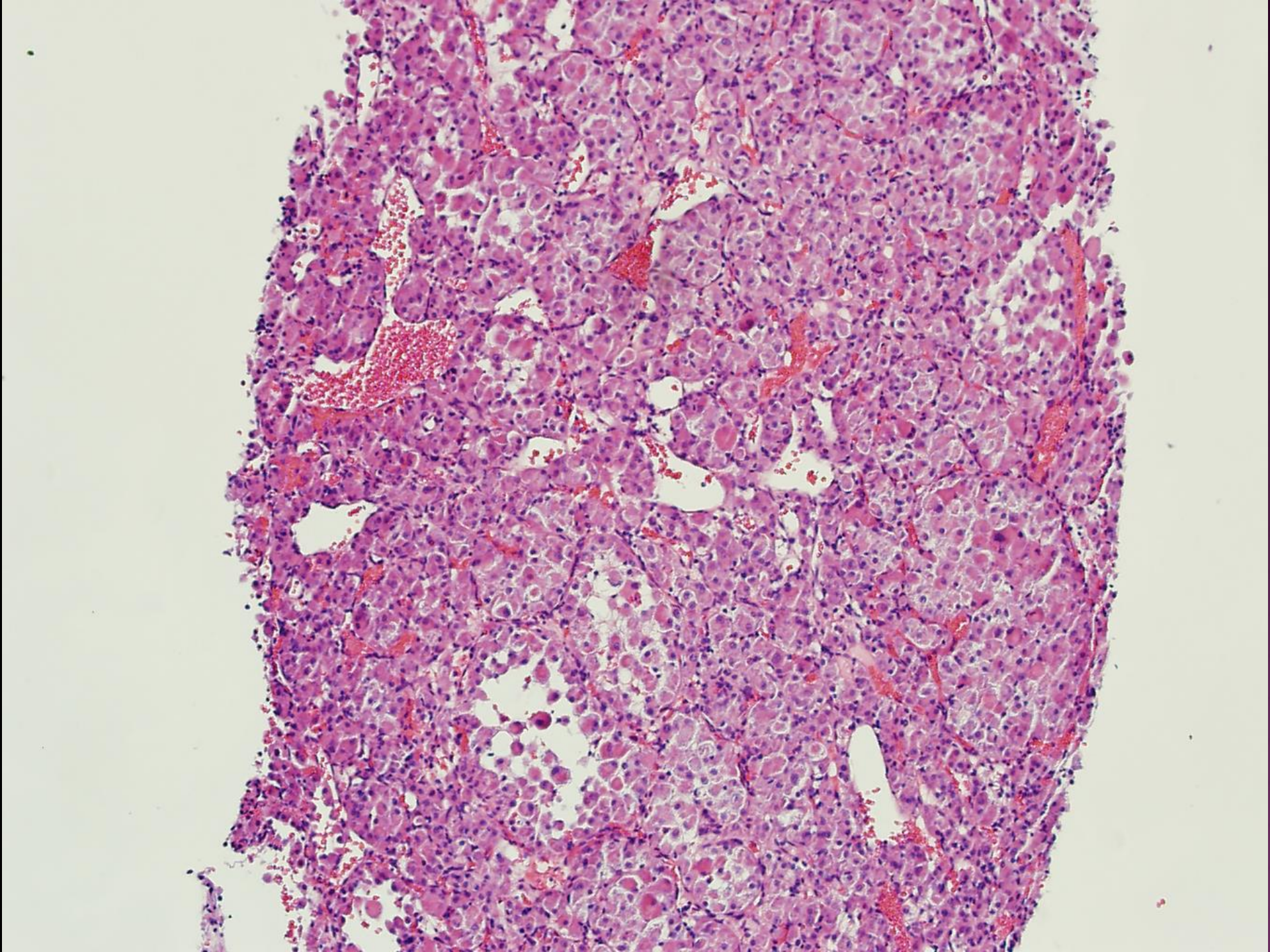
- **Part II**
  - Review classification of neuroendocrine tumors of the breast
  - Review primary vs metastatic
  - Rare tumors of the breast: Small cell carcinoma and Adenoid cystic carcinoma

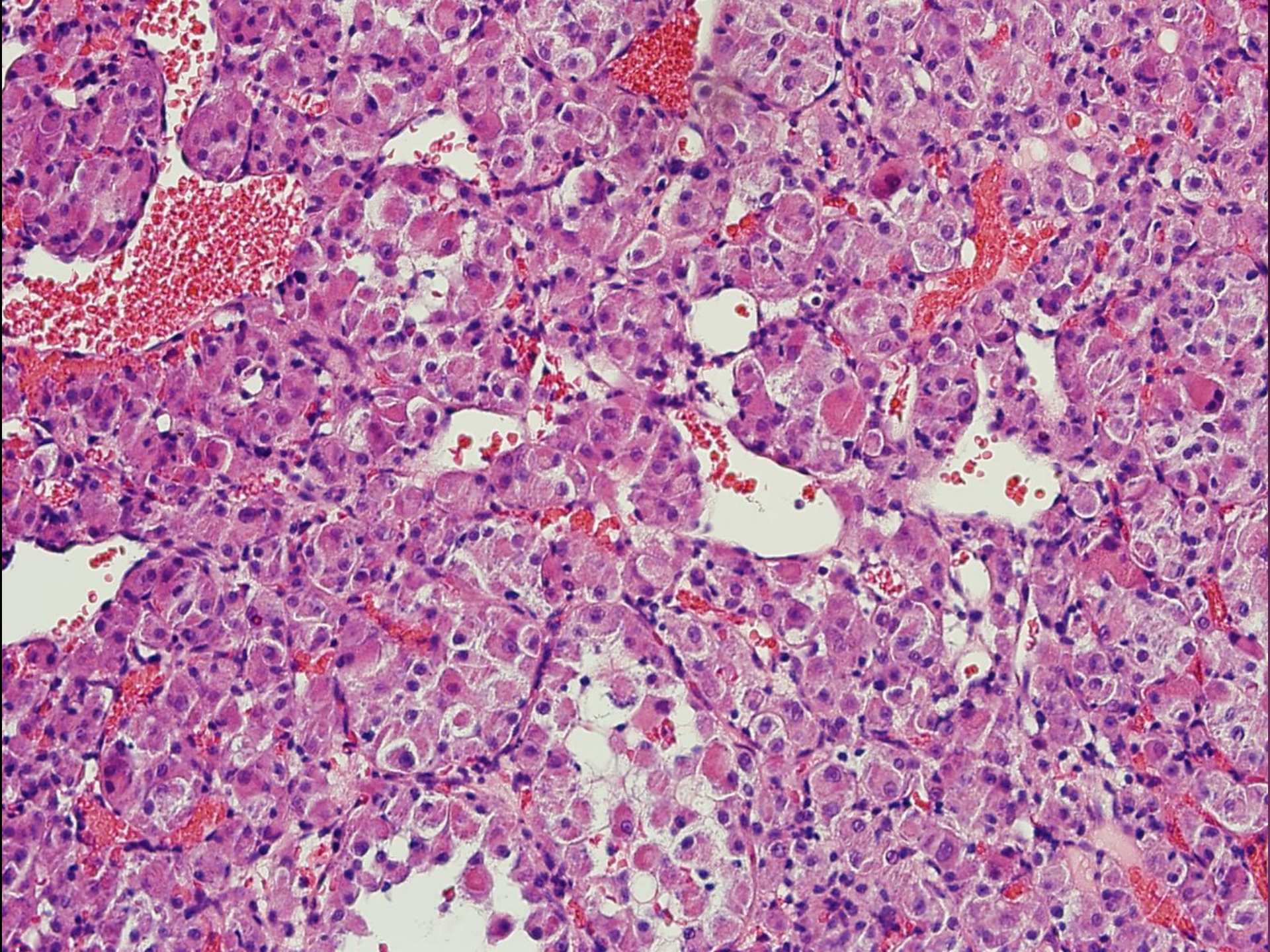
PART 1

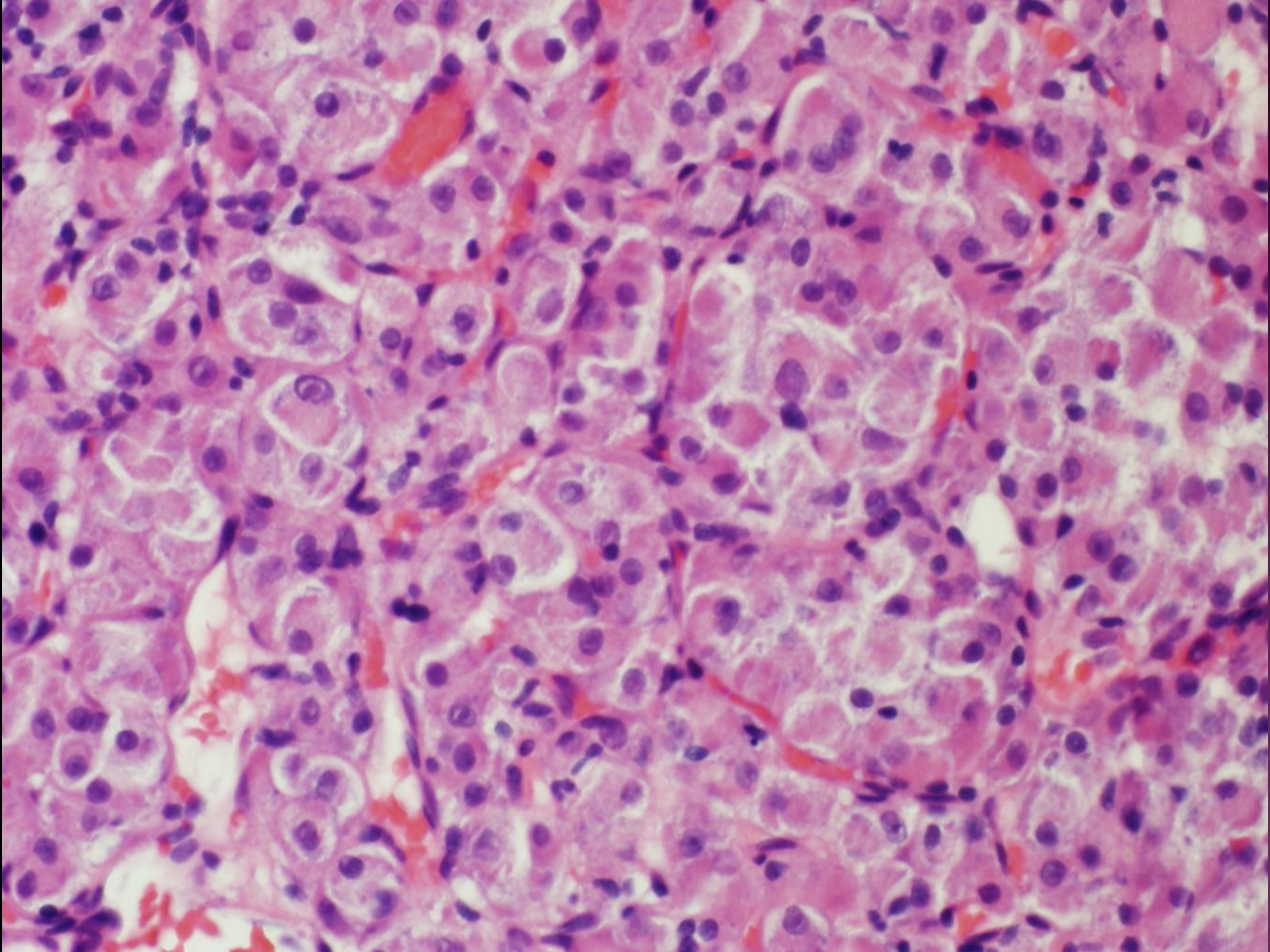
- Two cases with similar morphology but different origins

FIRST CASE

- 29 yo woman, pregnant
- Palpable breast mass
- U/S: 1.6cm mass at 9:00, 8cm from nipple
- Biopsy performed

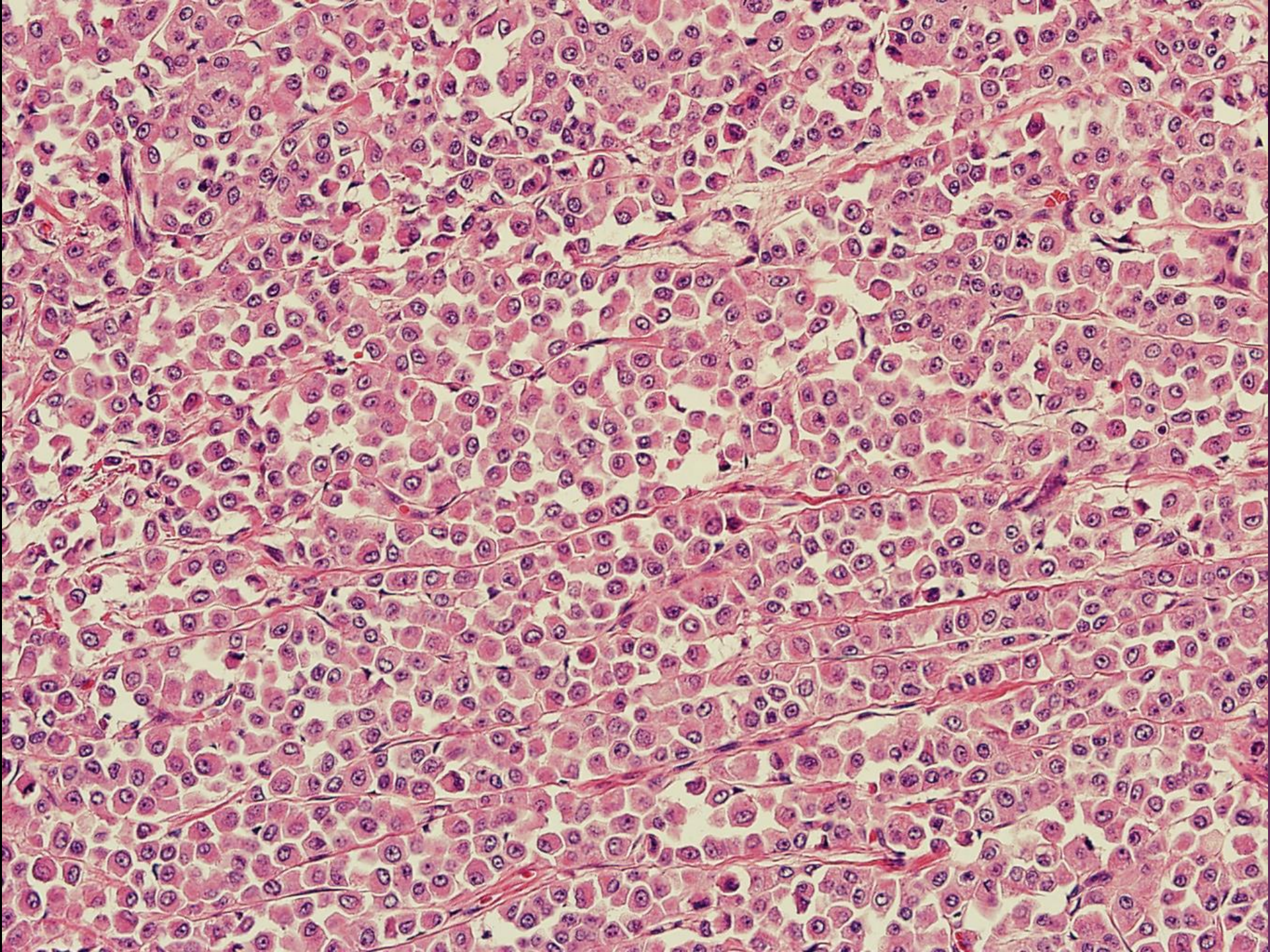


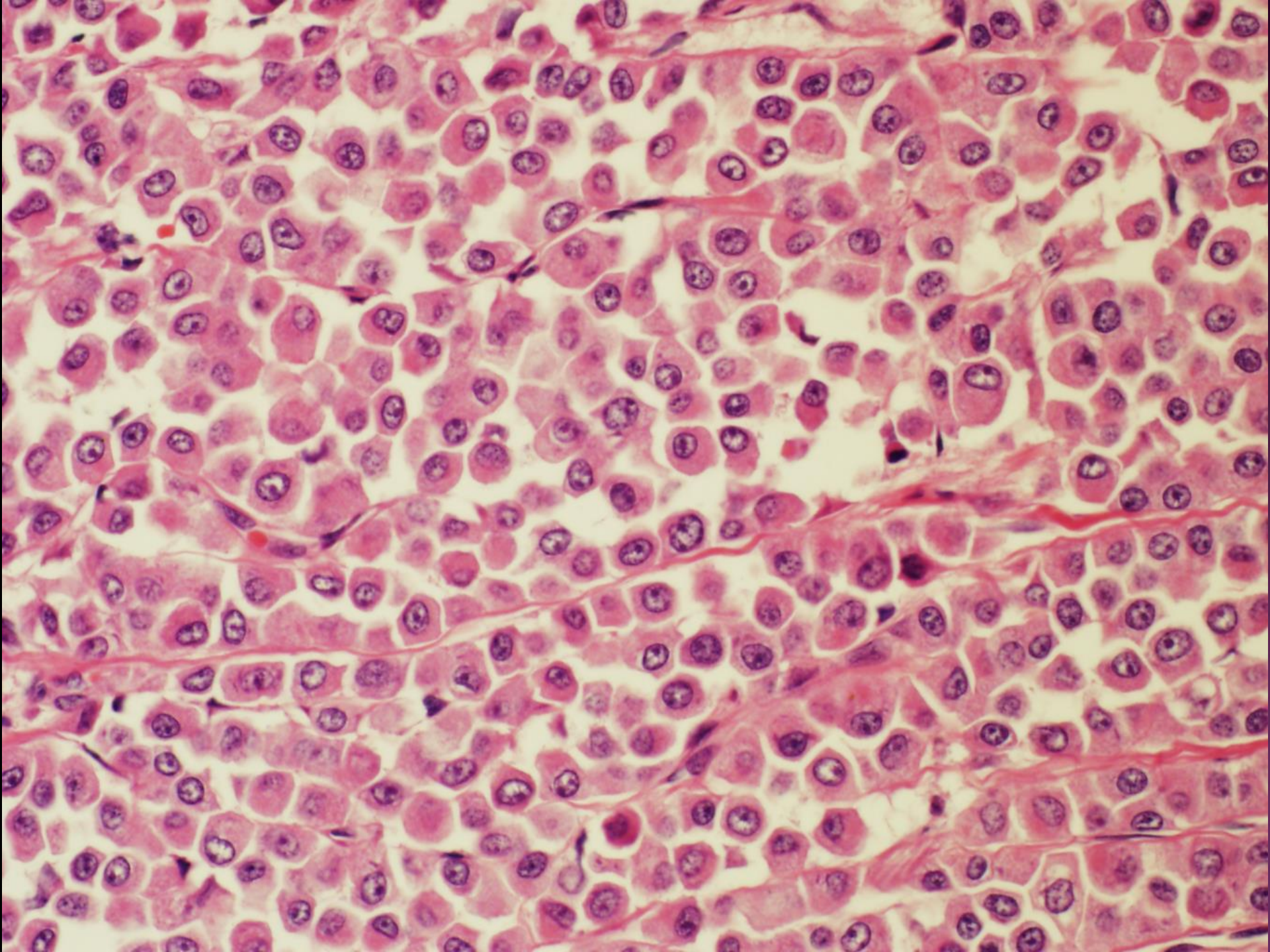




SECOND CASE

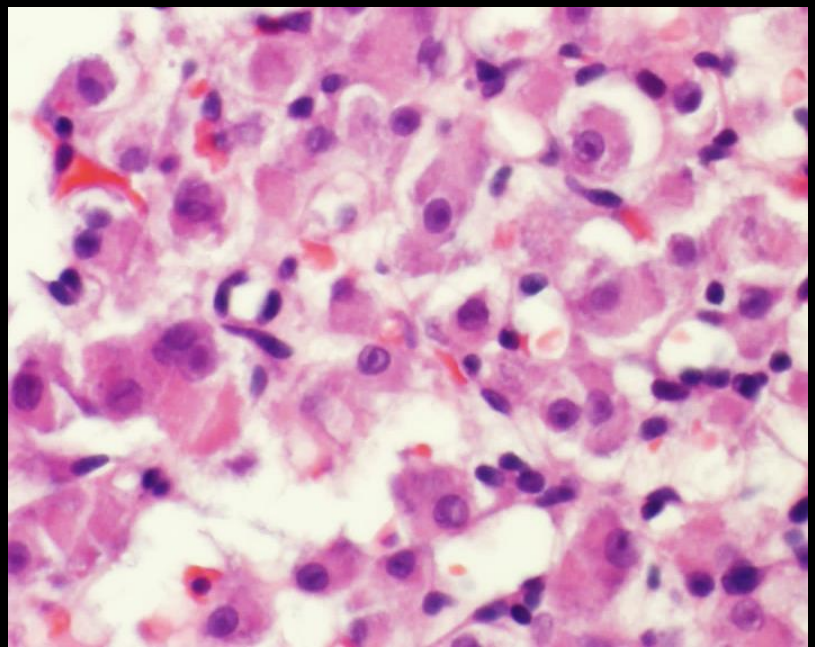
- 70 year old woman
- 2 masses in the right breast
- Biopsy-proven malignancy
- Excision performed



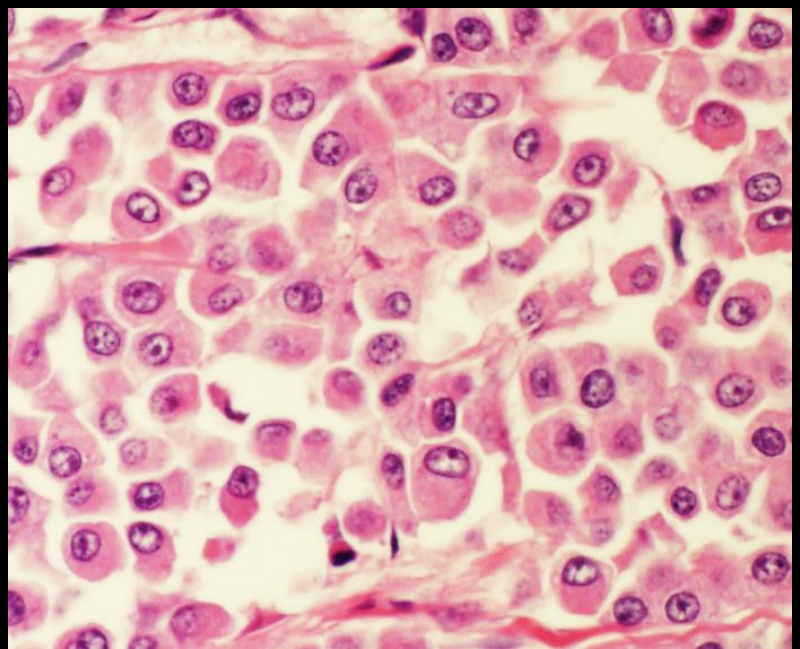


SIMILAR MORPHOLOGY

Case 1



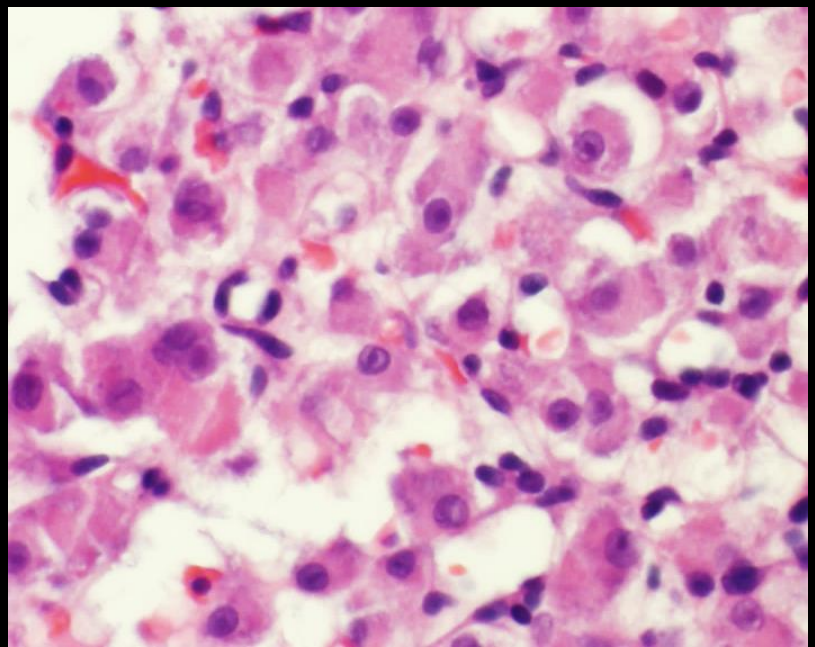
Case 2



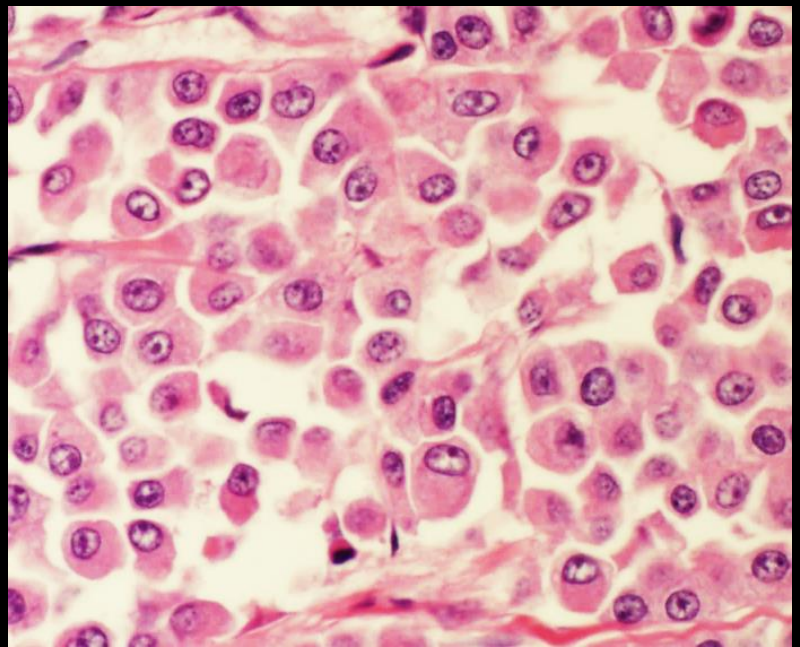
SURPRISE!

- One case is invasive lobular breast carcinoma
- One is a metastatic tumor

Case 1

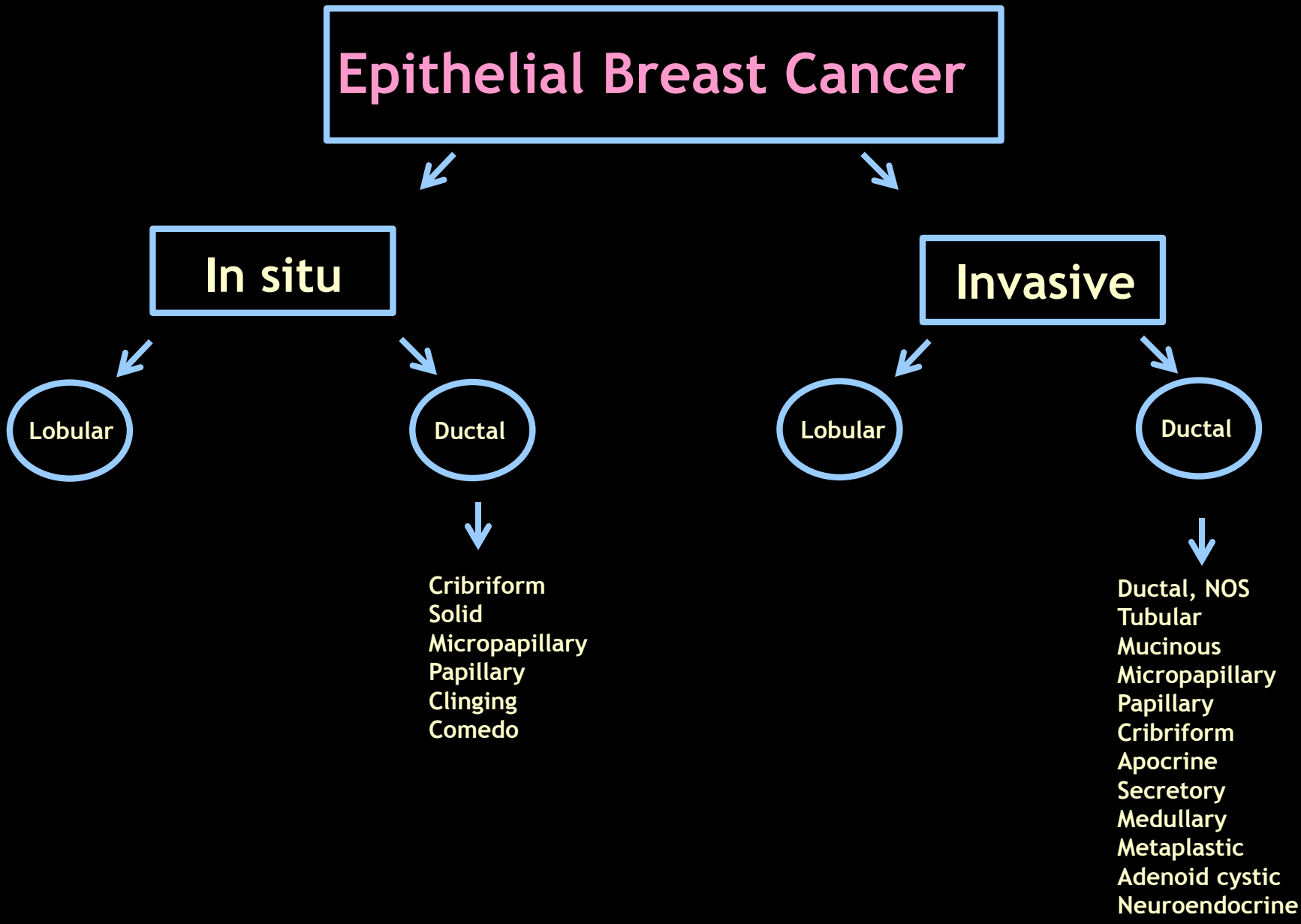


Case 2



INVASIVE LOBULAR CARCINOMA AND ITS MIMICS

- Lobular carcinoma and variants
- Mimics of lobular carcinoma
- Review w/u primary vs metastatic disease

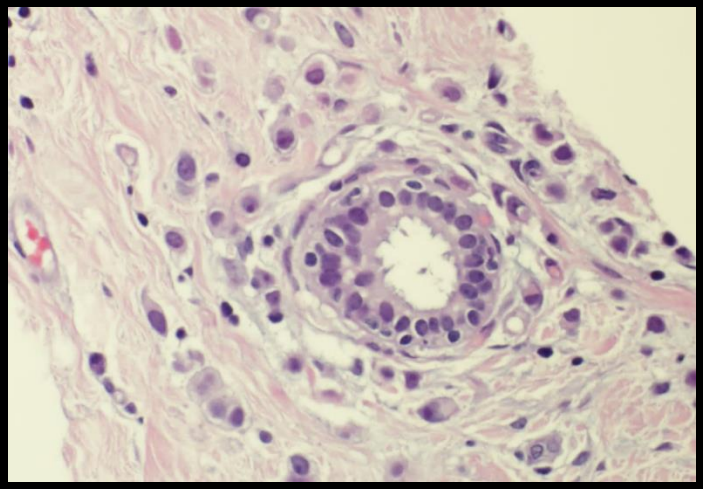

Epithelial Breast Cancer
In situ
Invasive
Lobular
Ductal
Lobular
Ductal
Cribriform
Solid
Micropapillary
Papillary
Clinging
Comedo
Ductal, NOS
Tubular
Mucinous
Micropapillary
Papillary
Cribriform
Apocrine
Secretory
Medullary
Metaplastic
Adenoid cystic
Neuroendocrine

INVASIVE LOBULAR CARCINOMA

- 5-15% of invasive breast carcinomas
- Frequently multifocal in ipsilateral breast
- Some reports of increased incidence of breast cancer in contralateral breast
- Palpable mass or mammographic or u/s abnormality, but may be subtle
- Mass may not be identifiable grossly

INVASIVE LOBULAR HISTOLOGY

- Classic type + variants:
  - Loosely cohesive cells
  - Intracytoplasmic lumina with eosinophilic mucin and eccentrically placed nuclei
  - Linear growth
  - Concentric growth pattern around ducts



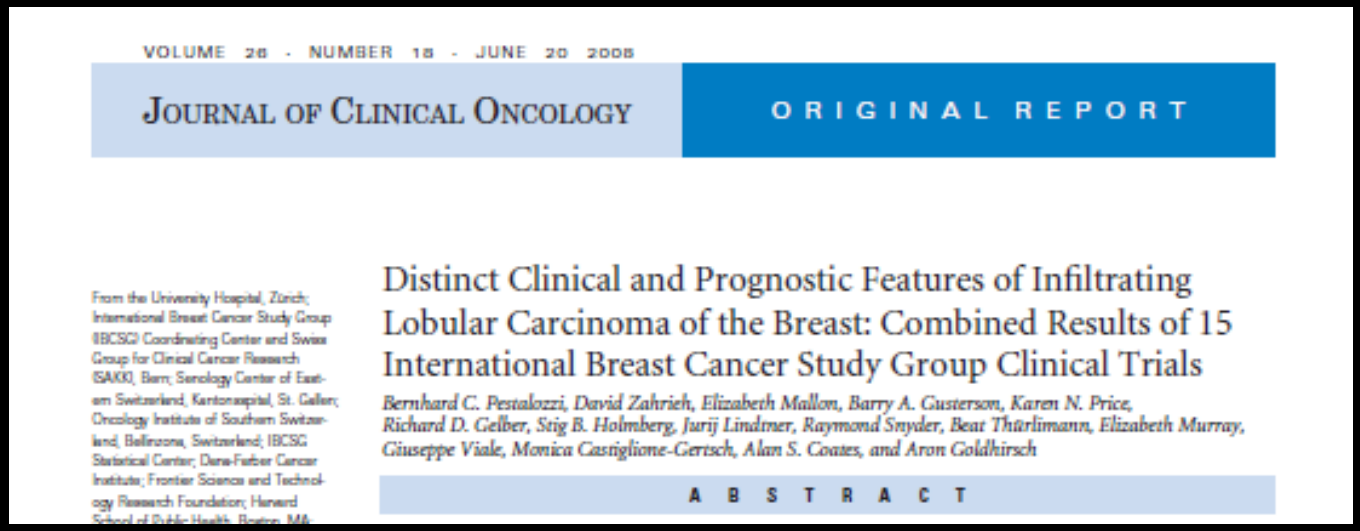
LOBULAR VS DUCTAL

- Lobular
  - Shows loss of E-cadherin
  - Usually ER/PR+
  - Rarely HER2+
  - Less likely to show lymphovascular invasion
  - Poor response to chemotherapy
  - Negative margin status difficult to achieve
  - Mets: bone, GI, meninges, ovary, serosa

LOBULAR VS DUCTAL

- Ductal
  - ER/PR/HER2 varies
  - Variable response to chemotherapy
  - Margin status varies
  - Mets: more likely to lung

- Ultimate question:
  - Is there is a prognostic difference?
  - It’s complicated!



VOLUME 26 · NUMBER 18 · JUNE 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Distinct Clinical and Prognostic Features of Infiltrating Lobular Carcinoma of the Breast: Combined Results of 15 International Breast Cancer Study Group Clinical Trials

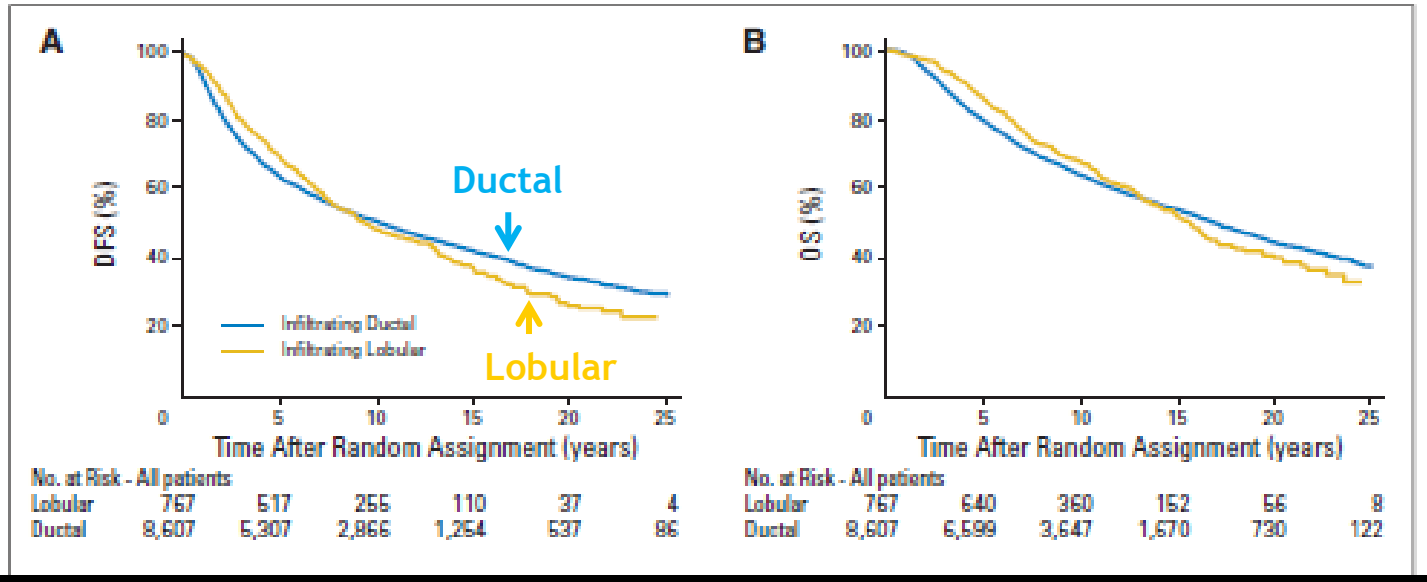
Bernhard C. Pestalozzi, David Zahrieh, Elizabeth Mallon, Barry A. Gusterson, Karen N. Price, Richard D. Gelber, Stig B. Holmberg, Jurij Lindtner, Raymond Snyder, Beat Thürlimann, Elizabeth Murray, Giuseppe Viale, Monica Castiglione-Gertsch, Alan S. Coates, and Aron Goldhirsch

From the University Hospital, Zürich; International Breast Cancer Study Group (IBCSG) Coordinating Center and Swiss Group for Clinical Cancer Research (SAKK), Bern; Senology Center of Eastern Switzerland, Kantonsspital, St. Gallen; Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; IBCSG Statistical Center; Dana-Farber Cancer Institute; Frontier Science and Technology Research Foundation; Harvard

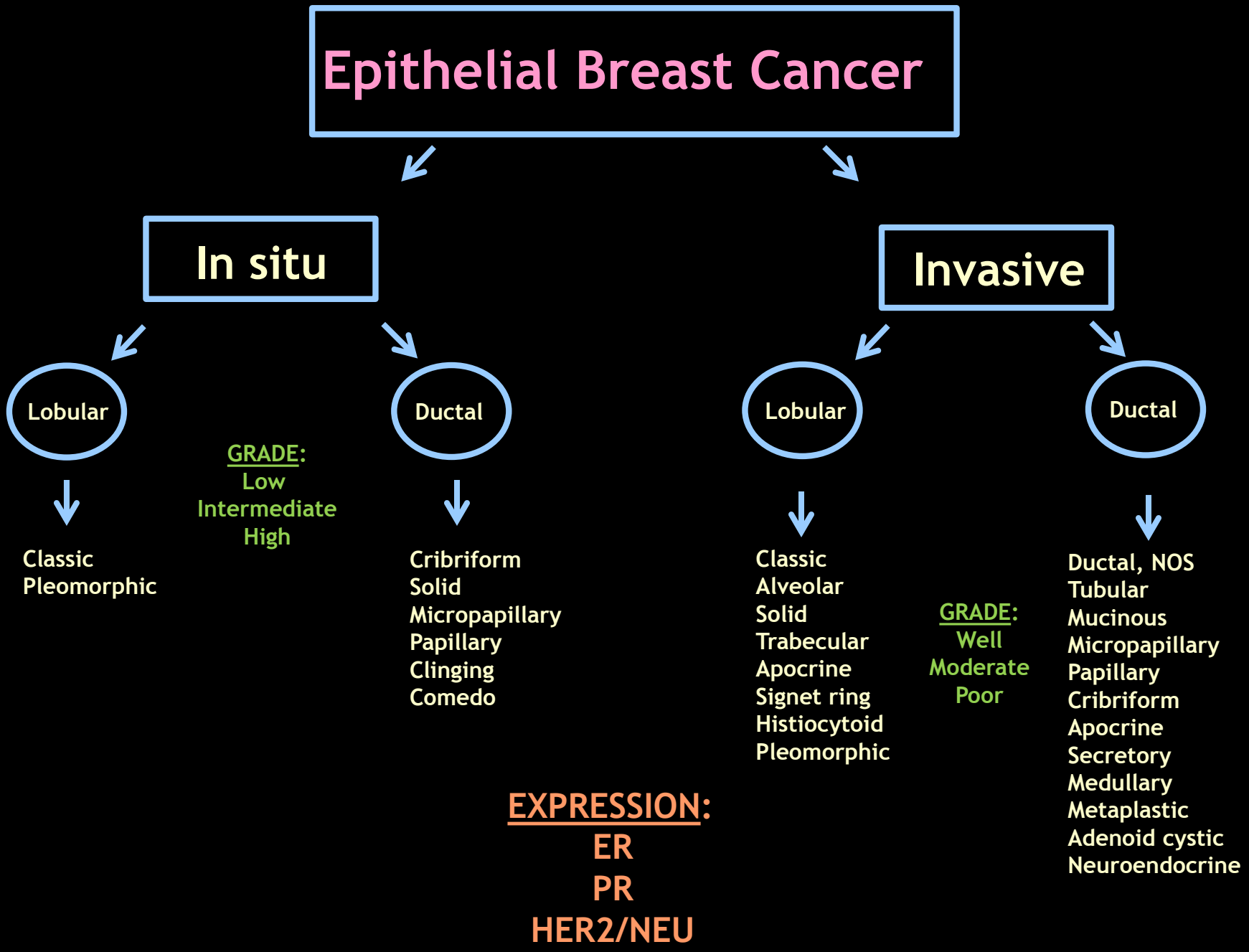
ABSTRACT

- Retrospective
- Patients enrolled in the International Breast Cancer Study Group Clinical Trial 1978-2002
- 9,374 patients with either pure IDC or ILC
- Median follow-up of 13 years

Disease Free Survival (DFS) and Overall Survival (OS)



- Within the first 10 years, risk of death was 16% lower for ILC than IDC.
- After 10 years, risk of death was 50% higher for ILC than IDC.


Epithelial Breast Cancer
In situ
Invasive
Lobular
Ductal
Lobular
Ductal
GRADE:
Low
Intermediate
High
Classic
Pleomorphic
Cribriform
Solid
Micropapillary
Papillary
Clinging
Comedo
Classic
Alveolar
Solid
Trabecular
Apocrine
Signet ring
Histiocytoid
Pleomorphic
GRADE:
Well
Moderate
Poor
Ductal, NOS
Tubular
Mucinous
Micropapillary
Papillary
Cribriform
Apocrine
Secretory
Medullary
Metaplastic
Adenoid cystic
Neuroendocrine
EXPRESSION:
ER
PR
HER2/NEU

INVASIVE LOBULAR VARIANTS

- Based on architecture and cytology
- Architecture:
  - Classic
  - Solid
  - Alveolar
  - Trabecular
- Cytology:
  - Signet ring
  - Apocrine
  - Histiocytoid
  - Pleomorphic

Breast Cancer Res Treat (2012) 133:713–723
DOI 10.1007/s10549-012-2002-z

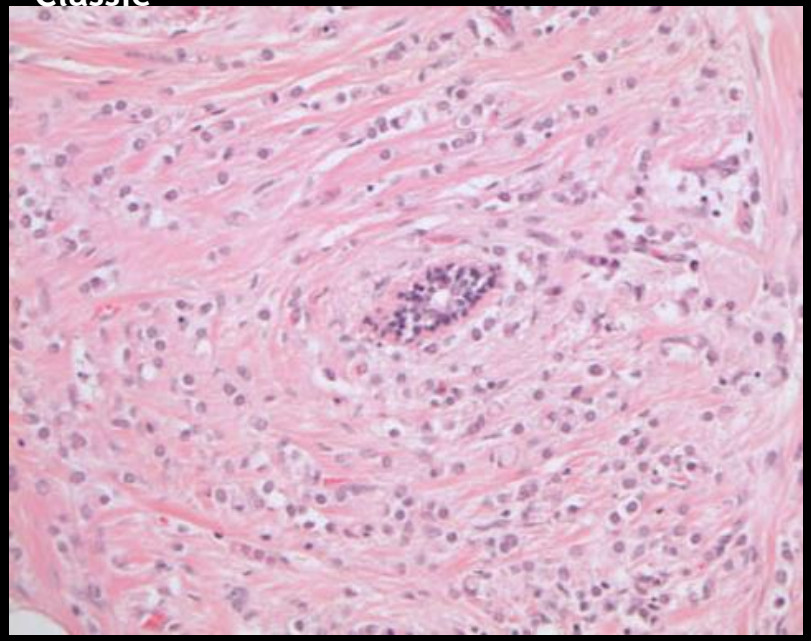
CLINICAL TRIAL

Invasive lobular breast cancer: subtypes and outcome

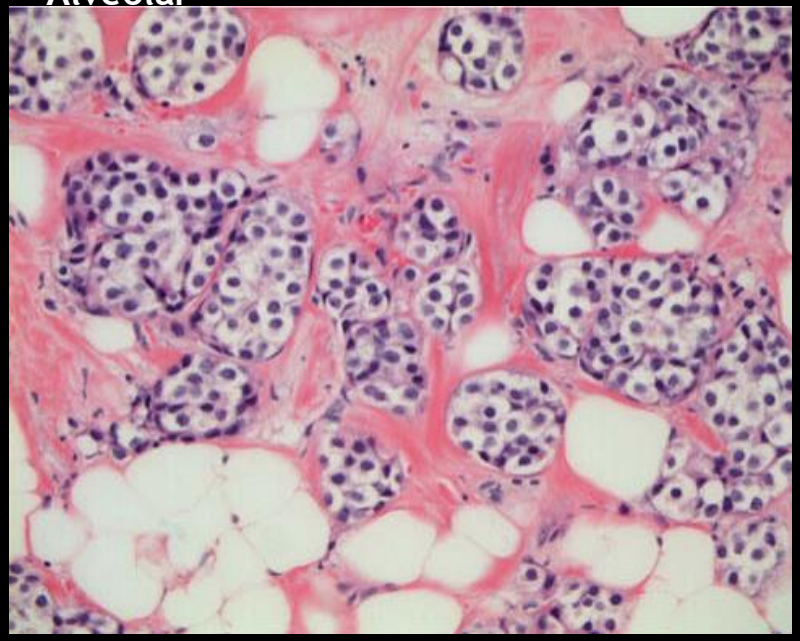
Monica Iorfida · Eugenio Maiorano · Enrico Orvieto · Patrick Maisonneuve · Luca Bottiglieri · Nicole Rotmensz · Emilia Montagna · Silvia Dellapasqua · Paolo Veronesi · Viviana Galimberti · Alberto Luini · Aron Goldhirsch · Marco Colleoni · Giuseppe Viale

- Studied prognosis of classic ILC vs variants
- 981 patients with pure ILC
- Classified as classic (including alveolar, solid, trabecular) or mixed non-classic (including pleomorphic, signet ring, histiocytoid and apocrine)
- Median follow up 6.4 years for DFS and 7.4 years for OS

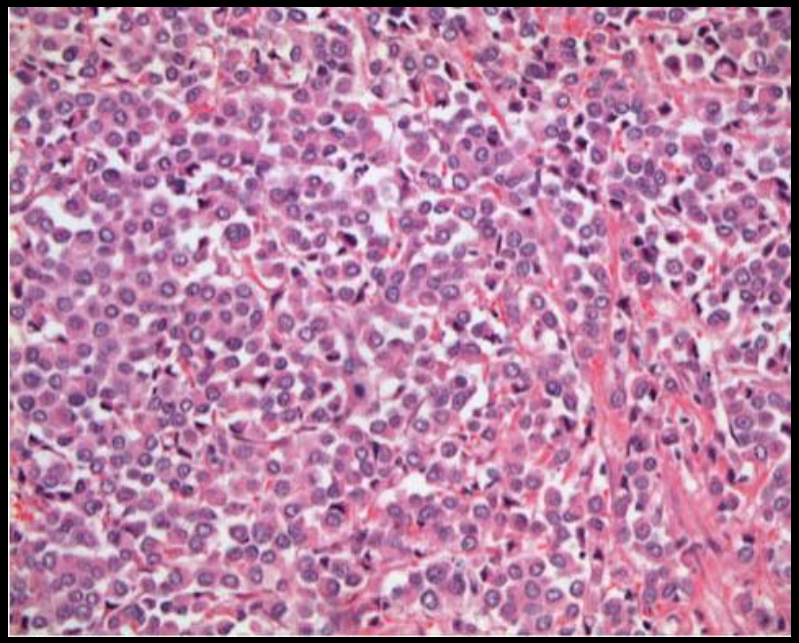
Classic



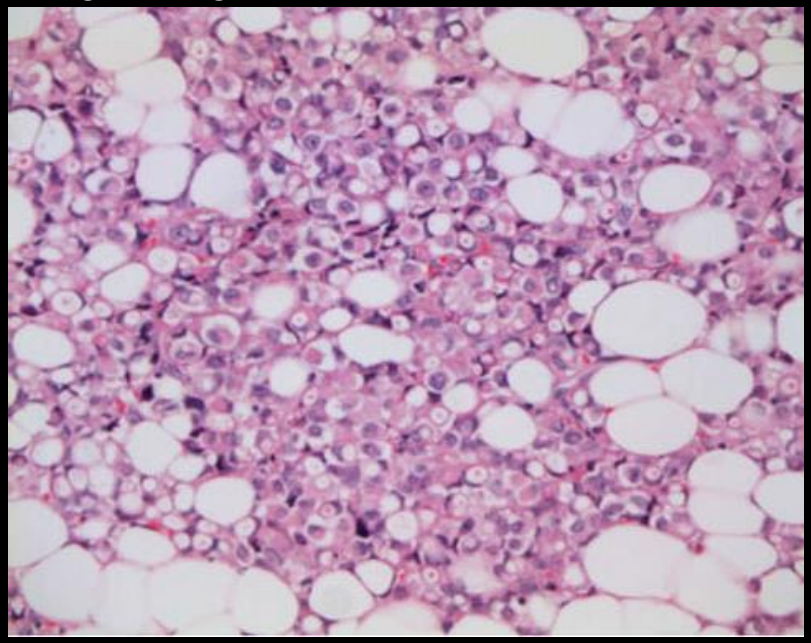
Alveolar



Solid



Signet ring

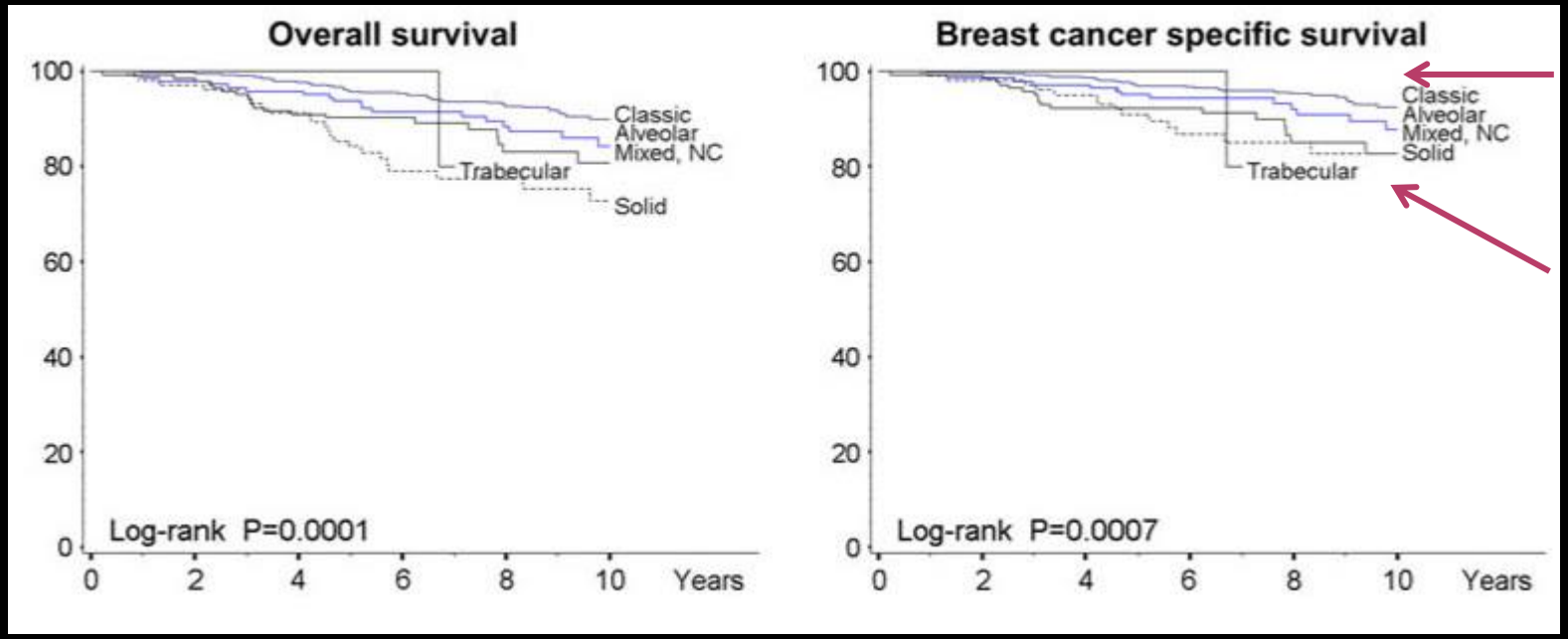


RESULTS

- Classic (55.8%), alveolar/trabecular (18.8%), solid (10.6%), mixed non-classic (14.8%)

- Classic: >50% grade 1
- Mixed non-classic: 58.6% grade 3
- Solid: 37.5% grade 3

- Overall, 96.5% were ER+
- Overall, Based on IHC, 48.5% were Luminal B



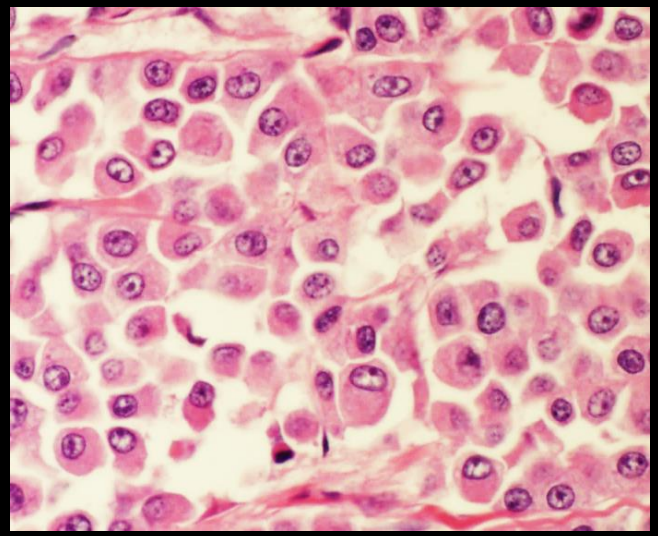
- Multivariate analysis
- Significantly different outcomes between classic vs non-classic and solid types
- Independent prognostic factors: age >70, large tumor size and positive nodes

CONCLUSION

- ILC is a heterogeneous disease
- Different histologic subtypes with different grades, different behaviors and different response to treatment
- Selected subgroups may benefit from tailored therapy

PLEOMORPHIC INVASIVE LOBULAR CARCINOMA

- First described by Page in 1987
- Growth pattern of classic ILC
- Nuclei 4x the size of a lymphocyte
- Hyperchromasia
- Nuclear irregularity
- Prominent nucleoli
- Increased mitotic activity



Available online at www.sciencedirect.com
SciVerse ScienceDirect
Annals of Diagnostic Pathology 16 (2012) 185–189
Annals of DIAGNOSTIC PATHOLOGY

Clinicopathologic and biomarker analysis of invasive pleomorphic lobular carcinoma as compared with invasive classic lobular carcinoma: an experience in our institution and review of the literature

Melissa Jacobs, MD, Fang Fan, MD, PhD*, Ossama Tawfik, MD, PhD
Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, Kansas 66160, USA

Table 1
Patient and tumor characteristics (PLC vs ILC)

		PLC (n = 7)	ILC (n = 58)	*P*
Age (y)		35-69	30-88	.20
Grade	I	0/7	11/58	.59
	II	5/7	47/58	.62
	III	2/7	0/58	**.01**
LVI present		2/7	7/58	.25
Lymph node	Unknown	0/7	4/58	>.99
	N0	4/7	37/58	.70
	N1a	1/7	12/58	>.99
	N2a	0/7	2/58	>.99
	N3a	2/7	3/58	.09
ER ≥ 1%		4/7	All positive	**.001**
Her-2		All negative	All negative	>.99
Ki-67 ≥ 10%		5/7	7/58	**.002**
Follow-up (median, 29 mo)	None	1/7	2/58	.30
	NED	5/7	51/58	.25
	Metastases	1/7	4/58	.45
	Deceased	0/7	1/58	>.99

LVI indicates lymphovascular invasion; NED, no evidence of disease.

Significant:

Grade

ER

Ki67

Not Significant:

HER2

F/u

BOTTOM LINE

- Pleomorphic invasive lobular carcinoma is a distinct entity
- E-cadherin negative
- Often higher grade, higher Ki67
- May be ER-
- Has implications for anti-estrogen therapy and chemotherapy

OTHER IMPLICATIONS

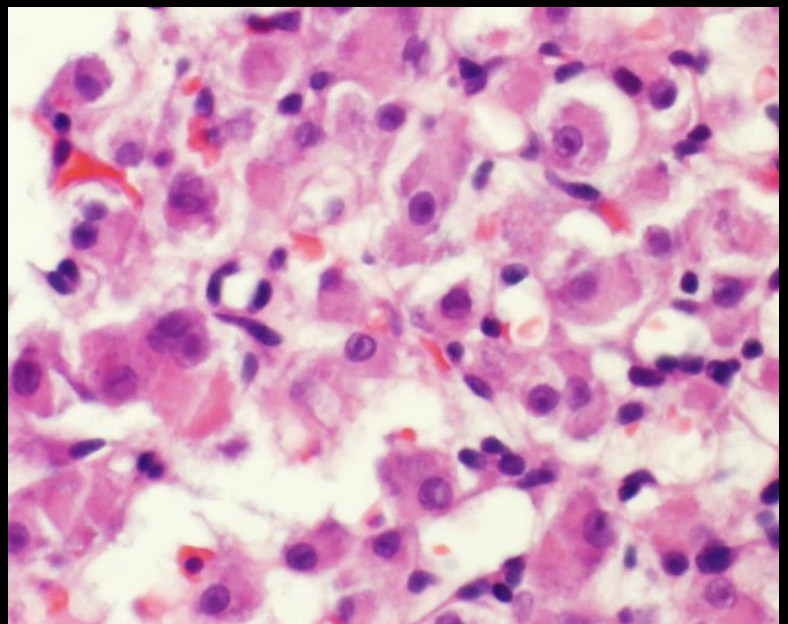
- Non-classical morphology
- Fairly rare occurrence
- Need to consider other tumors

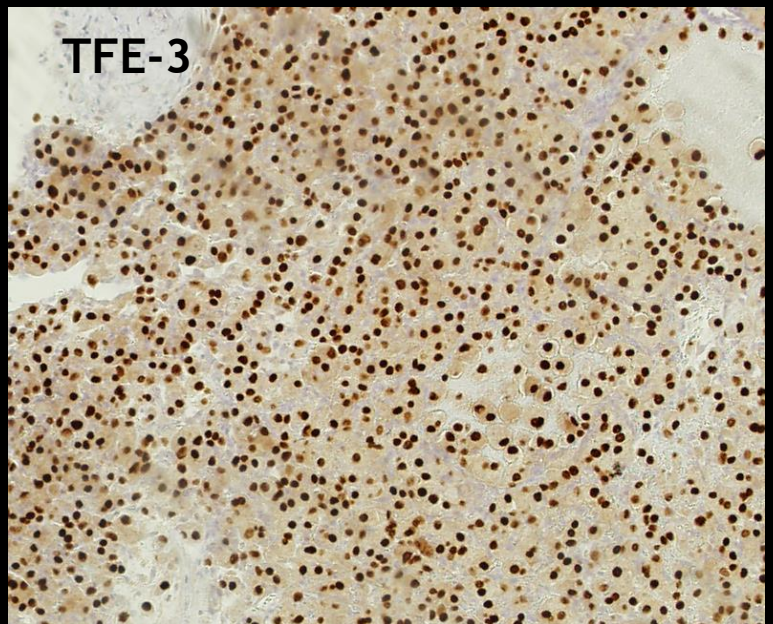
MIMICS OF INVASIVE LOBULAR

- Breast
  - Apocrine carcinoma
  - Acinic cell carcinoma
  - Secretory carcinoma
- Metastatic
  - Melanoma
  - Gastric carcinoma
  - Renal cell carcinoma
  - Hepatocellular carcinoma
  - Alveolar soft part sarcoma

OUR CASE

- Patient had a known history 10 years before
- Alveolar soft part sarcoma of the leg
- Now with widely metastatic disease
- Brain, lungs, breast





PRIMARY VS METASTATIC

- Clinical history
- Have a low threshold for “other”
- ER can be positive in metastatic lesions
- ER can be negative in breast tumors

USEFUL IMMUNOHISTOCHEMISTRY

	GCDFP15 (BRST2)	Estrogen Receptor	Progesterone Receptor	PAX8	Gata 3
Infiltrating ductal carcinoma	60-70%	75%	50-60%	0%	92%
Infiltrating lobular carcinoma	60-70%	>95%	80%	0%	100%
Lung adenocarcinoma	0-1%	<5%	<5%	0%	8%
Ovarian adenocarcinoma	1-5%	50-100%	40-90%	90-100%	6%
Endometrioid adenocarcinoma	negative	70%	70%		7%
GI adenocarcinoma	negative	<5%	1-10%	0%	<5%
Pancreatic adenocarcinoma	negative	negative	0-5%	0%	37%
Cholangiocarcinoma	negative	negative	30%		9%
Thyroid carcinoma	negative	20%	30%	100%	<10%
Germ cell tumors					40-100%
Urothelial carcinoma					84-100%
Mesothelioma					58%

Adapted from Surgical Pathology Criteria http://surgpathcriteria.stanford.edu/

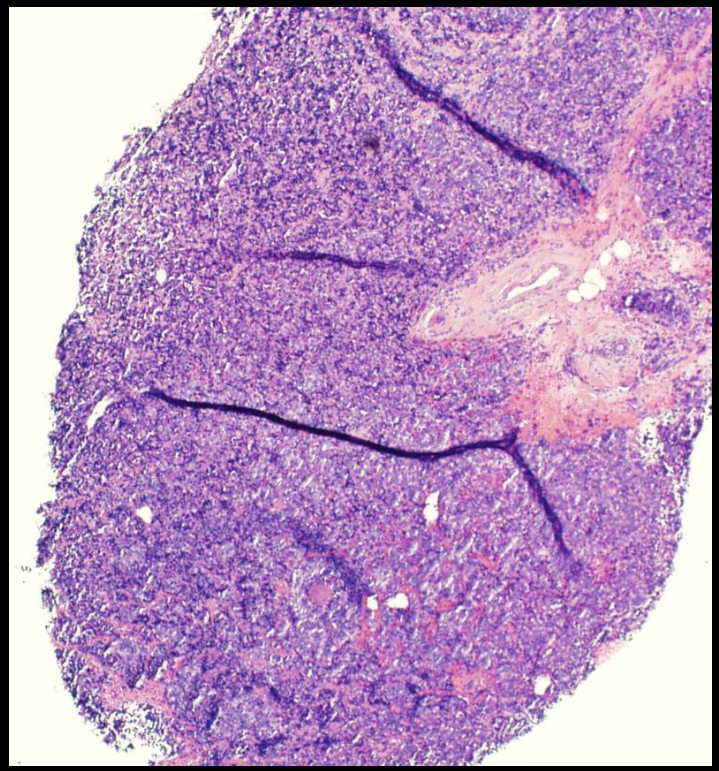
GATA3 column from Miettinen M, McCue PA, Sarlomo-Rikala M, et al. A Multispecific but potentially useful marker in surgical pathology. Am J Surg Pathol, 38(1):13-22. 2014.

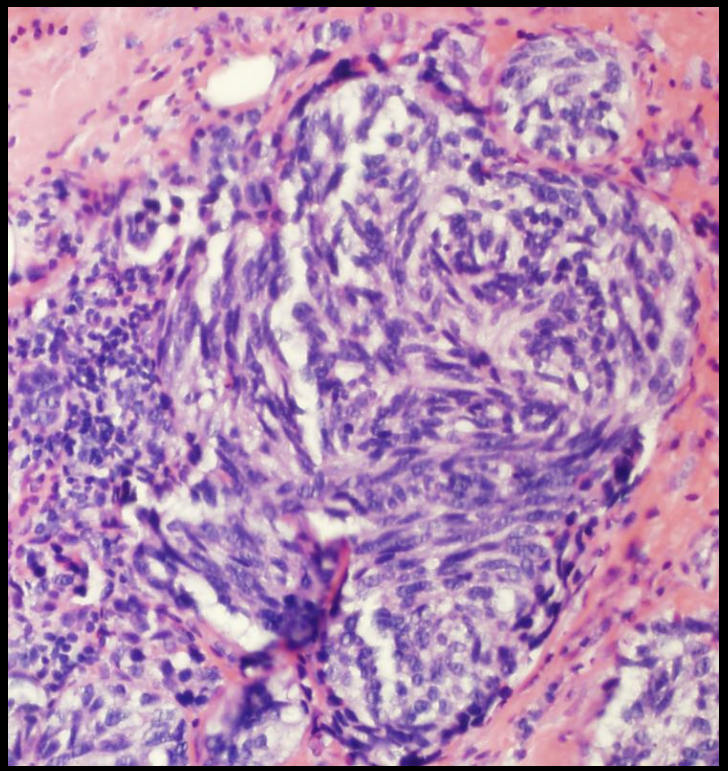
PART 2

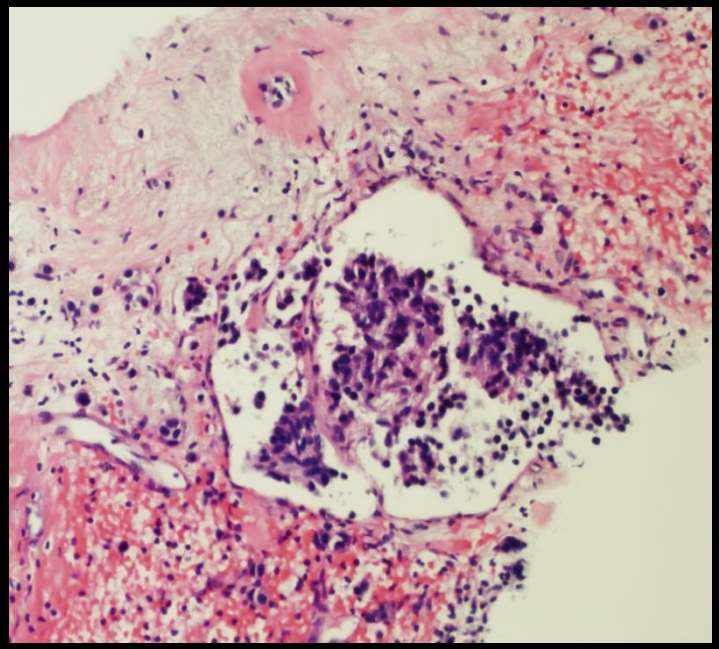
- Two consult cases, similar on first blush and both initially given the wrong diagnoses.

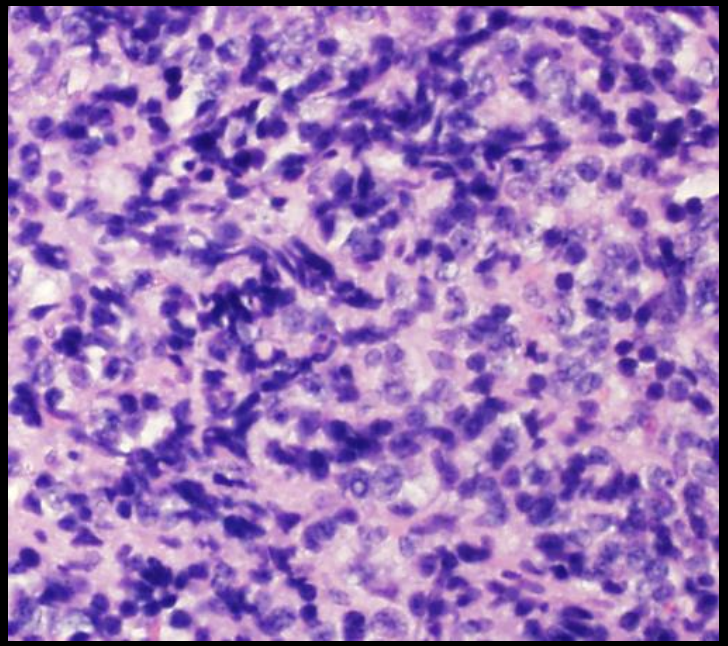
FIRST CASE

- 73 yo woman with a left breast mass
- Core biopsy performed



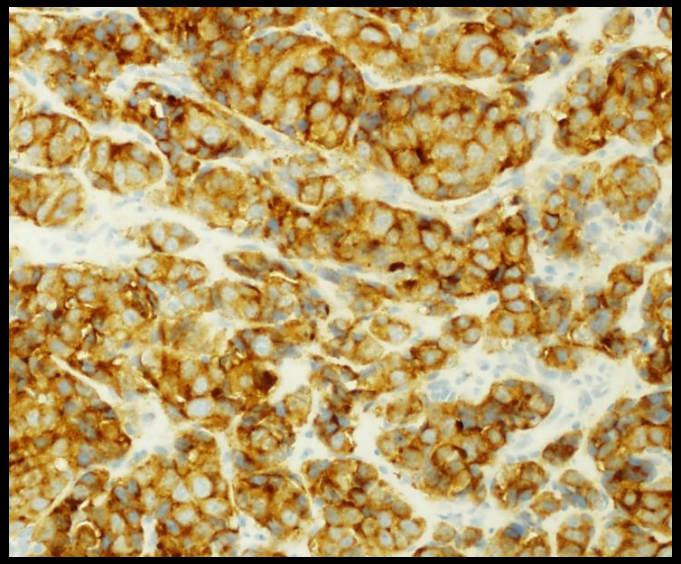






OUTSIDE HOSPITAL STUDIES

- Ancillary studies:
  - **POSITIVE: AE1/AE3, CAM5.2, CK7, ER (weak, 20%), Synaptophysin, Chromogranin**
  - **NEGATIVE: CK20**



Synaptophysin

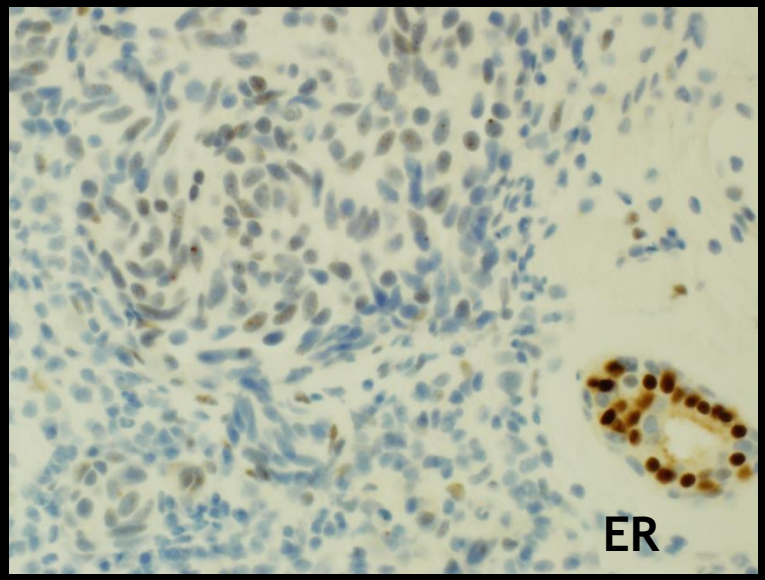
INTERPRETATION

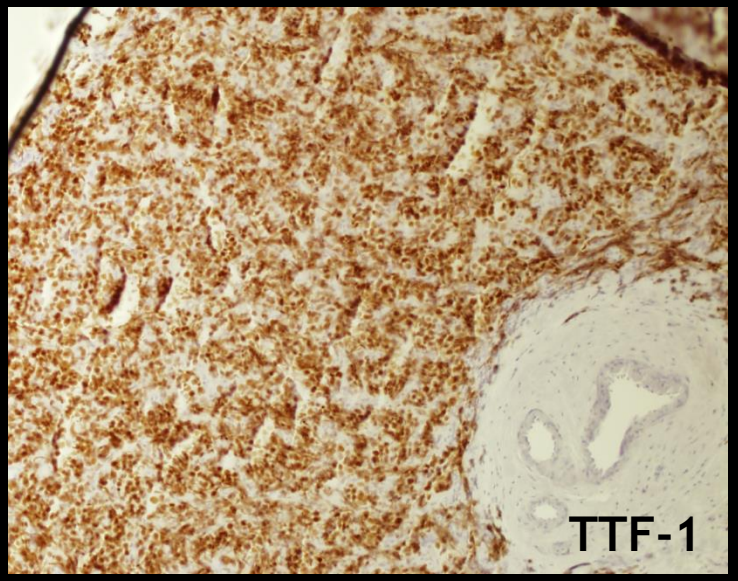
- Due to positivity for Estrogen receptor, Synaptophysin and Chromogranin, the tumor was called “poorly differentiated invasive ductal carcinoma with neuroendocrine features.”

- Our in house oncologist agreed.
- To us, the work-up was incomplete.

ADDITIONAL HISTORY AND STAINS

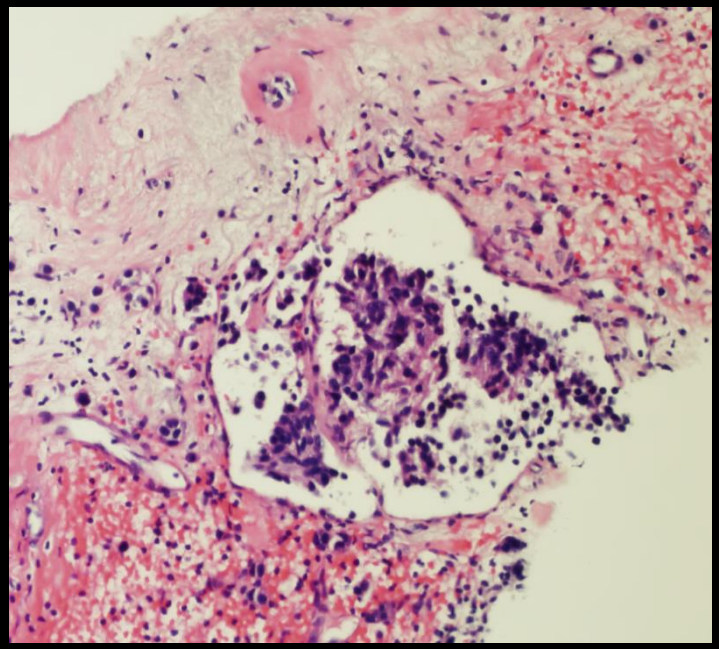
- Patient had lesions in bone, breast and lung.
- We performed additional stains:
  - **POSITIVE: TTF-1 (diffuse, strong)**
  - **NEGATIVE: PR (0), HER2 (0)**





NEW INTERPRETATION

- Metastatic neuroendocrine tumor, most likely of primary lung origin.



LVI

SURPRISE!

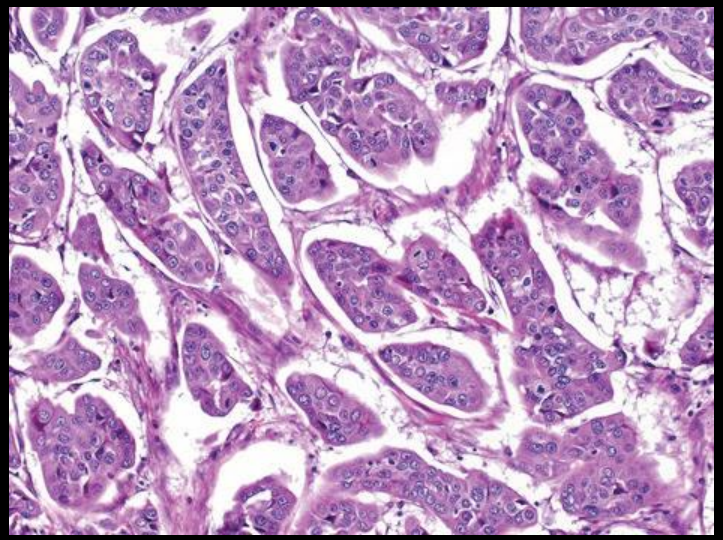
IDC of breast with neuroendocrine features

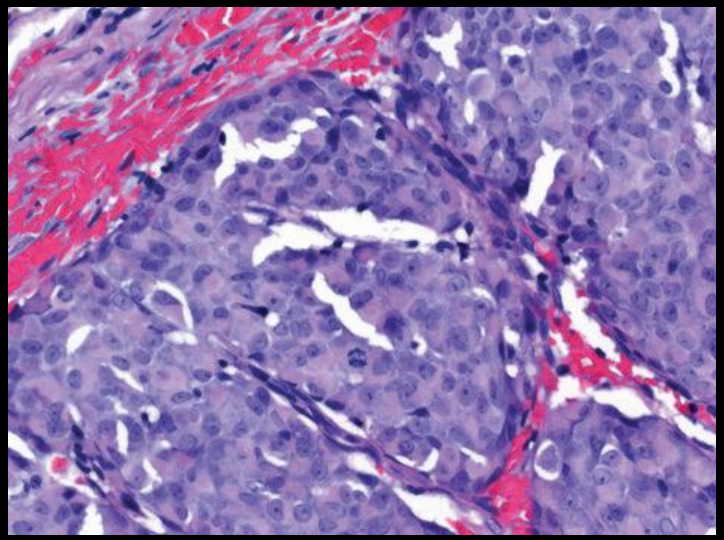
↓

Metastatic NET from lung

DISCUSSION POINTS

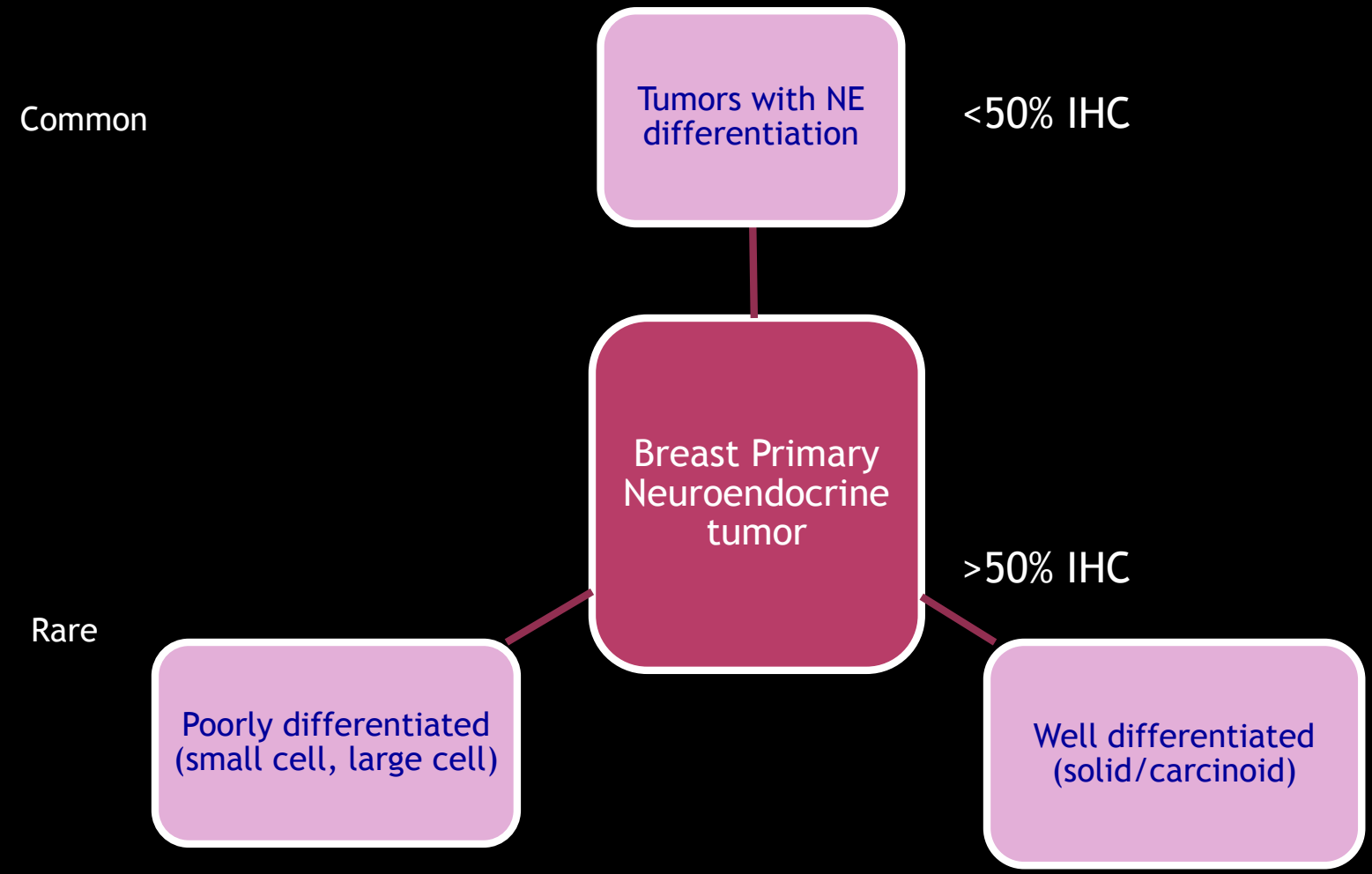
- Neuroendocrine tumors of the breast: classification and diagnosis





Wachter DL, Hartmann A, Beckmann MW, et al. Expression of neuroendocrine markers in different molecular subtypes of Breast Carcinoma. Biomed Research International Volume 2014.

CATEGORIES (WHO 2003)



TUMORS WITH NEUROENDOCRINE DIFFERENTIATION

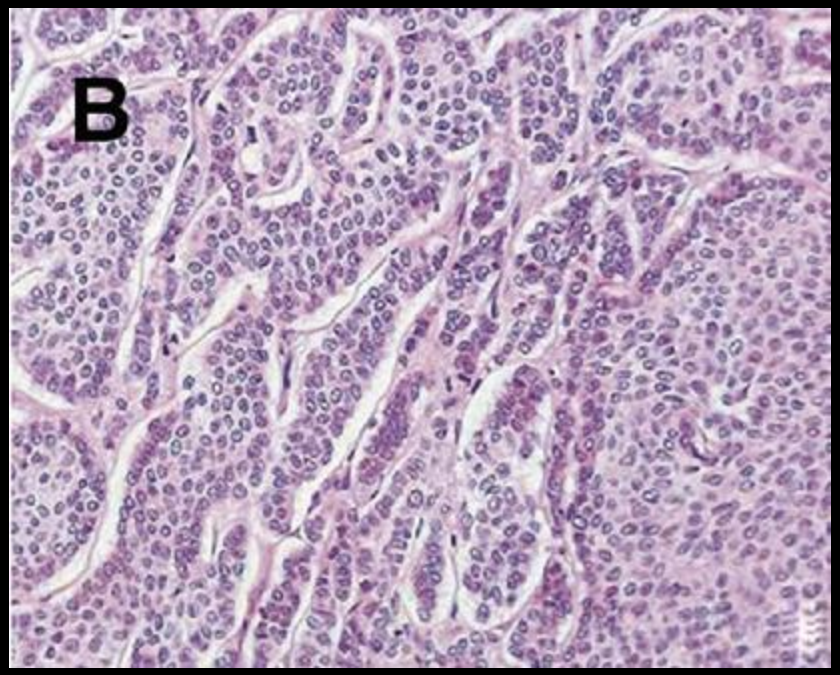
- Uncertain how many cases this includes
- Lack cyto-architectural features of true neuroendocrine tumors
- Often post-menopausal
- IDC-NOS, mucinous, solid papillary included
- Show scattered expression of endocrine markers such as Synaptophysin and Chromogranin in <50% of cells (WHO 2003)

PROGNOSIS OF TUMORS WITH NE DIFFERENTIATION

- Uncertain
- Some report no prognostic significance
- Others report better prognosis
- Most important: Grade, Stage, ER/PR/HER2
- Bottom line:
  - No need to test every tumor for NE Diff
  - Some NE staining does not = NEC

SOLID/CARCINOID-LIKE

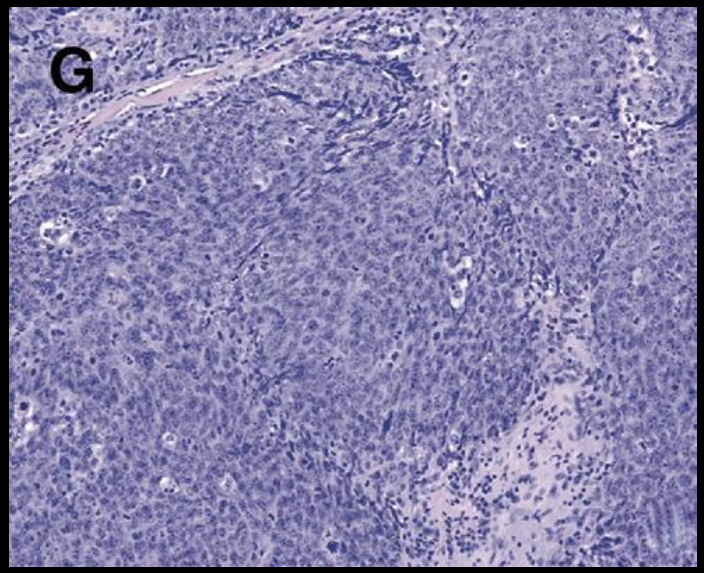
- <1% of breast cancers
- Morphologically indistinguishable from carcinoids from other sites
- Presence of DCIS and/or LVI may help
- Majority ER/PR+
- HER2 negative



Righi L, Sapino A, Marchio C, et al. Neuroendocrine Differentiation in breast cancer: established facts and unresolved problems. Seminars in Diagnostic Pathology (2010) 27, 69-76.

POORLY DIFFERENTIATED

- Small/large cell neuroendocrine carcinomas
- Morphologically indistinguishable from lung
- TTF-1 does not help: may be positive
- In situ carcinoma may help
- Variable expression of NE markers
- Prognosis?



Righi L, Sapino A, Marchio C, et al. Neuroendocrine Differentiation in breast cancer: established facts and unresolved problems. Seminars in Diagnostic Pathology (2010) 27, 69-76.

Small Cell Carcinoma of the Breast

A Clinicopathologic and Immunohistochemical Study of Nine Patients

Sandra J. Shin, M.D., Ronald A. DeLellis, M.D., Liang Ying, B.A., and Paul Peter Rosen, M.D.

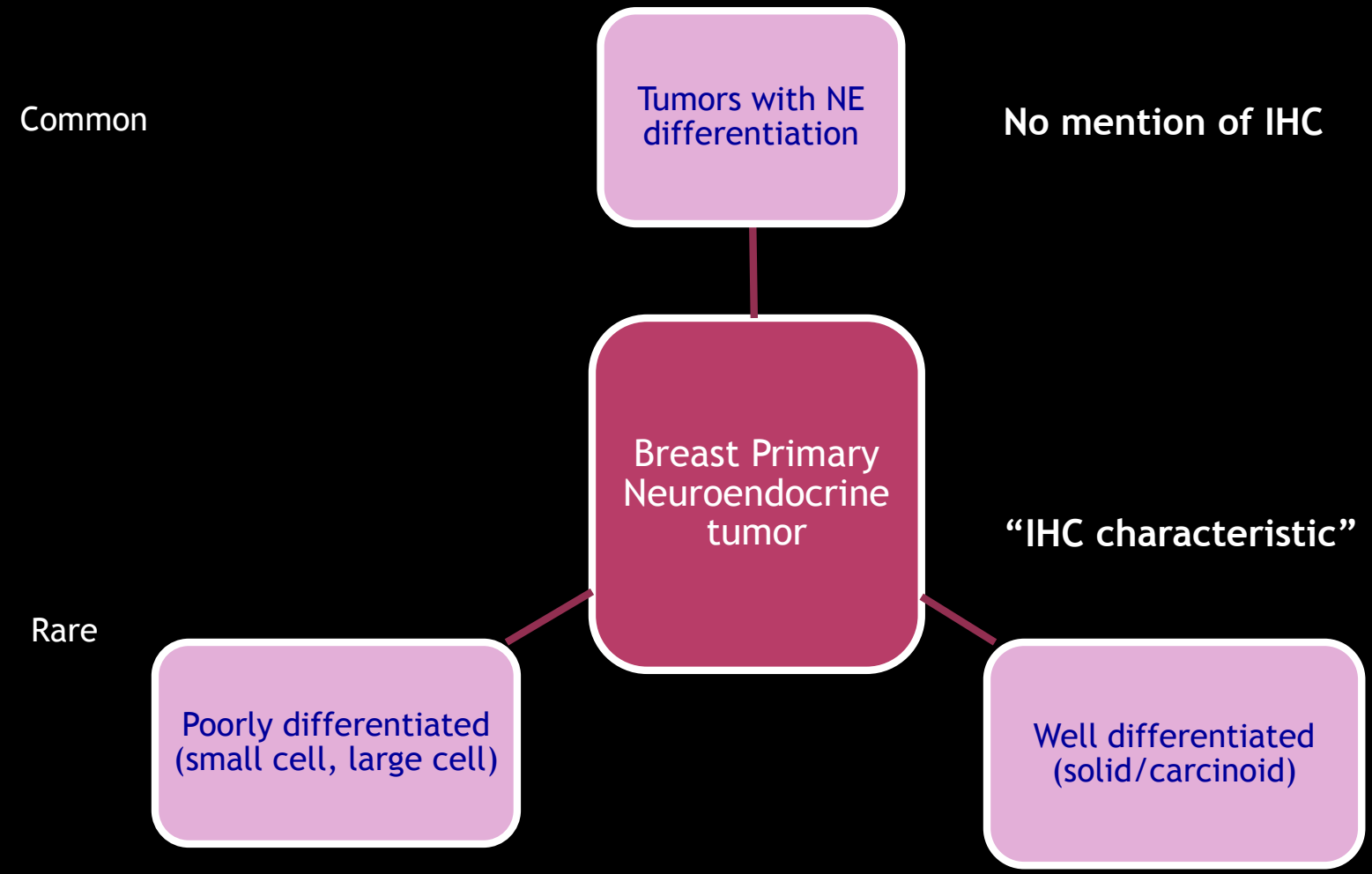
The American Journal of Surgical Pathology *24(9): 1231–1238, 2000*

- 9 patients diagnosed with primary small cell ca
- Treatment: mastectomy or lumpectomy with or without ALDN
- Follow-up 3-35 months
- All patients alive
- Conclusion: Primary small cell carcinoma of the breast is not as aggressive as at other sites

ISSUES WITH NE CLASSIFICATION

- >50% expression is arbitrary
- Most appropriate IHC marker for NET's?
  - Panel is recommended
  - Synaptophysin and chromogranin
  - Others: NSE, CD56
- Some tumors with cyto-architecture of neuroendocrine tumors are negative for markers of NE differentiation

CATEGORIES (WHO 2012)

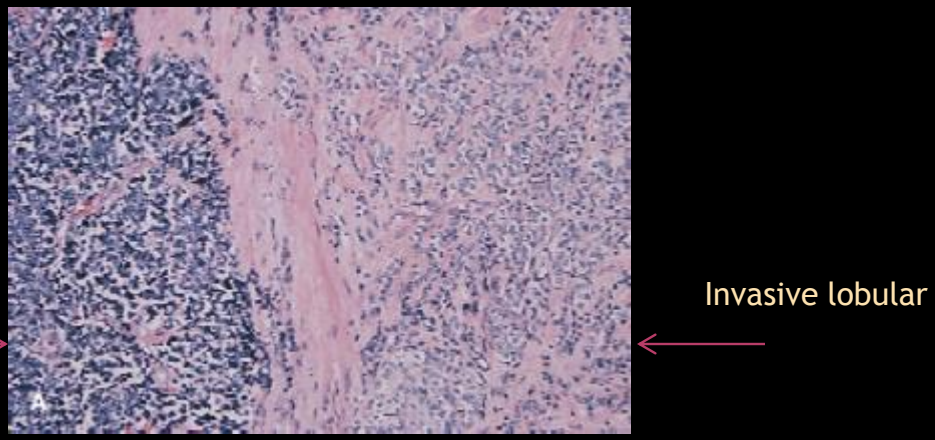


NEUROENDOCRINE TUMORS OF THE BREAST: SUMMARY

- Breast carcinoma with endocrine differentiation is relatively common
- True primary neuroendocrine carcinoma of the breast is rare (<1%)
- Any neuroendocrine tumor of the breast should be distinguished from metastatic neuroendocrine tumors if possible

INTERESTING POINT

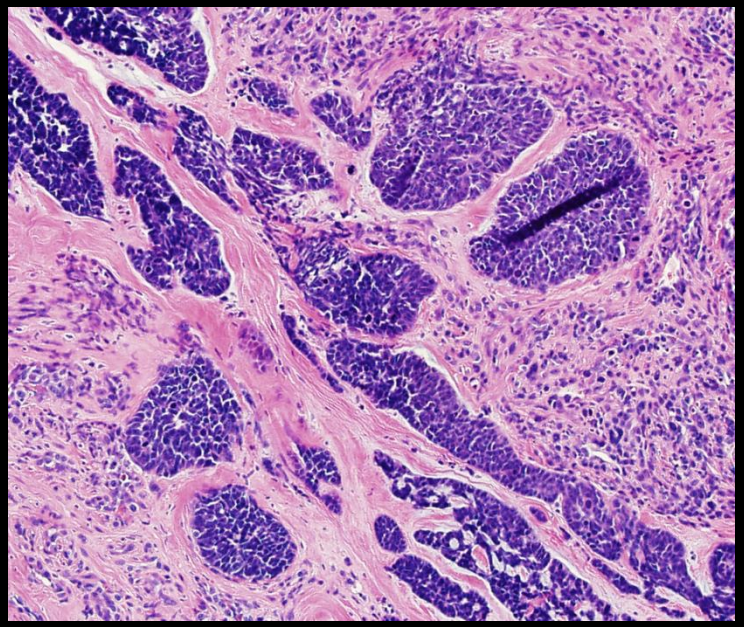
- 4 patients showed dimorphic tumor growth, showing small cell carcinoma co-existing with invasive lobular, ductal NOS, metaplastic and mixed types.

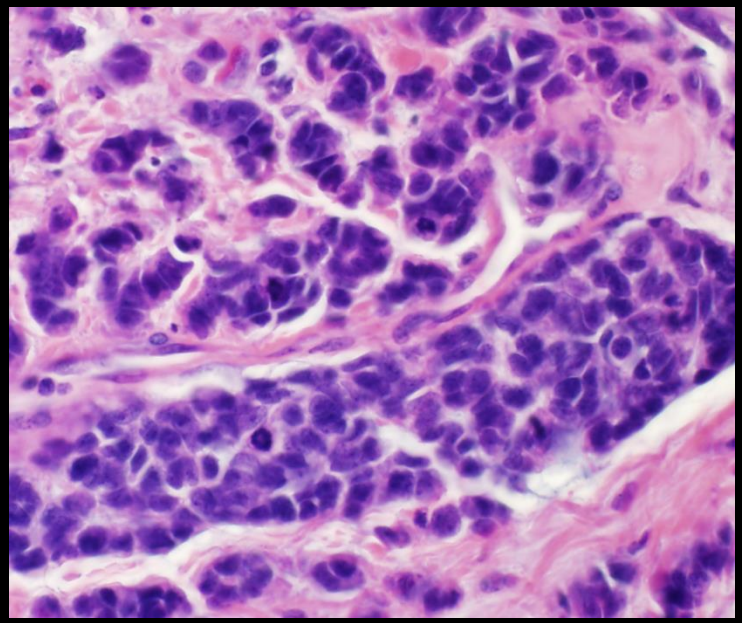


Shin, SJ, DeLellis RA, Ying L, Rosen PP. Small cell carcinoma of the Breast: A Clinicopathologic and Immunohistochemical Study of Nine Patients. *Am J Surg Path* 24(9): 1231-1238, 2000

SECOND CASE

- 2010: 71 yo woman, 3cm mass in right breast
- Outside hospital case- excision performed





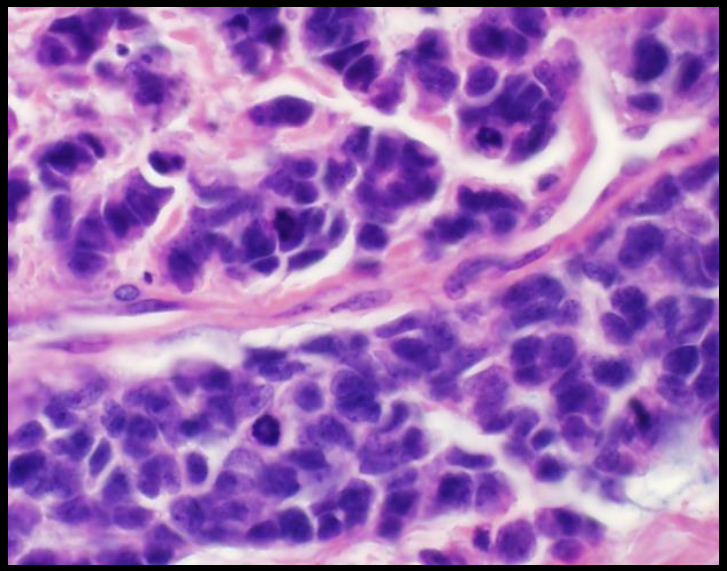
ORIGINAL INTERPRETATION

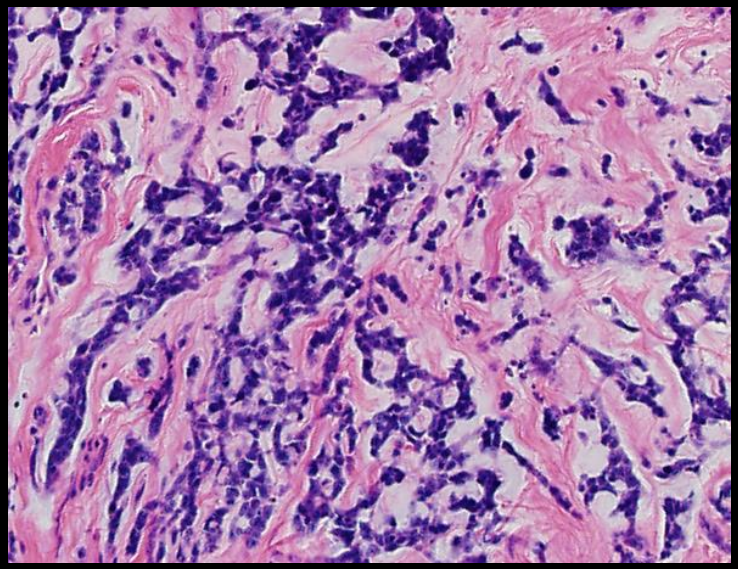
- 6 negative lymph nodes.
- Stains: Pan-K and NSE (+), ER/PR/HER2 (-), Synaptophysin (-), Chromogranin (-).
- Diagnosis: poorly differentiated small cell neuroendocrine carcinoma.

- Patient received 6 cycles of Carboplatin, Taxol and radiation.
- Developed severe neuropathy and recurrence in 2014.

CASE REVIEWED

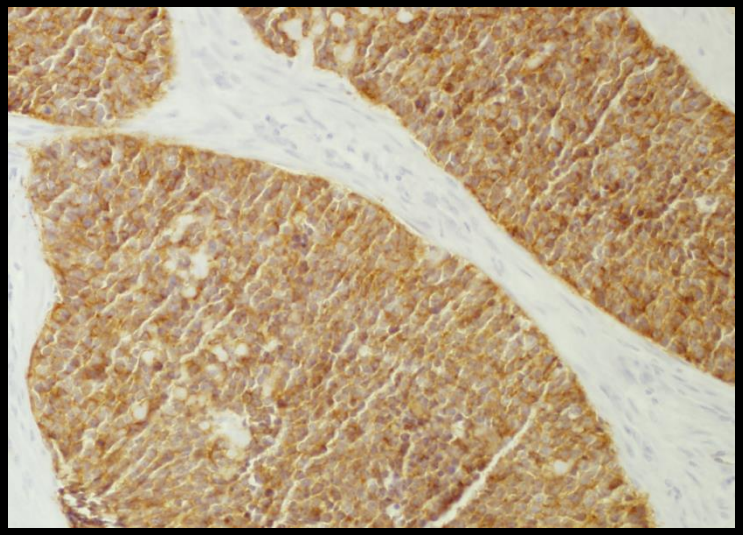
- Small round blue cell tumor.
- Sheets and clusters.
- Mitotically active (15/10).
- Areas of necrosis and LVI.
- Intervening hyaline and myxoid stroma.





STAINS: RECAP AND NEW

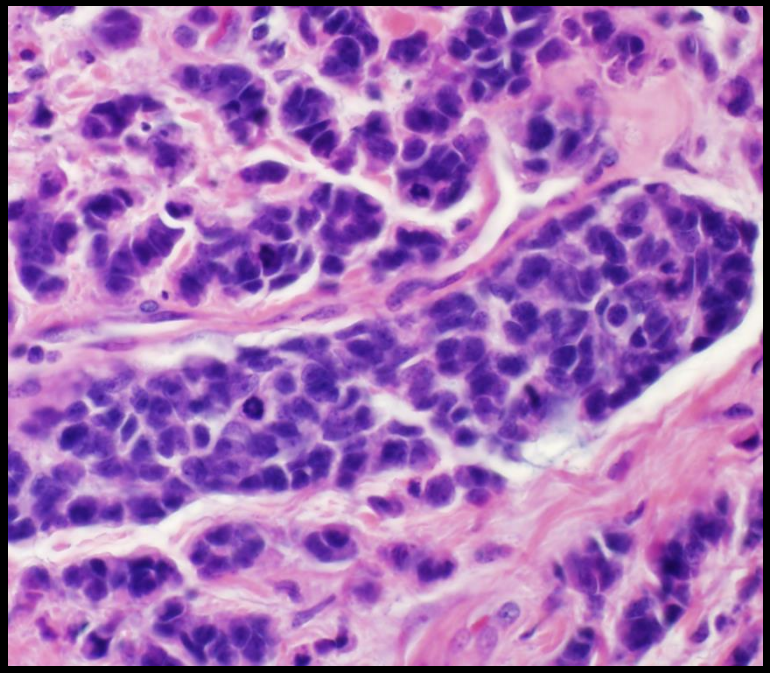
- SMA and p63: Negative
- Synaptophysin, Chromogranin: Negative
- CK7: Positive (patchy)
- NSE: Positive
- CD117: Positive (patchy to diffuse)

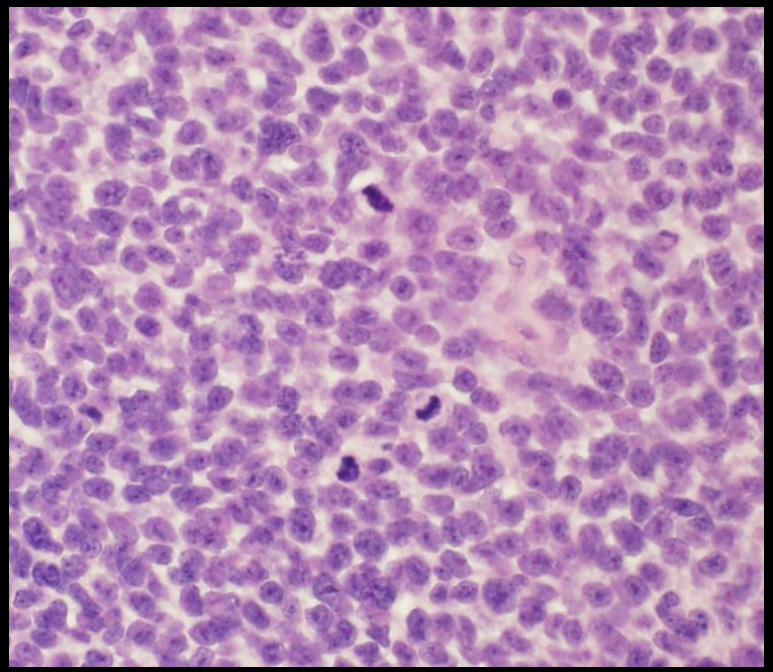


CD117

MORPHOLOGY + STAINS

- New diagnosis:
  - Adenoid cystic carcinoma of the breast, solid type with basaloid features



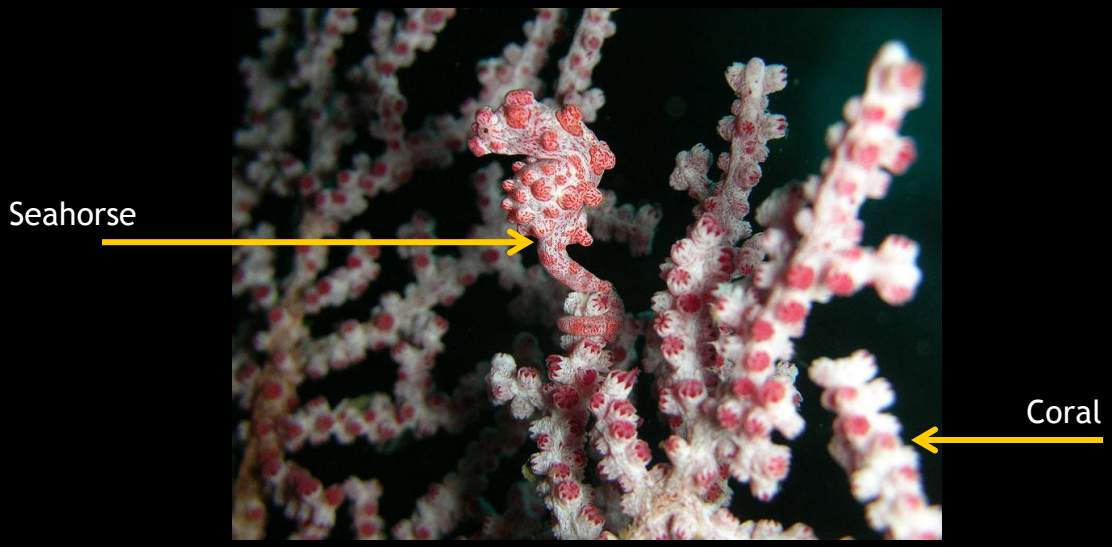


SURPRISE!

Primary small cell neuroendocrine carcinoma

↓

Primary adenoid cystic carcinoma



ADENOID CYSTIC CARCINOMA OF THE BREAST

- Rare: 0.1% of breast carcinoma
- Morphologically indistinguishable from Adenoid cystic in salivary gland, lung, cervix
- 6^{th}-7^{th} decade
- Subareolar region common
- Good prognosis

ADENOID CYSTIC CARCINOMA

- Architectural patterns:
  - Trabecular, tubular, cribriform, solid
- Histology triplet:
  - Epithelial cells
  - Myoepithelial cells – bulk of tumor
  - Matrix

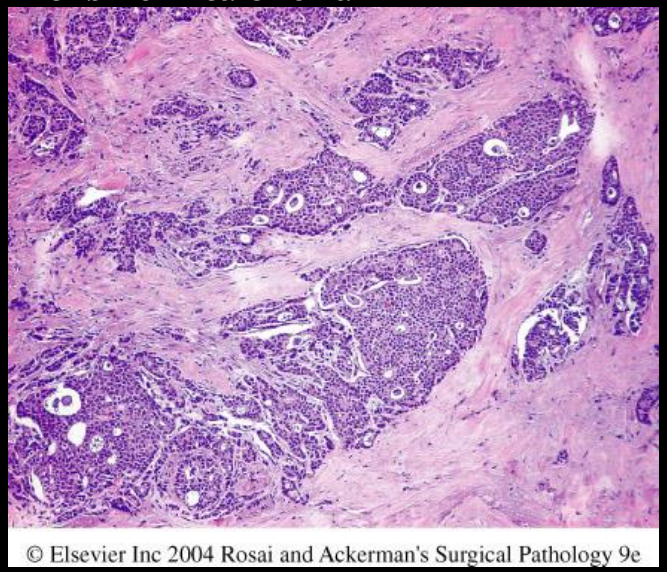
ADENOID CYSTIC CARCINOMA

- Epithelial cells
  - Eosinophilic cytoplasm, round nuclei
  - Forms real glands
  - CK7, CD117+
- Myoepithelial cells
  - Basaloid: small, dark, scant cytoplasm
  - Pseudolumens
  - p63, SMA, Calponin+
- Matrix
  - PAS-d+

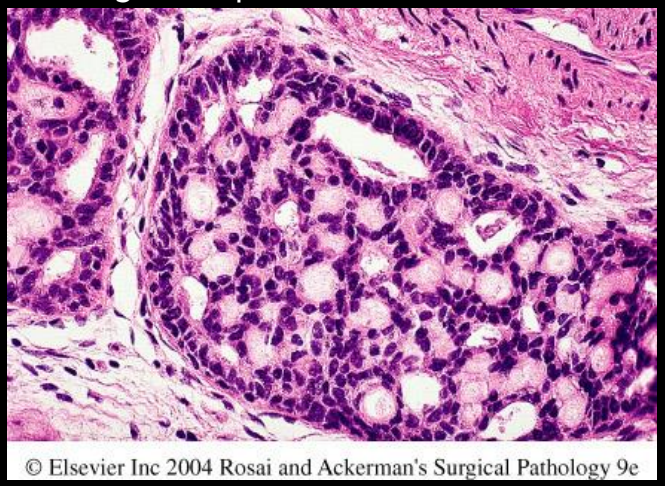
DIFFERENTIAL

- Malignant
  - Cribriform carcinoma
    - DCIS
    - Invasive
- Benign
  - Collagenous spherulosis

Cribriform carcinoma



Collagenous spherulosis



HOW TO DISTINGUISH?

- Adenoid cystic
  - Infiltrative with two cell populations
  - ER,PR, HER2 negative
  - *CD117 positive*
- Invasive Cribriform carcinoma
  - Usually ER/PR positive
  - Lacks myoepithelial cells
- Cribriform DCIS
  - Myoepithelial cell markers around periphery
- Collagenous spherulosis
  - Incidental
  - Not infiltrative
  - Lack cytologic atypia

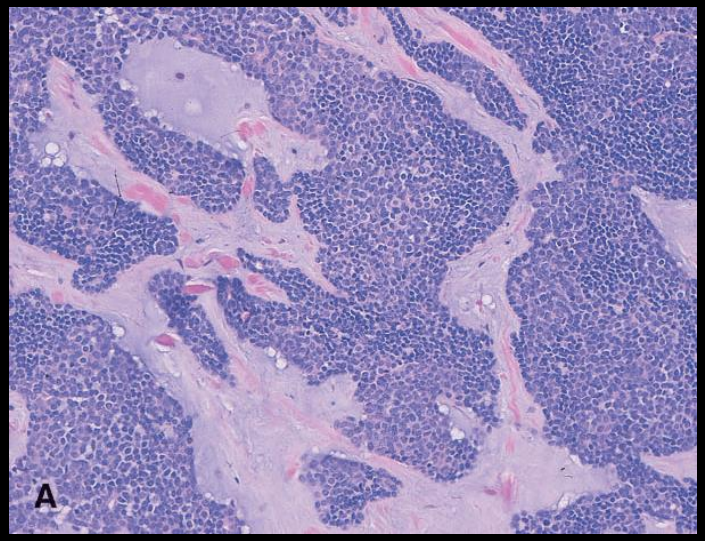
GRADING: PROPOSED METHODS

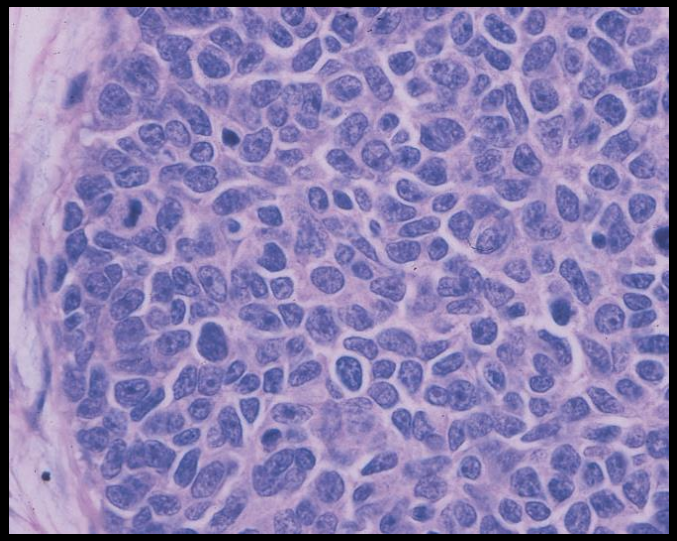
- 1. Most common
  - Nottingham grade (I-III)

- 2. Salivary gland method:
  - Ro, et al. *Hum Pathol* 18: 1276-1281, 1987
    - Grade 1: no solid areas
    - Grade 2: <30% solid
    - Grade 3: at least 30% solid

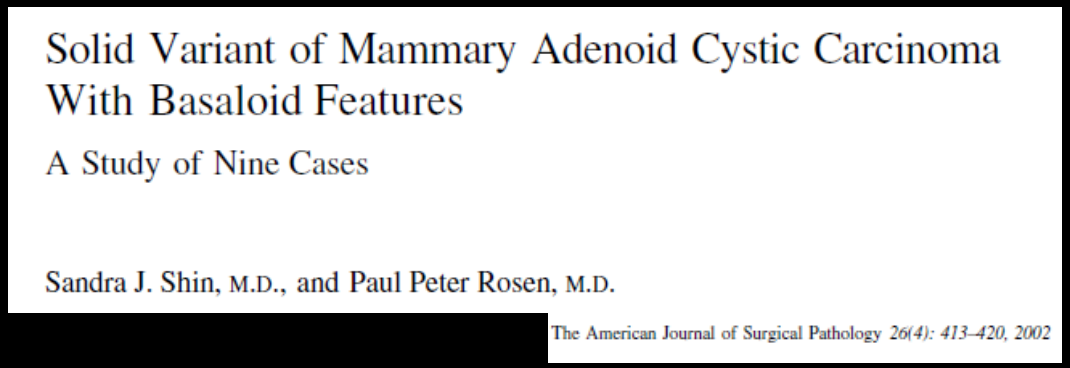
MORE AGGRESSIVE ADENOID CYSTIC VARIANTS?

- Some reports suggest the following:
  - Solid type (Ro, et al. *Hum Pathol* 18: 1276-1281, 1987)
  - Solid type with basaloid features (Shin, Rosen. Am J Surg Path 26(4): 413-420, 2002)





The American Journal of Surgical Pathology (26(4): 413-420, 2002.



Solid Variant of Mammary Adenoid Cystic Carcinoma With Basaloid Features

A Study of Nine Cases

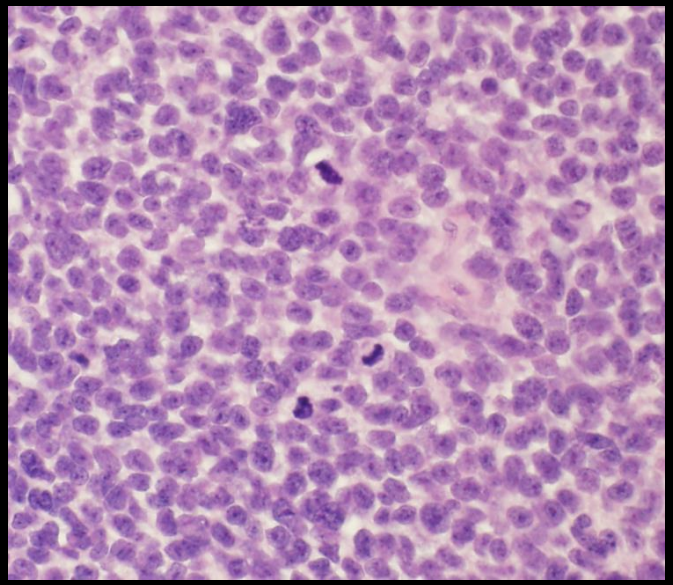
Sandra J. Shin, M.D., and Paul Peter Rosen, M.D.

The American Journal of Surgical Pathology 26(4): 413–420, 2002

- Each >90% solid with basaloid features
- Nuclear atypia moderate - marked in 8 cases
- Brisk mitotic activity in 50% of tumors
- No LVI or PNI
- Two cases with one positive axillary lymph node
- Management differed (surgical, radiation, endocrine)
- Follow-up:
  - 6 patients with no evidence of recurrent carcinoma (2-88 mo out)
  - 1 patient died of unknown causes; 1 lost to follow-up
- Conclusion: may be a worse ACC subtype, but still better than invasive ductal, NOS of similar size

DIFFERENTIAL

- Cribriform carcinoma (in situ, invasive)
- Collagenous spherulosis
- Lymphoma
- Small cell carcinoma
- Solid papillary carcinoma
- Metaplastic carcinoma



TEACHING CASE

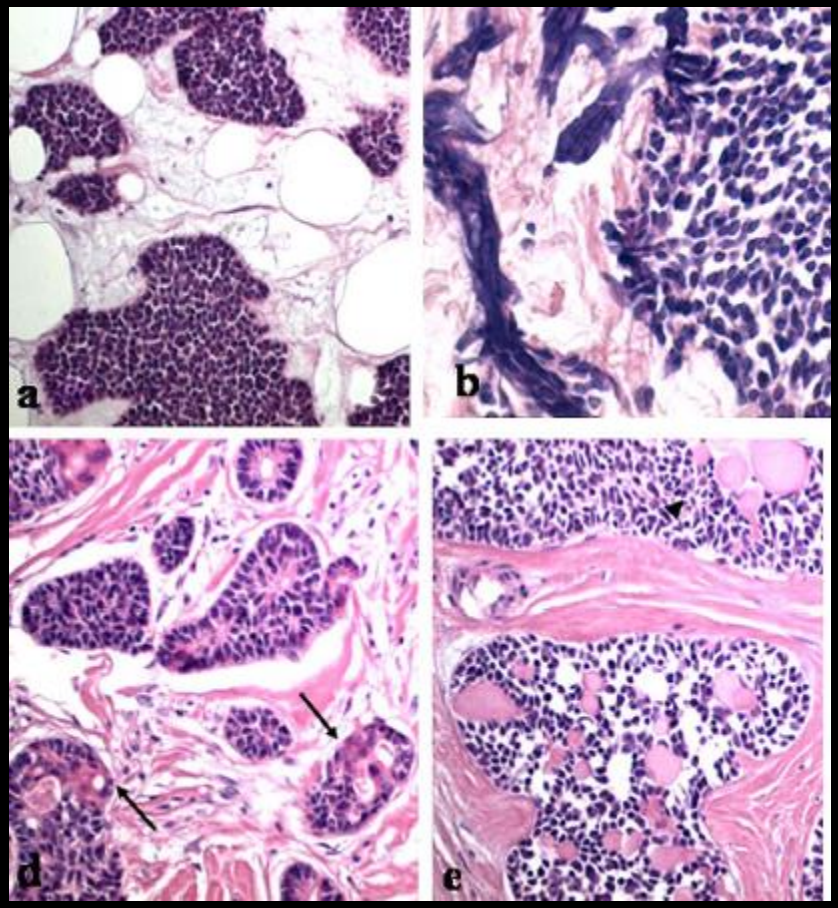
Solid variant of mammary "adenoid cystic carcinoma with basaloid features" merging with "small cell carcinoma"

Daniela Cabibi[a,*], Calogero Cipolla[b], Ada Maria Florena[a], Salvatore Fricano[b], Elisabetta Barresi[a], Salvatore Vieni[b], Vito Rodolico[a], Liborio Napoli[b]

Pathology – Research and Practice 201 (2005) 705–711

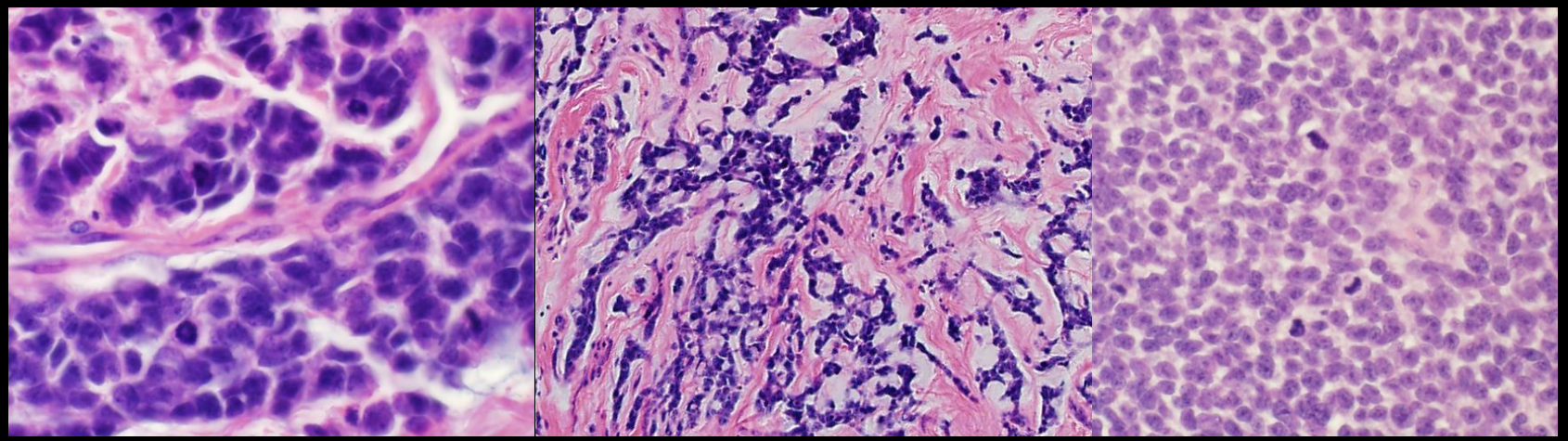
Small cell →
- Keratin and CD117+
- Synaptophysin, NSE+
- MIB-1 >30%

Adenoid cystic →
- Keratin and CD117+
- Synaptophysin, NSE-
- MIB-1 10%



OUR CASE: REVISITED

- Solid, basaloid with trabecular components showing matrix production
- Mitotically active
- CD117+, NSE+
- Originally called small cell carcinoma
- Possible collision tumor?



THANK YOU

Deer Valley in the summer