Carcinoma Lobulare

Caratteristiche Istopatologiche

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Infiltrating Lobular Carcinoma of the Breast

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Structure of this Presentation

White background: Dr. Salomon's Slides

(exactly the lecture prepared by Dr. Salomon for this conference)

Blue background: Dr. Sidoni's Slides
(containing remarks on controversial aspects of lobular neoplasias and lobular carcinomas)

Introduction: Infiltrating lobular carcinoma (ILC)

5-15% of invasive breast tumors

original definition : invasive form of the carcinoma arising in lobules and terminal ducts (Foote and Stewart 1941)

recent increase in the incidence (> 50 years)

Use of post-menopausal combined hormone replacement therapy ?

Better histological identification ?

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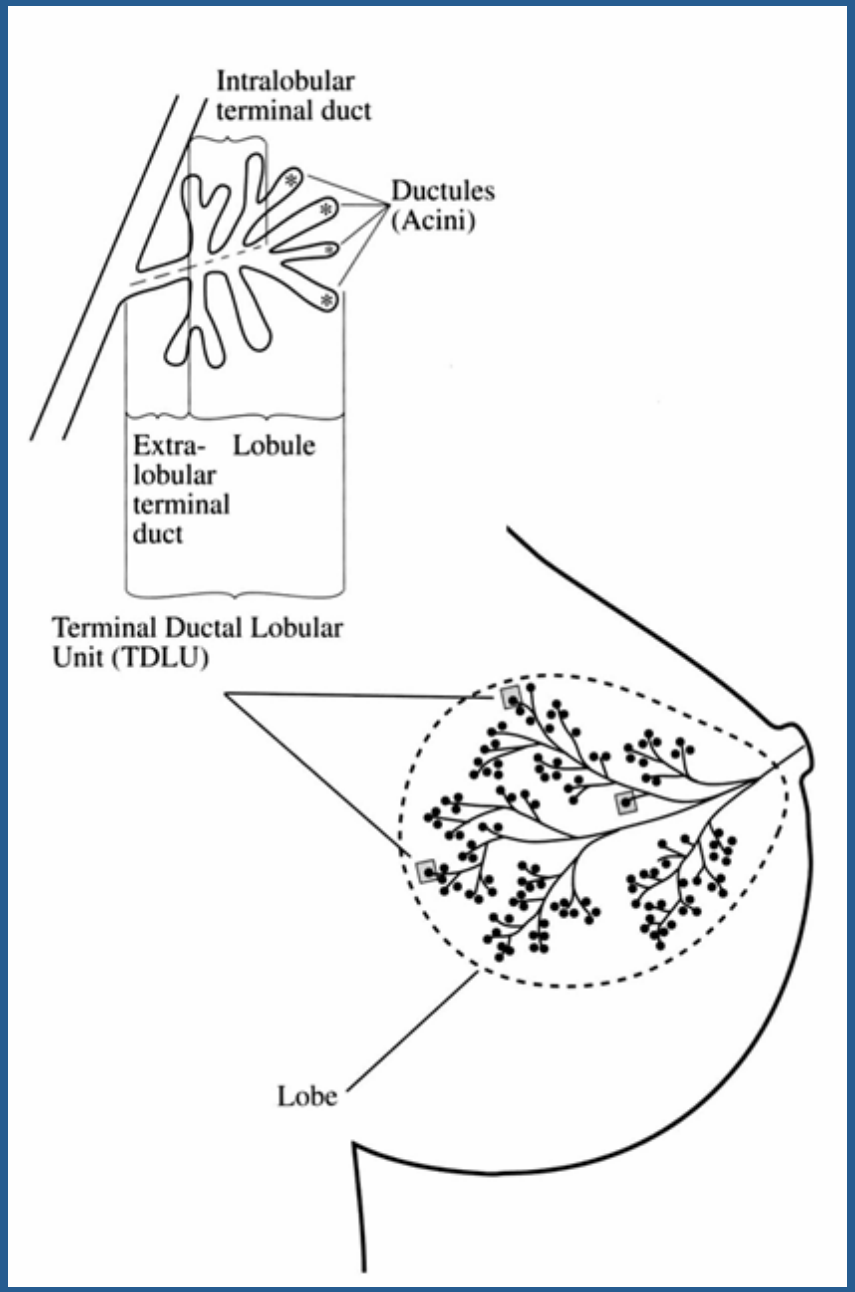


Semantic Considerations

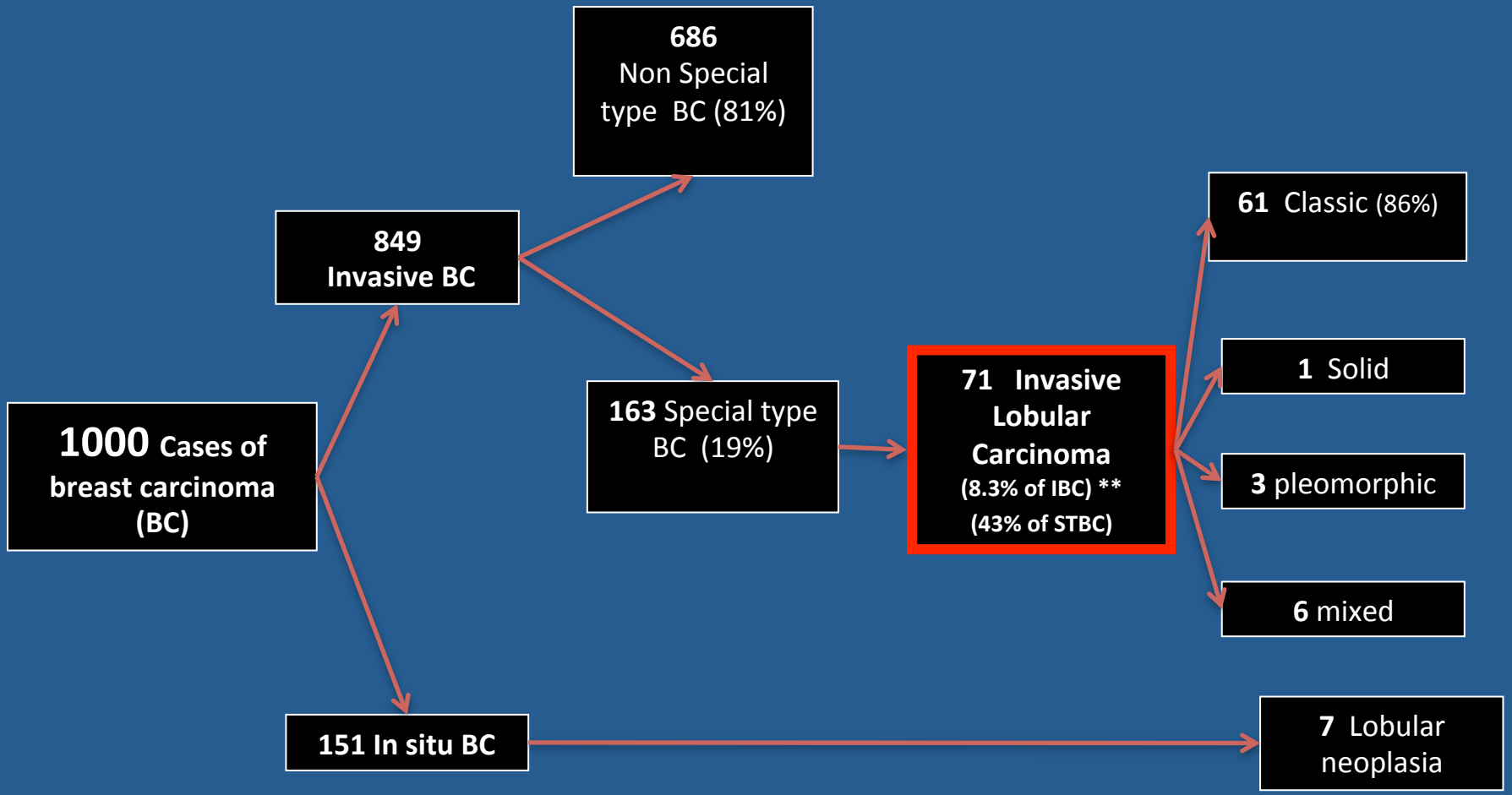
The terminology of ductal and lobular carcinomas is controversial as on purely histological grounds there is no justification for this nomenclature.

In fact both carcinomas (and their precursor lesions) originated from the Terminal Ductal Lobular Unit (TDLU).

Differences in their morphology are likely to reflect different mechanisms of carcinogenesis rather than the anatomical origin of the lesions.

On the other hand most of the supposed clinical and prognostic differences between these two histological types have been reconsidered in recent studies.

Histopathological subdivision of 1000 consecutive breast carcinomas * (Pathologic Anatomy and Histology – Perugia Medical School - 2009-2013)



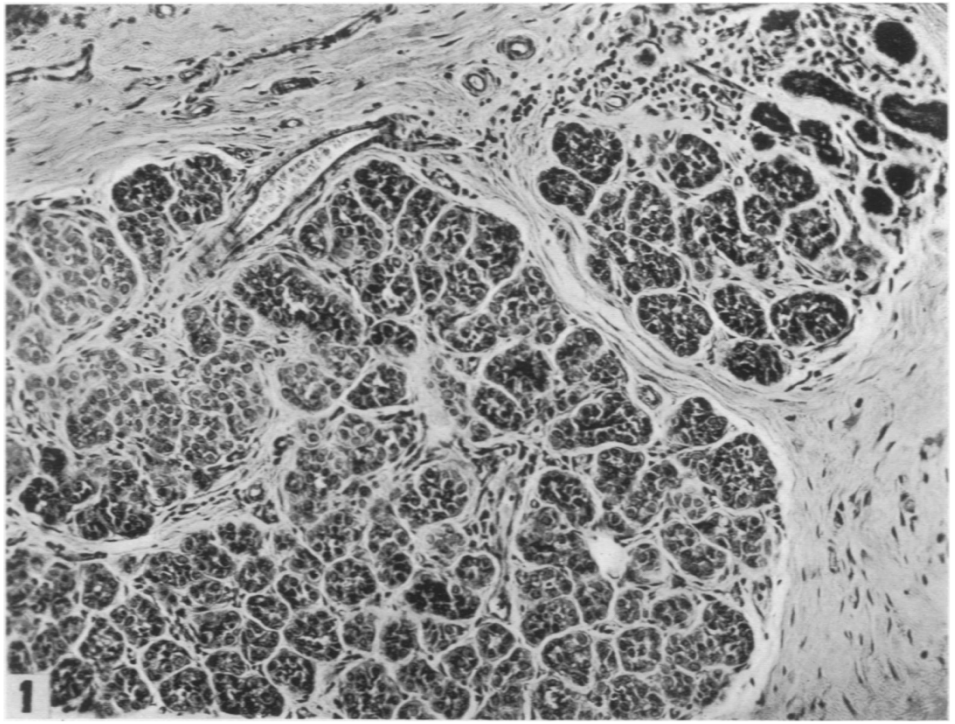
*according to the 2012 WHO classification
** 5-15% in pertinent literature

LOBULAR CARCINOMA IN SITU *

A Rare Form of Mammary Cancer

Frank W. Foote, Jr., M.D., and Fred W. Stewart, M.D.
(*From the Pathological Laboratories of the Memorial Hospital, New York, N.Y.*)

American Journal of Pathology. Vol. XVII Plate 93



* Received for publication November 25, 1940.
Presented at the Forty-First Annual Meeting of the American Association of Pathologists and Bacteriologists, New York City. April 11, 1941.
† For the American Society of Clinical Pathologists.

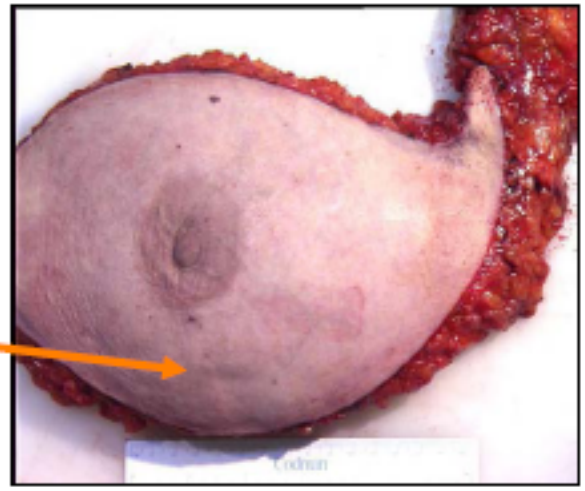
Clinical presentation

Age :

median age 45 to 57 years (= Invasive Ductal Carcinoma = IDC)
2% of breast carcinomas before 35
11% of breast carcinomas after 75

Clinical examination :

vague thickening or induration
nipple or skin retraction
central location
no Paget's disease



Contralateral cancer: higher risk than IDC (RR = 1.5 to 1.8)

(metachronous or synchronous)

Multicentricity: 31% , twice higher than IDC

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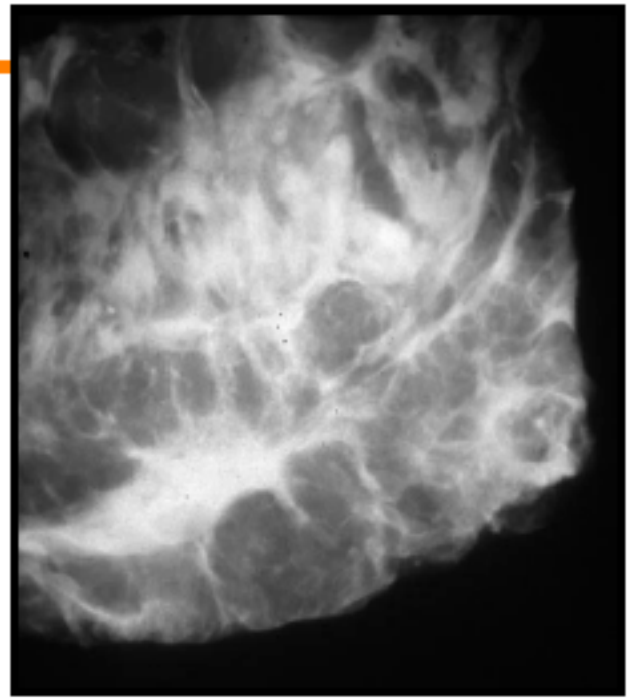
Radiological presentation

Mammography

- architectural distortion
- microcalcifications not frequent
- lesion not visible on all views
- size difficult to evaluate



Ultrasound

- irregular hypoechoic mass,
- posterior acoustic shadowing

Magnetic Resonance Imaging

better assessment of

- multifocality, bilaterality
- size

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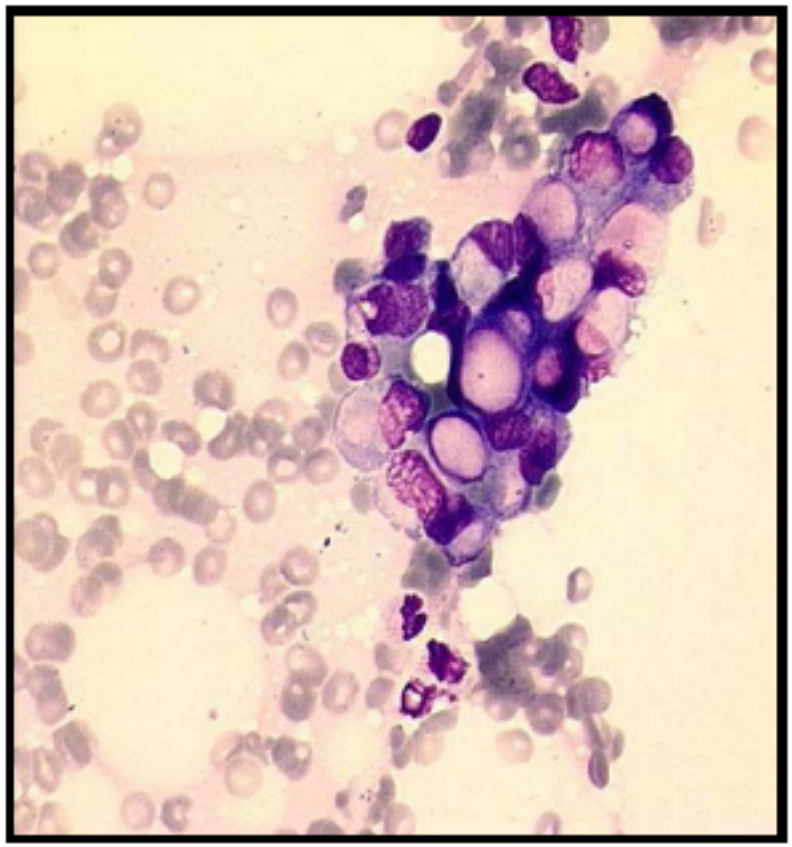
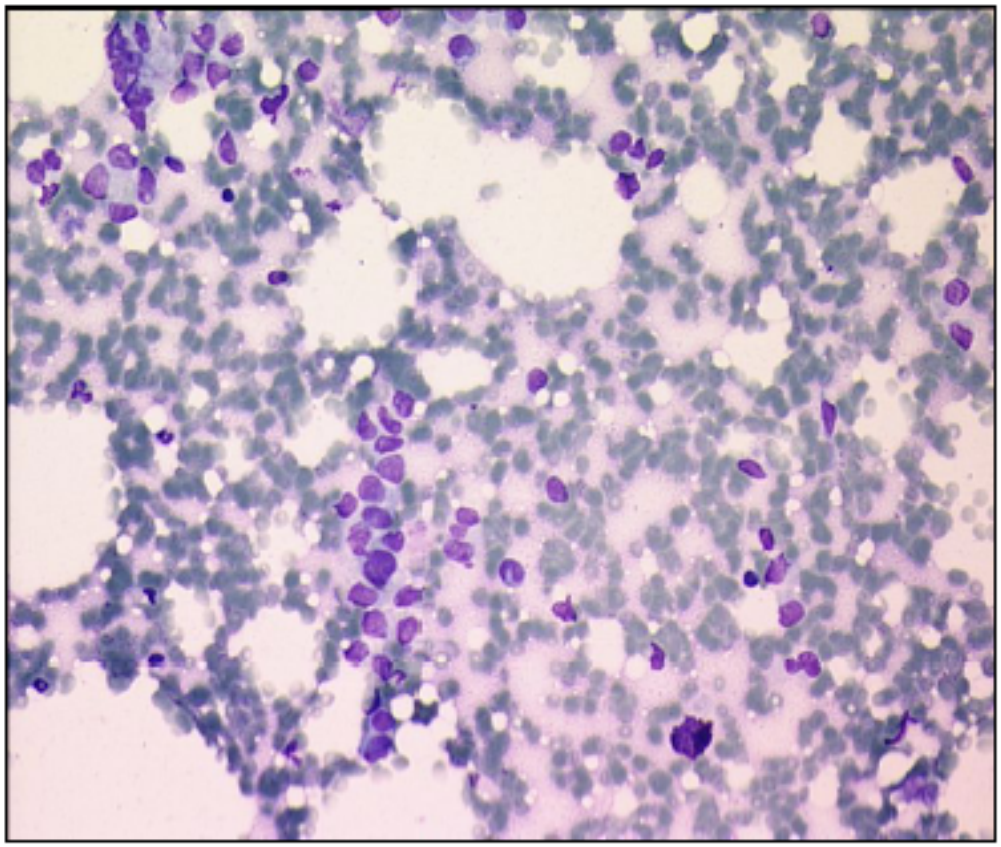
Diagnostic procedures

fine needle aspiration : hypocellular ⇒ hyposensitive





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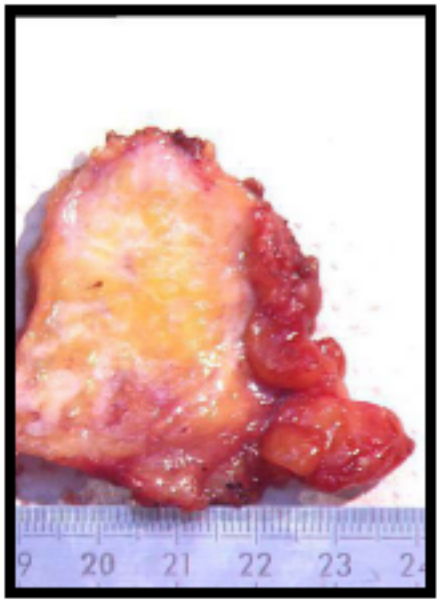
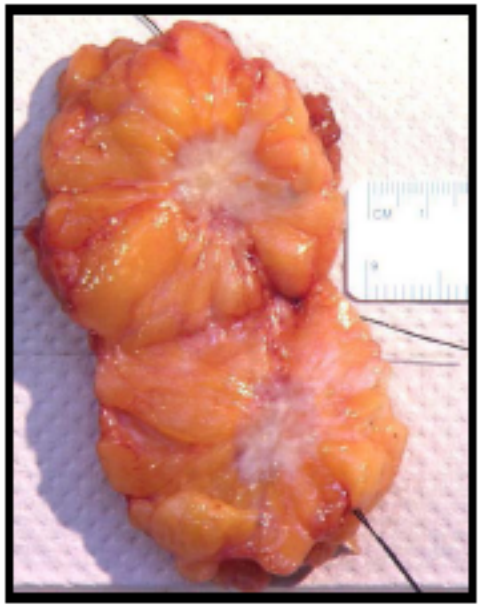
Pathological gross features

Irregular and poorly defined mass

Size larger than in IDC: ILC 19% > 5cm / IDC 12% > 5cm



ILC



IDC

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Histopathology

specific features > 90% of the tumor

classical type

variants :

architectural patterns

- alveolar
- solid

mixed features

cytological aspects

- pleomorphic
- signet ring cell carcinoma

in common : lack of cell to cell cohesion

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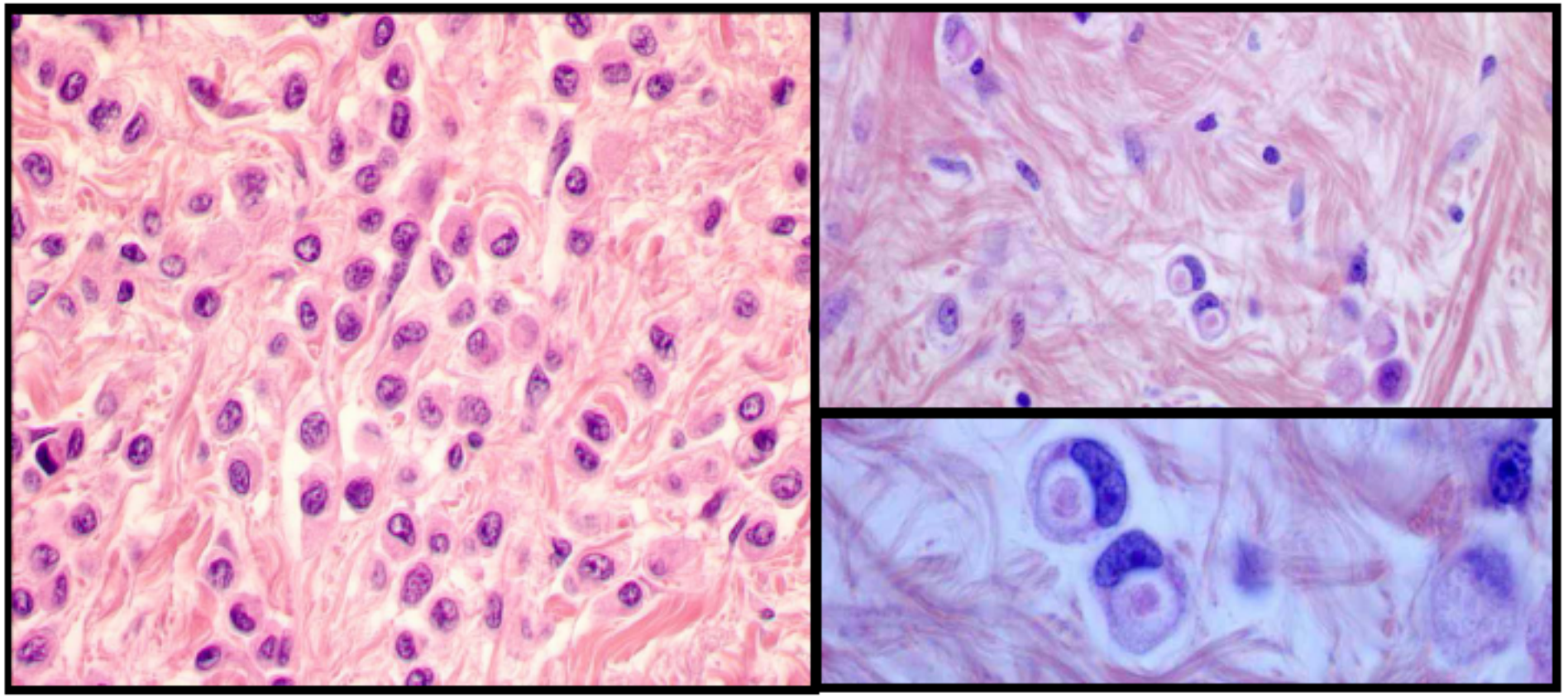
Classical ILC



Non cohesive small cells,
low proliferation rate (< 10 mitoses / 10 HPF),
intracytoplasmic vacuoles or lumens (in a minority of the cells in 64% of the cases), no necrosis, rare lymphoid infiltrate

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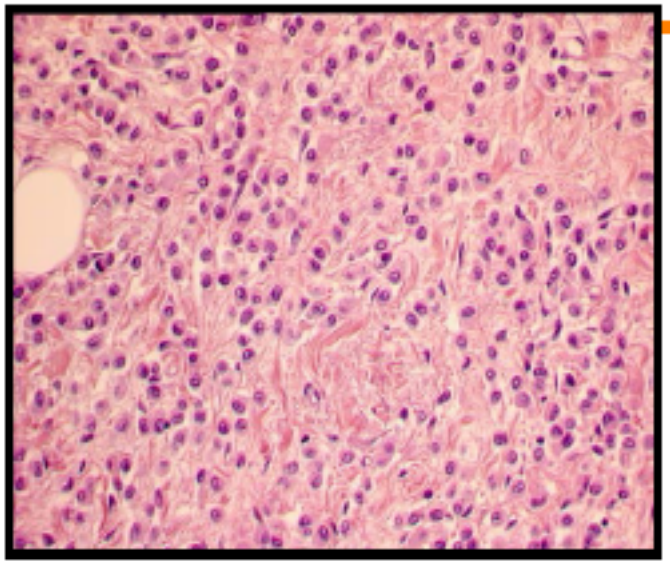
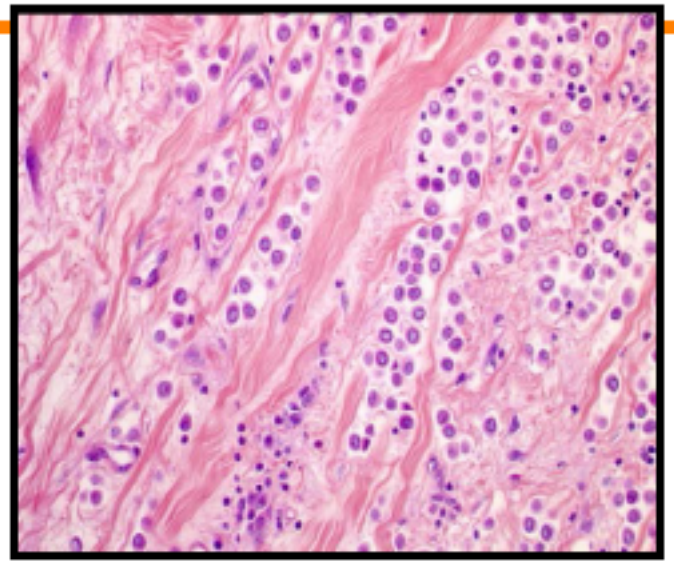
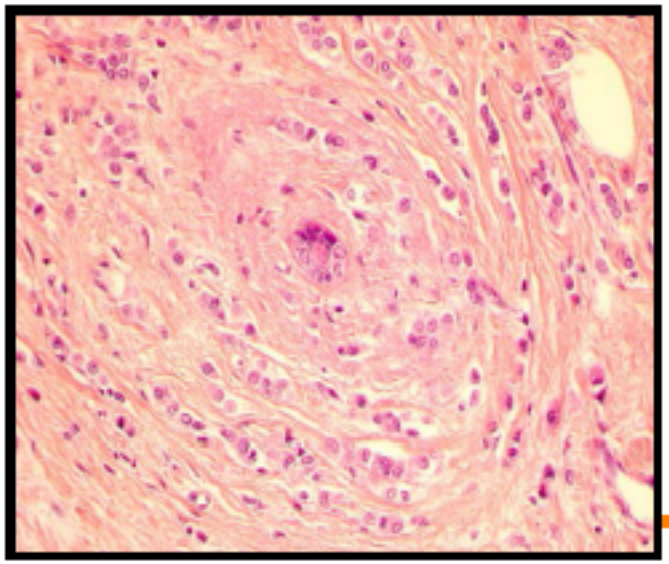
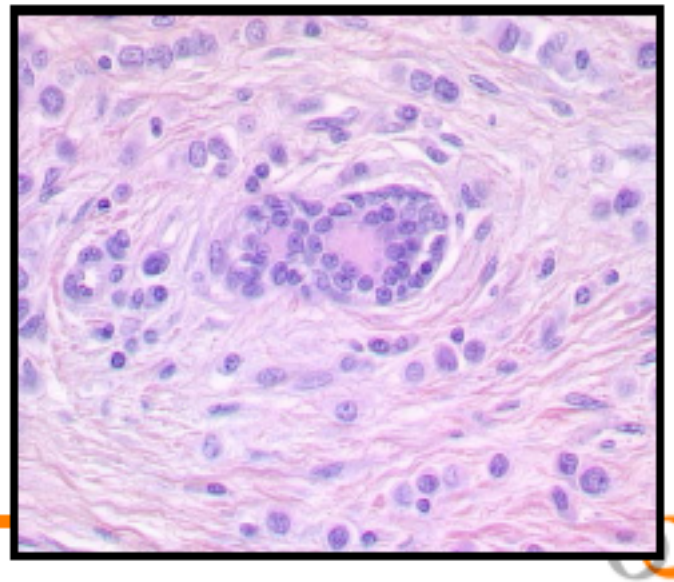
Classical ILC



Isolated cells







Concentric pattern around normal ducts

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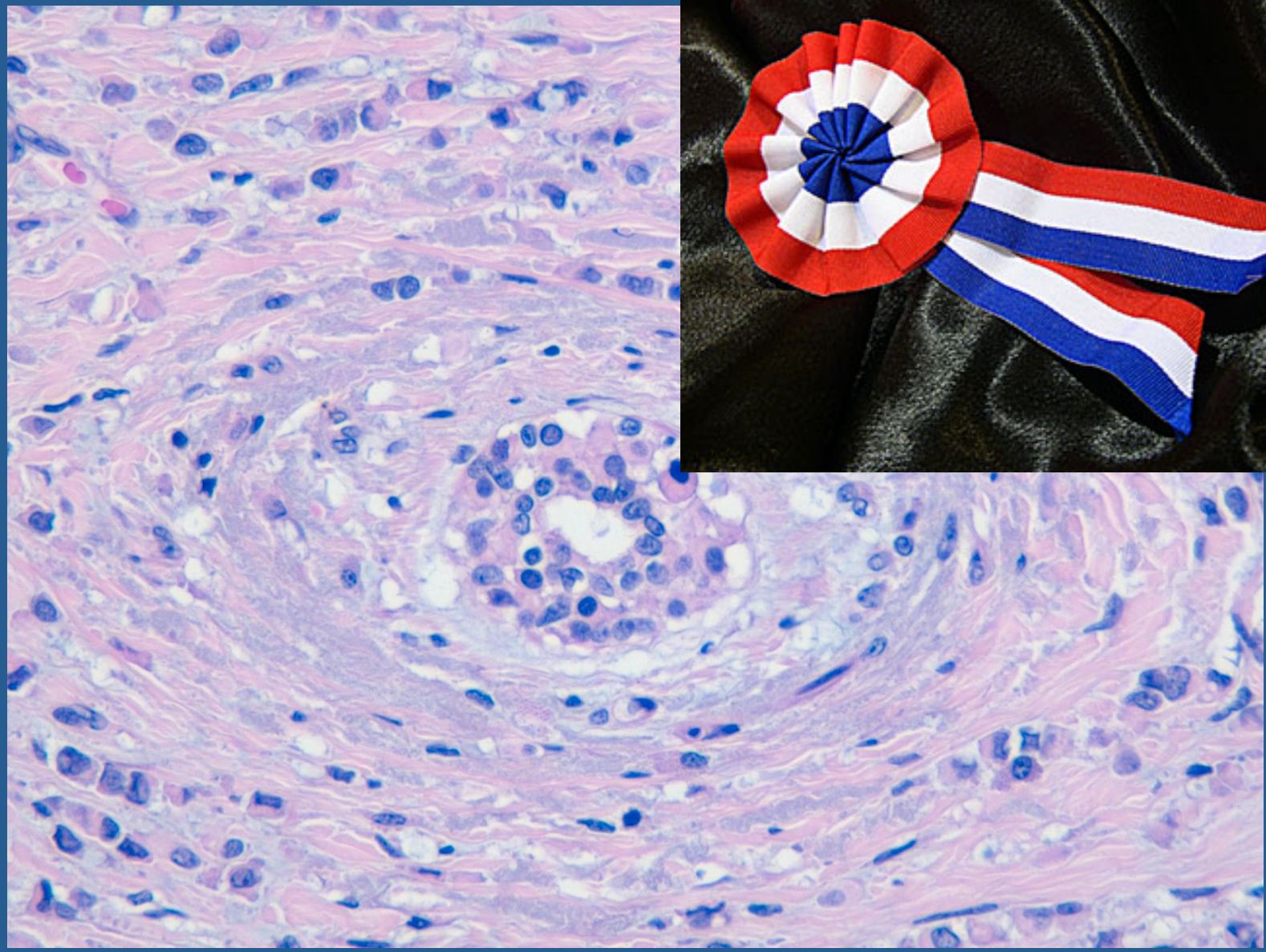
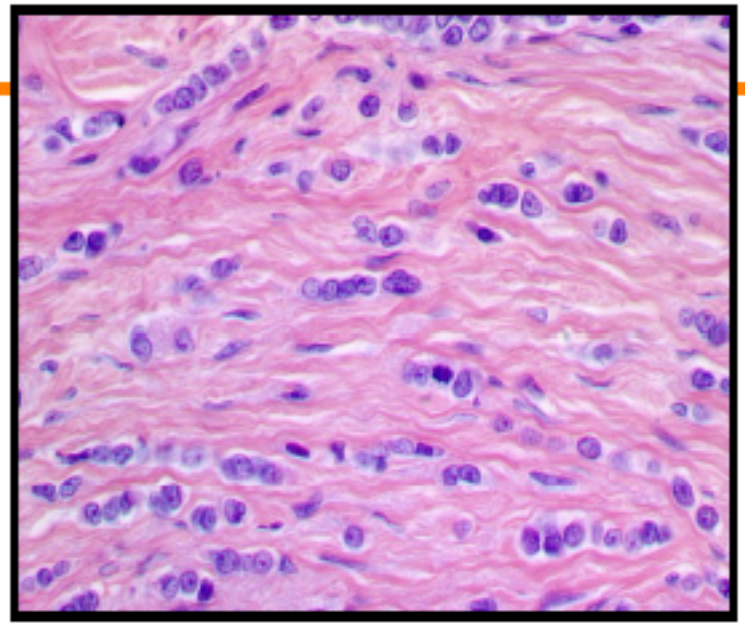
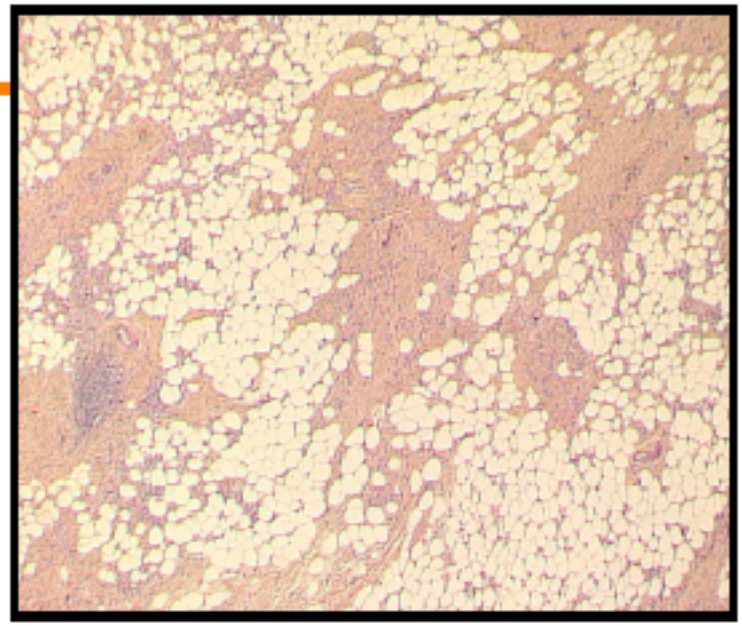


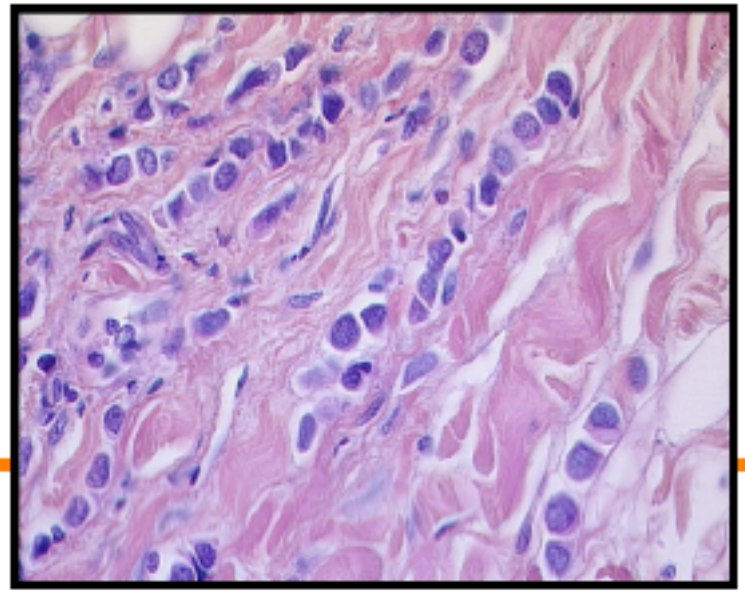
Classical ILC

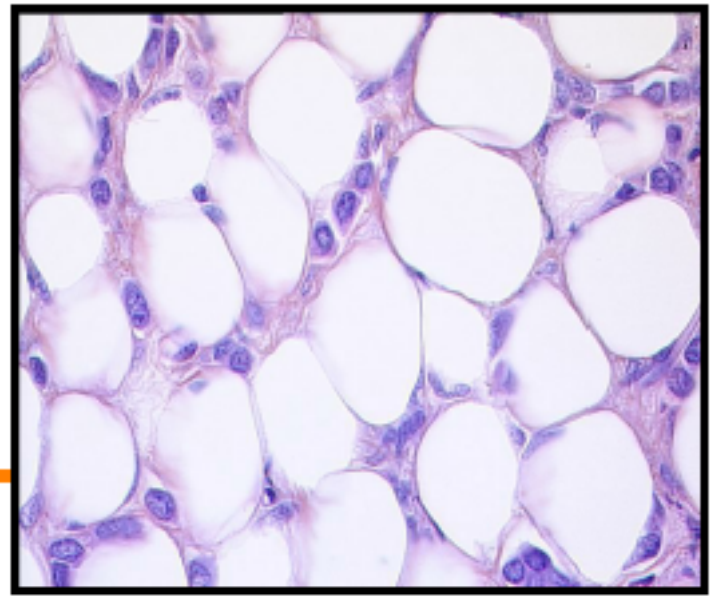


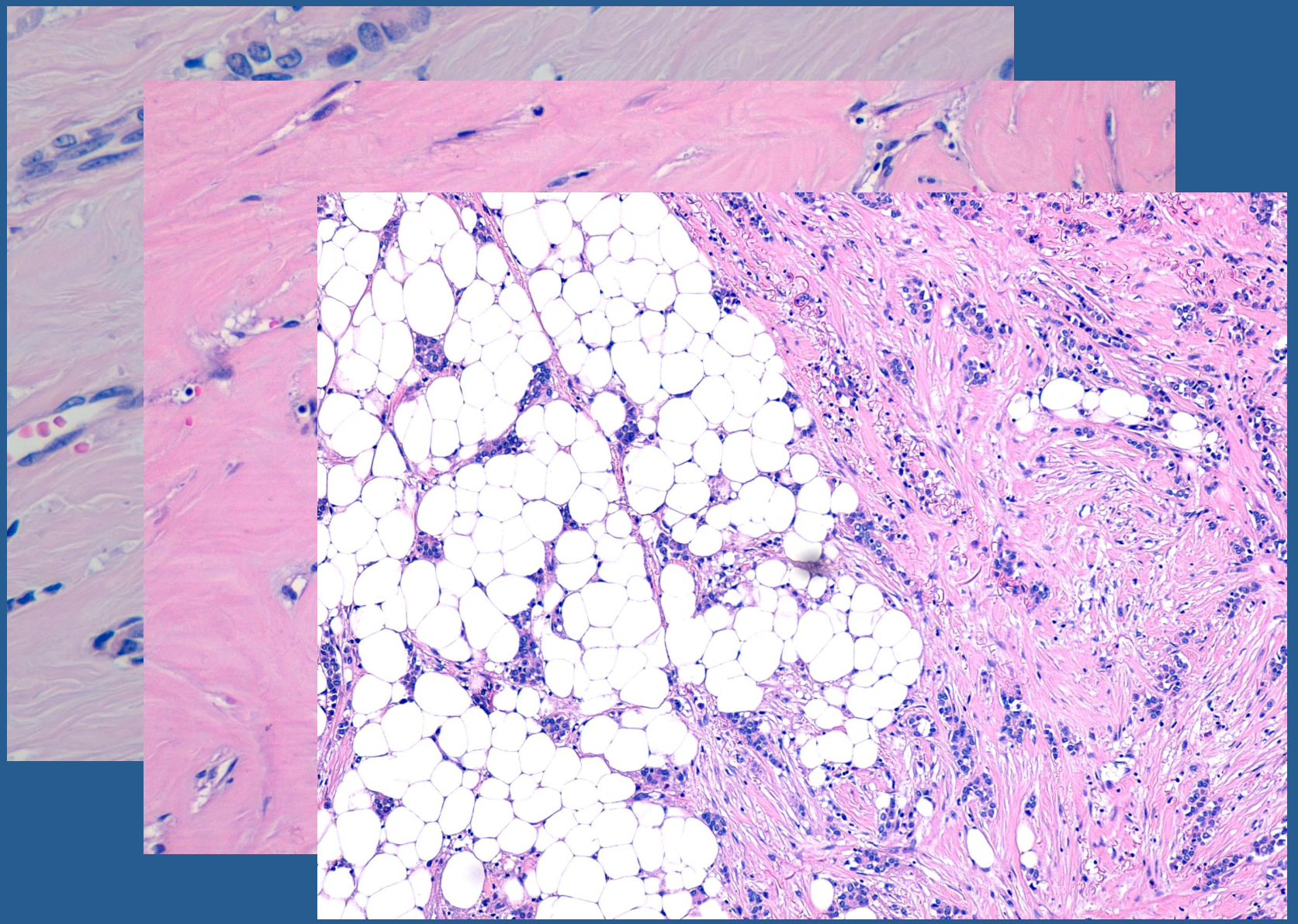
Single file and linear cords in the stroma



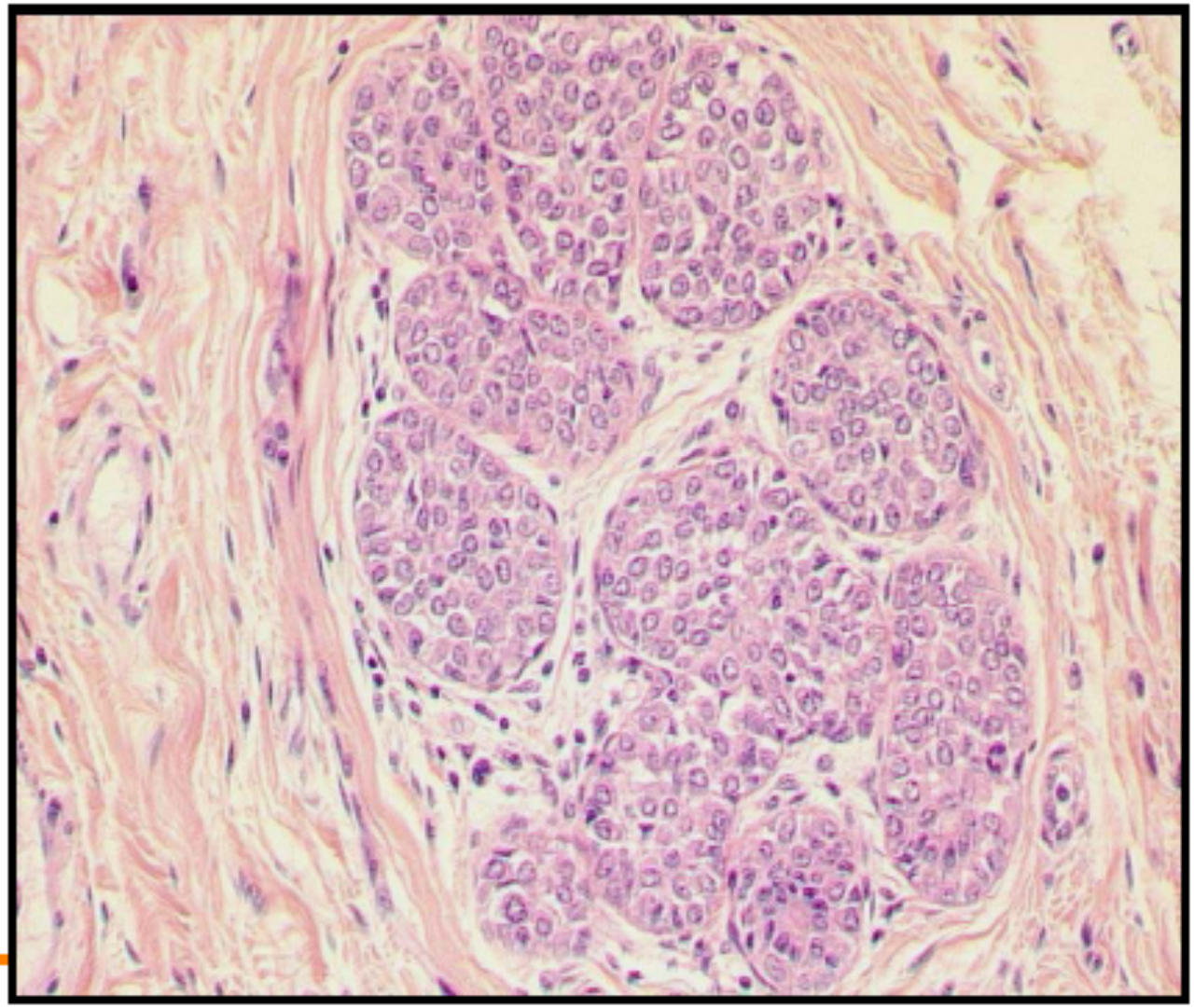
in the adipose tissue







Lobular carcinoma *in situ* associated in 60 to 90% of the cases



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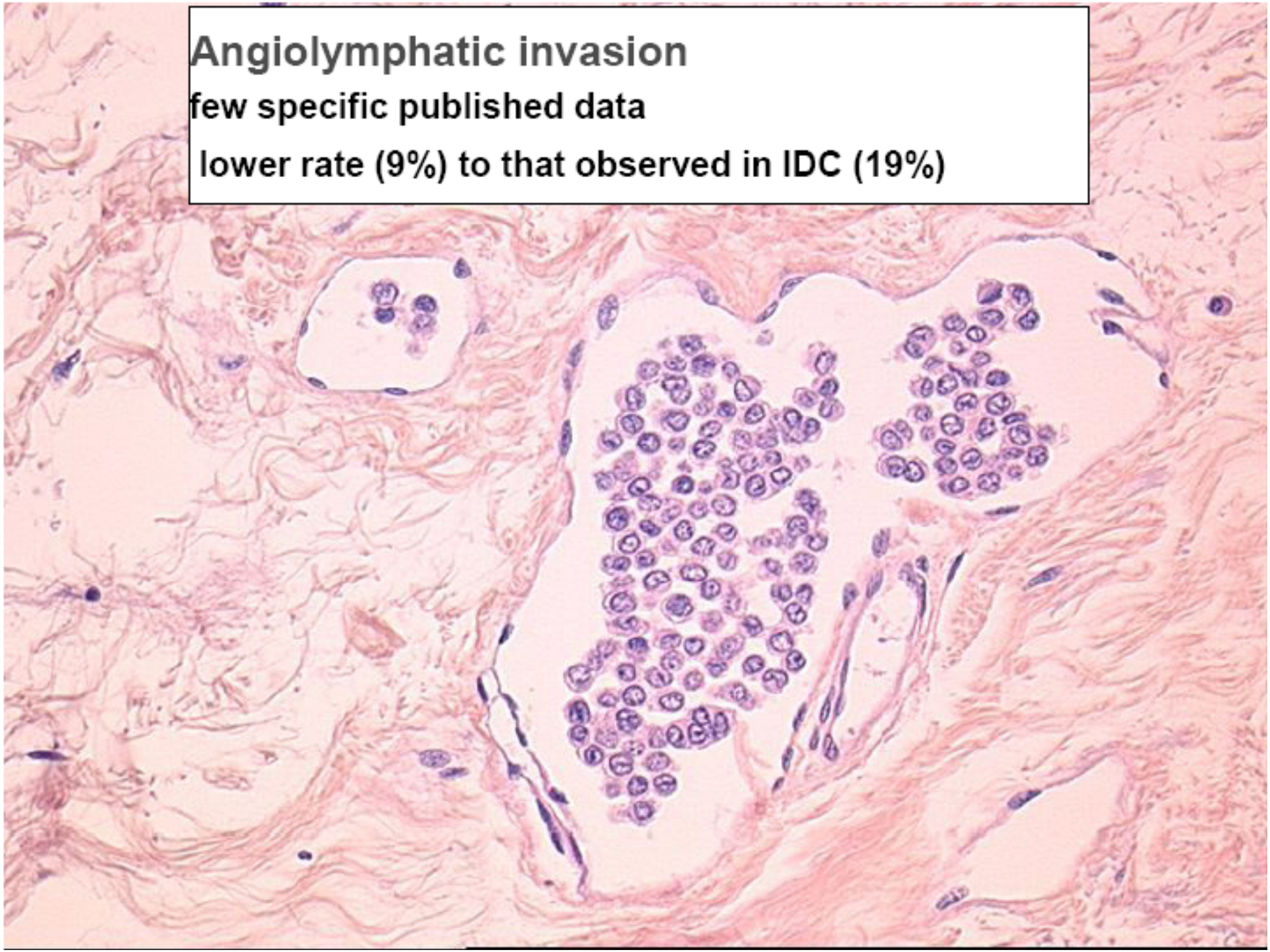
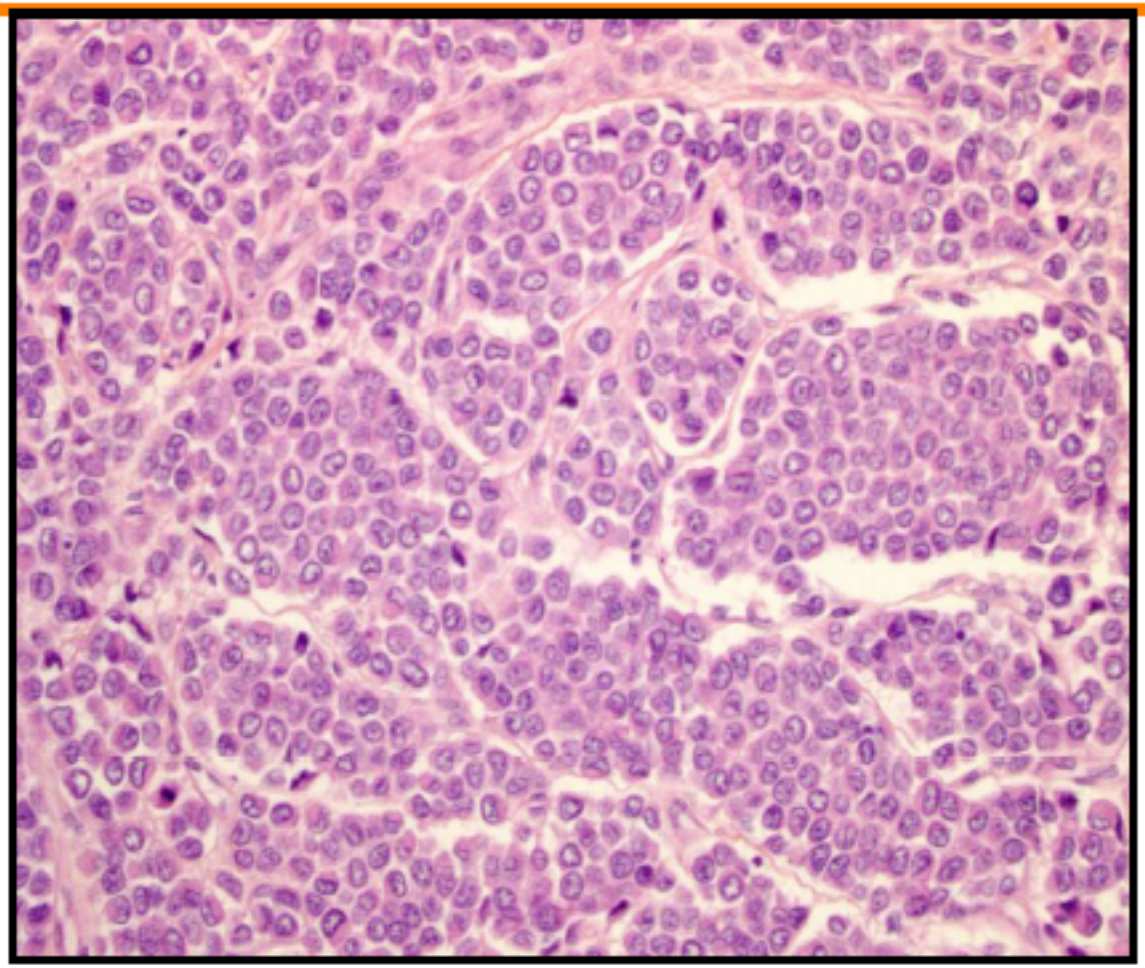

Angiolymphatic invasion
few specific published data
lower rate (9%) to that observed in IDC (19%)

ILC alveolar variant



Clusters of at least 20 cells, that lack cell to cell cohesion, separated by thin bands of stroma

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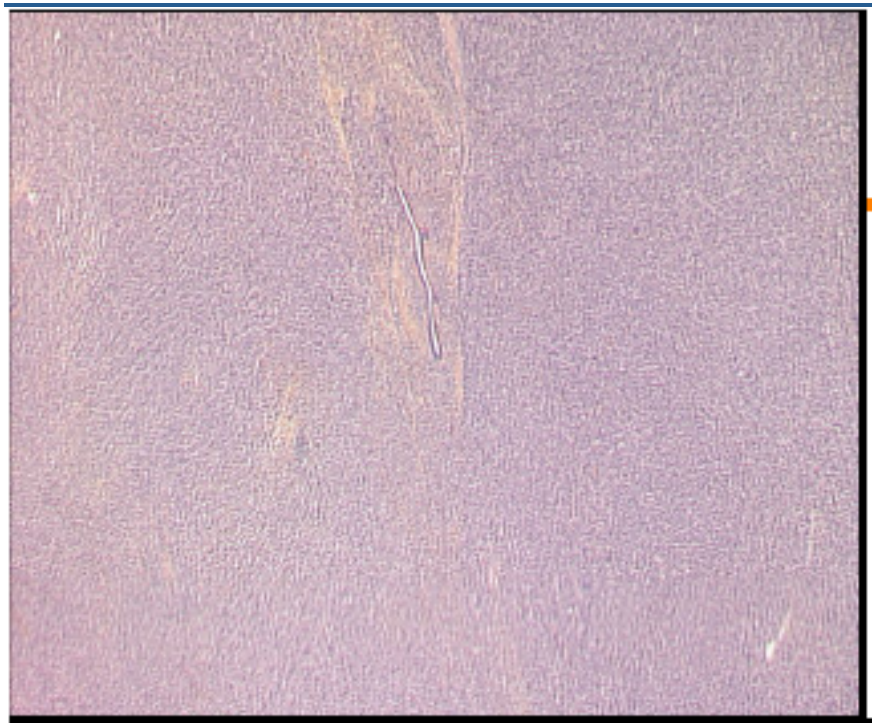
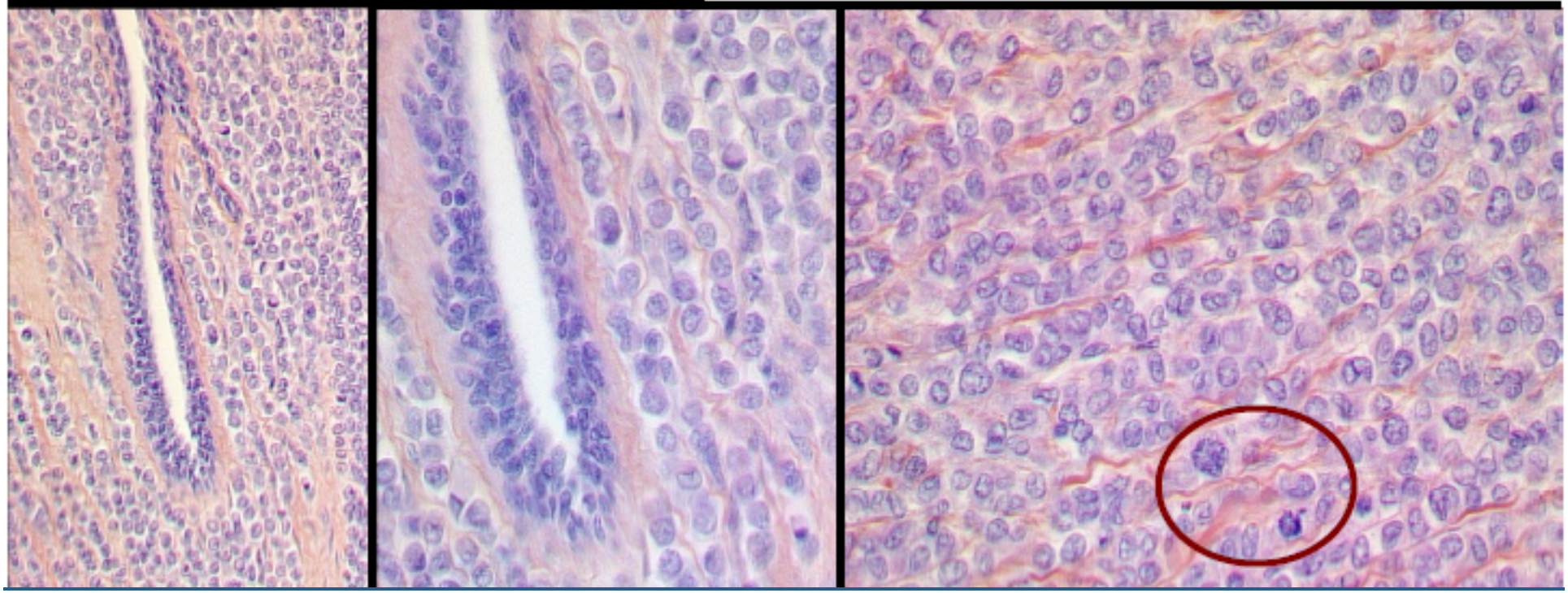
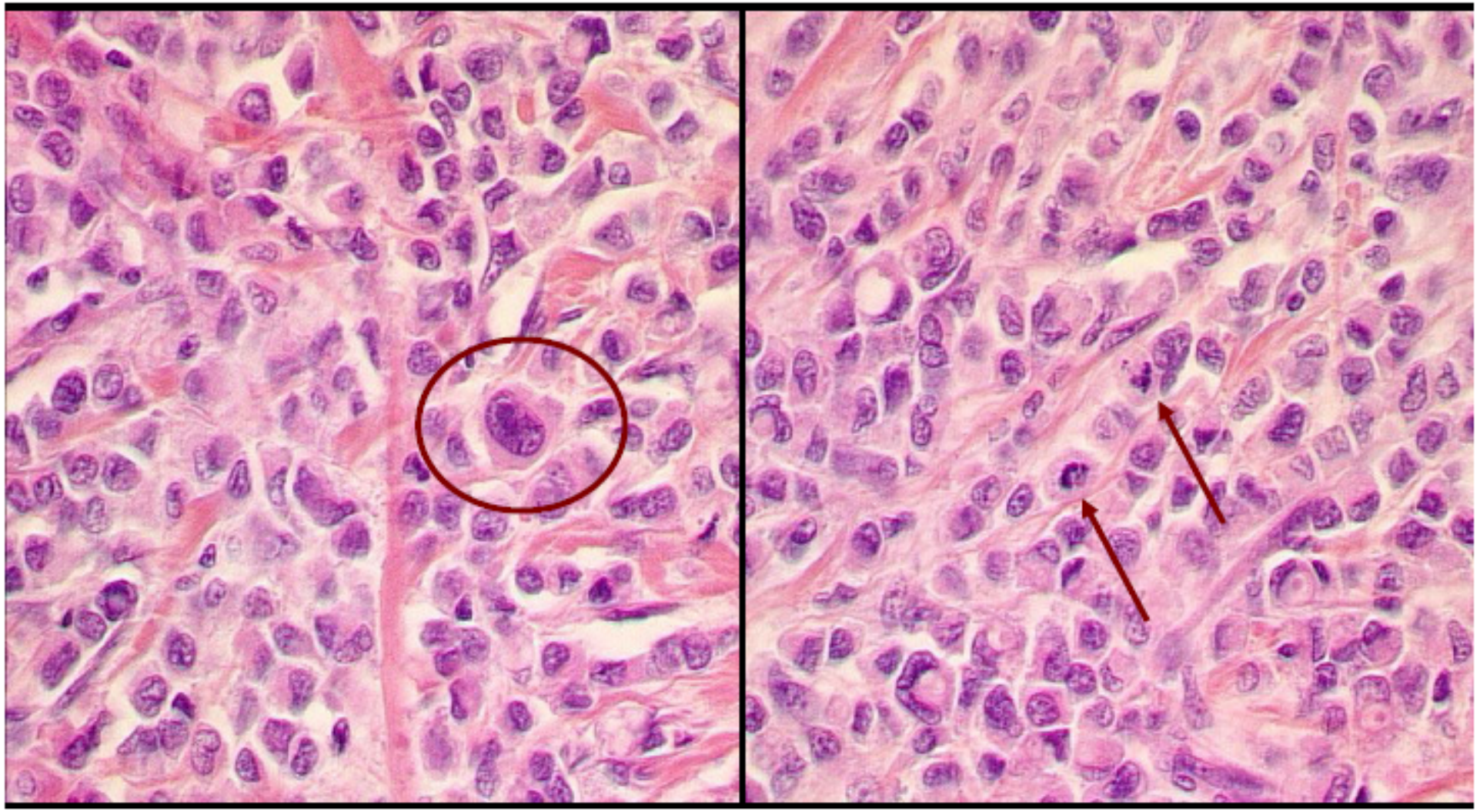


ILC solid variant :

solid sheets of uniform cells
with often more mitosis
and anisocaryosis

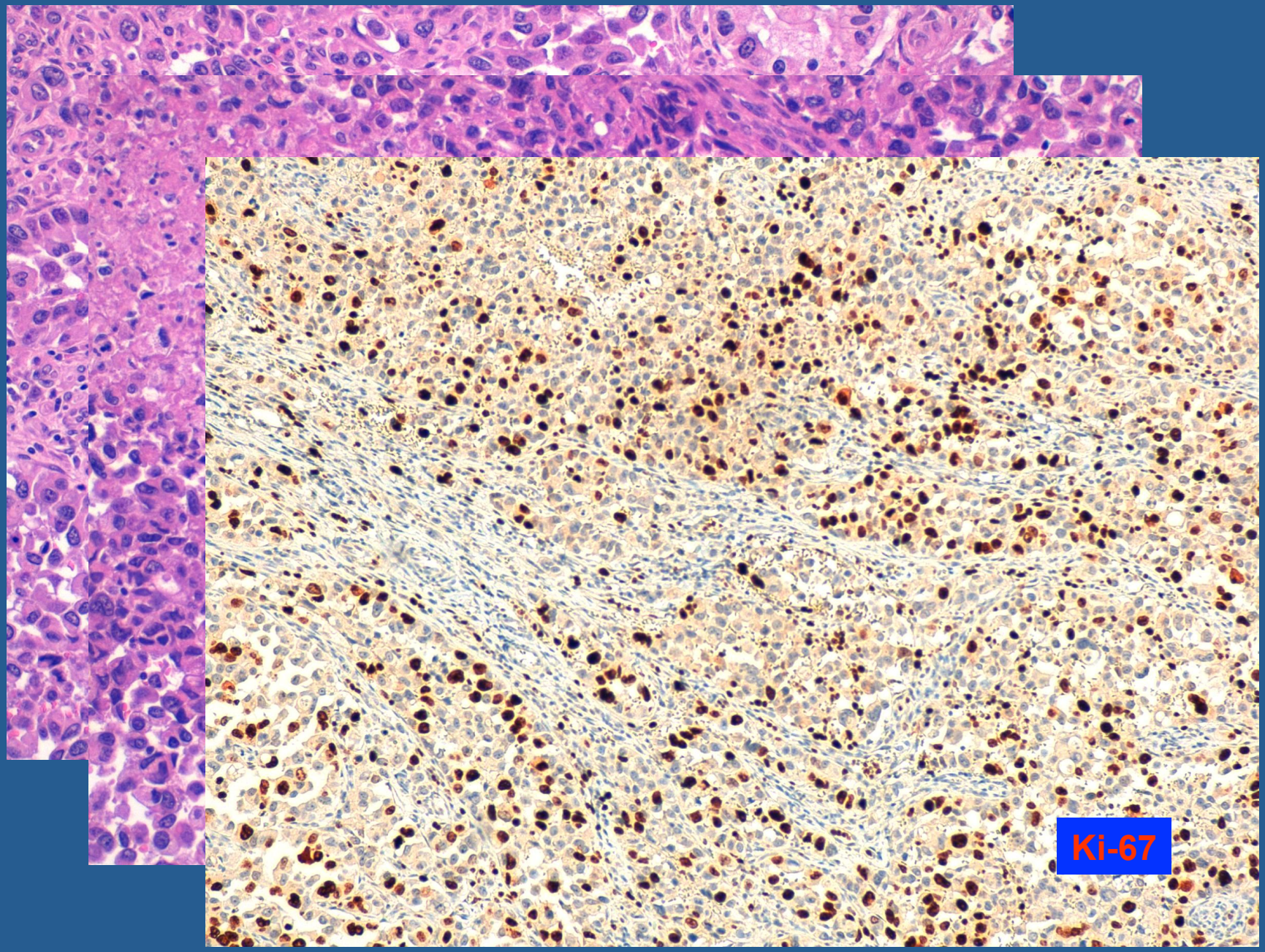


ILC pleomorphic variant

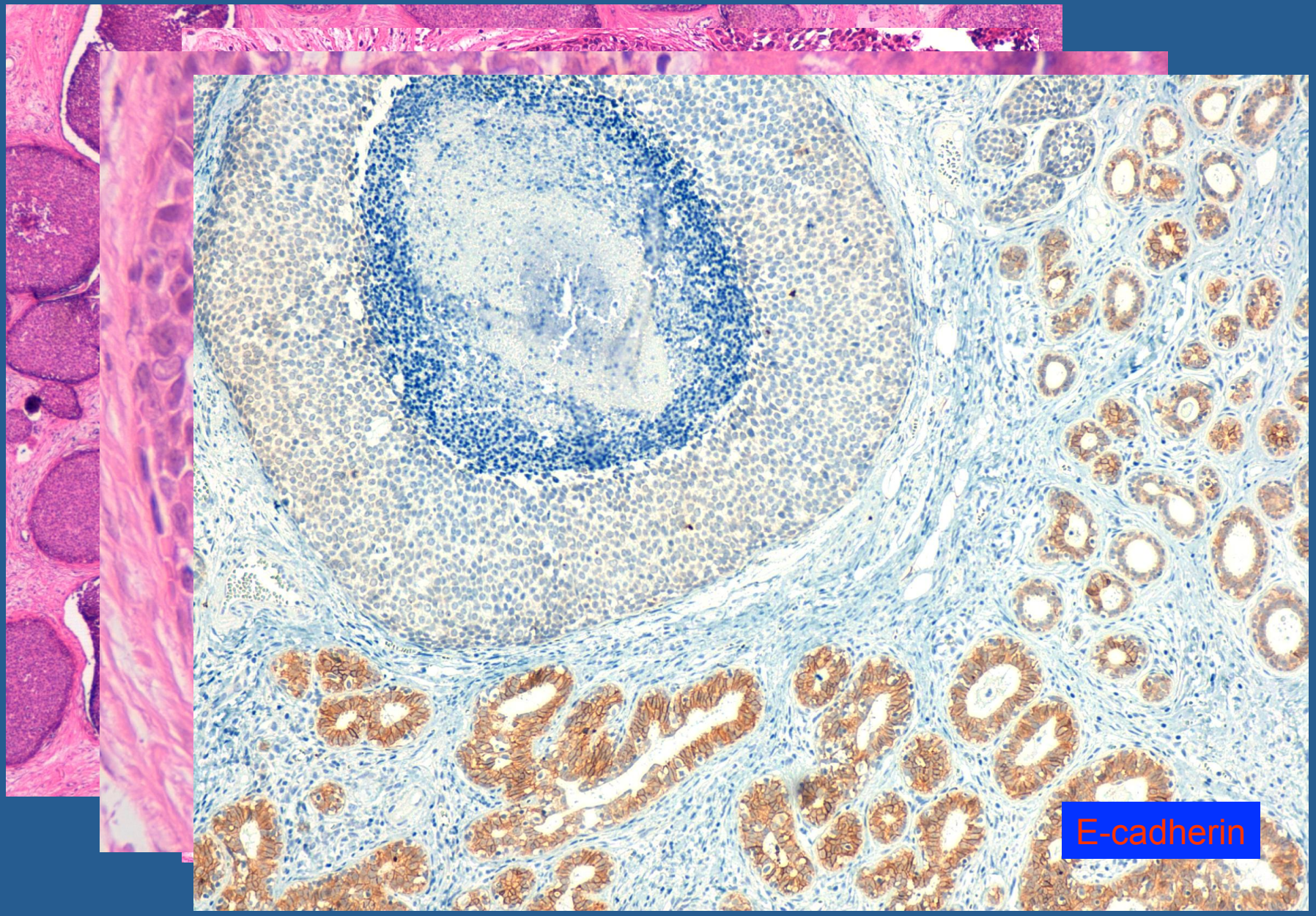


Non-cohesive cells, nuclear grade 2 or 3,
higher rate of mitoses (2.5 to > 10 mitoses / 10 HPF)

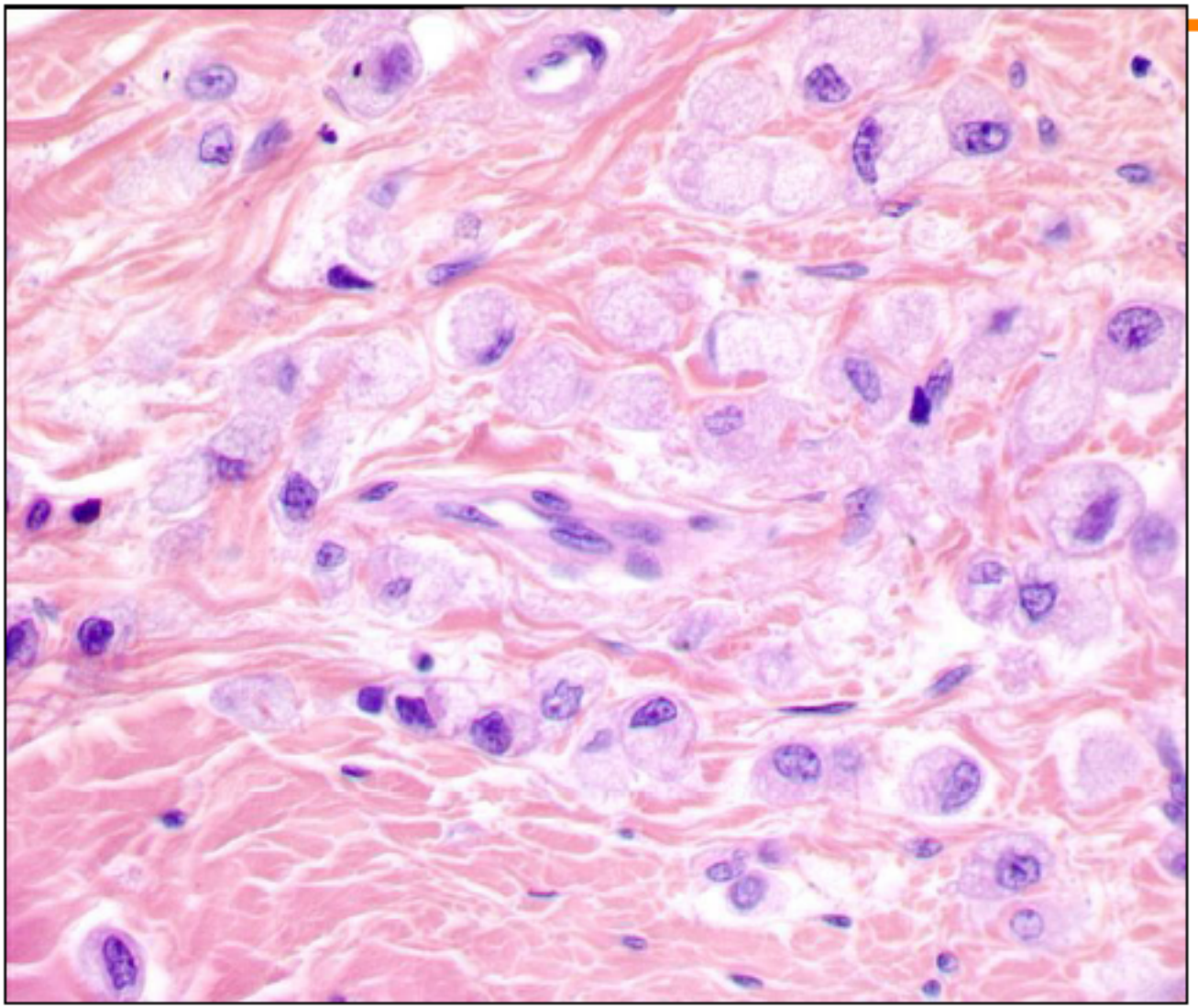
Pleomorphic lobular carcinoma (PLC)

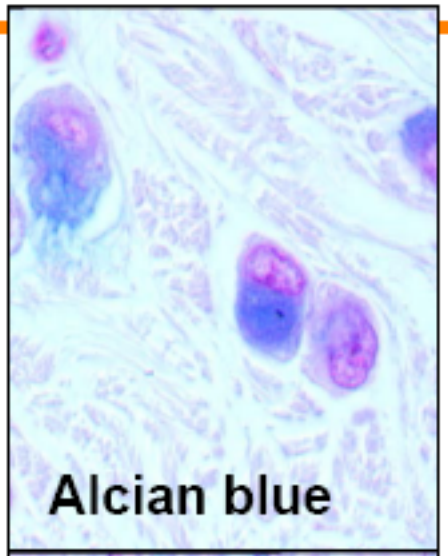


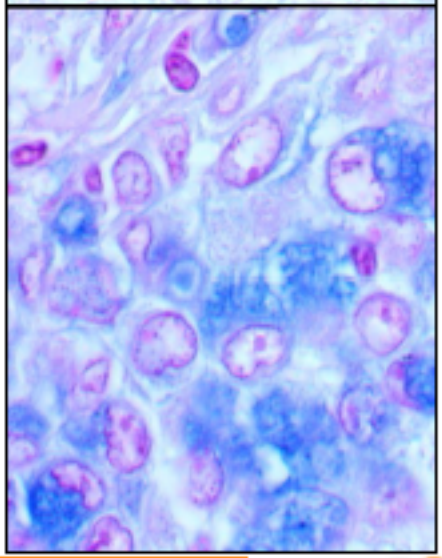
Frequently associated with the homologue in situ counterpart (PLCIS)



Signet ring cell is not a ILC variant in WHO 2012 classification.







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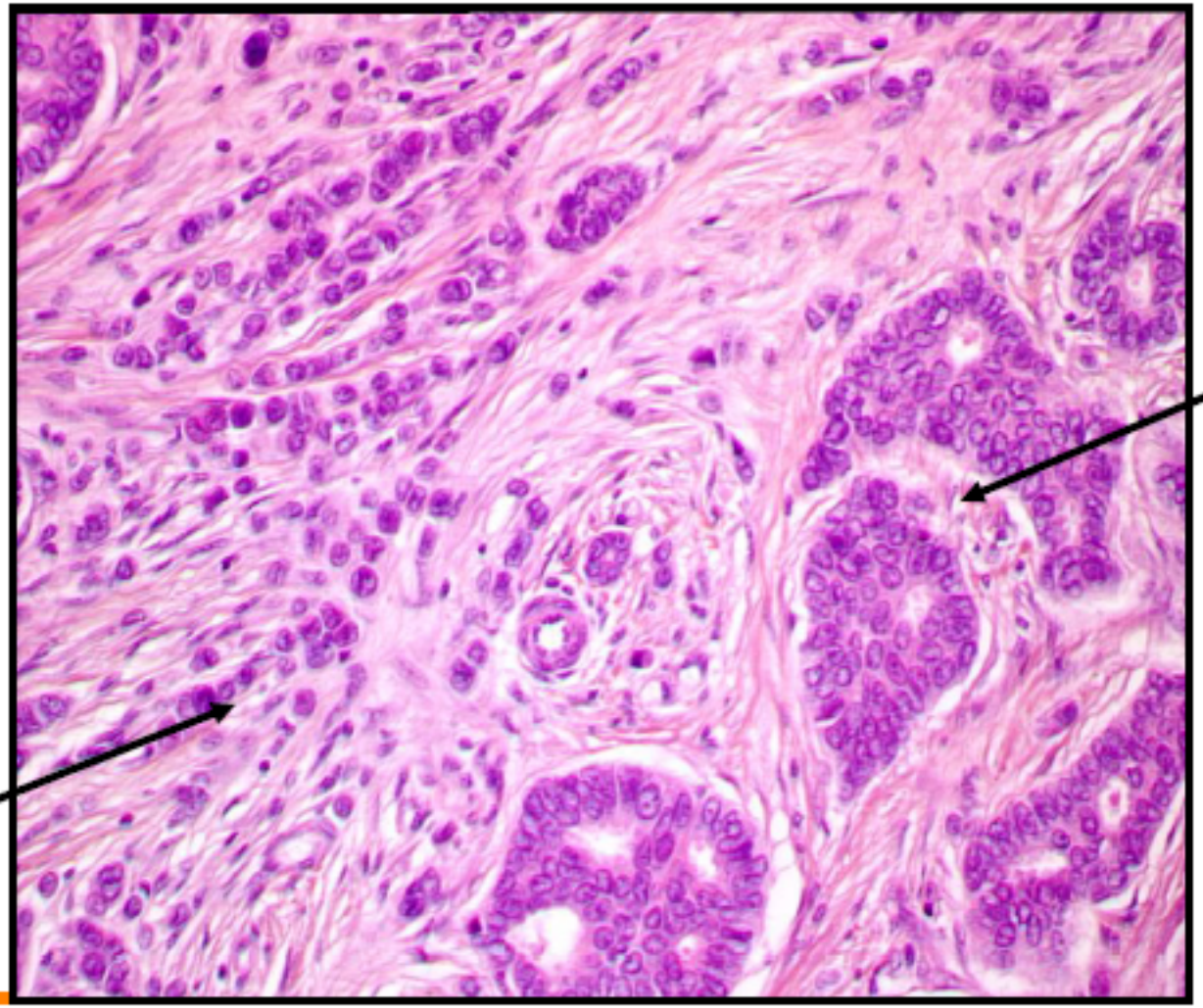
Mixed ductal and lobular carcinomas

2 to 5% of breast carcinomas



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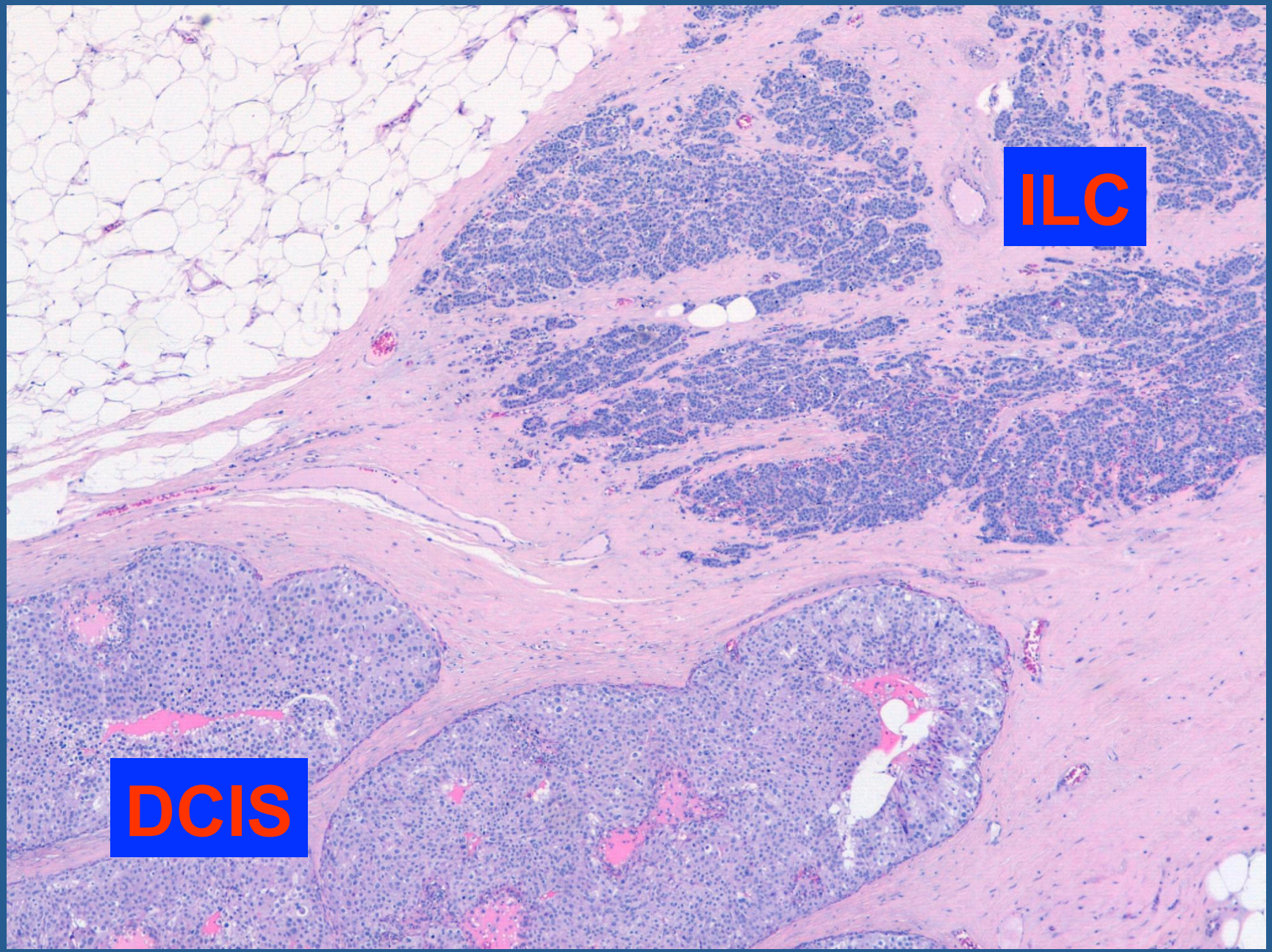
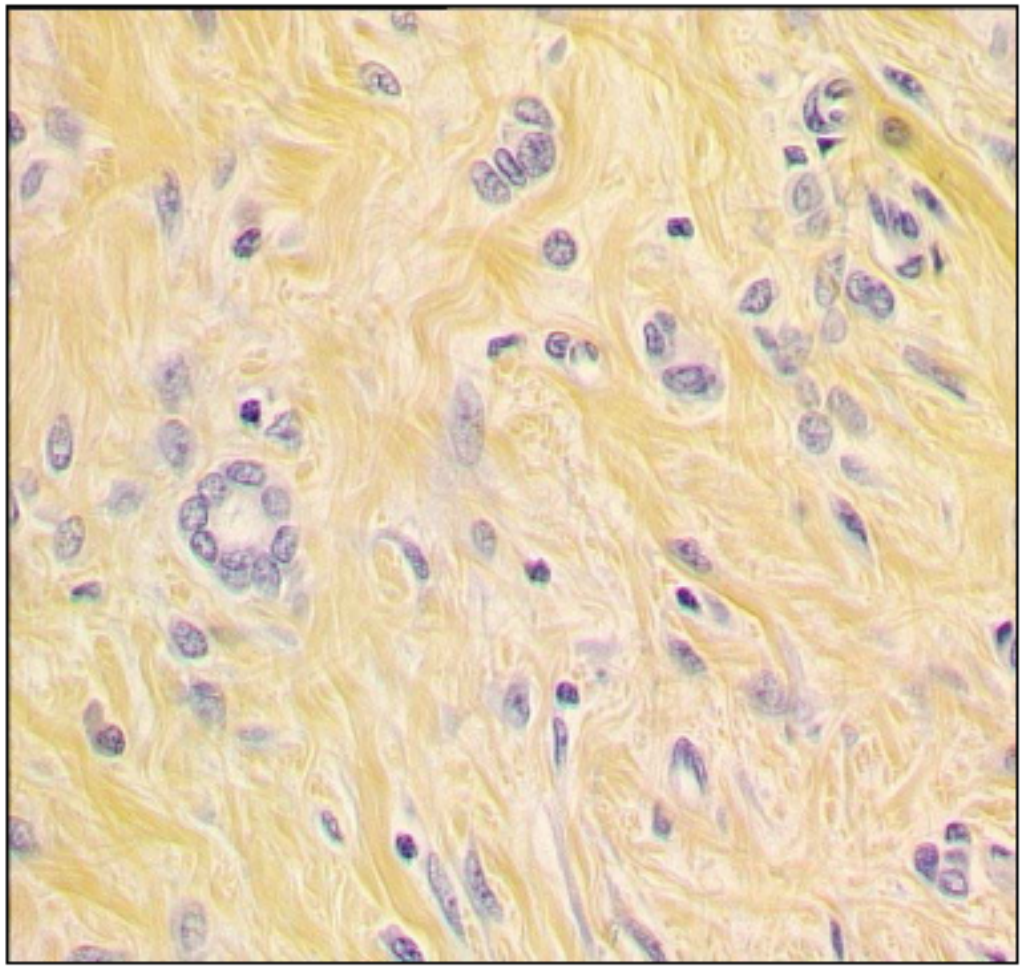
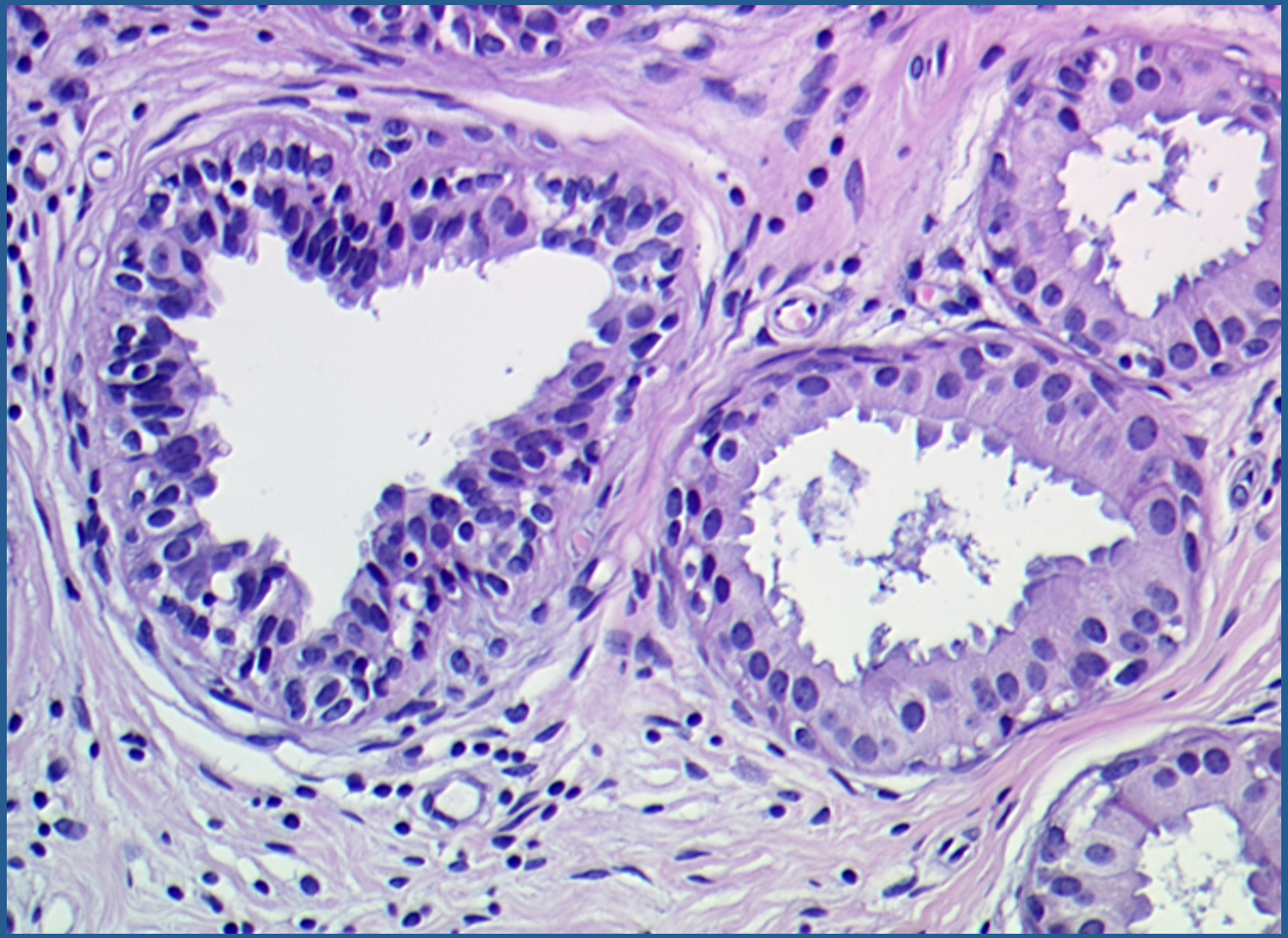

ILC
DCIS

Tubulo-lobular carcinoma : is an ILC variant (WHO 2012 classification)



Tubules lined by cohesive cells (one cell thickness)

associated to isolated cells or cells arranged in a linear pattern



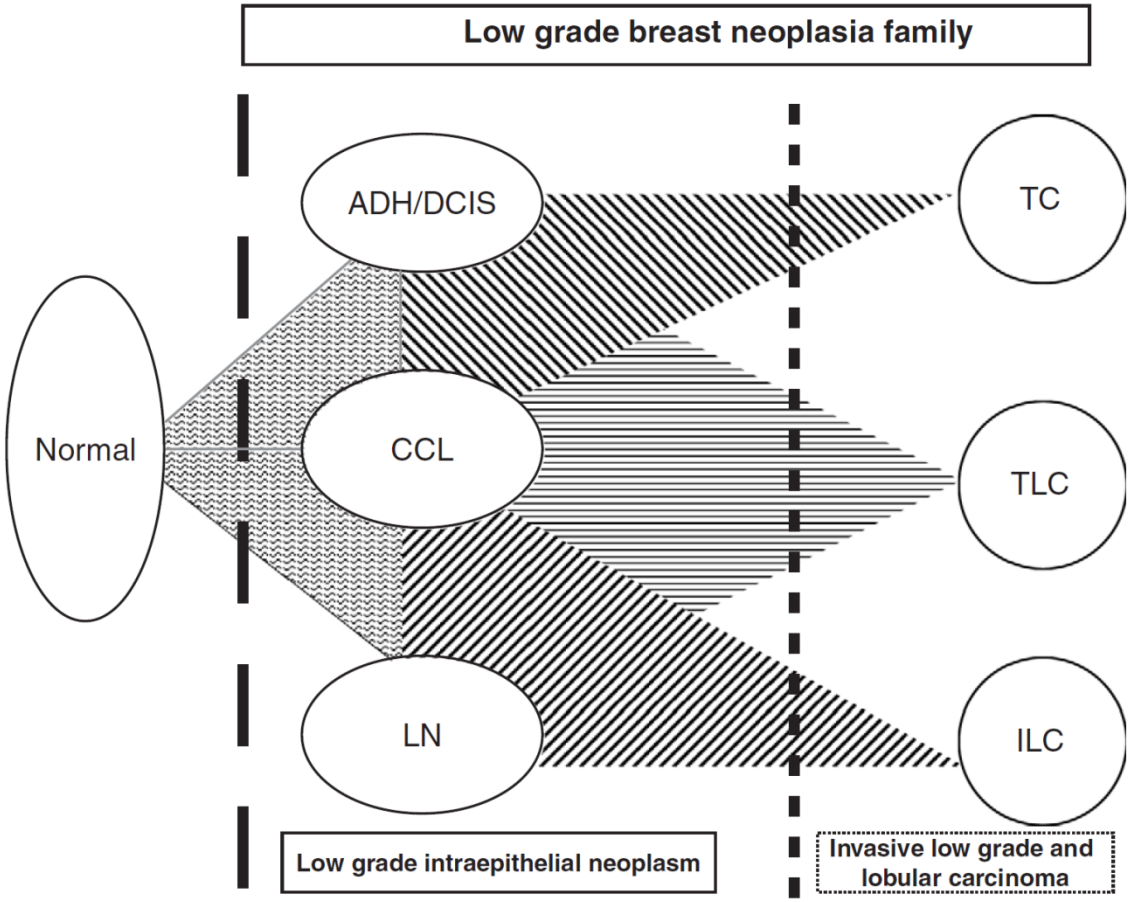
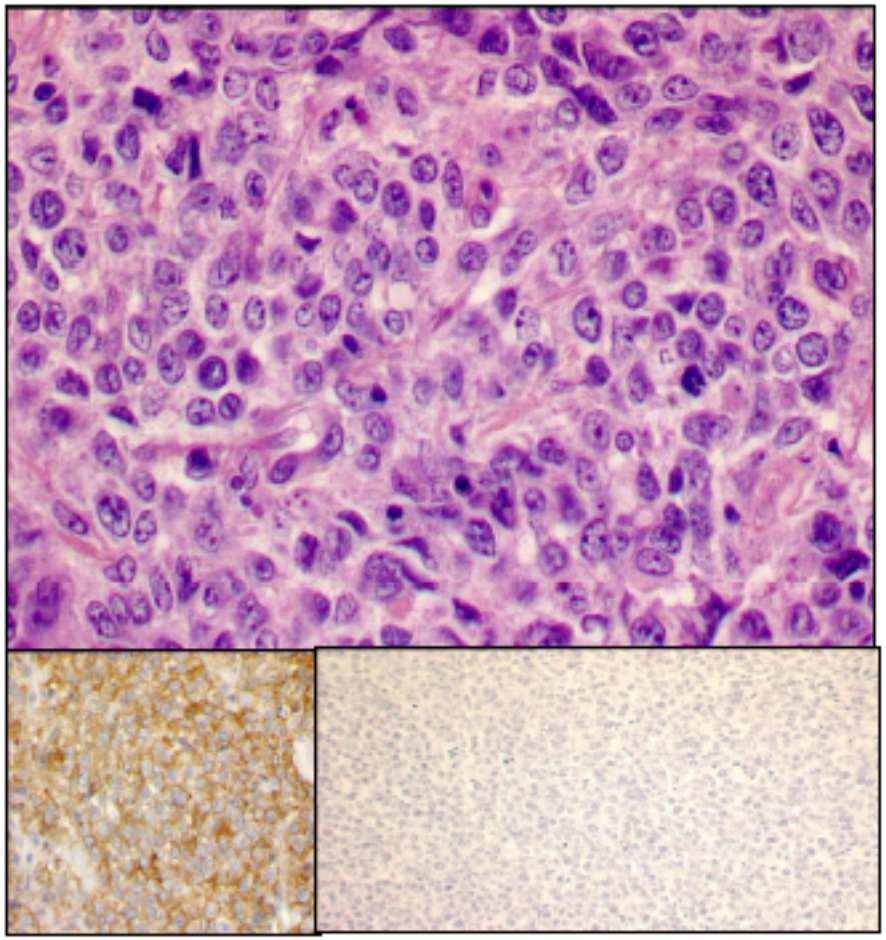


FIGURE 9. Evolutionary pathways of low grade breast neoplasia.

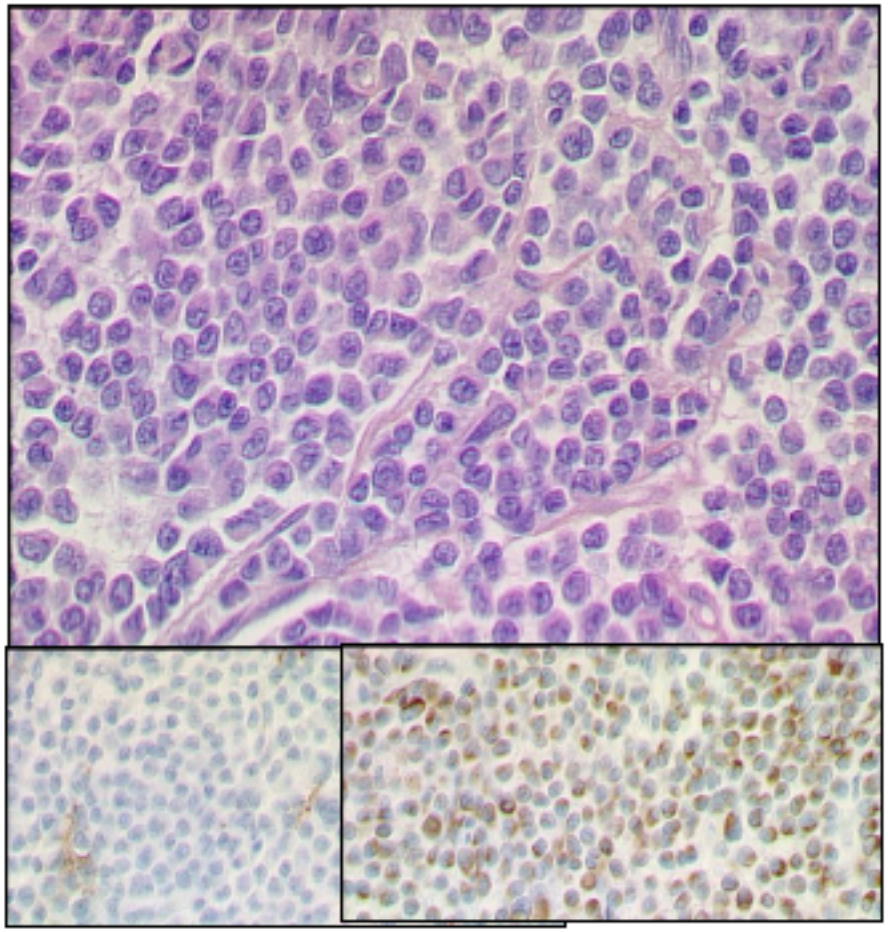
Differential diagnosis

between

large B cell lymphoma and a solid lLC



CD 45 Pan keratin



CD 45 Pan keratin

ILC current biological profile

	ILC		IDC
ER +	70 - 95%		85%
PR +	60 - 75%		60 - 75%
HER 2 +	0 - 5%		15 %
p53 +	classical	6%	30%
	pleomorphic	50%	
Ki67 +	10%		17%

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Genetic alterations of ILC

loss of chromosome 16q (LOH)

loss of E-cadherin gene function

correlation phenotype / genotype

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E-cadherin

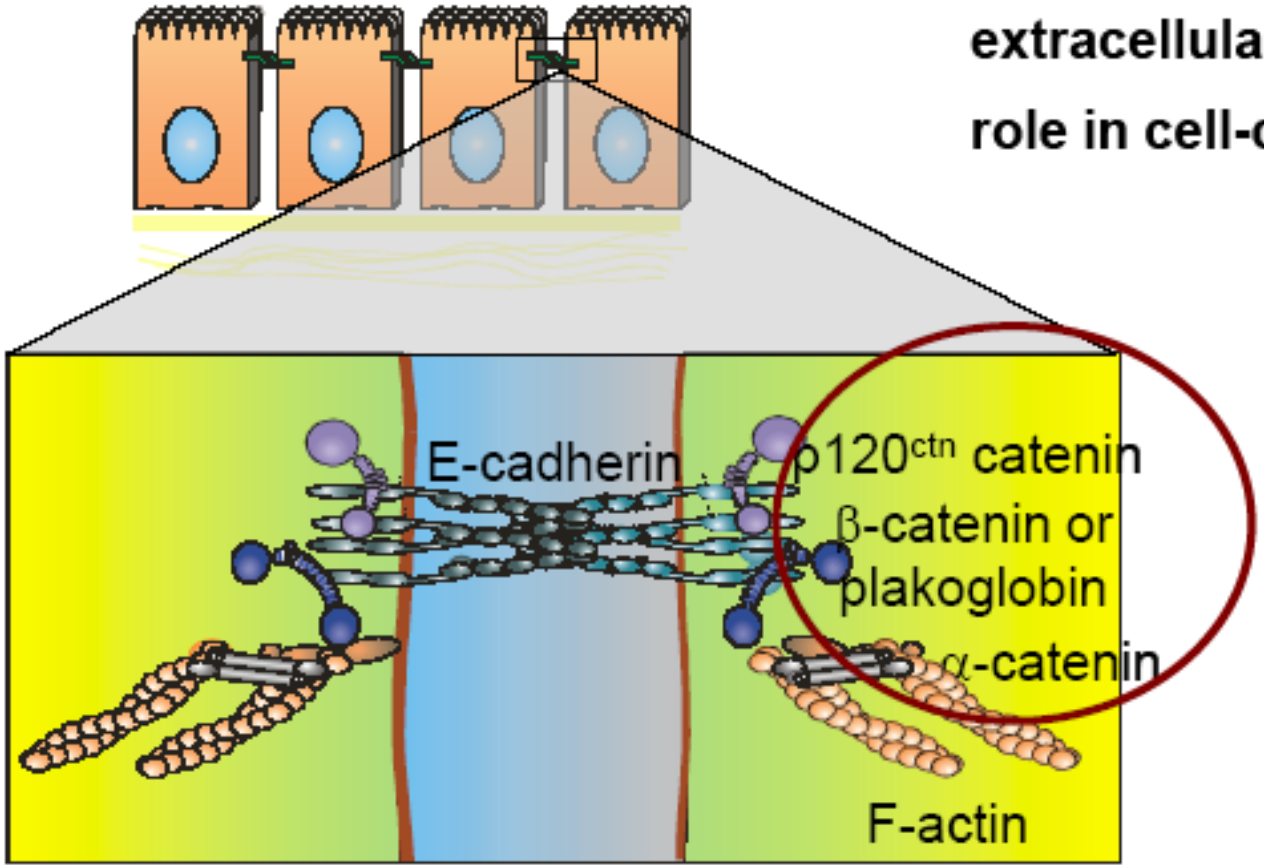
Gene: 16q22.1

tumor supressor gene

Protein: transmembrane protein

extracellular domain

role in cell-cell cohesion



Scheme adapted from van Roy

Genetic alterations of ILC
loss of E-cadherin gene function

1. Alteration of one allele: LOH long arm of chromosome 16:

63 to 87% of ILC versus 30% to 50% of IDC

2. Alteration of the remaining allele

mutation

- truncating
- region coding for the extracellular domain of the protein
- 56% of the ILC studied

transcription silencing

- E-cadherin promoter methylation (40% of the ILC studied)
- transcription repressing pathways (Snail, SIP1)

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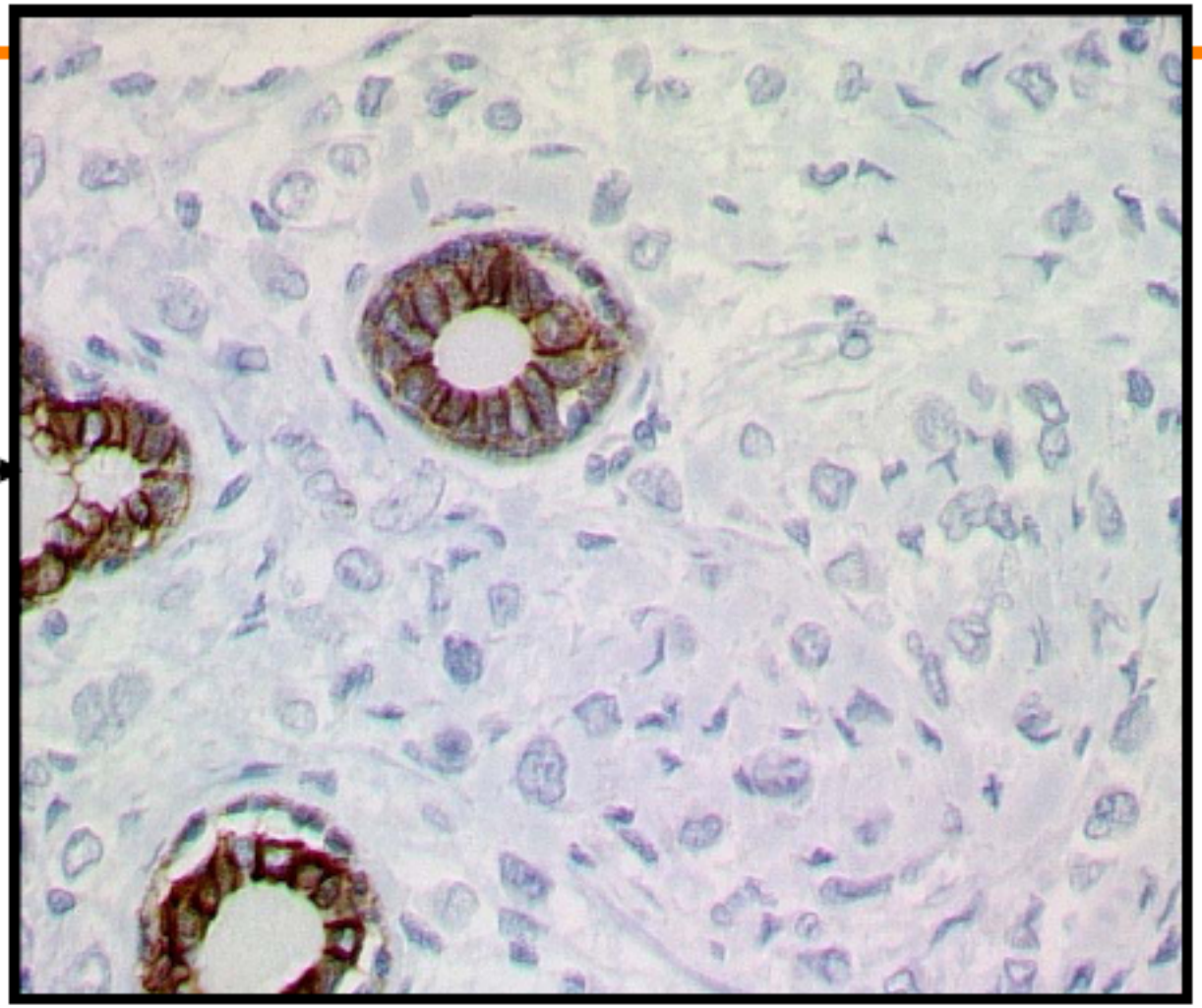
E-cadherin in ILC



lack of expression in 80 to 100%

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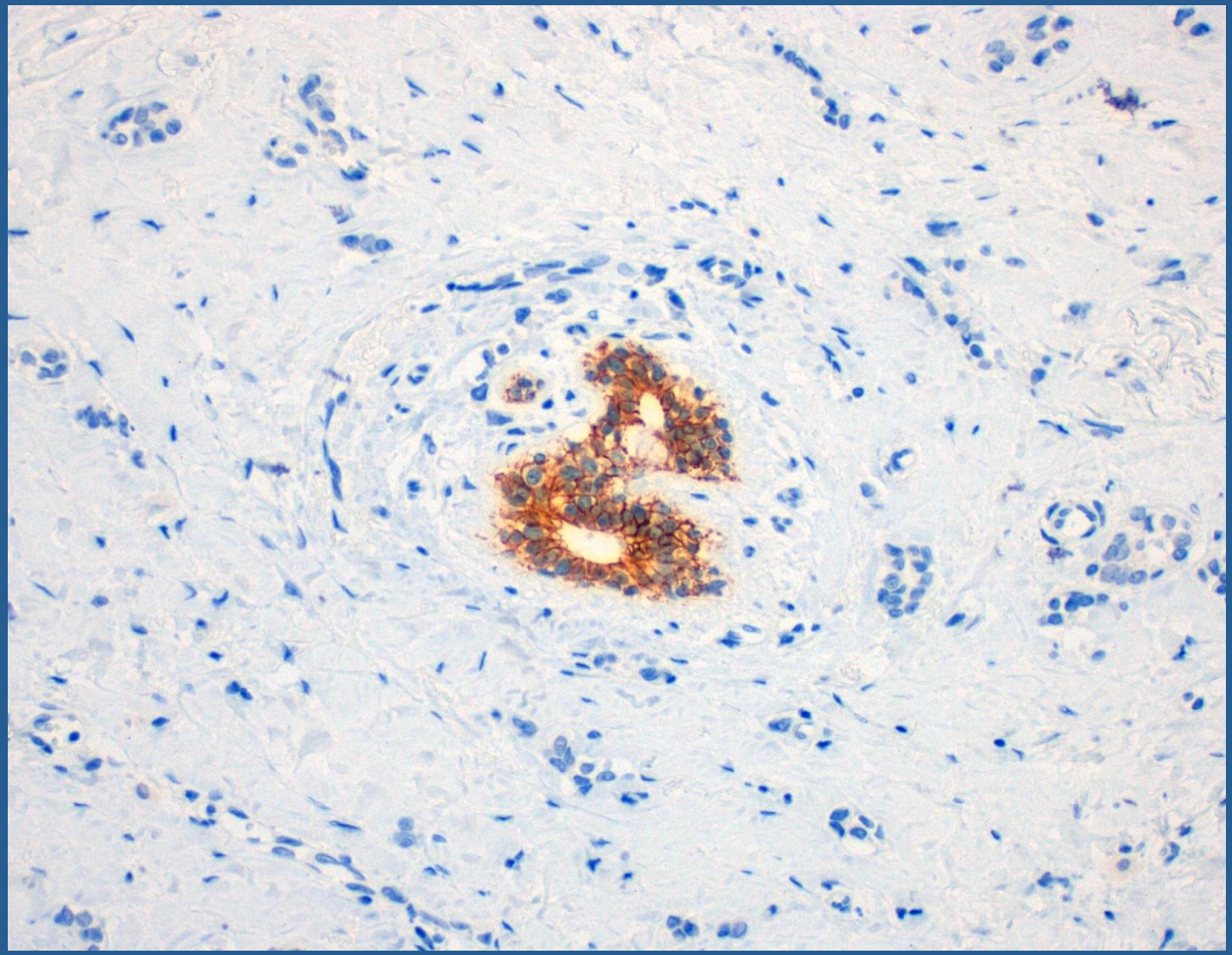
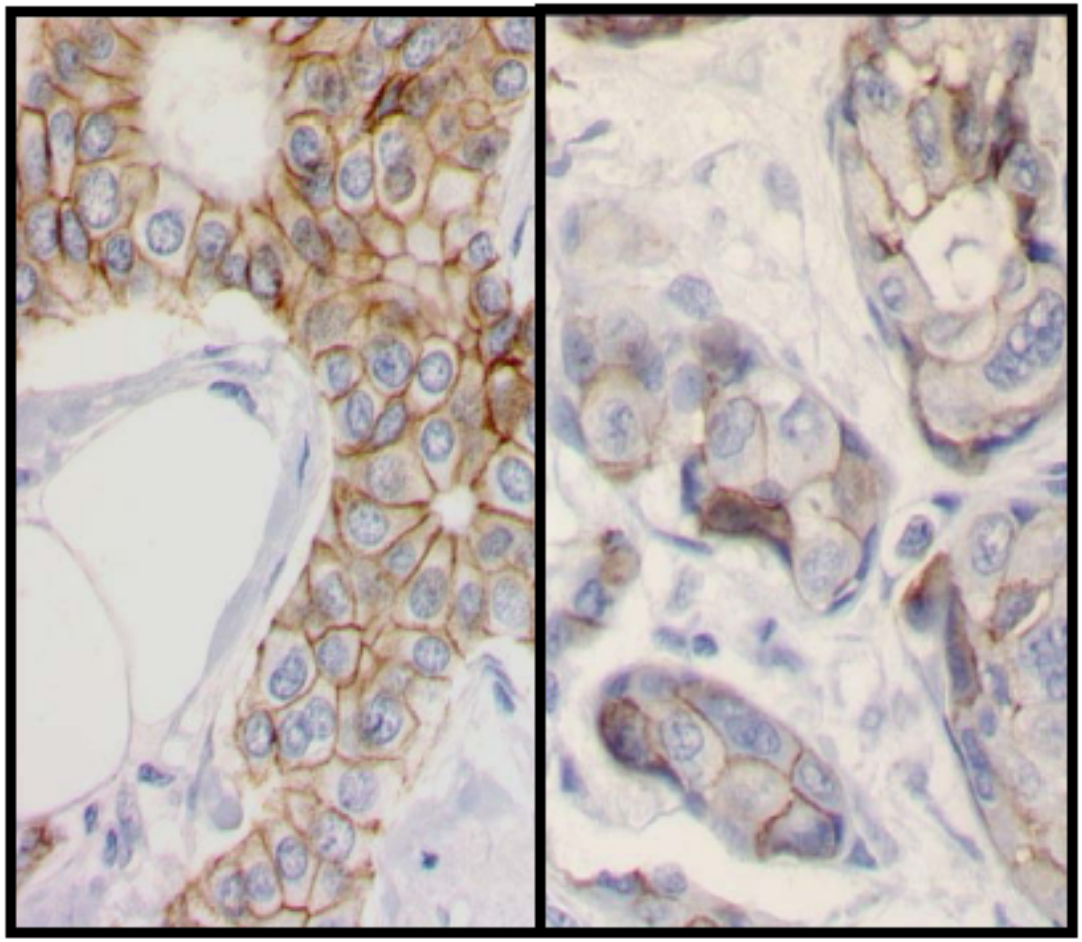


E-cadherin in IDC



decrease of staining: 30 to 40% of the cases

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In summary

E-cadherin	ILC	IDC
expression		
normal	10 - 15 %	70 - 60 %
decreased	~ 0 %	30 - 40 %
absent	80 - 100 %	0 %
mutation	56 %	0 %

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When to use E-cadherin staining ?

not currently needed for the definition of ILC

in cases with equivocal features

to distinguish ILC variants from IDC

⇨ pleomorphic, solid and alveolar

to identify mixed IDC and ILC

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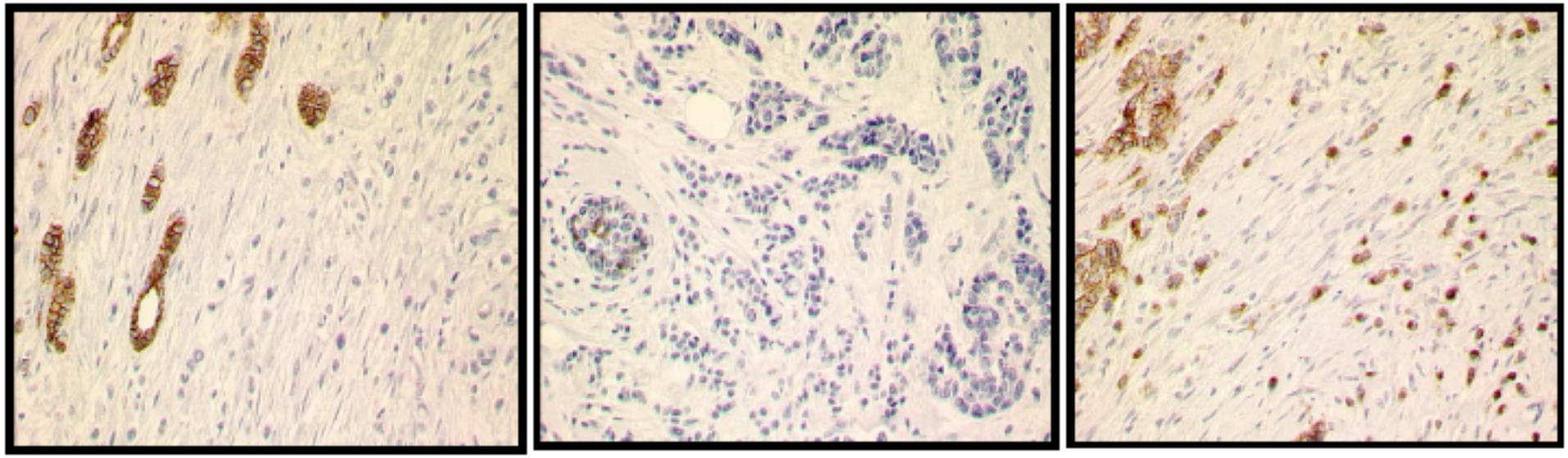
E-cadherin immunostaining
Mixed ductal and lobular carcinomas

Three different patterns of E-cadherin expression



IDC + and ILC –

ILC and IDC –

ILC and IDC+

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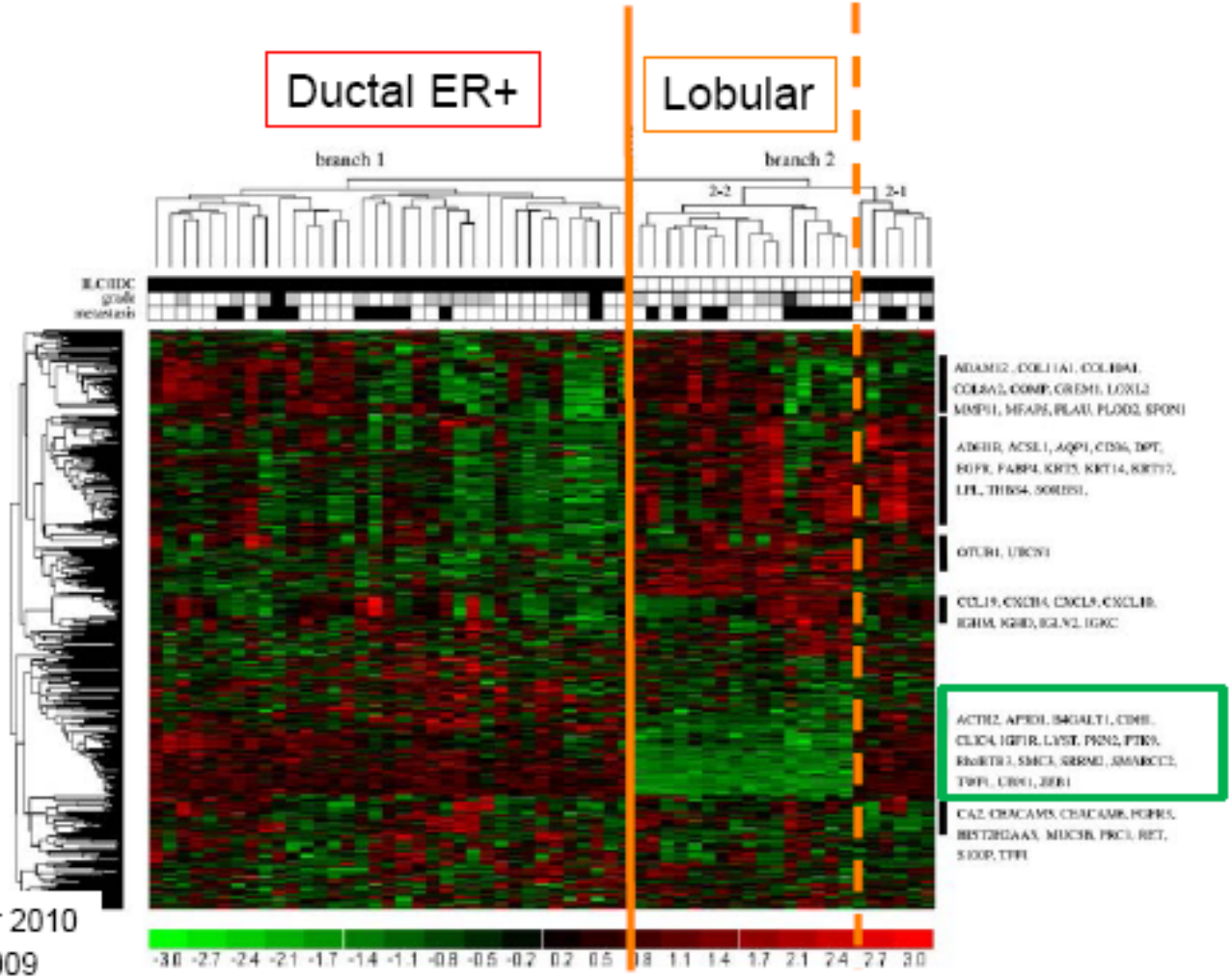
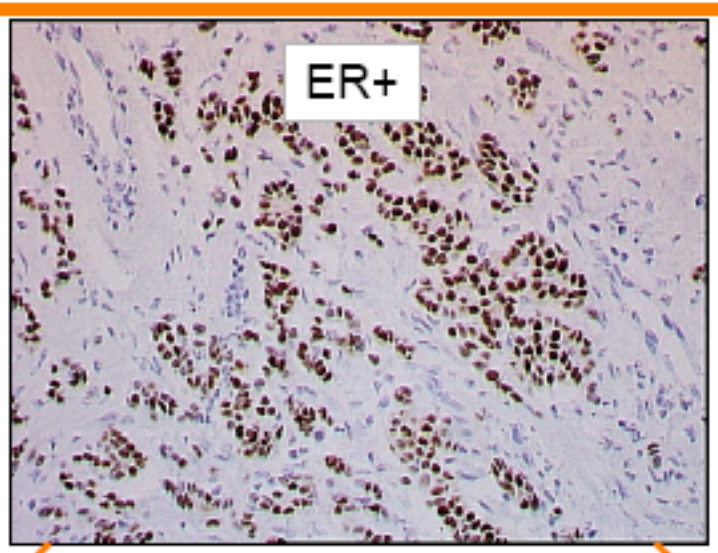
Others ILC specific biological features

Specific gene expression profile when compared to luminal invasive ductal carcinomas



Gruel *et al*, Eur J Cancer 2010
Weigelt *et al*, J Pathol 2009
Bertucci *et al*, Oncogene 2009

Lobular carcinomas are luminal carinomas A or B when grade 3 (pleomorphic), HER2 amplified or HER2 mutated



Ki67 < 14%
RP ≥ 20%

Luminal A

Ki67 ≥ 14%
RP < 20%

Luminal B

HER2 Amplification

HER2 Mutations (ILC)

HER2 Normal

Cheang et al, JNCI 2009
Kennecke et al, JCO 2010
Prat et al, JCO 2013
Bose et al, Cancer Discovery 2013

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ILC axillary lymph nodes metastasis :

Same rate to that observed in IDC (~ 40%)

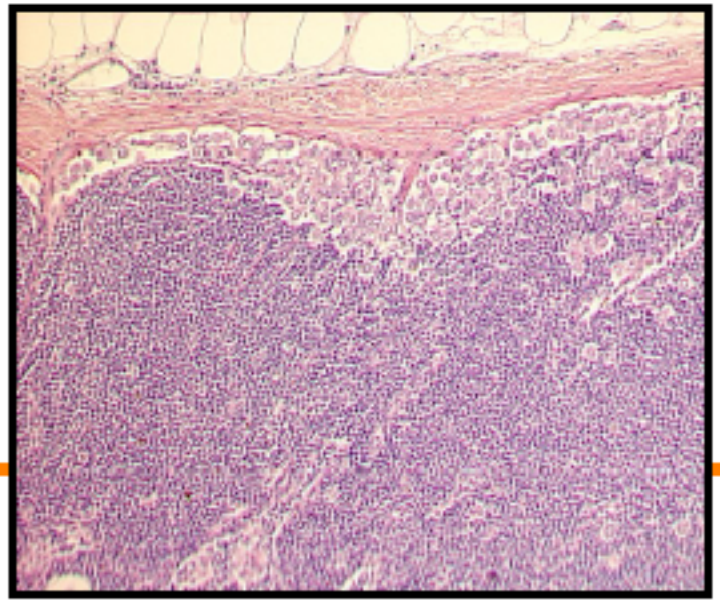
May be difficult to identify (single cells in sinuses)

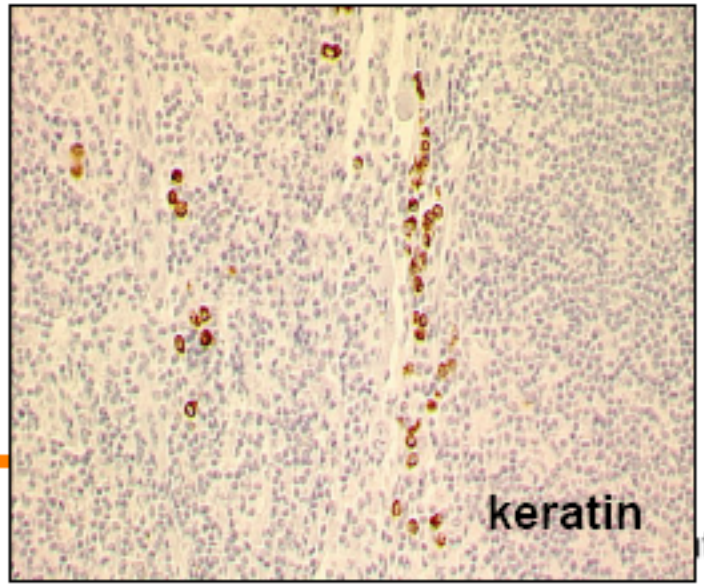
Immunostaining with anti-cytokeratins:

useful to distinguish isolated cells from histiocytes

not recommended systematically

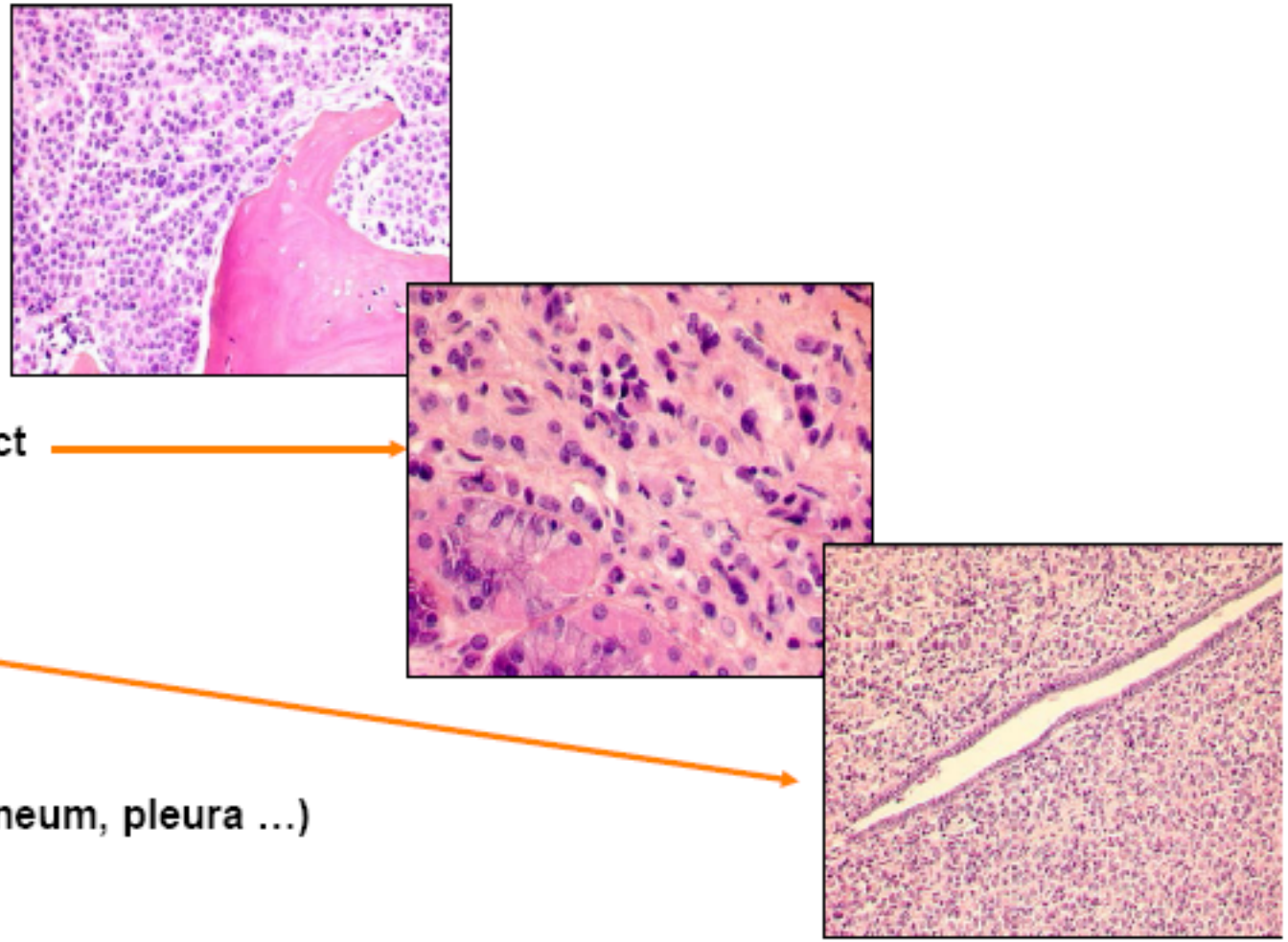
Sentinel lymph node procedure: feasible and accurate





Metastatic patterns of ILC: preferred sites of metastasis

- bone
- gastrointestinal tract
- ovaries
- uterus
- meninges
- others (skin, peritoneum, pleura …)



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Distant sites of first recurrence

Sites	ILC ($n = 179$; %)	IDC ($n = 2576$; %)	P
Lungs/pleura	9.0	17.6	0.0019
CNS	1.7	5.3	0.032
Ovary	2.2	0.7	0.0003
Gastrointestinal tract[a]	4.5	1.1	0.009
Nodes	15.5	22.0	0.018
Bone	34.6	35.5	NS
Skin[b]	31.8	27.3	NS
Liver	7.3	10.9	NS
Pituitary	0.5	0.1	NS

Percentages do not add up to 100% because of multiple metastatic sites in the same patient and infrequent or unknown sites not shown.
[a]Stomach, small bowel, colon, appendix, duodenum, and peritoneum.
[b]Soft tissue and skin.
CNS, central nervous system; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NS, not significant.

Breast Cancer Res 2004, **6**:R149-R156 (DOI 10.1186/bcr767)

Number of synchronous visceral metastasis of ILC

Metastasis	ILC	IDC
> 2 sites	6 - 42%	2.5 - 25 %

Ferlicot et al, Eur J Can 2004

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Prognosis of ILC

Determined by

nodal status

tumor size

histological grade

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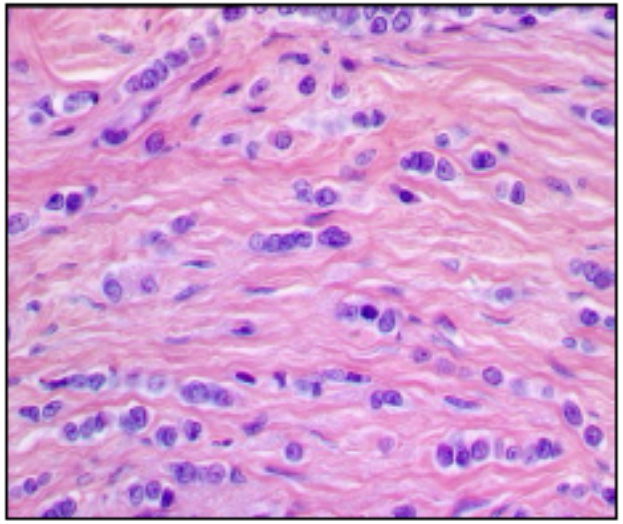
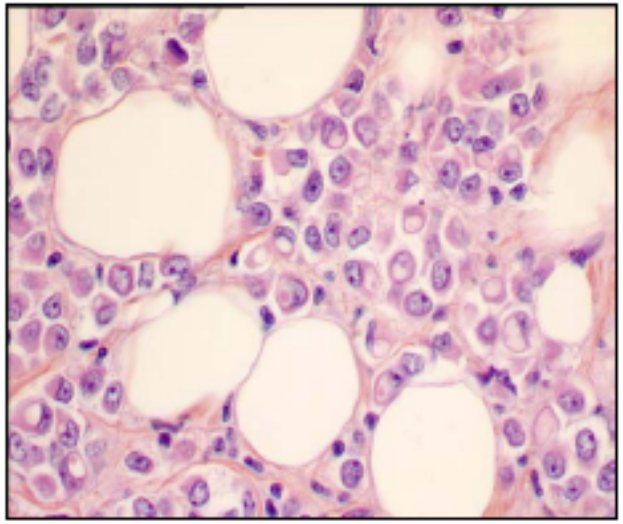
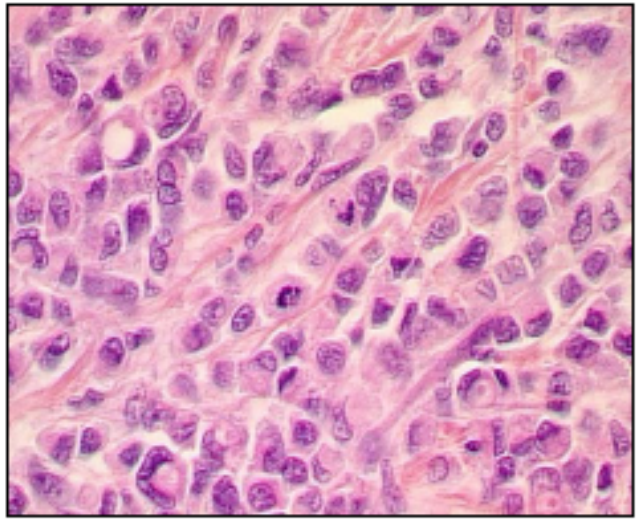
Prognosis of ILC
Histological grade (Elston and Ellis)







I II III

Tubule formation :	always 3
Nuclear pleomorphism :	1 , 2 or 3
Mitoses :	usually 1 , can be 2, rarely 3

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Prognosis of ILC : Histological grade (Elston and Ellis)

	ILC	IDC
grade I	35 to 50%	20%
grade II	43 to 54%	40 to 50%
grade III	7 to 11%	15 to 30%

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Prognosis of ILC Histological grade (Elston and Ellis)

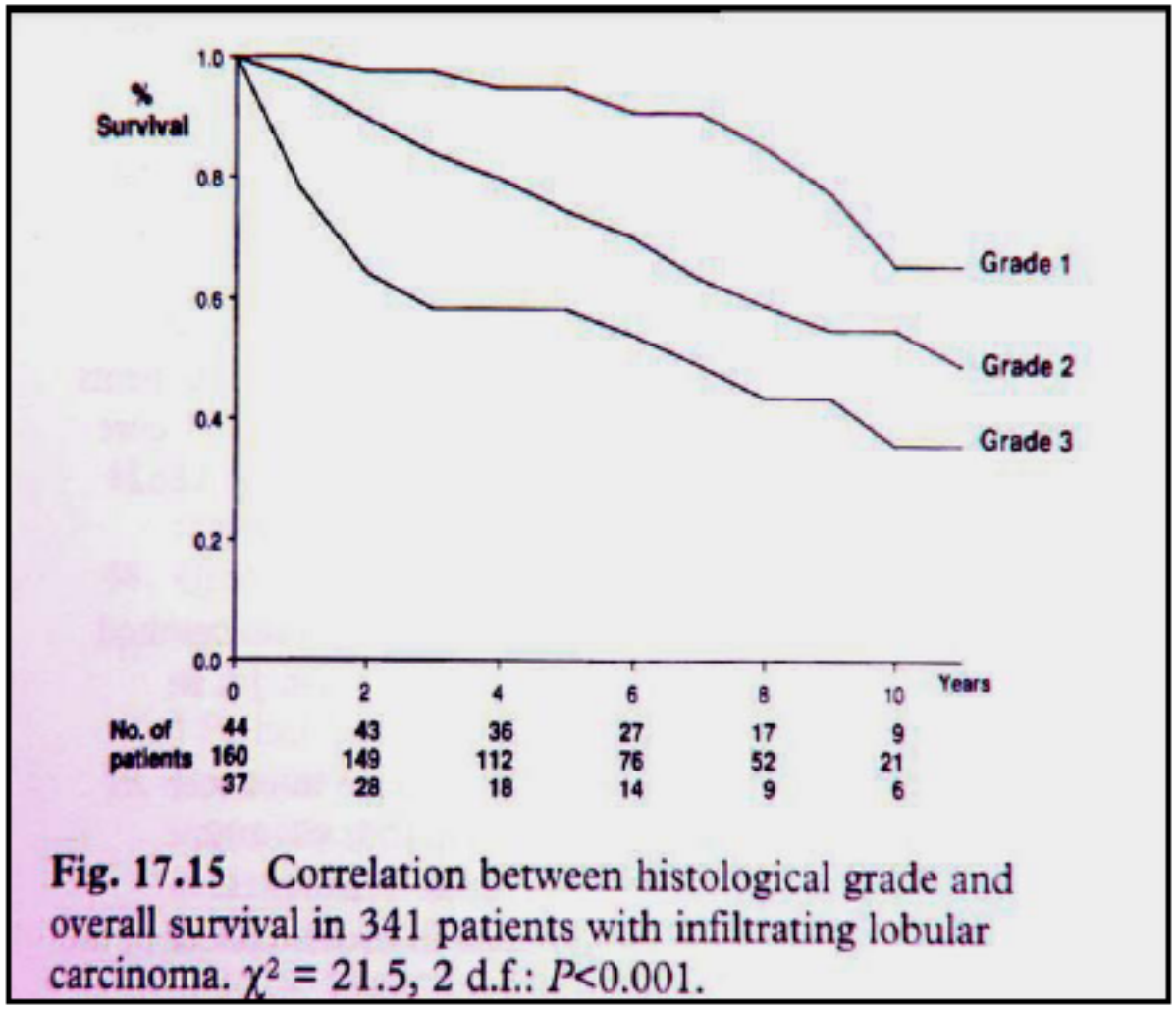

Fig. 17.15 Correlation between histological grade and overall survival in 341 patients with infiltrating lobular carcinoma. $\chi^2 = 21.5$, 2 d.f.: $P<0.001$.

From Elston and Ellis
***The Breast*, p 381,**

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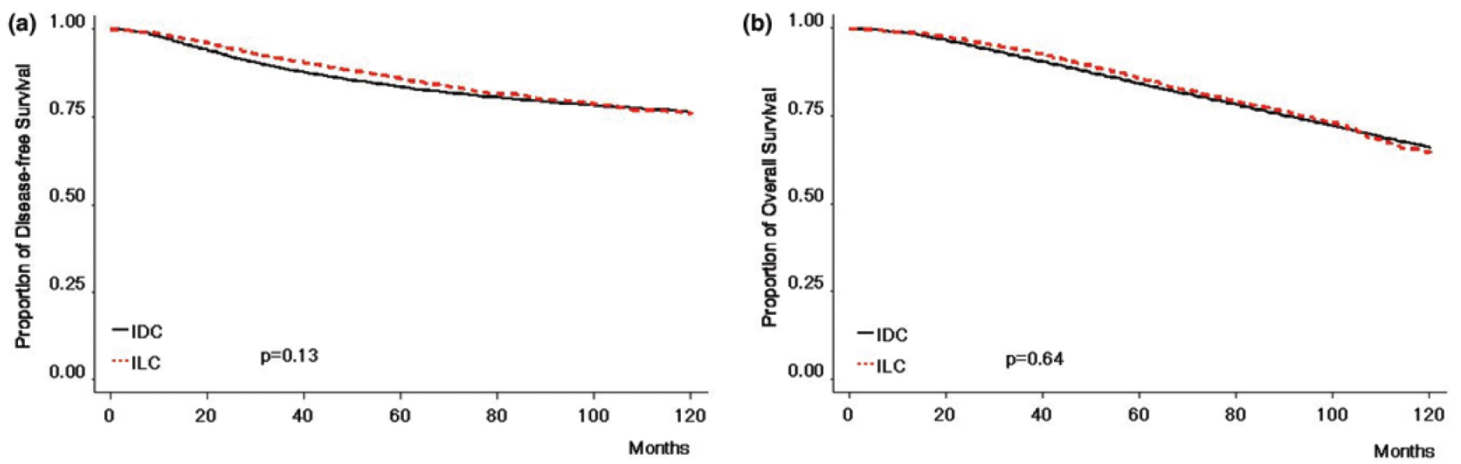
Available online http://breast-cancer-research.com/content/6/3/R149

Research article

Open Access

Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome

Grazia Arpino[1], Valerie J Bardou[2], Gary M Clark[1] and Richard M Elledge[1]



(a) The 5-year disease-free survival (DFS) was 85.7% (95% confidence interval [CI] 84.4–87.1%) for invasive lobular carcinoma (ILC) versus 83.5% (95% CI 83.1–84.0%) for invasive ductal carcinoma (IDC; $P = 0.13$). **(b)** The 5-year overall survival (OS) was 85.6% (95% CI 84.2–87.0%) for ILC and 84.1% (95% CI 83.7–84.6%) for IDC ($P = 0.64$).

* Based on 4140 ILC vs. 45169 IDC

Breast Cancer Res 2004, **6**:R149-R156 (DOI 10.1186/bcr767)

ILC treatment

Surgical :

conservative treatment depending on tumor size

LCIS at margins not associated with a higher risk of local recurrence

Systemic treatment :

Hormonotherapy:

high rates of response ⇔ ER and PR +

Preoperative Chemotherapy :

low rates of response ⇔ low proliferation, grade I, ER and PR +

Anti-HER2 therapy

low rates of HER2 positivity

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ILC : what is important in practice?

Classic ILC and variants = non cohesive cells

ILC should be graded

Specific biological profile:

E-cadherin genetic alteration and lack of E-cadherin expression

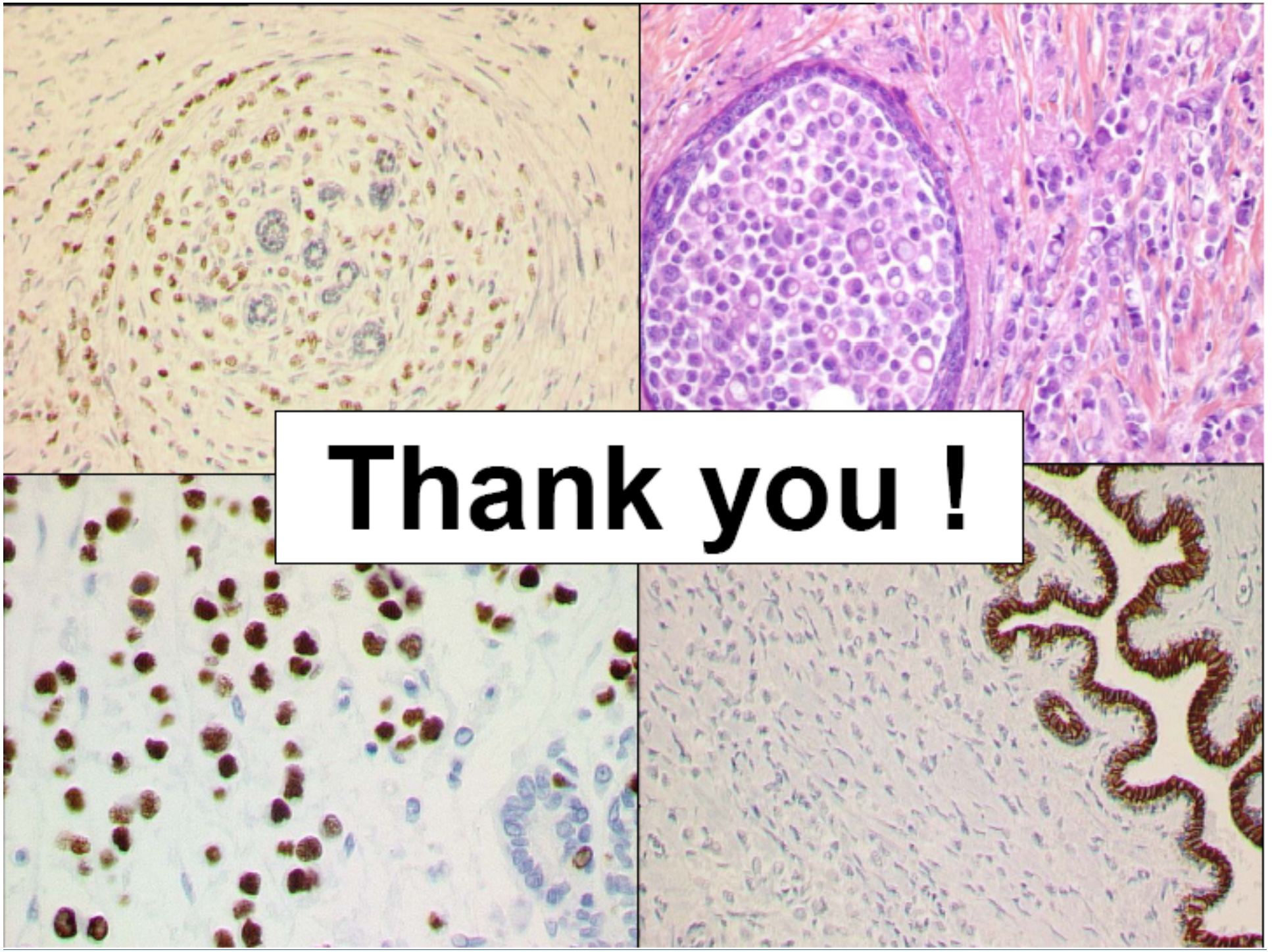
ER and PR +, low proliferation rates,

Specific gene expression profile pattern

Rare HER2 amplification, possible HER2 mutations

Metastatic profile (bone, urogenital, digestive, meninges)

Low rates of response to preoperative chemotherapy


Thank you !