In situ and invasive lobular carcinoma

Hiam Ali
Consultant pathologist
Trafford general hospital
UK

Lobular neoplasms

- LCIS/ ALH
- LIN (Lobular intraepithelial neoplasia)
- MIN (Hybrid lesions)
- LN (Lobular neoplasia)
- Variants of LCIS (indeterminate lesions)
- Incident & Management of LCIS and it’s variants
- Combination of LCIS with other lesions
- ILC (pleomorphic and tubulolobular)
- Molecular biology and cytogenetics

Non- invasive lob proliferation

- First described in 1941 by Foote and Stewart (Am J Surg Pathol)
- Historically divided into ALH & LCIS
- Morphological distinction between these two lesions is blurred
- They have a shared cytogenetic and molecular profile
- These two lesions represent a continuum with LCIS evolving from ALH
- This view proposed the term **lobular neoplasia** to include both lesions

LCIS/ALH

- **Classic LCIS/ALH are multicentric and bilateral**

- **Risk indicator for the subsequent development of Inv Ca in either breasts & after a prolonged period of time OR not at all (the risk is more with LCIS than ALH).**

  Bodian CA et al, Cancer 1996

- **This view forms the basis for B3 categorisation of LCIS/ALH on CNB- NHSBSP**

One cannot leave this subject without discussing which term is most appropriate to designate the condition currently called lobular carcinoma in situ. The writer is in agreement with the increasing number of workers who are dissatisfied with the designation
of 'carcinoma' for this condition… The dissatisfaction with the term 'carcinoma' in this context remains and is to a great extent justified… the term 'carcinoma' is too emotive and alarming to patient and to surgeon. It seems that the name ***'lobular neoplasia****,' adopted by Haagensen (1971), satisfies our need for a different name. It does not dismiss LCIS as a 'marker' while, at the same time, it does not elevate it to the frightening stature of a 'carcinoma.' It is short, accurate, and reasonably distinctive."*

J.G. Azzopardi

Problems in Breast Pathology, 1979, p. 232

LCIS/ALH

- Both do not produce a palpable mass
- Generally an incidental path. diagnosis in patients who undergo biopsies for other reasons
- **The management for both is the same**

Bodian CA et al, Cancer 1996
Haagensen et al, Cancer 1974
Lattes et al, Pathol Res Prac 1980

LIN (LCIS/ALH)

- Tavassoli subdivided LIN into 3 grades:

- LIN1: partial or complete replacement of the acinar epithelium- **NO** distension (ALH)

- LIN2: cells fill & **distend** some or all acini- acinar outline remains distinct (**stroma**)

- LIN3: (Type A)- Confluent acinar distension (**NO** stroma)

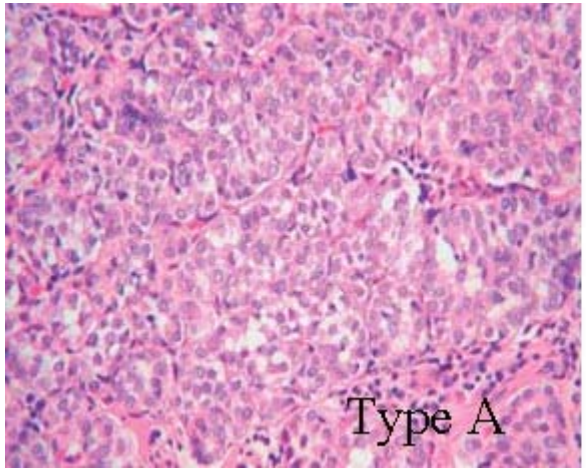
  (Type B)- Pleomorphic variants- high grade variants (signet ring cell, histiocytoid, apocrine cell), with or without acinar distension

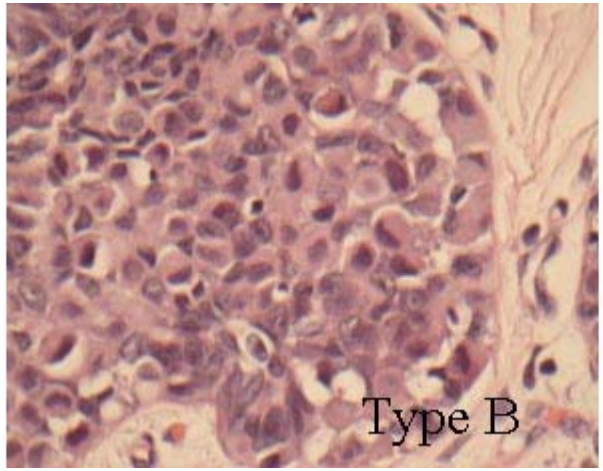
LIN

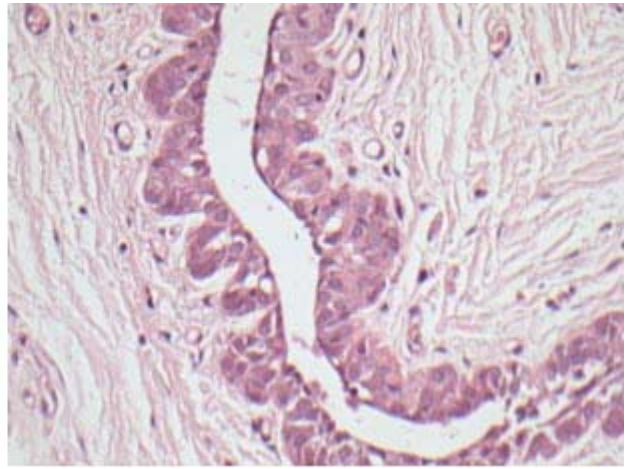
Tavassoli: for practical purposes:

- Low-grade (the most common type)
  LIN1, LIN2, LIN3 -TypeA

- High grade- pleomorphic variants (rare variant)- LIN3 -TypeB







LCIS

Microscopy

- **Classical- solid, occlusive proliferation of relatively uniform population of loosely cohesive and often small round cells with scant cytoplasm (Type A)**
- **Pleomorphic-there is variation in nuclear size with eosinophilic or clear cytoplasm (Type B)**
- **The neoplastic cells may extend to the adjacent terminal ducts (pagetoid spread)**

LCIS

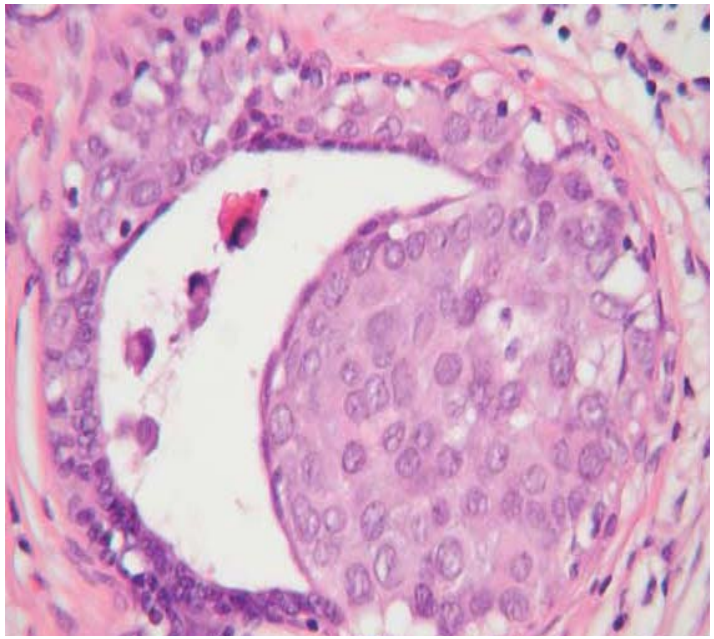
- **Mostly LCIS is easy to distinguish from DCIS**
- **There are areas of overlap;**
  CIS with Indeterminate Histologic features;
  LCIS variants
- **The distinction between LCIS and DCIS has an important therapeutic implications**

E-cadherin & CK34 BE12

- **E-cadherin is negative in LCIS/ ILC**
- **E-cadherin almost always positive in DCIS**

- **CK34BE12 is positive in 90-95% of LCIS/ILC**
- **CK34BE12 is negative in 85-90% of DCIS**

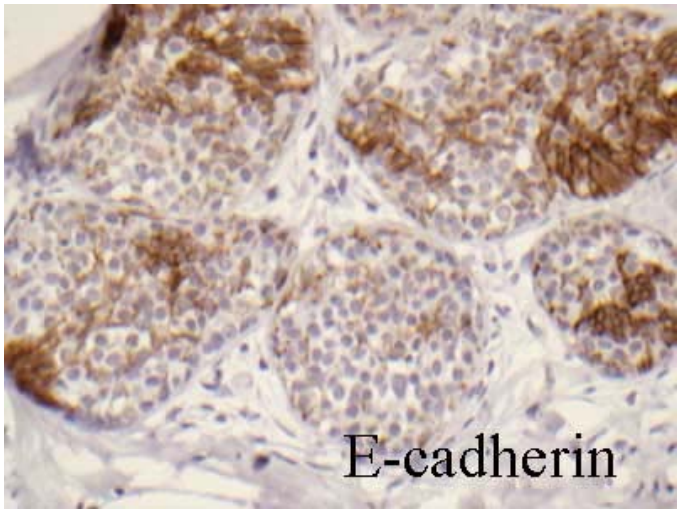
Mastracci et al, Mod pathol 2005;18
Maluf et al, Am J Surg Pathol, 2001;25
Acs et al, Am J Cli Pathol, 2001;115



Areas of Overlap Between LCIS and DCIS

- DCIS could extend into lobules and be mistaken for LCIS (cancerization of lobules) and LCIS could involve extralobular ducts mimicking DCIS

Jacob TW et al, To excise or not to excise? Am J Surg Pathol, 2002



Areas of Overlap Between LCIS and DCIS

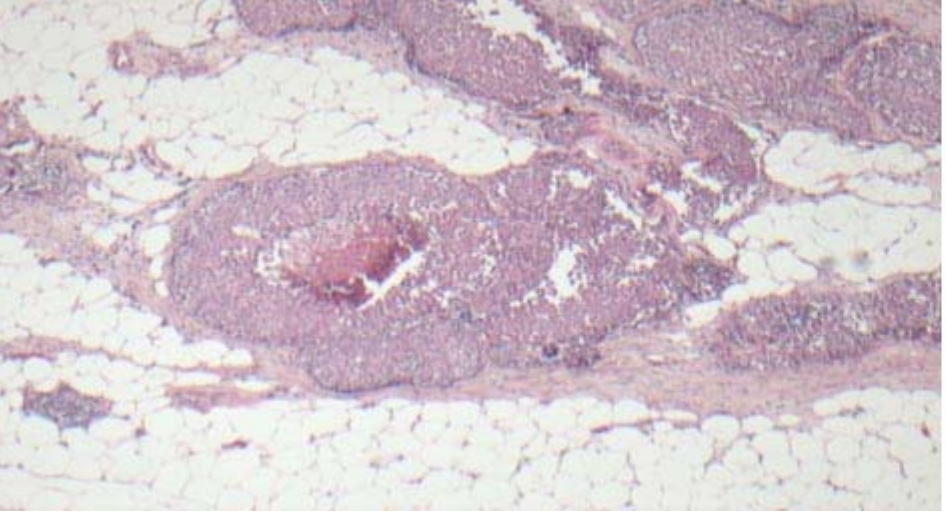
- DCIS and LCIS can coexist in the same breast and even in the same TDLU

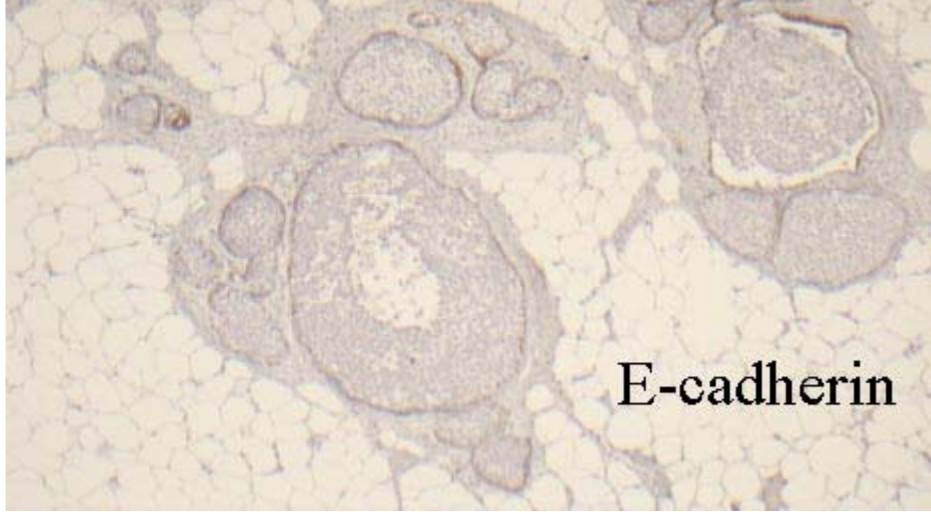
  Rosen PP, Coexistance LCIS and DCIS in a single lobular-duct unit. Am J Surg Pathol, 1980

  Fisher ER, 5-year observations concerning LCIS, Cancer, 1996

CIS with Indeterminate Histologic features (Pleomorphic variants (PLCIS)

- Group 1- LCIS with necrosis
- Group 2- LCIS with pleomorphism
- Group 3- Histological overlap with DCIS





Pleomorphic LCIS

Group one

- In Situ Carcinoma with cytologic and architectural features typical of LCIS but exhibiting areas of **comedo (central) necrosis**
- All **lack E-cadherin** expression by IHC

  Jacobs TW, . Am J Surg Pathol 2001

- The exact classification and management of such lesions has been the topic of much debate, with a spectrum of opinions regarding the degree of necrosis that is permissible in LCIS

  Page (against), Diag Hist of the Bt, 1987

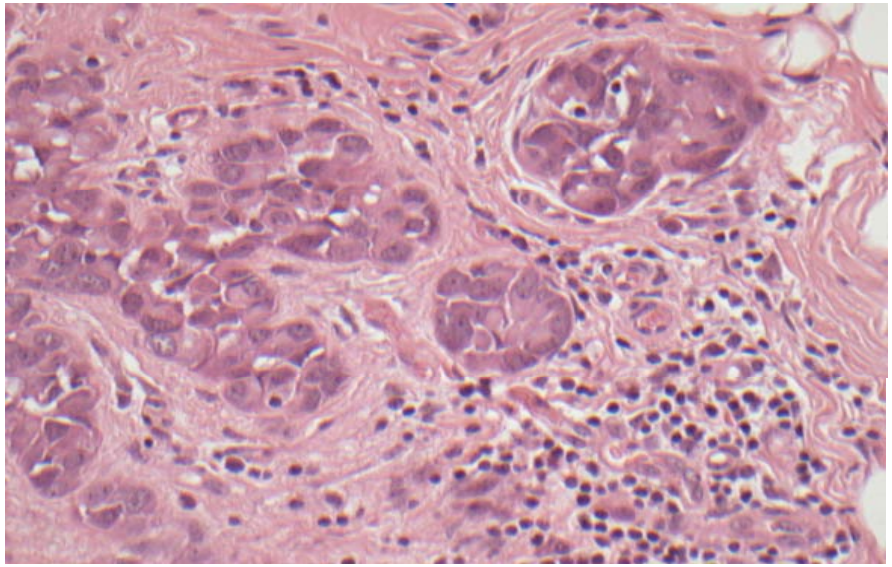
  Tavassoli (with), Pathol of the Bt, 1999

Pleomorphic LCIS
Group 1

- **Tavassoli**: Advices that LCIS with necrosis should be managed similar to DCIS, believing that this is a reflection of “far advanced lobular neoplasia”

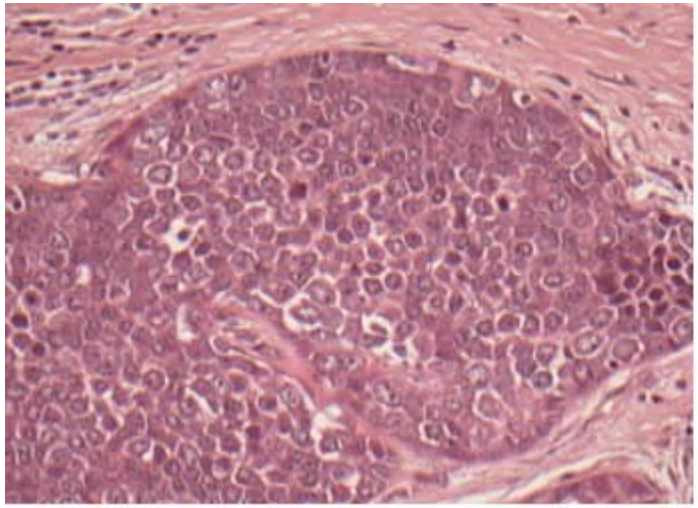
- Other authors have supported Tavassoli;

  Koerner F, et al, uncommon morphologic pattern of lobular neoplasia, Ann Diagn Pathol, 1999

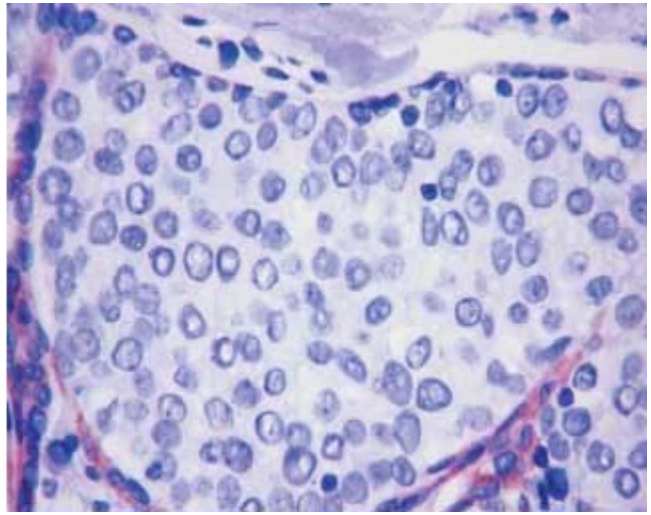


Pleomorphic LCIS
(PLCIS)
Group 2

- ISC with growth pattern similar to LCIS BUT cytologically similar to high grade DCIS)



Pleomorphic LCIS
(Group 2)



- **Discohesion of cells**
- **Plentiful mitoses**
- **High degree of pleomorphism**
- **With or without comedo type necrosis**
- **Resemble high grade DCIS**
- **Molecular profile can resemble high grade DCIS**
- **ER & PR negative & HER2 positive**
- **All PLCIS are negative for E-cadherin by IHC**

Middleton LP et al, PLCIS: Morphology, IHC and molecular analysis. Am J Pathol 2000

Sneige N et al, Mod Pathol 2002

Pleomorphic LCIS (Group 2)

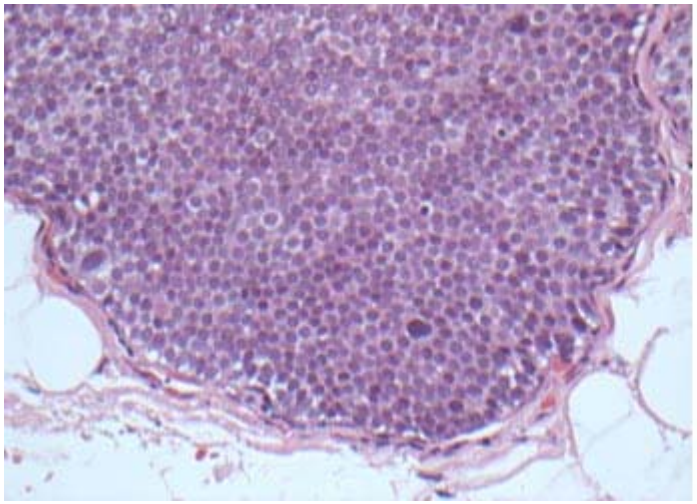
- Associated with PILC

  Frost AR et al, PLCIS, Pathol case Rev 1996
- Isolated PLCIS

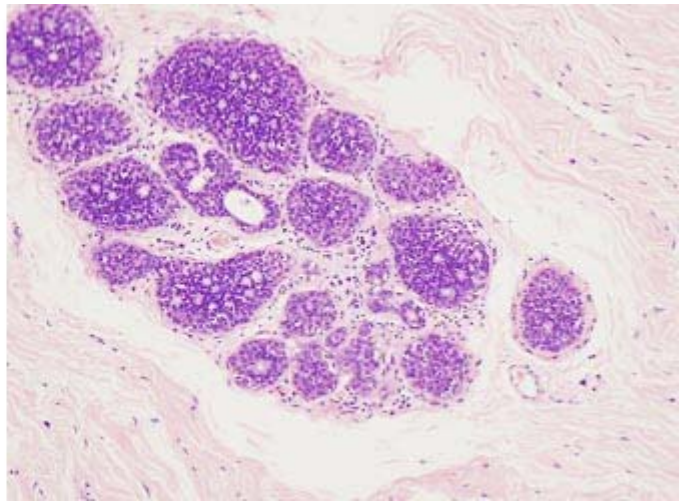
  Sneig N et al, clinical, histopathological, and biological features of PLCIS, Mod pathol 2002
- UNKNOWN: if the level and laterality of breast cancer risk associated with PLCIS is similar to LCIS or DCIS
- One case of recurrence and that case was not adequately excised initially

  Sneige N, Clin, histo, and biologic features of PLCIS of the bt, a report of 24 cases, Mod Pathol 2002

- Summary: The molecular profile of PLCIS implying a high grade biology, and data, although limited, support a more aggressive treatment approach- the evidence has not reached levels leading to universal acceptance of this strategy.



LCIS
(Group 3)



- Having features of both LCIS and DCIS, rendering categorization very difficult if not impossible on routine histology
- Small monomorphic cells, with or without cytoplasmic vacuoles similar to classical LCIS

BUT

The cells grow in a solid, cohesive, mosaic pattern suggestive of solid-pattern DCIS

OR

Show microacinar-like structures, suggestive of DCIS

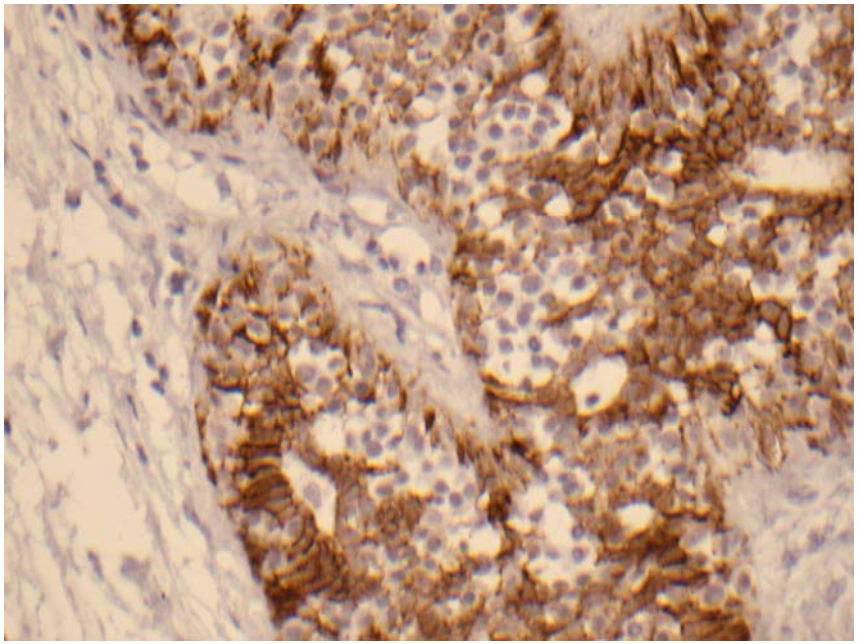
LCIS- Group 3

Shows E-cadherin immunostaining hetrogenesity

- 30% positive (akin to DCIS)
- 35% Negative (akin to LCIS)
- 35% both positive & negative tumour cells within the same ductal-lobular space, suggesting: mixed DCIS & LCIS phenotype

Jacobs TW et al, CIS with indeterminate features: role of E-cadhherin staining in categorization,

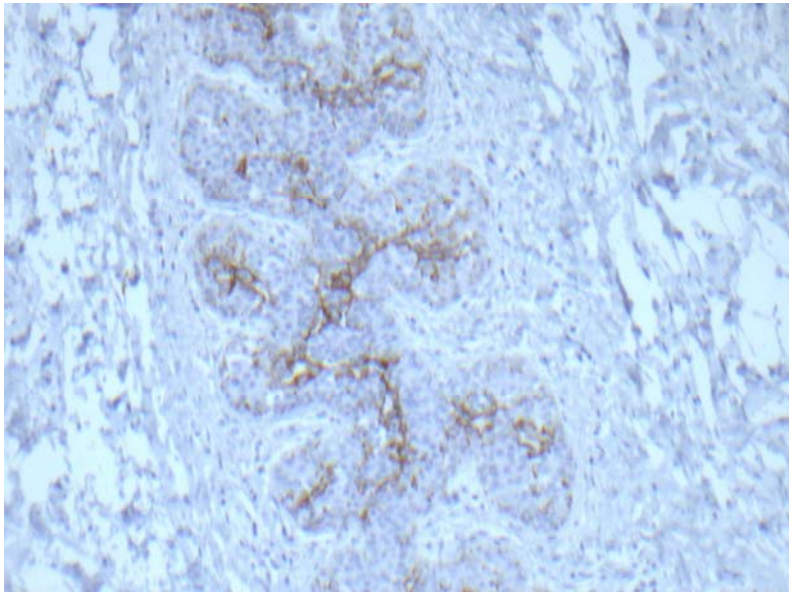
Am J Surg Pathol 2001



Pleomorphic LCIS
Group 3A

- 30% positive E-cadherin (akin to DCIS) and probably represent true cases of DCIS with morphologic “artifacts” on H&E mimicking LCIS
- These cases are best treated as DCIS.

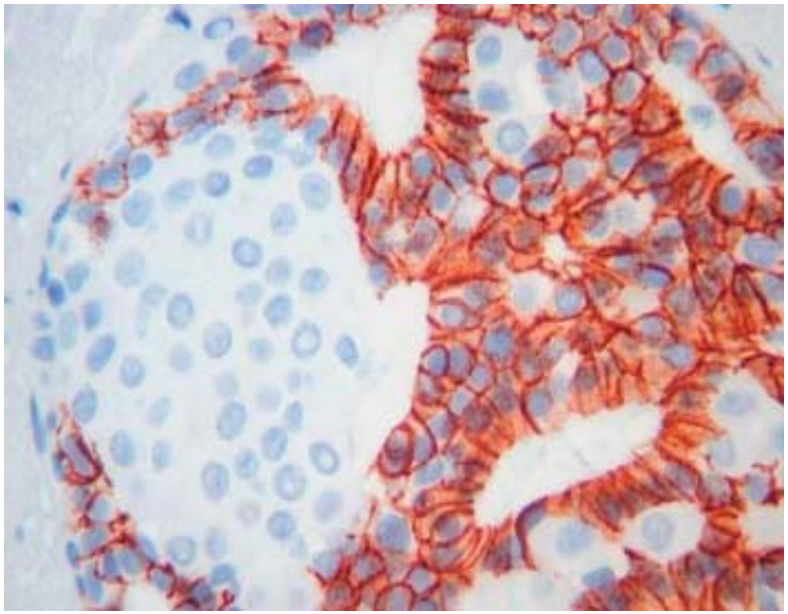
  Jacobs WT, Pathol case review 2003



LCIS
Group 3B

- 35% Negative E-cadherin (akin to LCIS)
- Can have residual E- cadherin positive epith/myoepith cells within the involved lobule- producing illusion of DCIS- like structures
- Most likely represent true cases of LCIS

Goldstein et al, Am J Clin Pathol 2001



LCIS Group

3C

(E-cadherin)

True cases of DCIS & LCIS

- E-cadherin positive and negative TUMOUR cells in the same breast or even in the same ductal-lobular system (not partial immunoreactivity of individual cells)

Rosen PP, Am J Surg Pathol 1980

“ ductolobular ca in situ” (Fisher et al)

LCIS- Group 3C
(LCIS + DCIS)

- **Long term follow up these cases behaved closer to DCIS than LCIS**

  (higher proportion of subsequent ipsilateral cancers that developed after a shorter time)

  Goldstein et al, Cancer 2001;92

- **Until further clinical outcome data are available , it is prudent therefore that cases that show both E-cadherin –positive and –negative cells in the same ductal-lobular space should be treated as for DCIS rather than LCIS**

  Jacobs TW, Path case Review, 2003

Hybrid lesions (MIN)

- Tavassoli (1999)-

  Mammary intraepithelial neoplasia (MIN)

- E-cadherin and CK34BE12 are either both positive OR both negative

  -Positive hybrid lesions (positive E-cadherin & CK34BE12)

  -Negative hybrid lesions (negative E-cadherin and CK4BE12)

Incidence of LCIS

- Data are limited
- Ranging from 0.5%-3.9%-surgical series

  Anderson JA, Cancer 1997
- Under 2% in most CNB series

  Renshaw AA et al, Am J Clin Pathol 2002
- Incidance of variant LCIS in unknown but probably lower than 2%

Incidence of LCIS

Liberman Let al, Am J Roentgenol 1999

- Correlated CNB **histology** and Bt **imaging** with subsequent **surgical** follow up.
- **LCIS** in **16** of **1315 CNB** (1.2%), with subsequent surgical Excision performed in **14**
- ***3 of 14 had Carcinoma***

  5 cases with high risk lesions- RS 3, ADH 2- **One** DCIS

  4 cases of variant LCIS- **One** DCIS and **One** ILC

  5 cases of LCIS alone- None had carcinoma on excision

Incidence of ALH

Liberman Let al, Am J Roentgenol 1999

- In the same study there were **4**/1315 cases of "incidental" **ALH** diagnosed on CNB who underwent surg. Excision:
- 2/4 had LCIS
- 2/4 had benign findings with no residual ALH

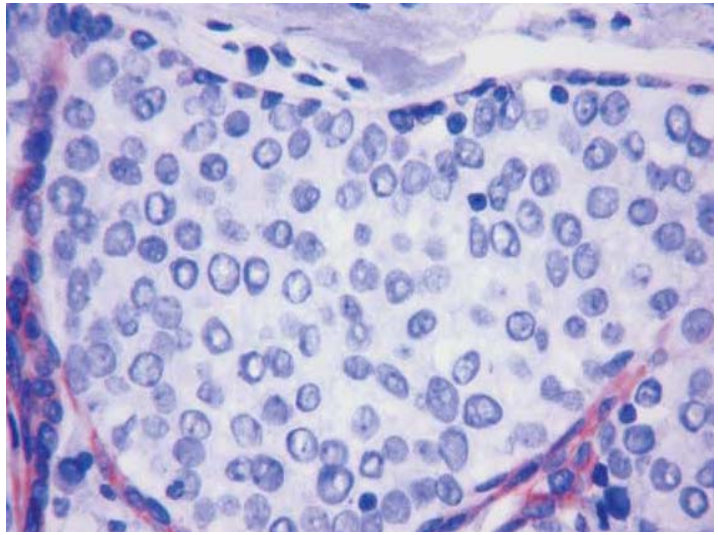
LCIS& ALH

Berg et al , Radiology 2001

- **25**/ 1400 consecutive cases of CNB (1.8%) had either LCIS or ALH- **15** had subsequent surgery

- **8**/10 **LCIS** were excised- **3** ADH (radiologically- 5 microcal. &3 for Mass lesion)

- **7**/15 **ALH** were excised- **ONE** DCIS (radiologically six microcal. & one mass lesion)



LCIS & E-cadherin

Pacelli et al, Am J Clin Pathol 2001

- Retrospective review of 3401 cases of CNB
- ALH, LCIS & variants- **30**/3401

  12/3401 **ALH** (**7**/12 had Surgical Excision - **NONE** had Inv or In Situ Carcinoma)

  13/3401 **LCIS** (**7**/13 had Surgical excision- **NONE** had Invasive or In Situ Carcinoma)

  5/3401 **mixed LCIS & DCIS** (ALL E-cadherin negative suggesting a lobular phenotype- **5**/5 had surgical excision- **3**/5 (60%) had **Inv Ca**.

Management Classical LCIS Vs DCIS

- **LCIS- often managed by careful observation (with the addition of tamoxifen)**
- **Trt of DCIS is aimed at eradication (WLE, Excision with Radiotherapy, or mastectomy)**
- **Assessment of the microscopic margin status is clinically important in DCIS but not in LCIS**

  Schnitt et al, LCIS: current concepts and controversies. Seminar diagnostic Pathol 1999

Management of LCIS/ALH

Liberman Let al, Am J Roentgenol 1999

- Patients with a diagnosis of LCIS/ALH on CNB**, a surgical excision** is warranted if another:
- **high-risk lesion** such as RS or ADH is present
- **OR** if there is **radiologic-pathologic discordance**
- **OR** if LCIS is of pleomorphic variant or has some **histological features that overlap** with DCIS (even if E-cadherin is negative by IHC)

Philpotts et al, Radiology 2000

Berg et al, Radiology 2001

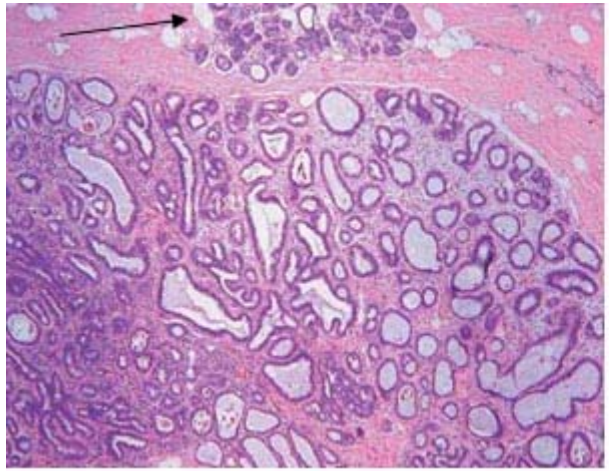
Elsheikh et al, Mod Pathol 2001

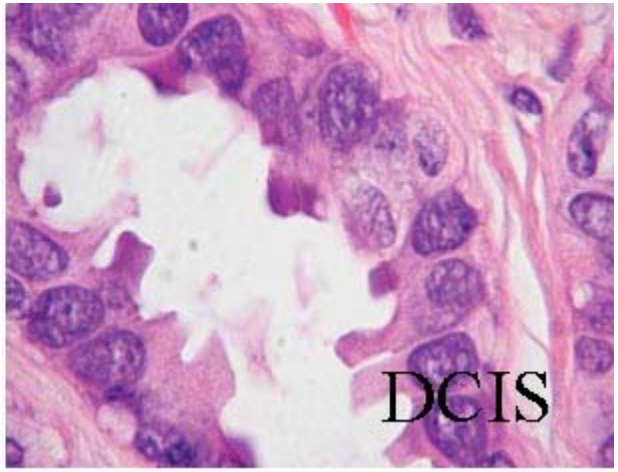
Management of LCIS/ALH

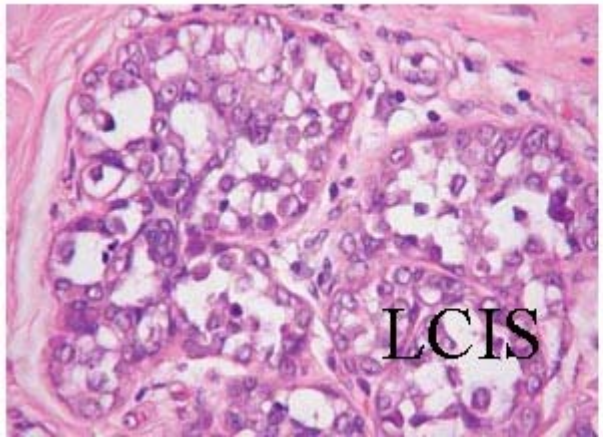
- Surgical excision might **Not** be necessary if:

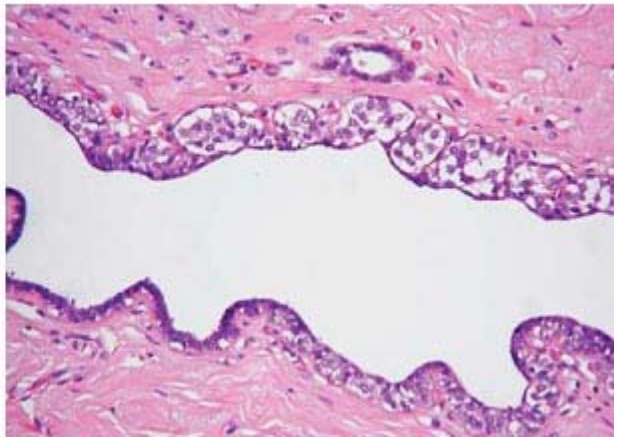
- LCIS or ALH is an incidental finding
- Good radiologic-pathologic correlation

Combination of LCIS with other lesions

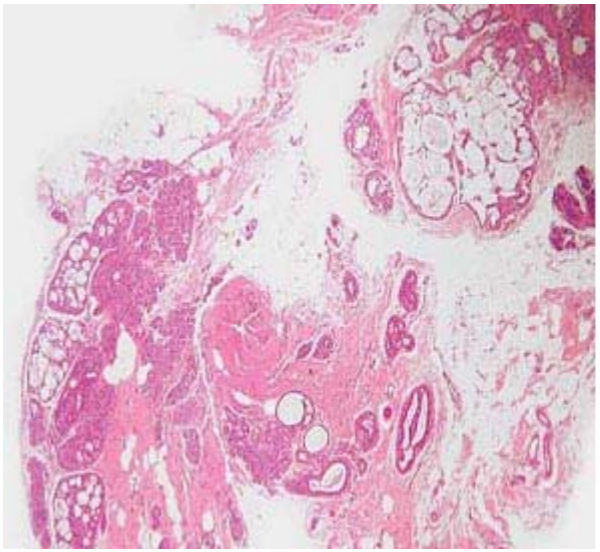


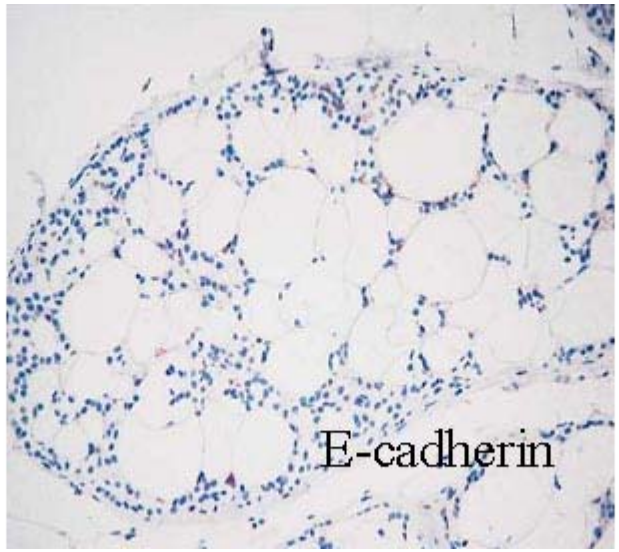


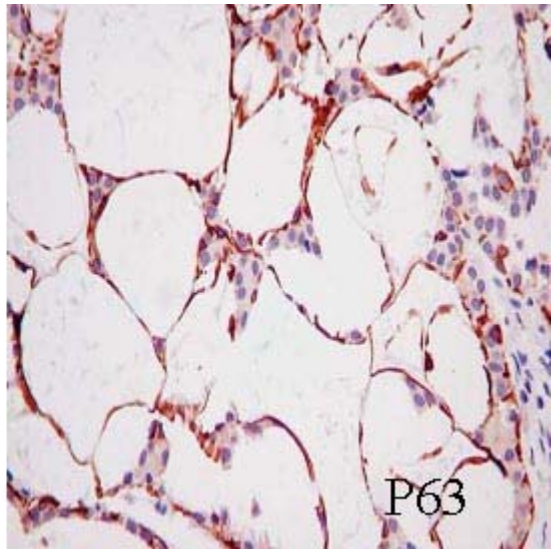




Combination of Lobular neoplasia with DCIS Flat type (Low & high nuclear grade atypia)







- Combination of **Mucinous spherulosis** and **Lobular neoplasia**
- Main DD is DCIS, cribriform variant
- **E-cadherin** demonstrate the negative neoplastic lobular cells
- **63** demonstrates the positive myoepithelial cells which are involved in mucinous spherulosis (earliest stage of collagenous spherulosis)
- *Sgroi D et al, Am J Surg Pathol, 1995*

INVASIVE LOBULAR CARCINOMA

Invasive Lobular Carcinoma (clinical)

- Current use of oestrogen and progestin associated with increased risk of lob and tubular ca
- Lob ca continues to rise in incidence (unlike duct ca), mainly in women age 50 or more
- 5-year DFS 85.7% verses 83.5% IDC
- Data vary depending on treatment regimes

ILC
Imaging

- Harder to detect than IDC
- Difficult to measure
- No mammographic difference from IDC-NST
- False –ve on initial mammograms 19%
- 46% of which showed no evidence of malignancy in retrospect
- MRI –better results: 59% detected by mammogrm, 64% Ultrasound, **100%MRI**

Invasive Lobular Carcinoma (ILC)

- 14% of all Invasive breast carcinoma
- Grossly: occult , unapparent lesions to tumour that diffusely involve the breast
- Typically forms a hard tumour with irregular border
- Characterized by discontinuous and multifocal pattern
- 80% associated with LCIS

Grading of ILC

- Although it is possible to grade ILC on the basis of modified Bloom and Richardson grading system (Nottingham system)-encouraged by TNM).
- ILC will always get a score of 3 for tubule formation, and often 1 for mitotic activity.
- It is mainly the cytologic features that account for the variation in grading
- Others do not grade BUT type ILC

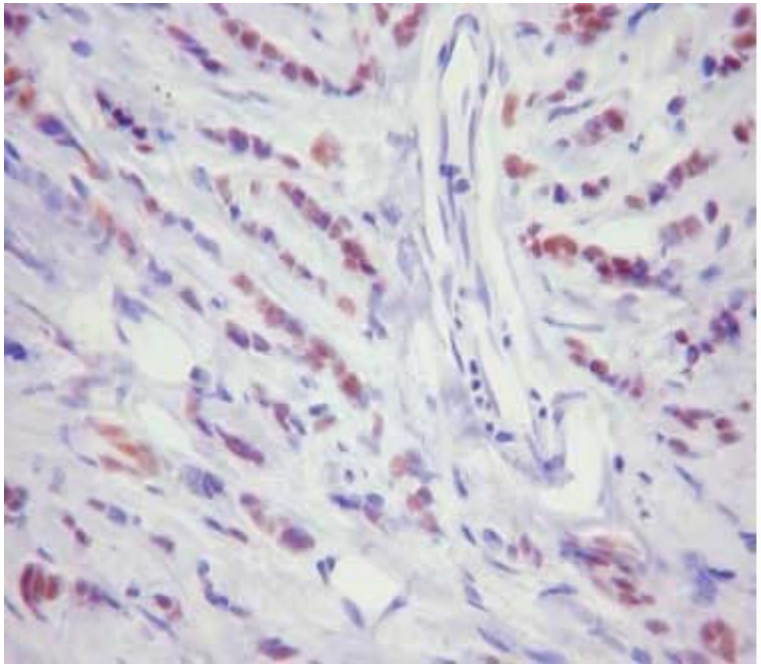
Bane AL et al, ILC: to grade or not to grade, Mod Pathol, 2005(18)

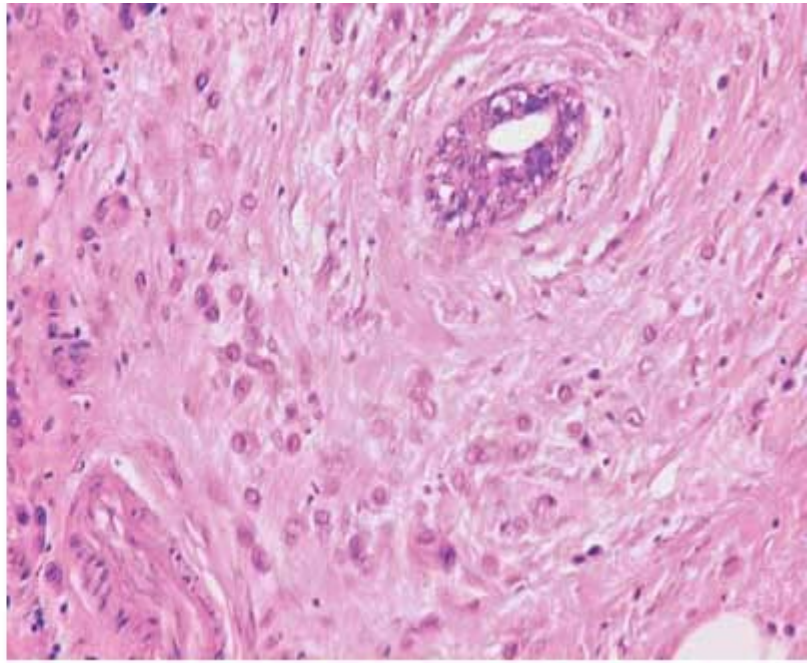
ILC- morphological diversity and variants

classification

classical

Variants





Classic ILC

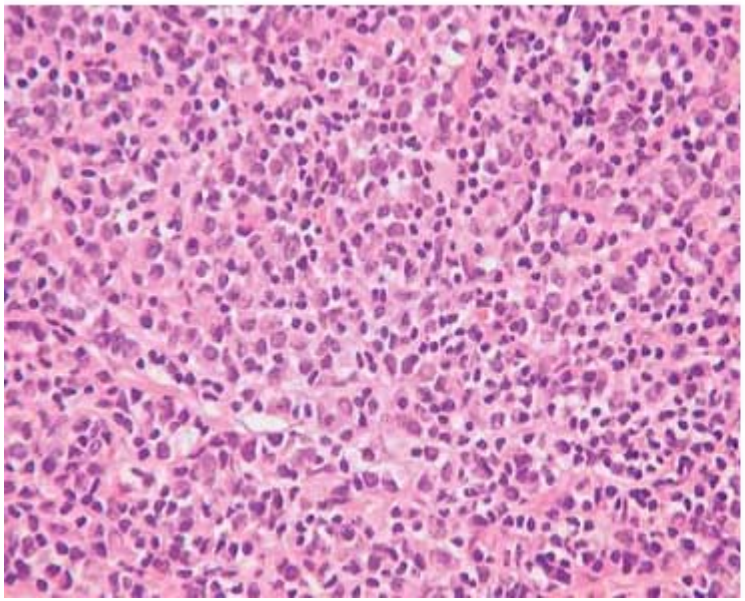
- Small or medium sized uniform cells
- “Single file” pattern and “targetoid” growth
- Discontinuous, infiltrative with irregular border
- Intracytoplasmic mucus & signet-ring cells identical to GIT signet-ring cell carcinoma

ILC

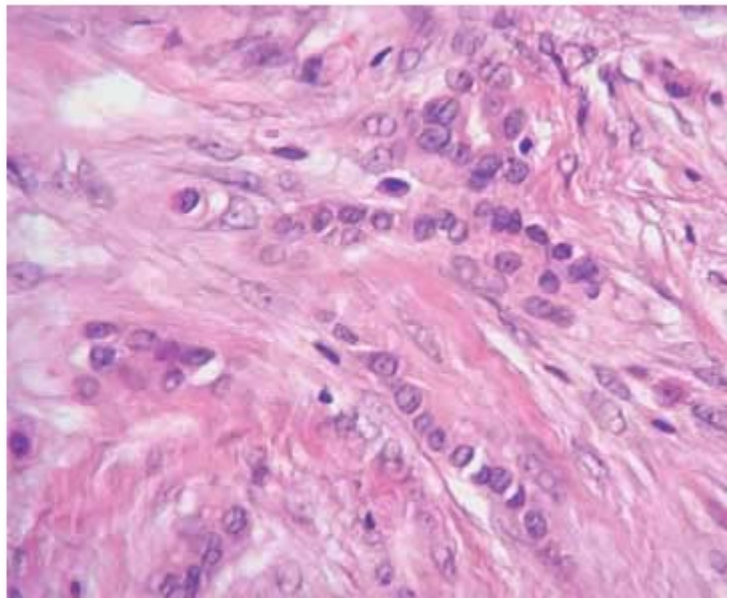
- Variants
  - Solid
  - Alveolar
  - Pleomorphic
  - **Tubulolobular**
  - Mixed (usually solid & alveolar)

Variants lesions have a worse prognosis than the classical lesion

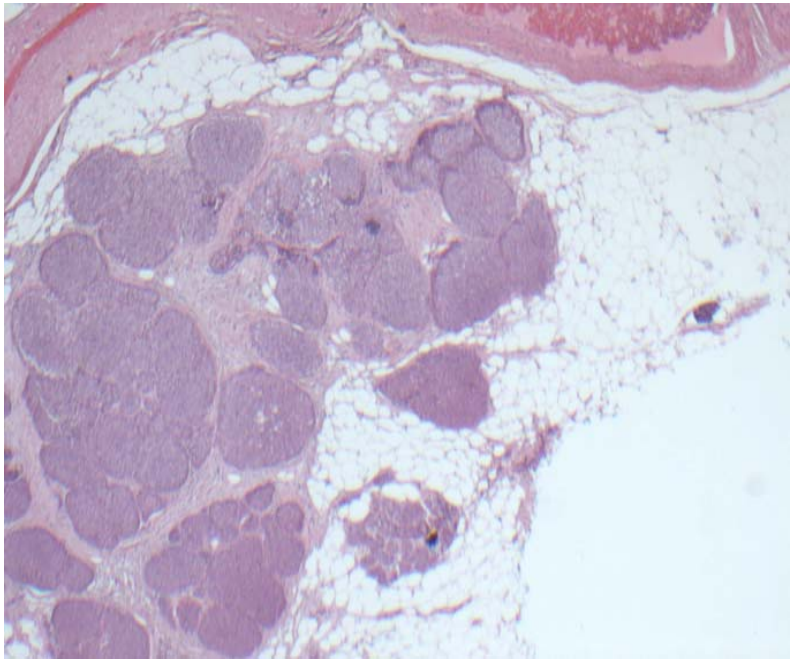
- Sparse cell variant (not widely recognised)



Solid
ILC

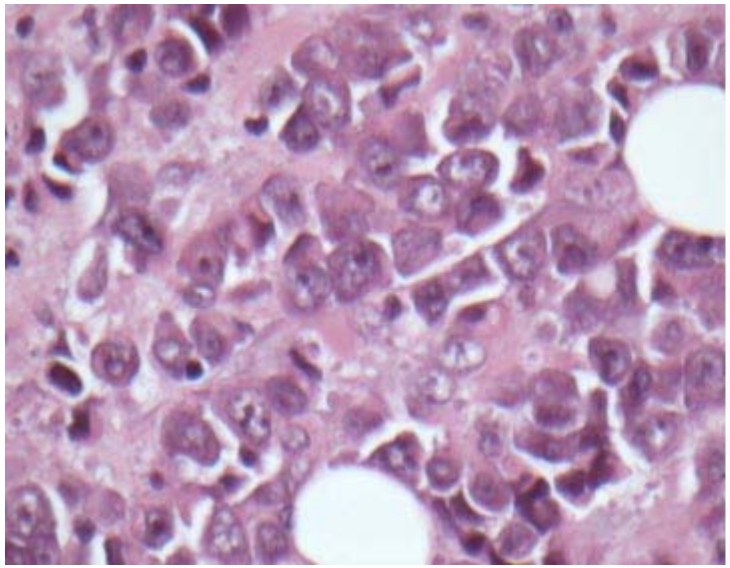


- Present in sheets
- Can mimic other solid round tumours
- High grade nuclei
- Single filing at the margin

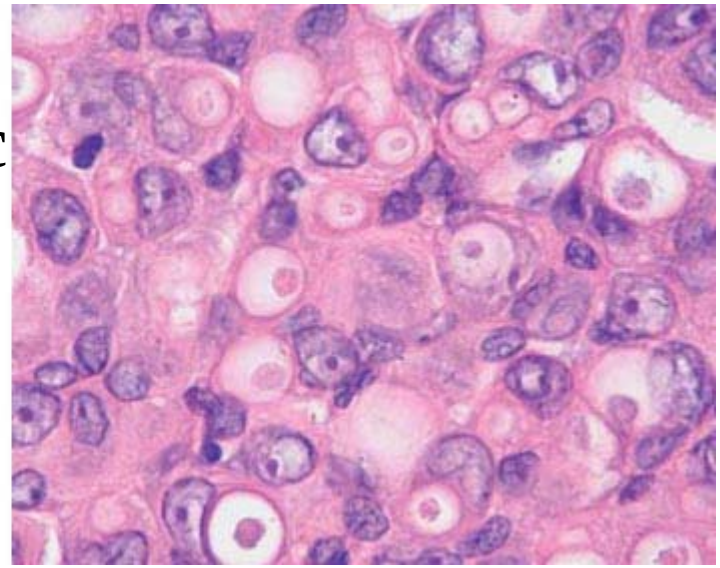


Alveolar ILC

- Rounded aggregates
- Invasion mimics LCIS
- Lacks myoepithelial/basal cells & basement membrane
- Often present in a mixed growth pattern

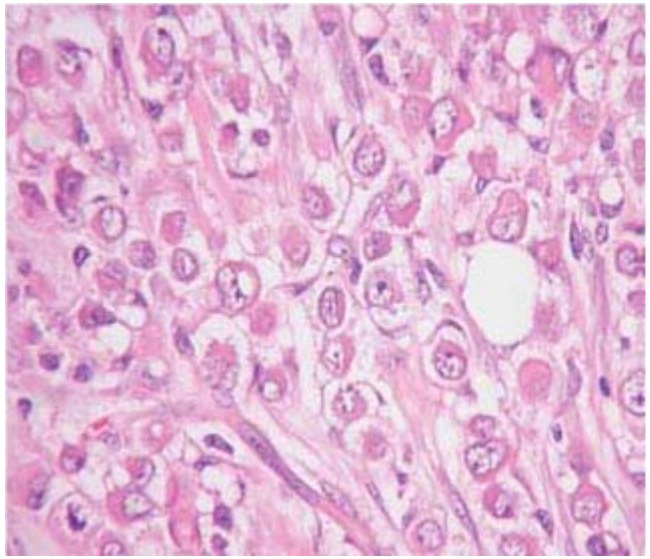


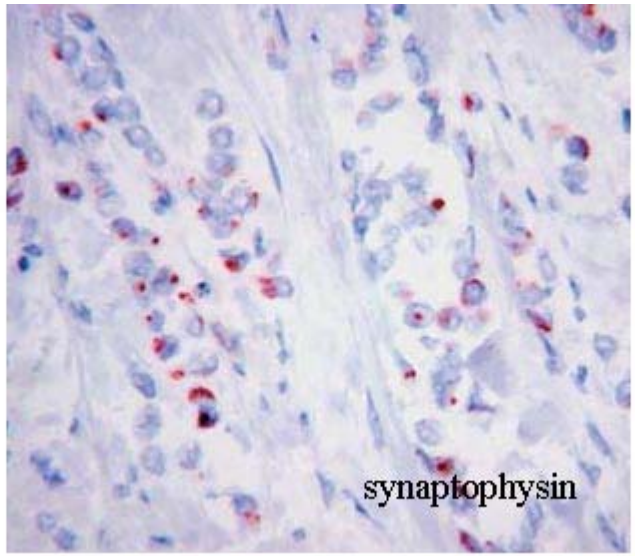
Pleomorphic ILC

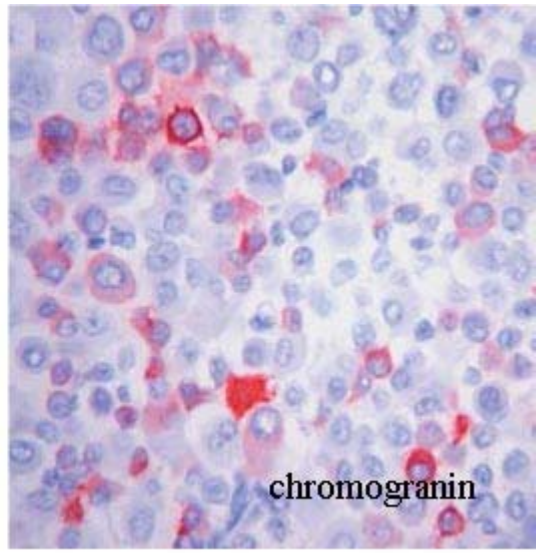


- Marked nuclear pleomorphism
- HER2 overexpression
- P53 positive
- ER & PR could be negative
- intracytoplasmic lumens containing centrally located eosinophilic material (targetoid cells).
- chromosomal changes more resemble grade lll IDC than grade l

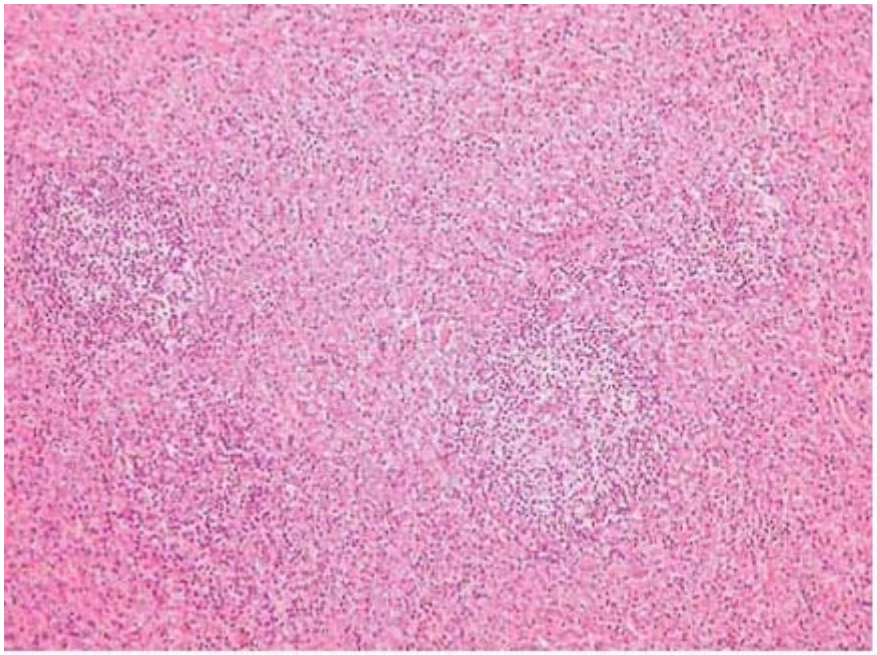
Middleton et al Am J Surg Pathol 2000

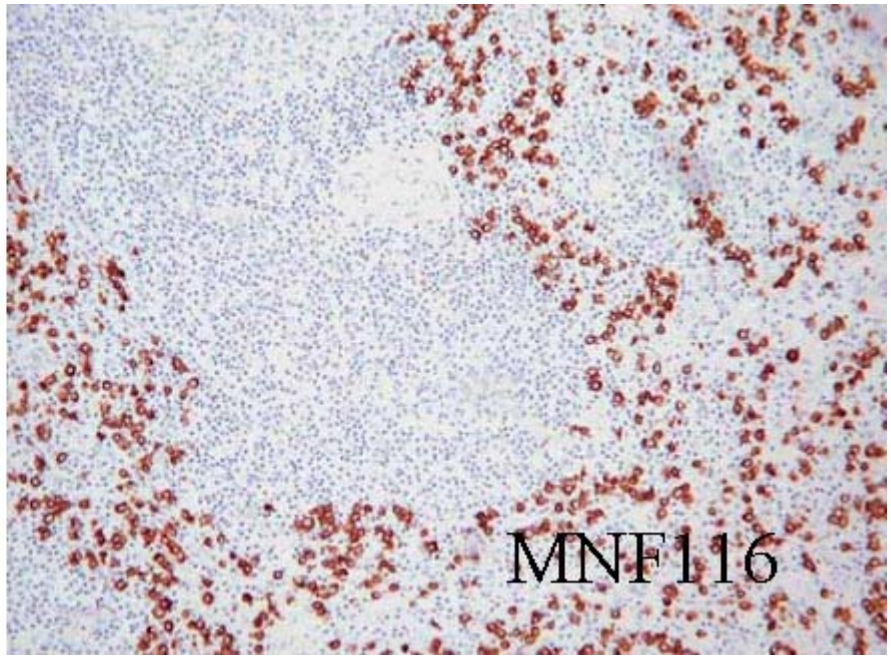






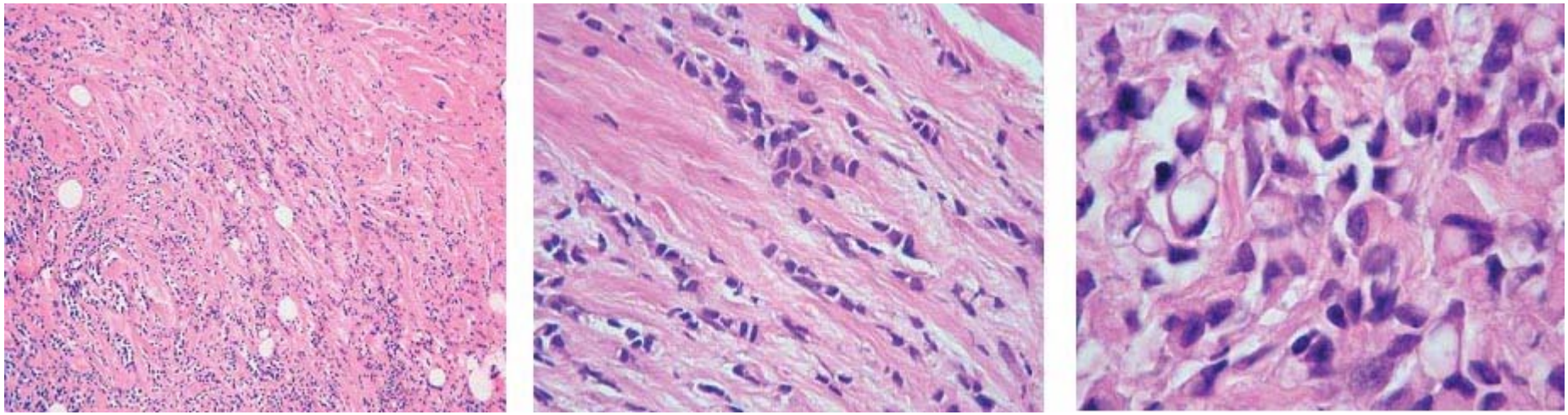
Pleomorphic variant of infiltrating lobular carcinoma with neuroendocrine differentiation.



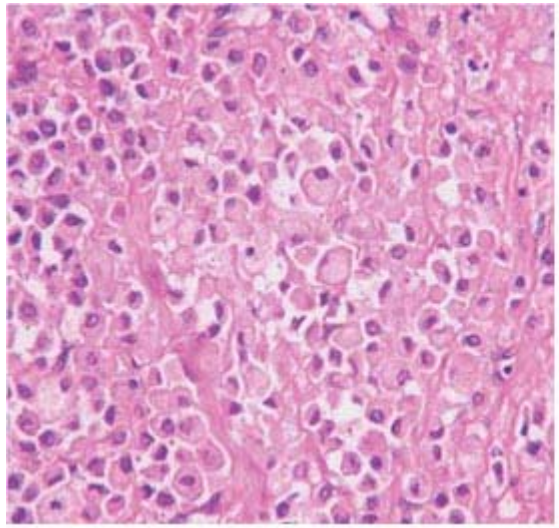
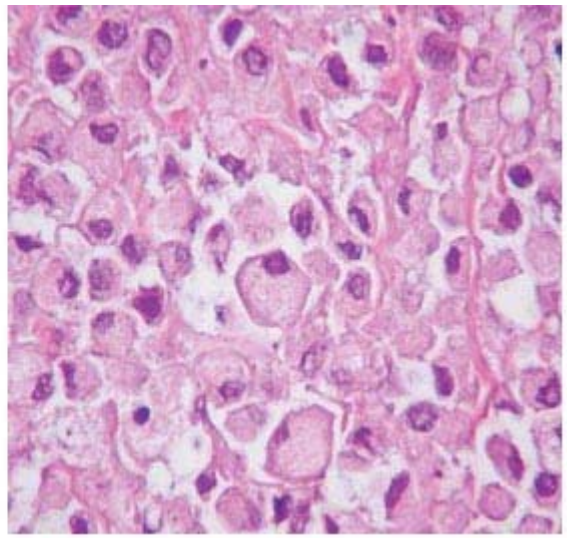
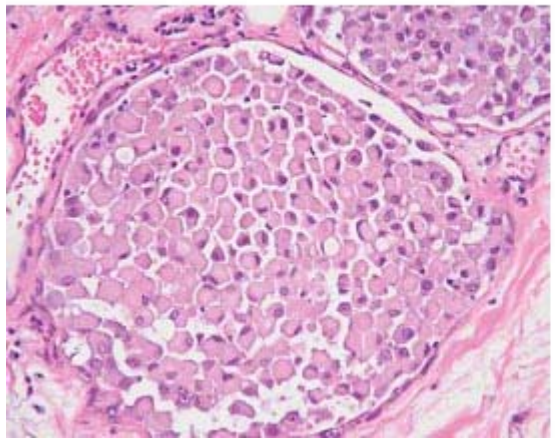
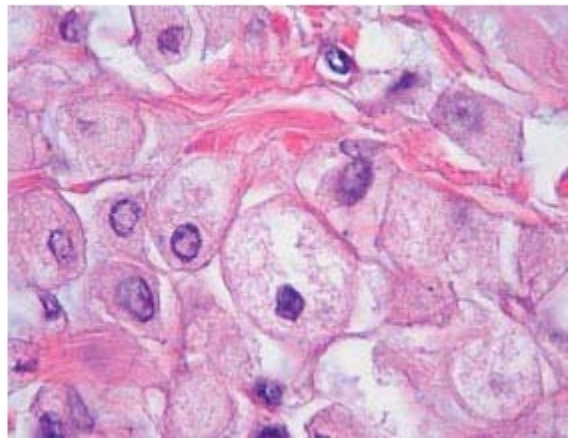


- **Pleomorphic variant of infiltrating lobular carcinoma simulating lymphoma**

  (lymphoma-like carcinoma).



Pleomorphic variant of Infiltrating lobular carcinoma with signet-ring cell component.

- **Histiocytoid variant of infiltrating lobular carcinoma (histiocytoid carcinoma).**

Histiocytoid Carcinoma

- **mainly BUT not exclusively found among ILC.**
- **It can be easily mistaken for inflammatory conditions**
- **Tumor cells commonly show granular immunoreactivities for gross cystic disease fluid protein-15 (GCDFP-15).**
- **Based on the morphology and IHC, several studies suggested that histiocytoid carcinoma represents**

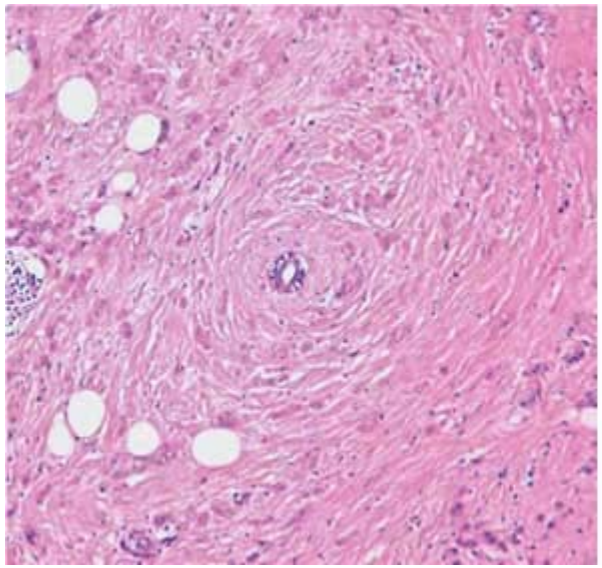
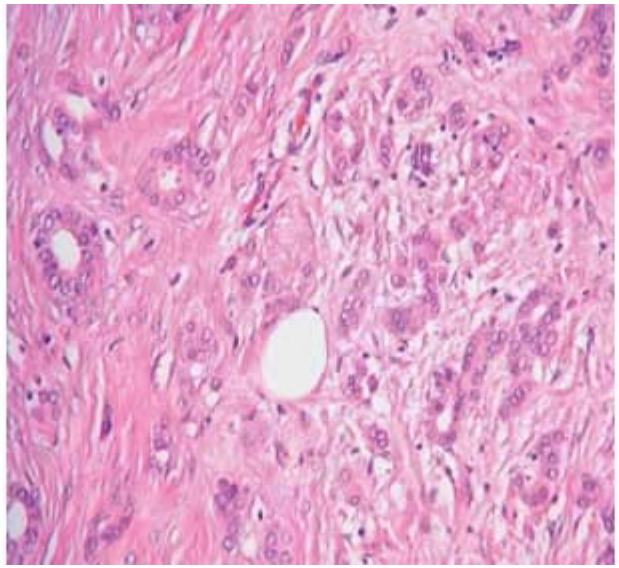
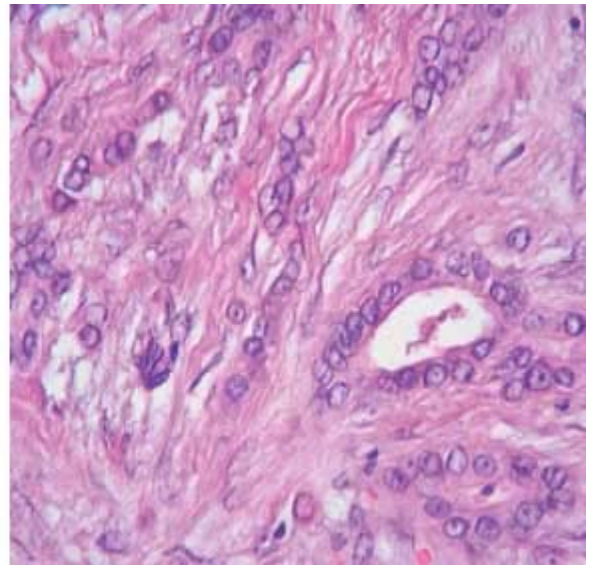
  a variant of carcinoma with apocrine

Grading of PILC

- It is important to keep in mind pleomorphic variant of ILC commonly do **not** show high mitotic activity.
- Such tumours should be regarded as **poorly differentiated carcinomas** based on the nuclear

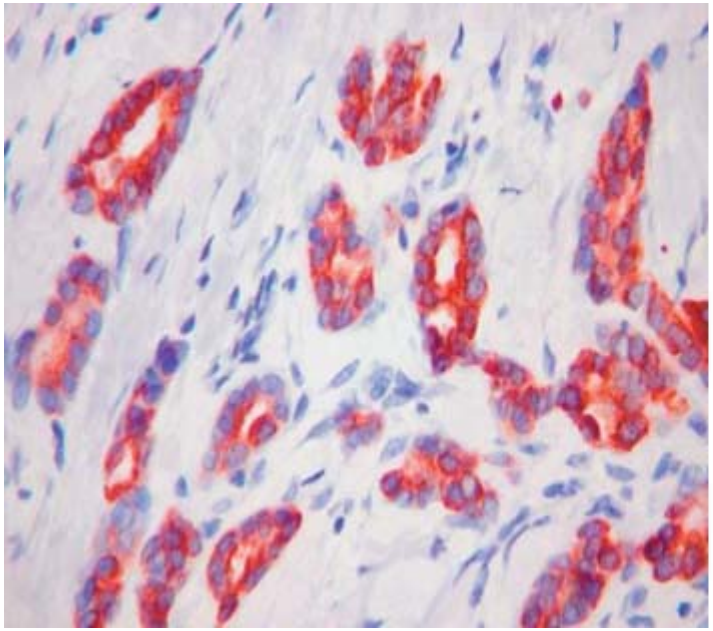
  grading system, regardless of their mitotic

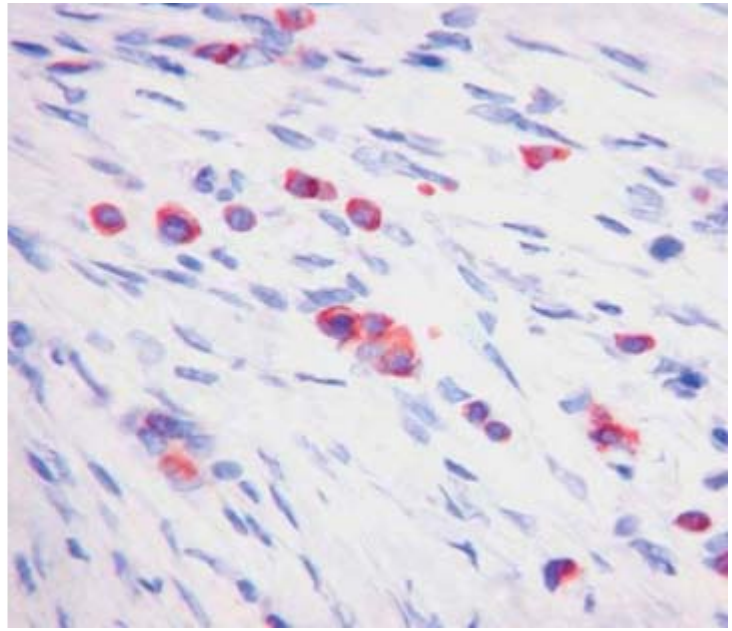
  activity (**G3**).

Tubulolobular ILC

- Classic Lob CA with single file and targetoid pattern
- Small calibre tubules
- It is distinct from tubular and lobular CA (tubular/lobular mixed)





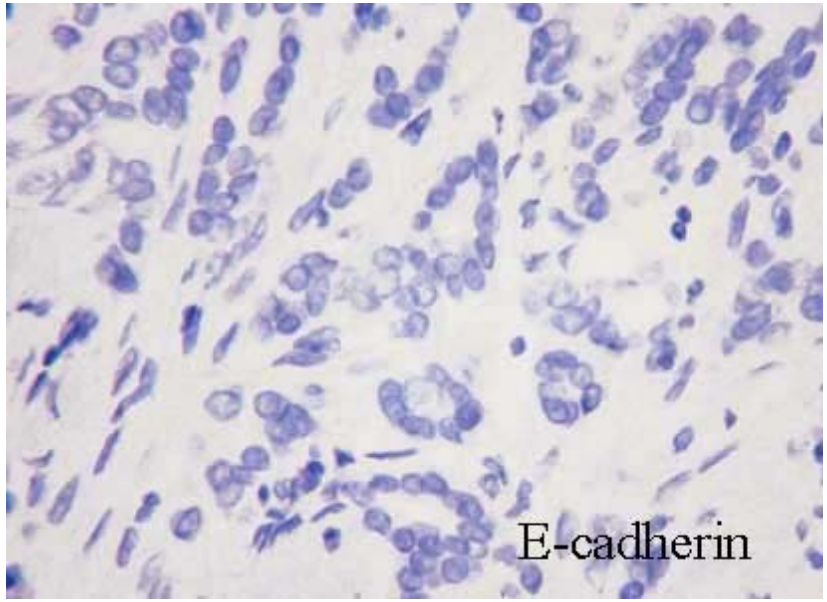
Tubulolobular Carcinoma

- **Most are Positive for E-cadherin and Negative for CK34 BE12 – more akin to ductal CA than ILC**

Wheeler DT et al, Am J Surg Pathol 2004;28(12)

Marchio C et al, Histopathology 2006;48(5)

Kuroda H et al, Virchows Arch 2006;448(4)



Tubulolobular Carcinoma

- Some tubulolobular Ca are negative with E-cadherin- more akin to ILC
- In other cases tumour cells are positive for both E-cadherin and CK34BE12 (positive hybrid tumour) OR negative for both E-cadherin and CK34 BE12 (negative hybrid tumour)

Monifar F, Essentials of Diagnostic Brest pathology, 2007

Tubulolobular ILC

Best prognosis of all lob CA subtype

Pereira H et alHistopathology 1995;27(3)

10 year survival

- 91% Tubulolobular CA
- 90% Tubular CA
- 71% Grade l ILC
- 55% Grade ll ILC

du Toit RS et al, Br J Cancer 1989;60(4)

Molecular pathology of classical lobular neoplasms

- **Typically E-cadherin negative**
  Berx G et al, EMBO J 1995;(14)

- **CK 34 BetaE12 (1, 5, 10 and 14) positive**
  Wheeler DT et al, Am J Surg Pathol 2004;28(12)

- **ER and PR positive**
  Arpino G et al, Breast Cancer Res 2004;6(3)

Molecular pathology of classical lobular neoplasms

- pleomorphic lobular carcinomas can be:
  ER and PR negative
  HER2 positive
  Middleton LP et al, Am J Surg Pathol 2000;24(12)

- Some ductal carcinomas share the molecular profile of Lobular carcinoma
  Tan DSP et al, J Pathol 1999;189(1)

Molecular pathology of classical lobular neoplasms

- Interestingly some rare families have been detected whose kindred have an inherited defect in the E-cadherin gene and who develop either lobular carcinoma or diffuse gastric carcinoma or both.

- *Keller G et al, Am J Pathol 1999;155(2):337-42.*

Cytogenetics of classical lobular neoplasms

- Support a continuum between ALH, LCIS and invasive lobular neoplasia.

Buerger H et al, Mol Pathol 2000;53(3)

Cytogenetics of classical lobular neoplasms

- **Classic ILC have relatively low numbers of changes compared to the rest of breast cancers: loss of 16q**

  Gain of 1p

  Resembling grade I ductal carcinomas and suggest that these tumours are closely related.

  Roylance R et al, Oncogene 2006;25(49)

Cytogenetics of classical lobular neoplasms

- **Recent studies on series of Lobular carcinoma:**

  Gain on 11p associated with
  FGFR1 gene amplification

  This observation holds out the intriguing possibility of a specific therapeutic target for these tumours

  Reis-Filho JS et al, Clin Canc res 200?


You see only what you look for
You recognise only what you know
THANK YOU