Breast cancer (BC) pathology and molecular biology

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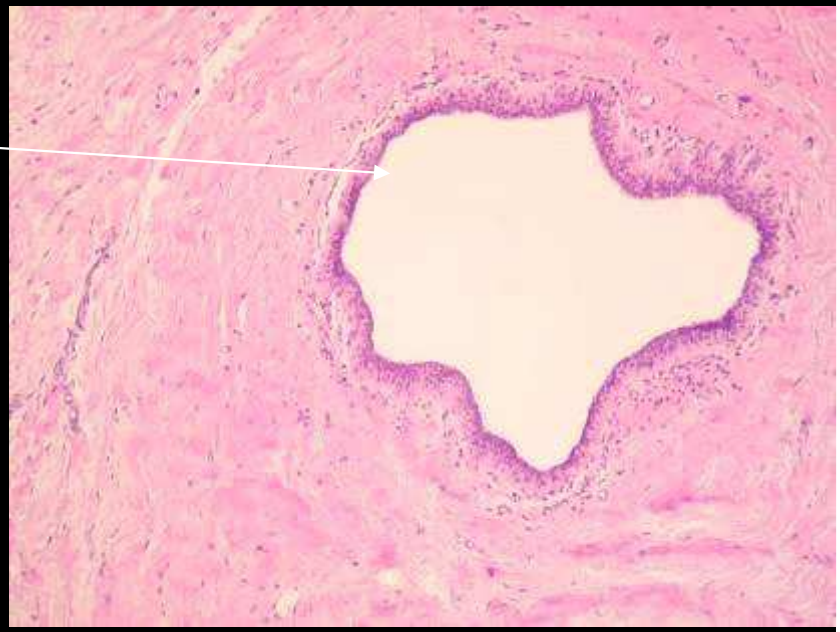
Normal microscopic anatomy

Duct



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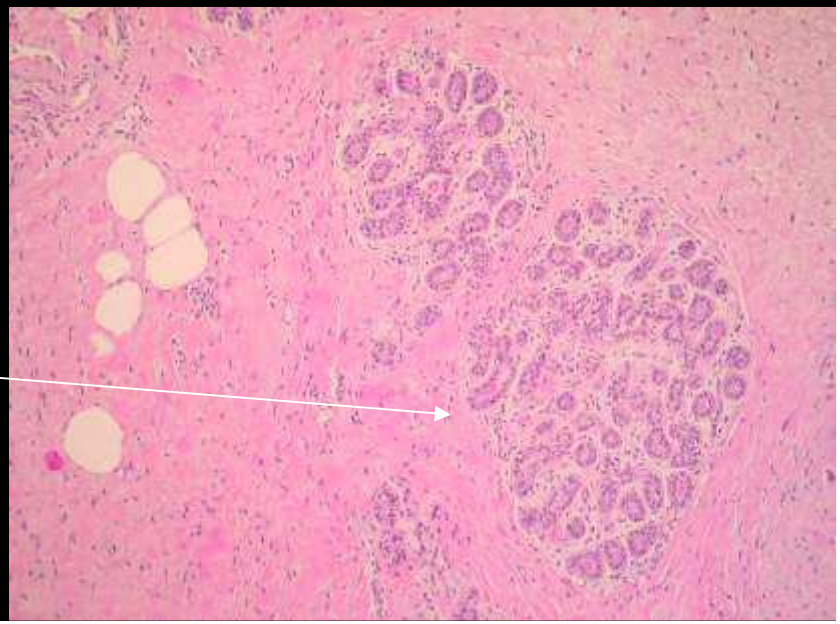
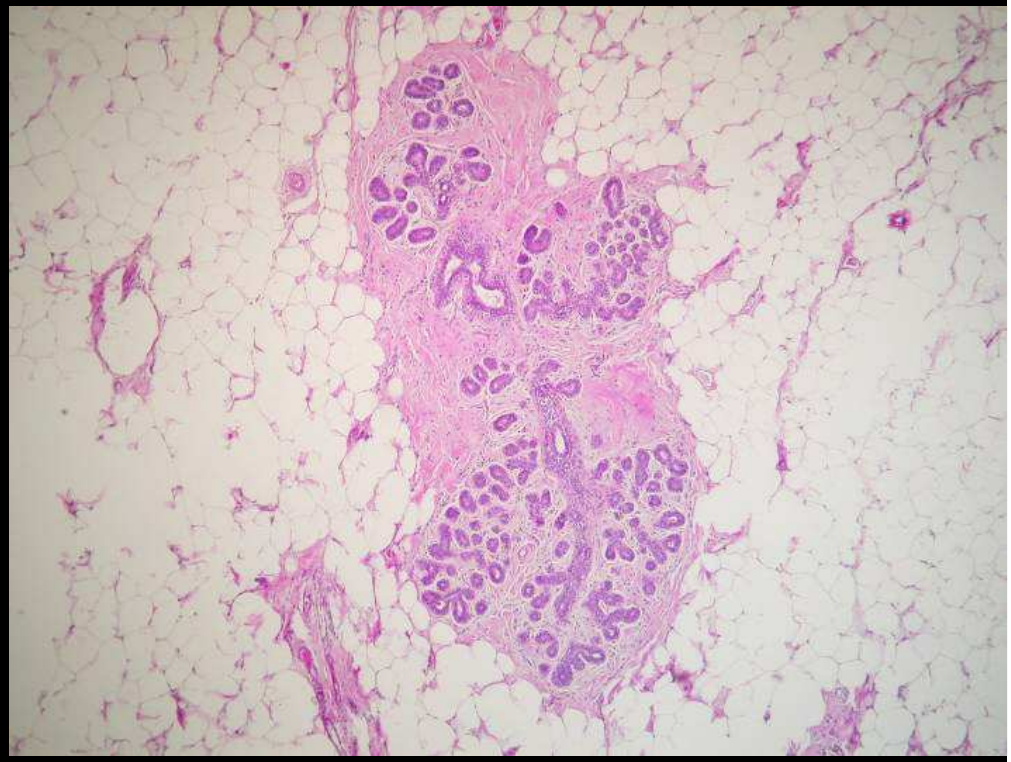


Lobule

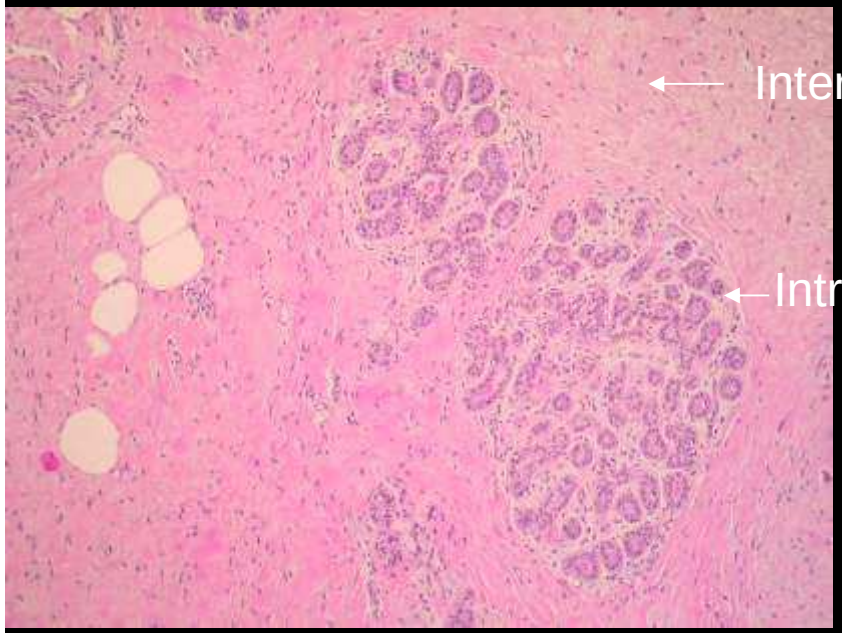
Terminal ductulolobular unit (TDLU)

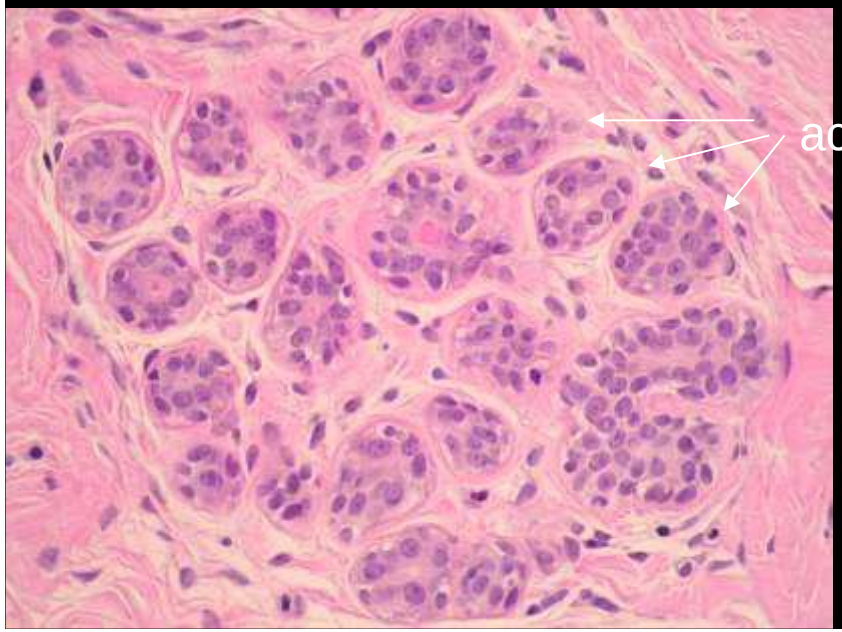


www....

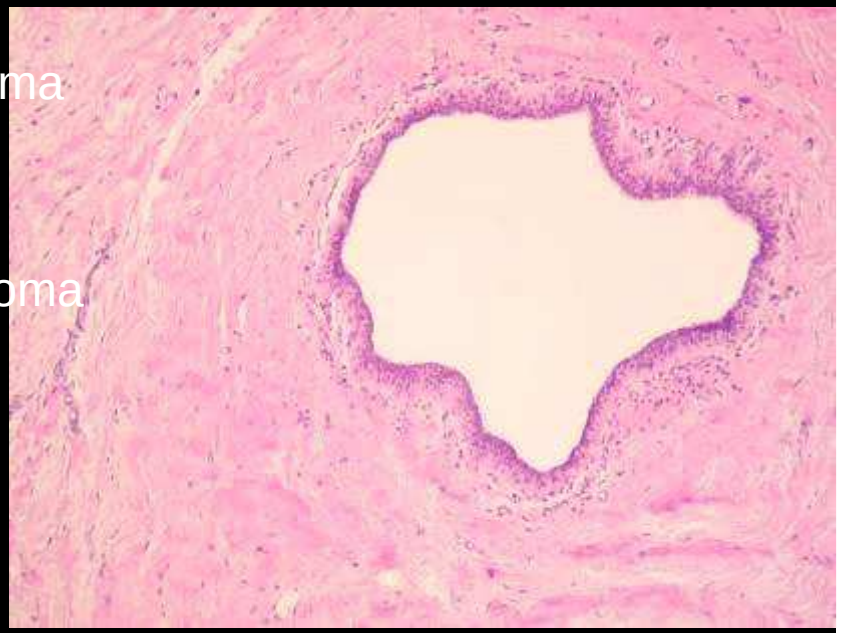
Normal microscopic anatomy

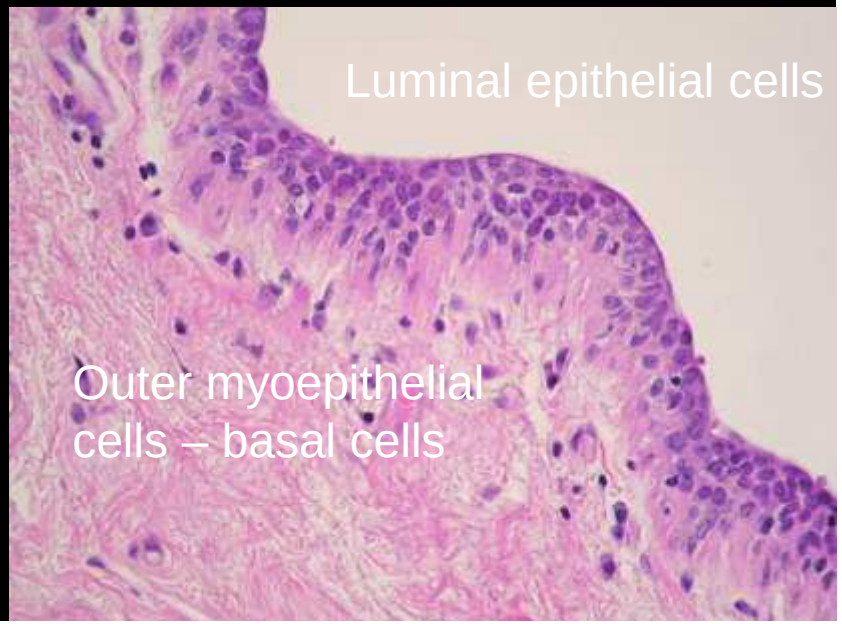
Lobules



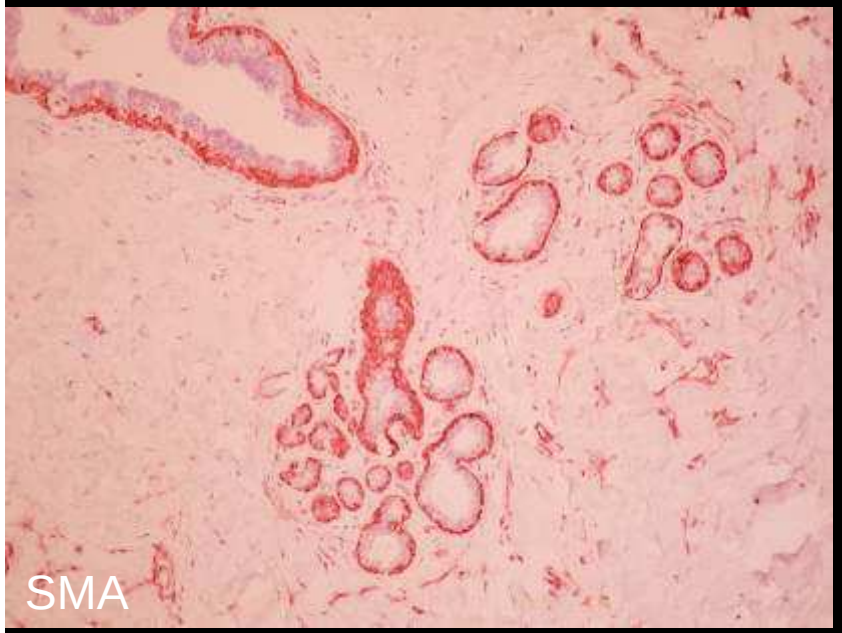


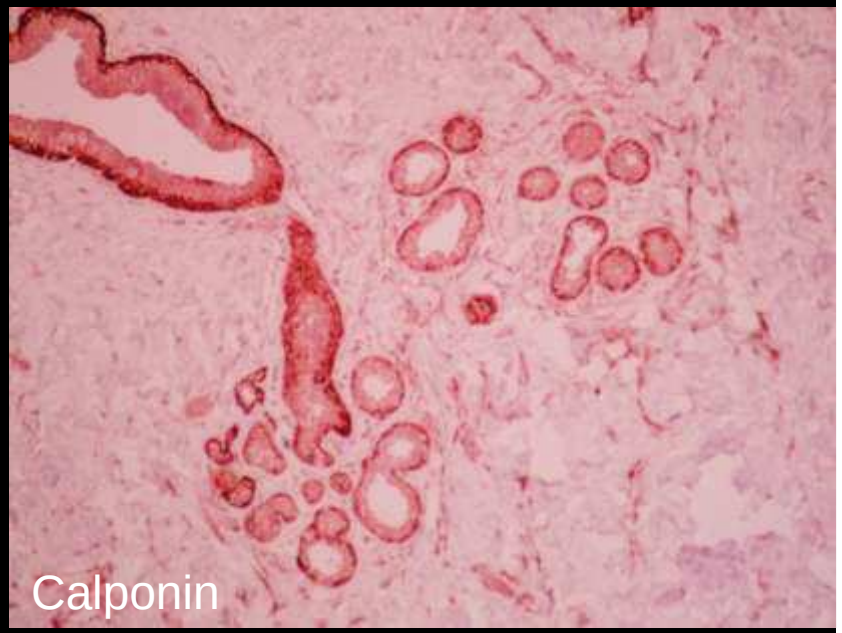
Duct

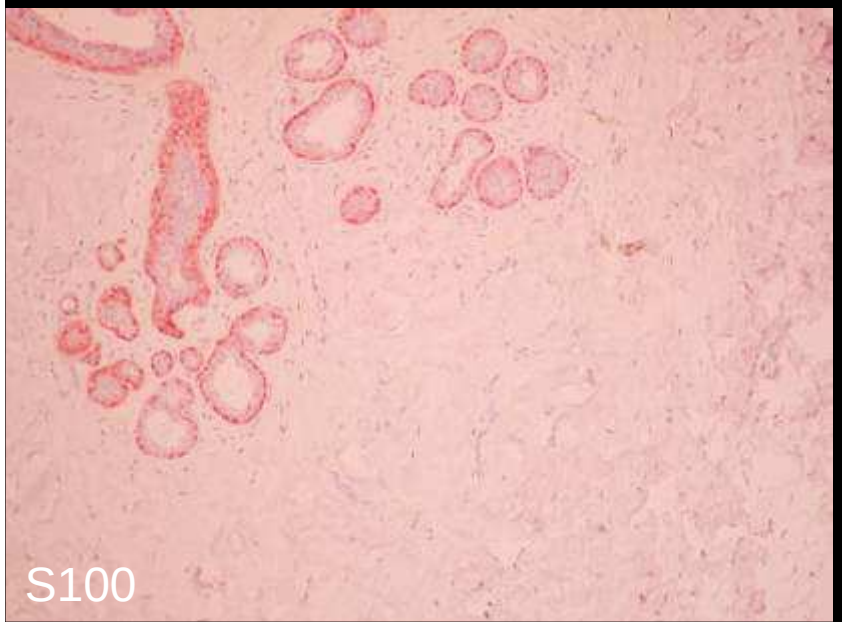


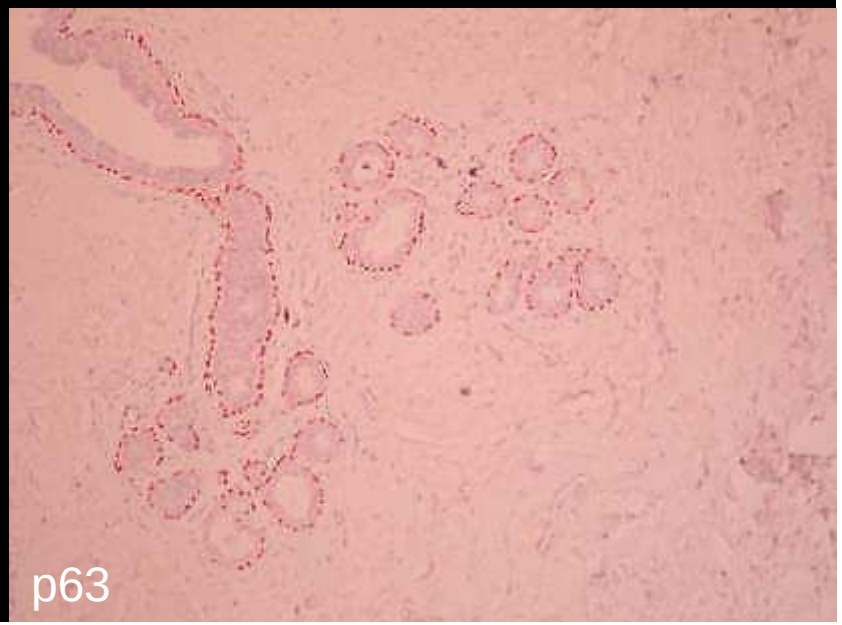


Normal structure (Myoepithelium)

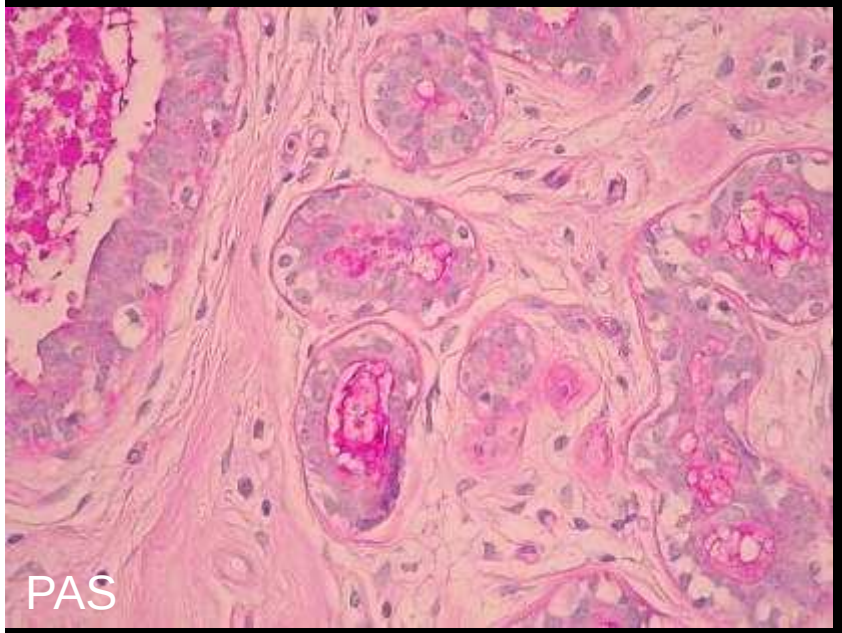


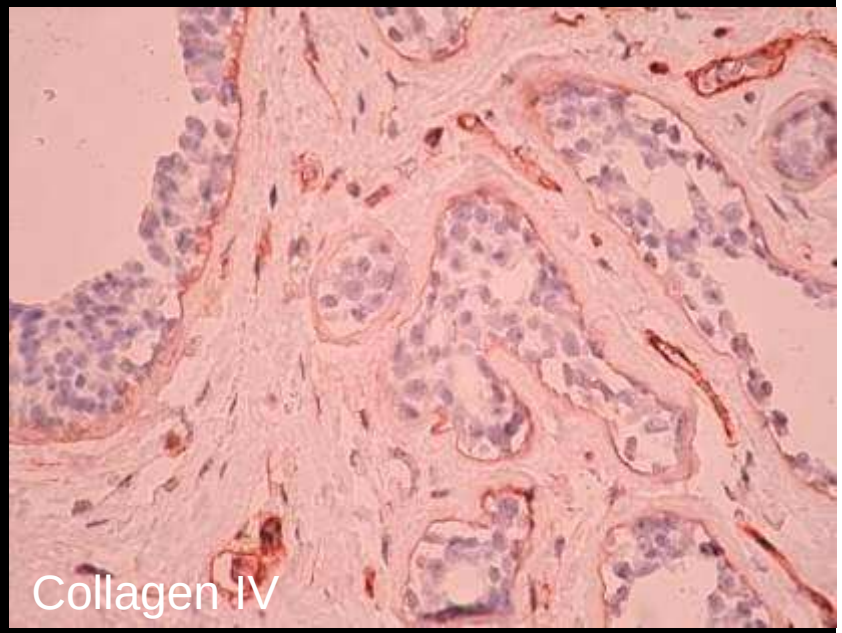


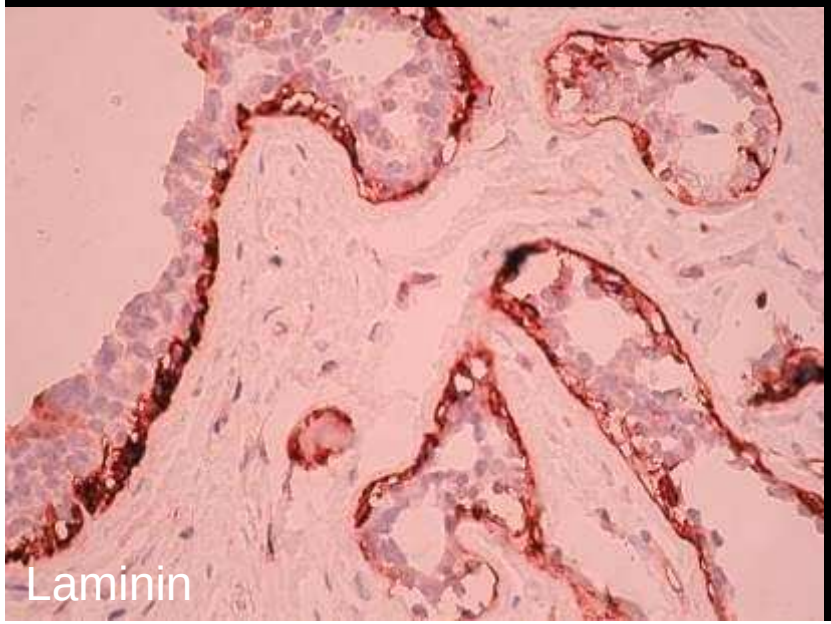




Normal structure (basament membrane)


PAS


Collagen IV

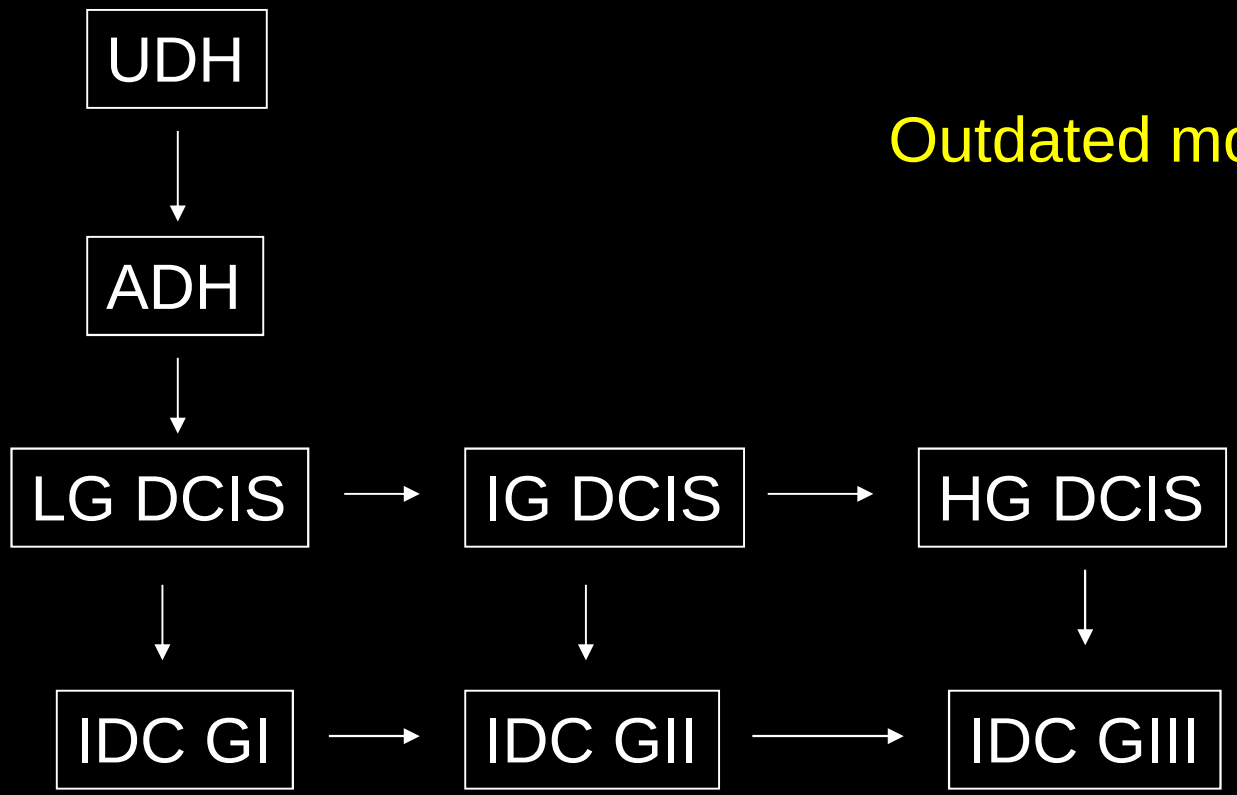

Laminin


Orcein – periductal elastic fibers

Breast cancer

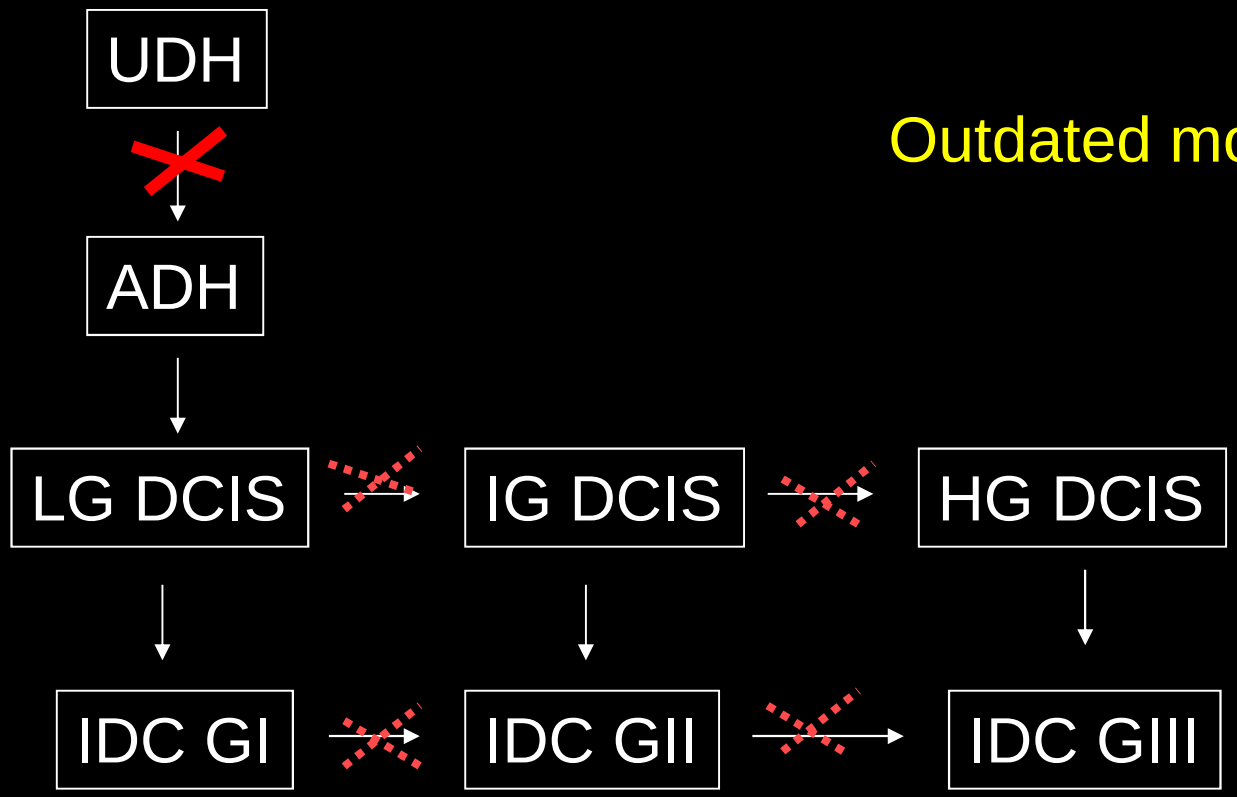
Rembrandt: Bathsheba in her bath (1654) - Louvre

Progression of BC (IDC) at the level of histological lesions



Outdated model

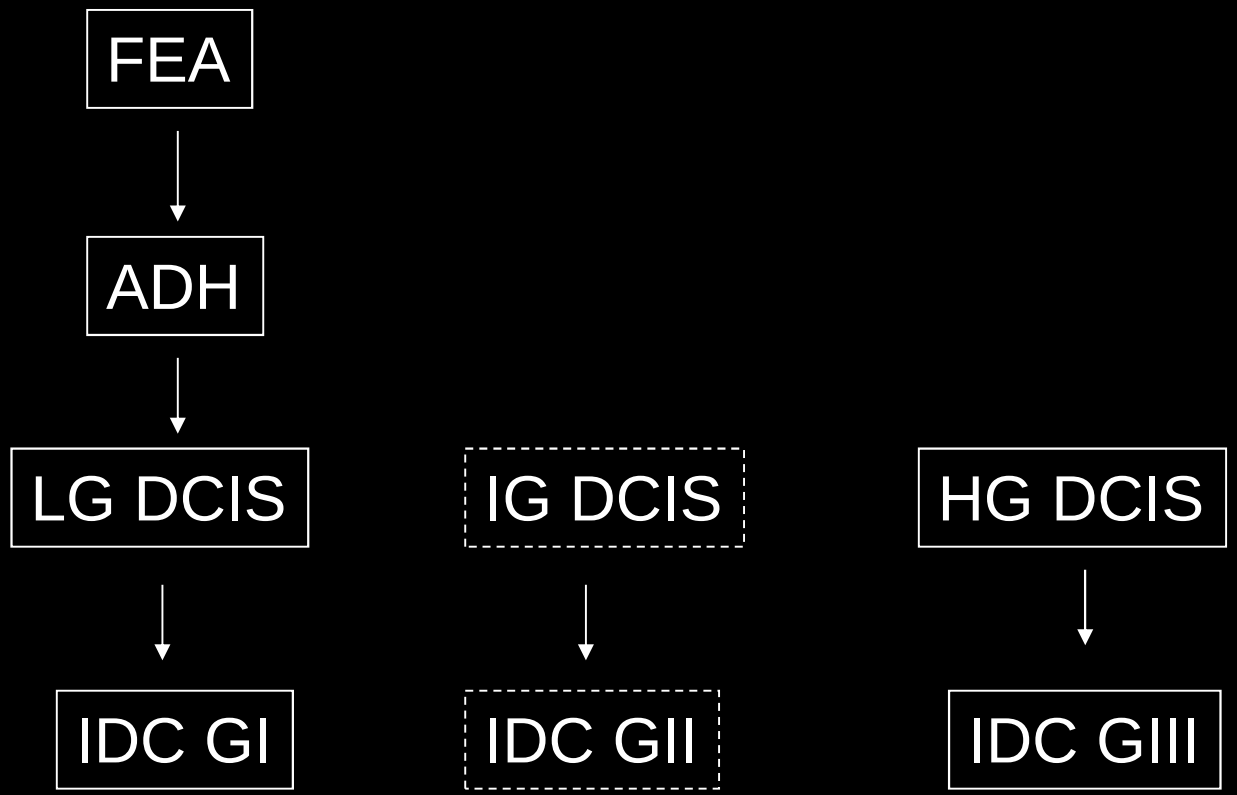
Progression of BC (IDC) at the level of histological lesions



Outdated model

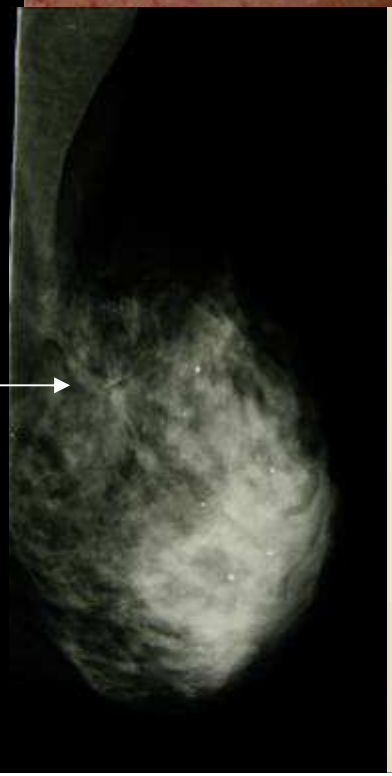
Usual type ductal hyperplasia does not progress into atypical ductal hyperplasia.

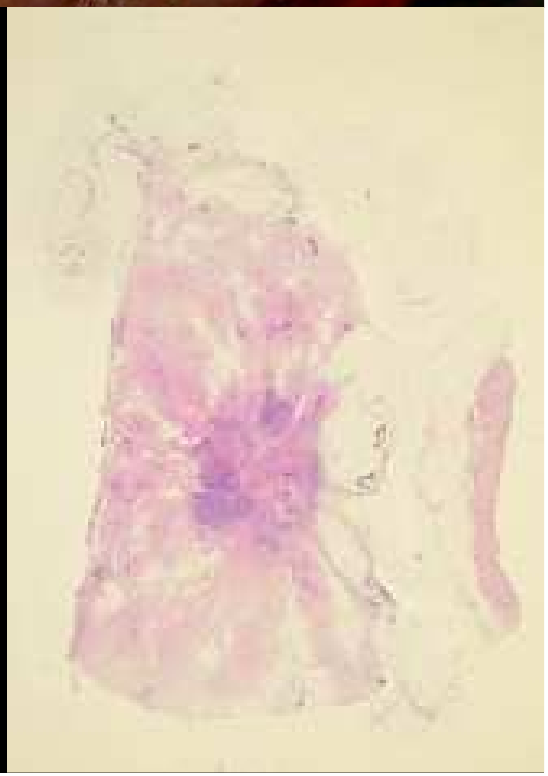
Progression of BC (IDC) at the level of histological lesions



Breast cancer

- Before the advent of breast cancer screening programs breast cancer was mainly detected as a symptomatic disease.
- In the era of BC screening many cases are detected in an asymptomatic (non-palpable) stage; many in the non-invasive or „in situ” phase





Breast cancer: in situ carcinoma

up to 25-30% of the screen detected cases

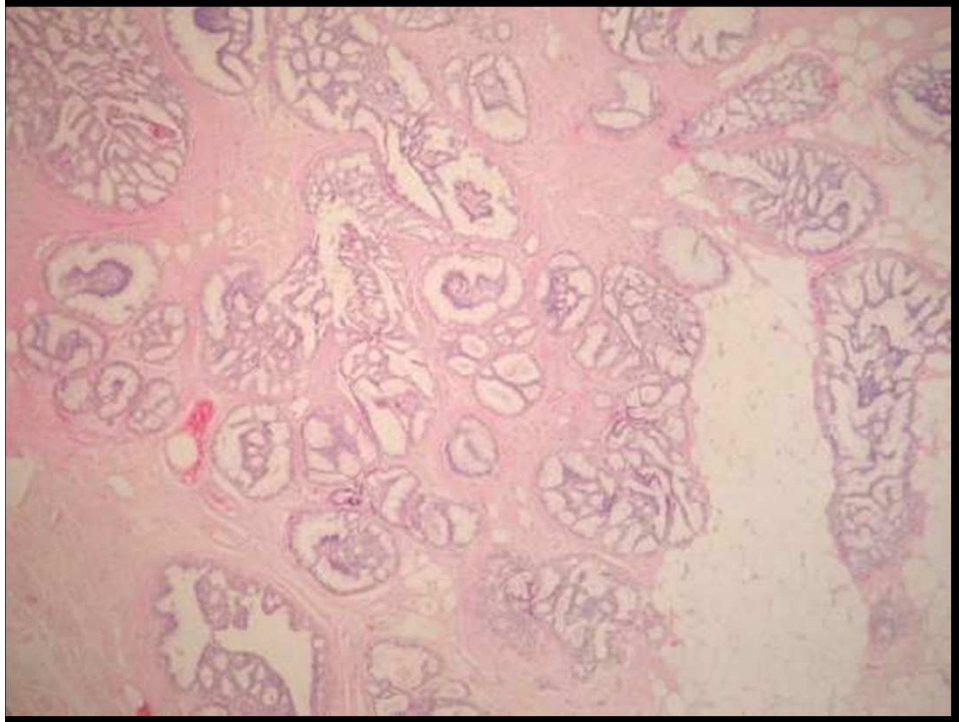
- IN SITU: myoepithelium and basement membrane borders them – NON-INVASIVE
- Ductal Carcinoma In Situ (DCIS)
- Lobular Carcinoma In Situ (LCIS)

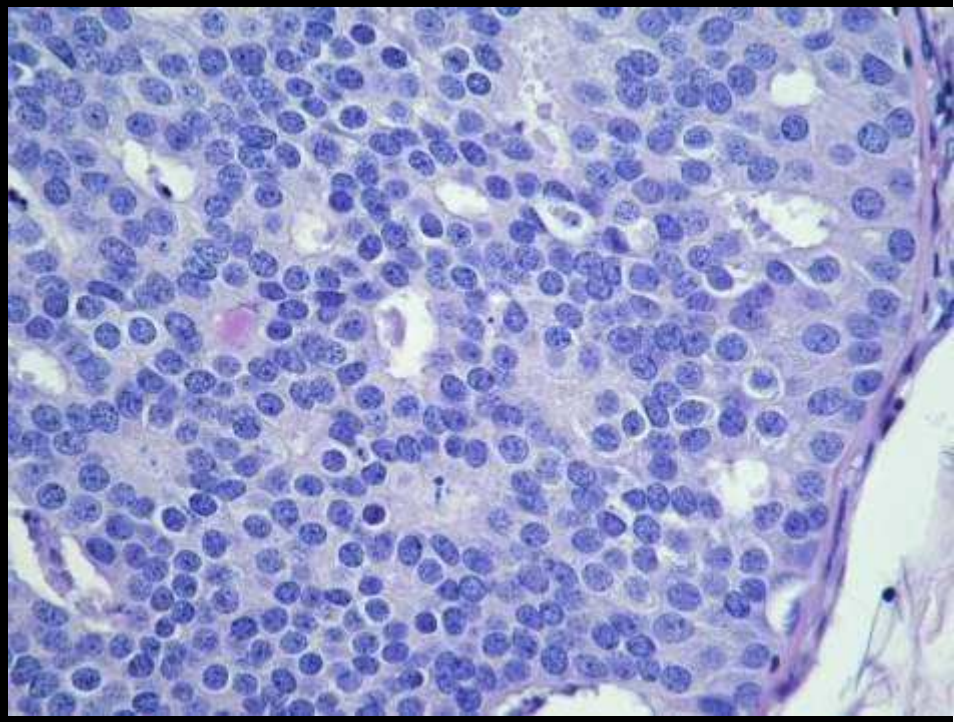
Both are traditional names and do not reflect the origin of the lesions; both arise from the terminal ductulolobular units

- Paget's disease of the nipple (in practice, always associated with in situ carcinoma of large lactiferous ducts or invasive carcinoma arising from this.

DCIS – cribriform pattern

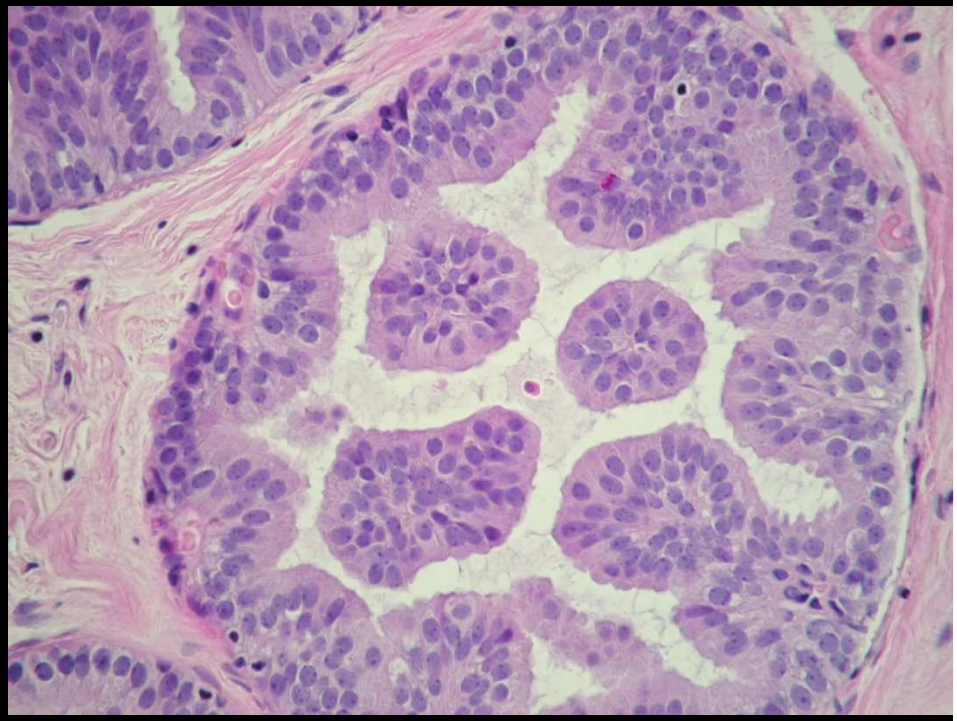
Rigid secondary lumen formation





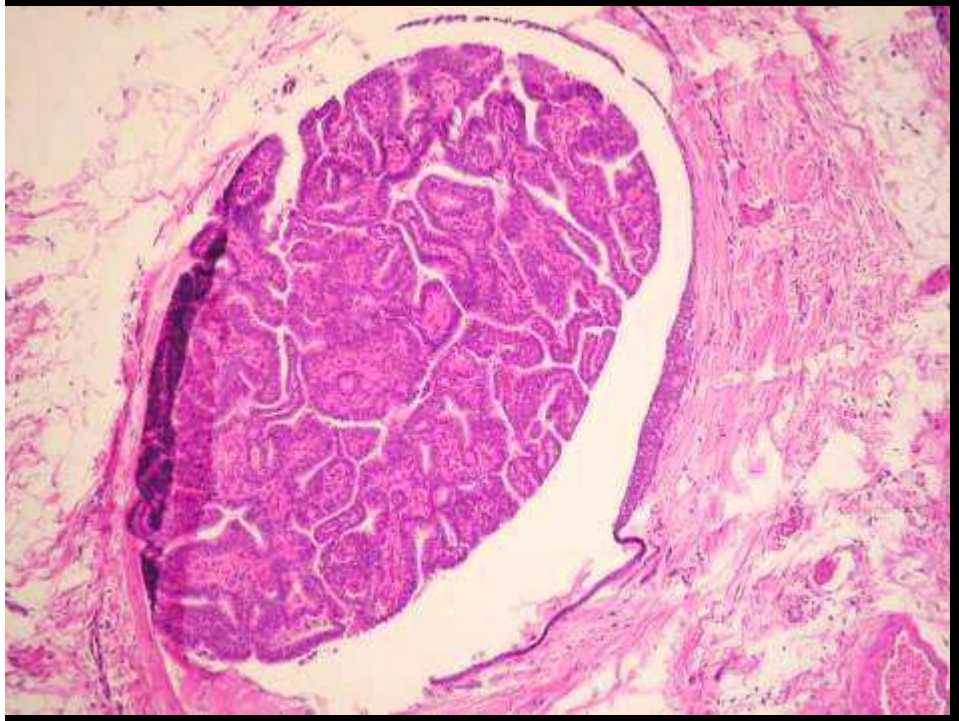
DCIS – micropapillary pattern

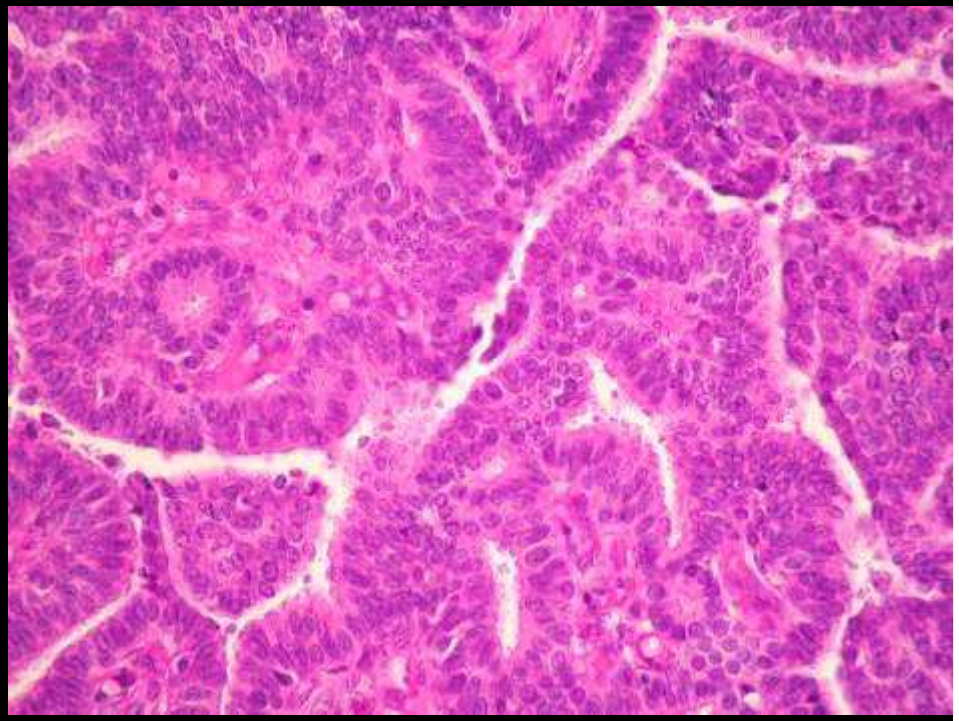
No fibrovascular cores



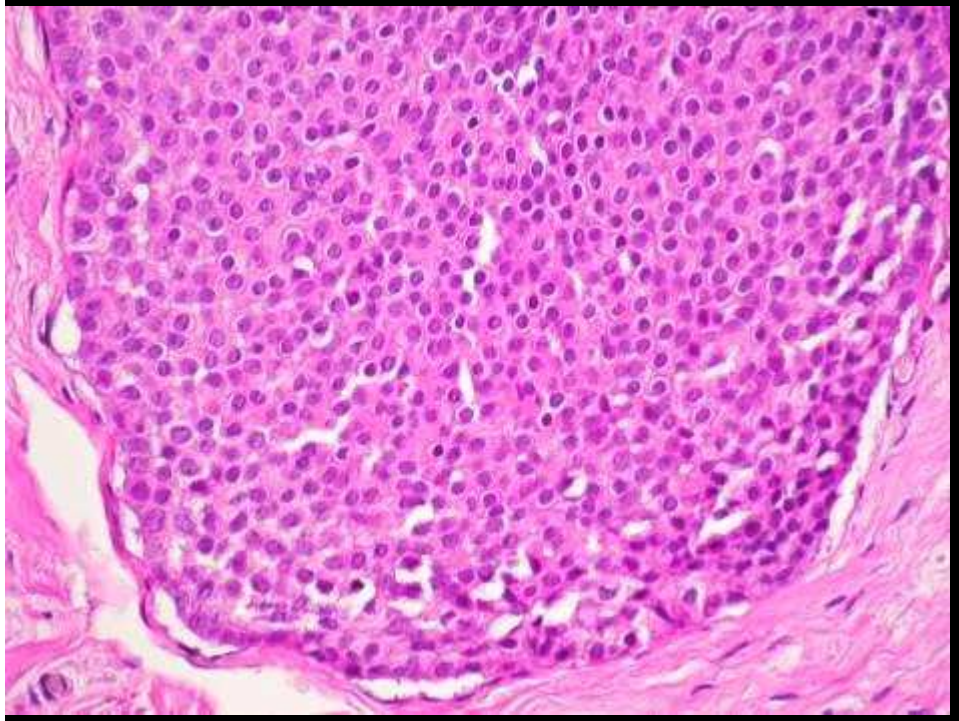
DCIS – papillary pattern

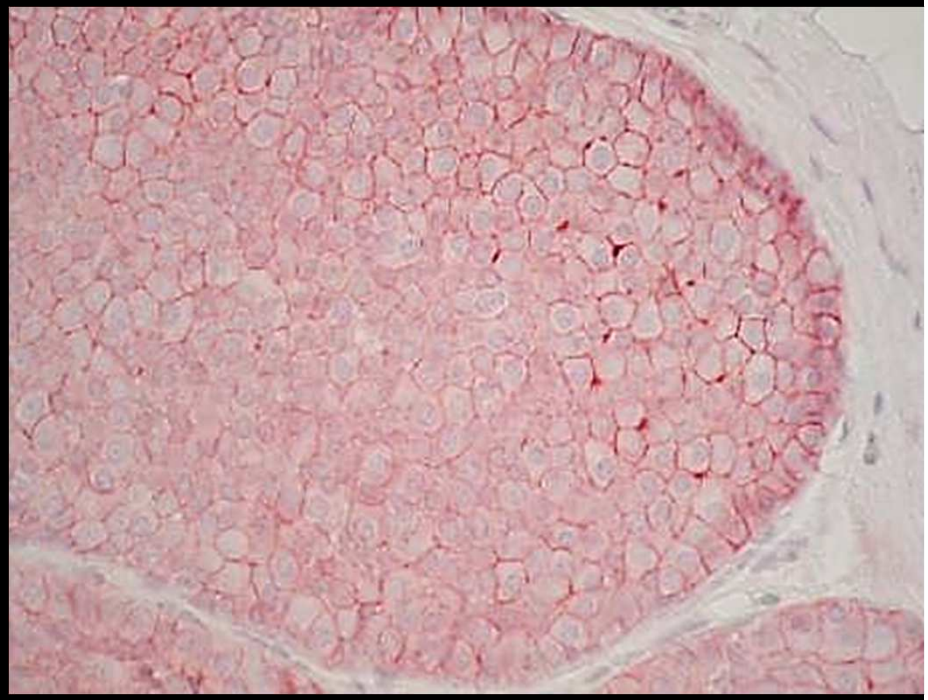
Lack of ME cells in the fibrovascular cores





DCIS – solid pattern

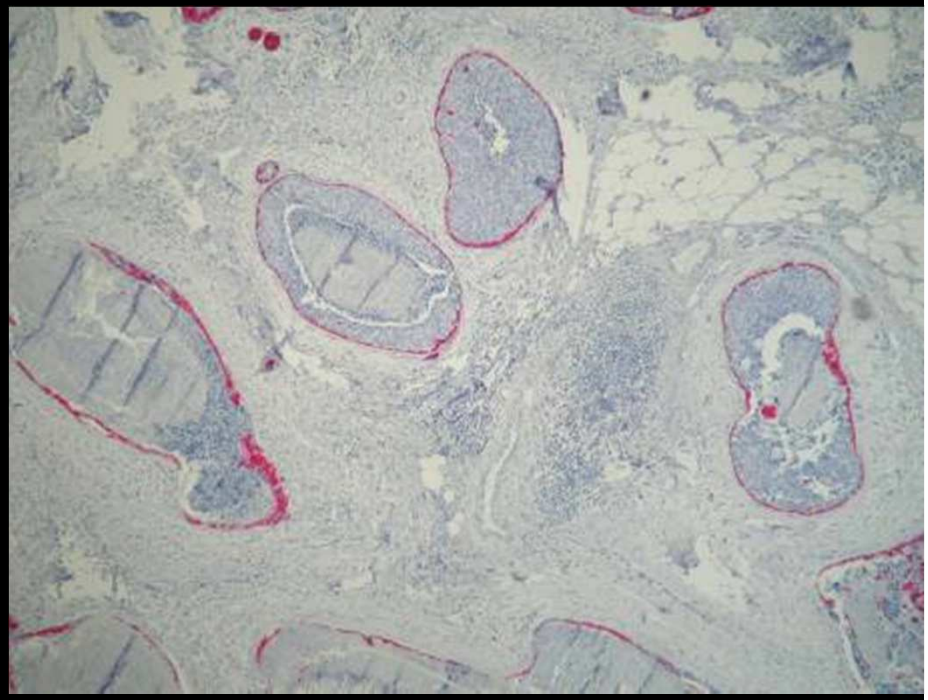




E-cadherin immunohistochemistry

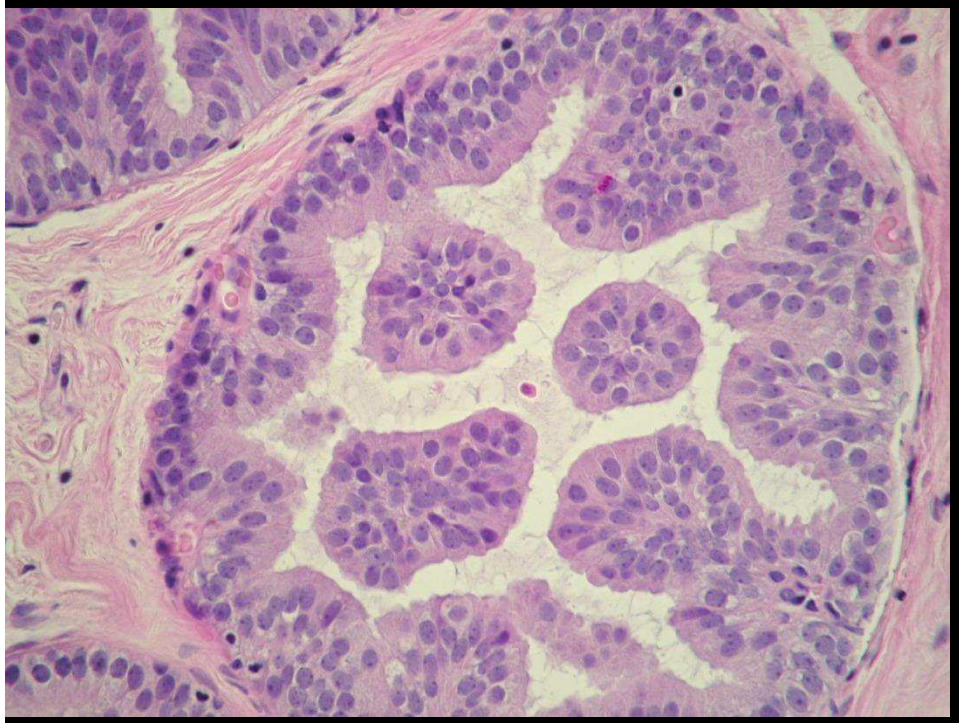
DCIS – comedo pattern

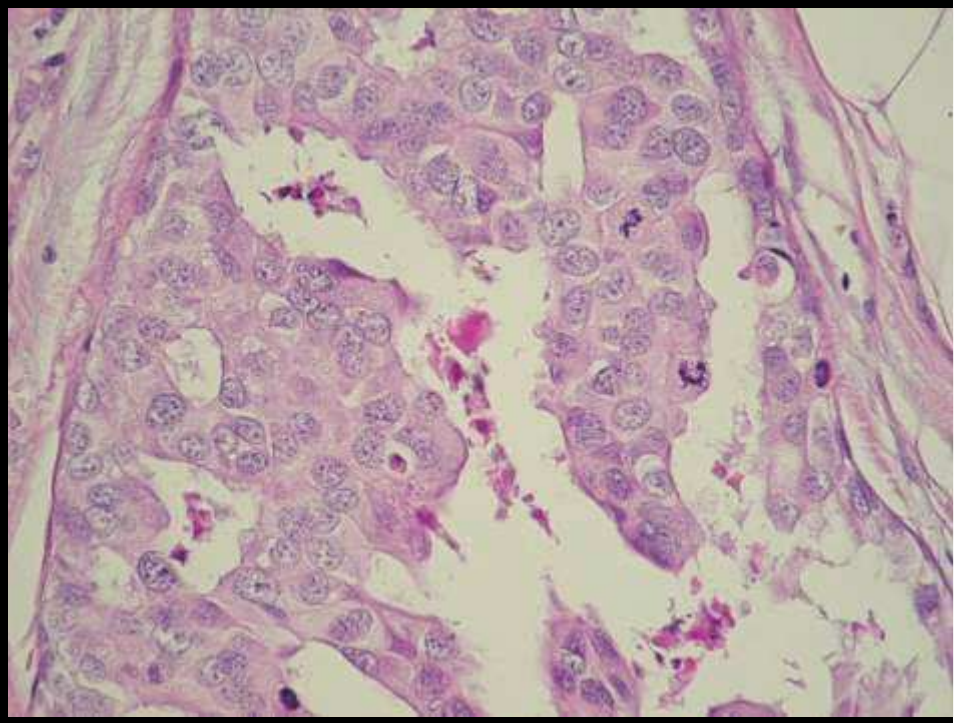
Central necrosis +/- casting microcalcification



Myoepithalial cell marker IHC

Low grade vs high grade DCIS

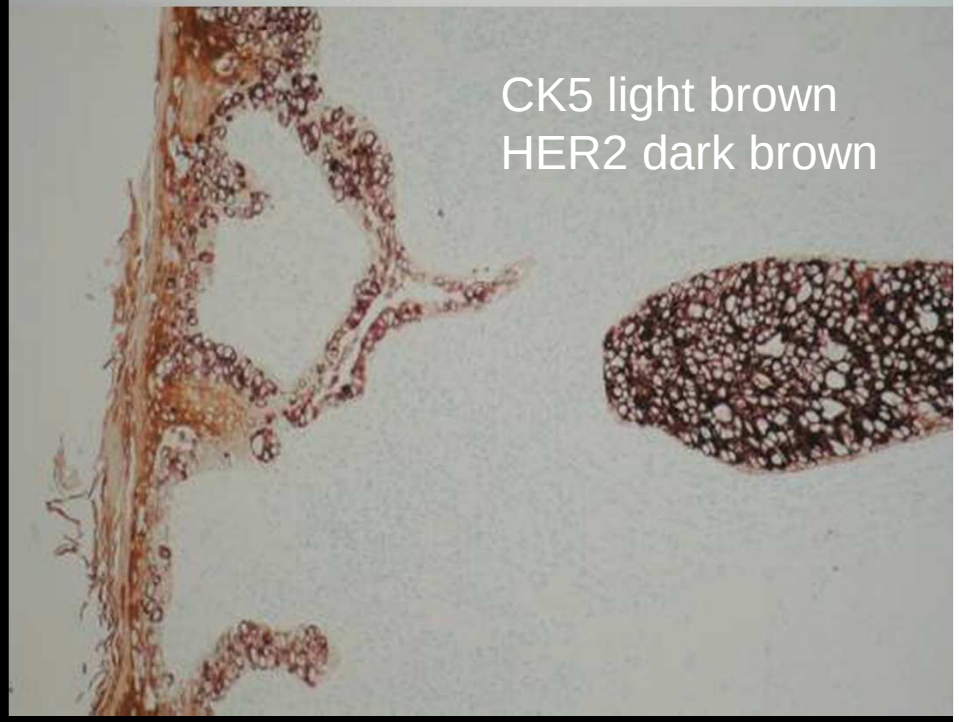




Do pattern and grade matter?

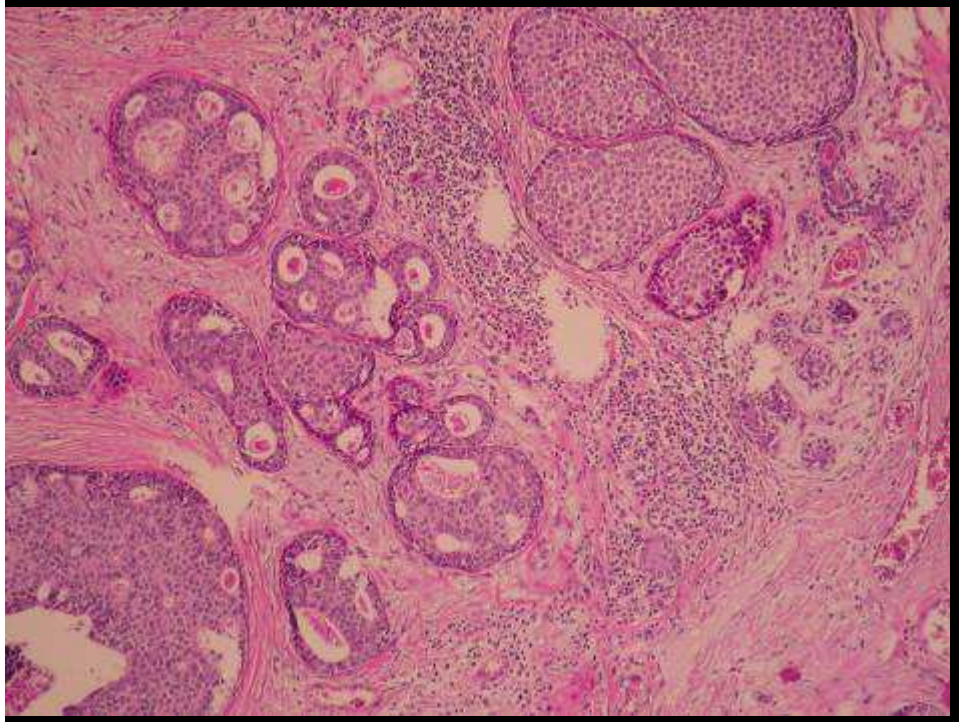
- Micropapillary DCIS is often larger than expected on the basis of microcalcifications.
- Micropapillary/cribriform are associated with different type of microcalcification than the comedo type (casting)
- Comedo necrosis and type is the type associated with fastest progression and worse prognosis.

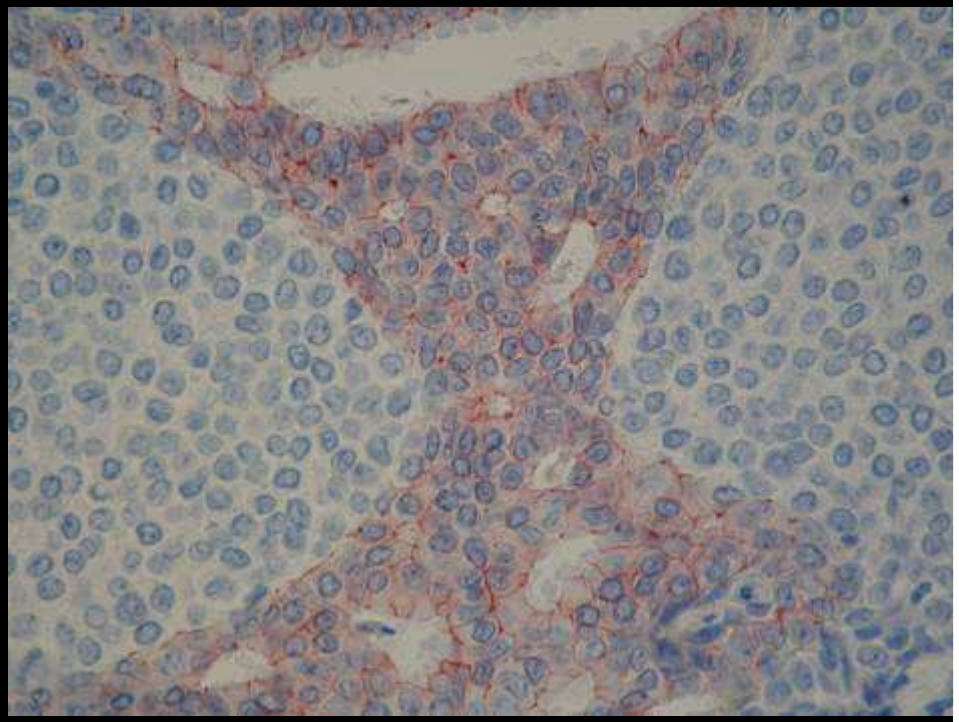
Paget's disease



CK5 light brown
HER2 dark brown

LCIS
(+LG cribriform DCIS in this example)

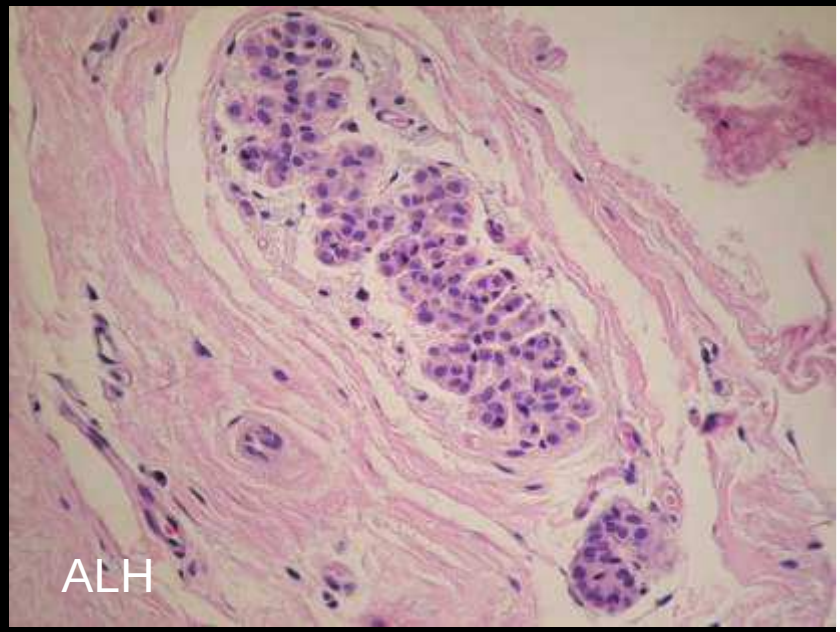


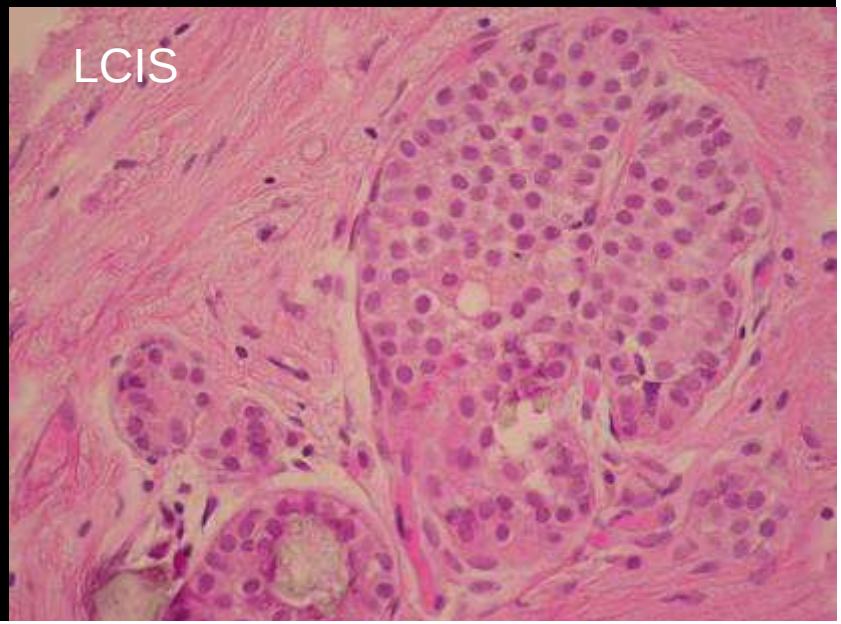


E-cadherin immunohistochemistry

The intraepithelial neoplasia concept

- ALH, LCIS are often referred to as lobular (intraepithelial) neoplasia (LN, LIN)
- ADH, DCIS are often referred to as ductal intraepithelial neoplasia (DIN)
- WHO 4th edition returned to ALH/LCIS & ADH/DCIS





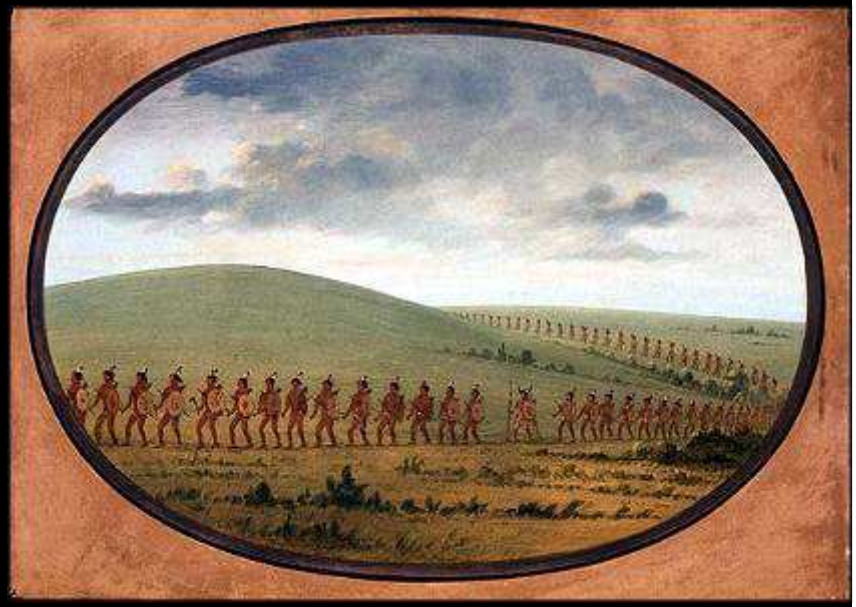
Invasive carcinoma - histological types

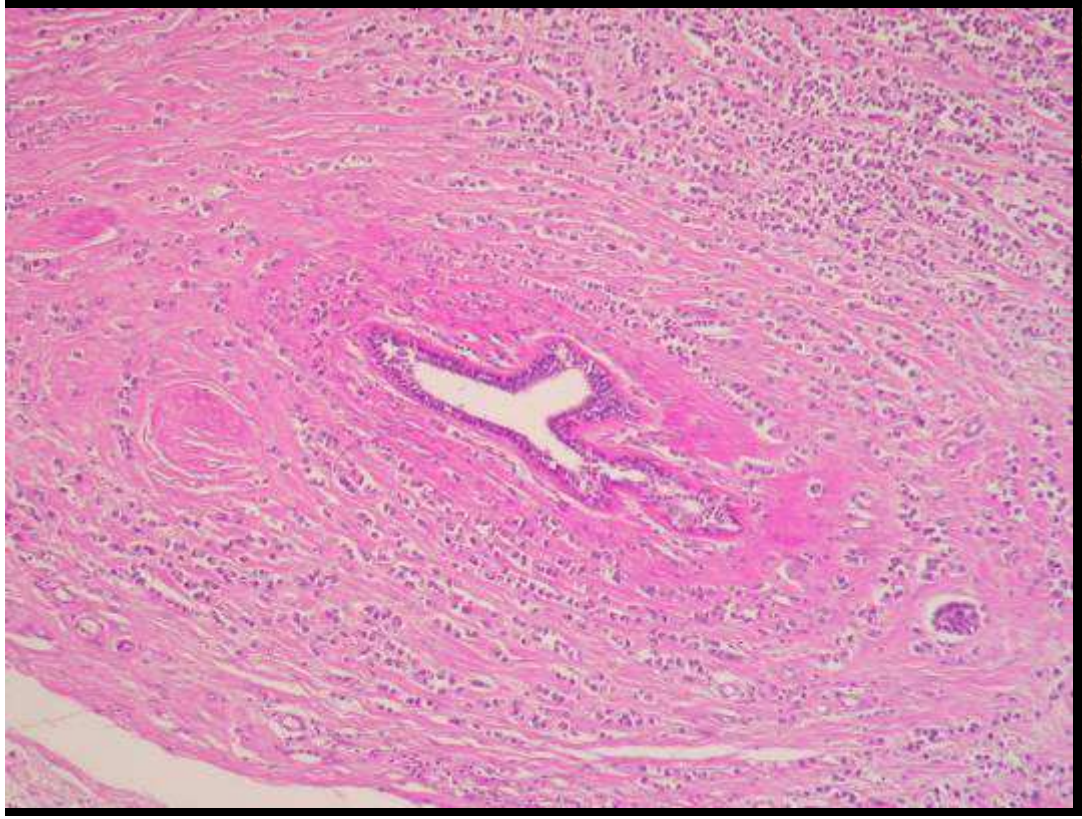
- Invasive ductal carcinoma NST (No Special Type) / NOS (Not Otherwise Specified) (about 80% of the invasive cases) WHO 4th ed
- Special type carcinomas
  - Invasive lobular carcinoma (~ 10%)
  - Tubular carcinoma and cribriform carcinoma (~ 6%)
  - Mucinous (colloid) carcinoma (~ 2%)
  - Medullary carcinoma (~ 2%)
  - Other less common types (e.g. micropapillary, papillary, metaplastic, … etc)

Invasive lobular carcinoma

Discohesive cells arranged in „indian files”, or in „geese lines”, often in a targetoid pattern around normal ducts

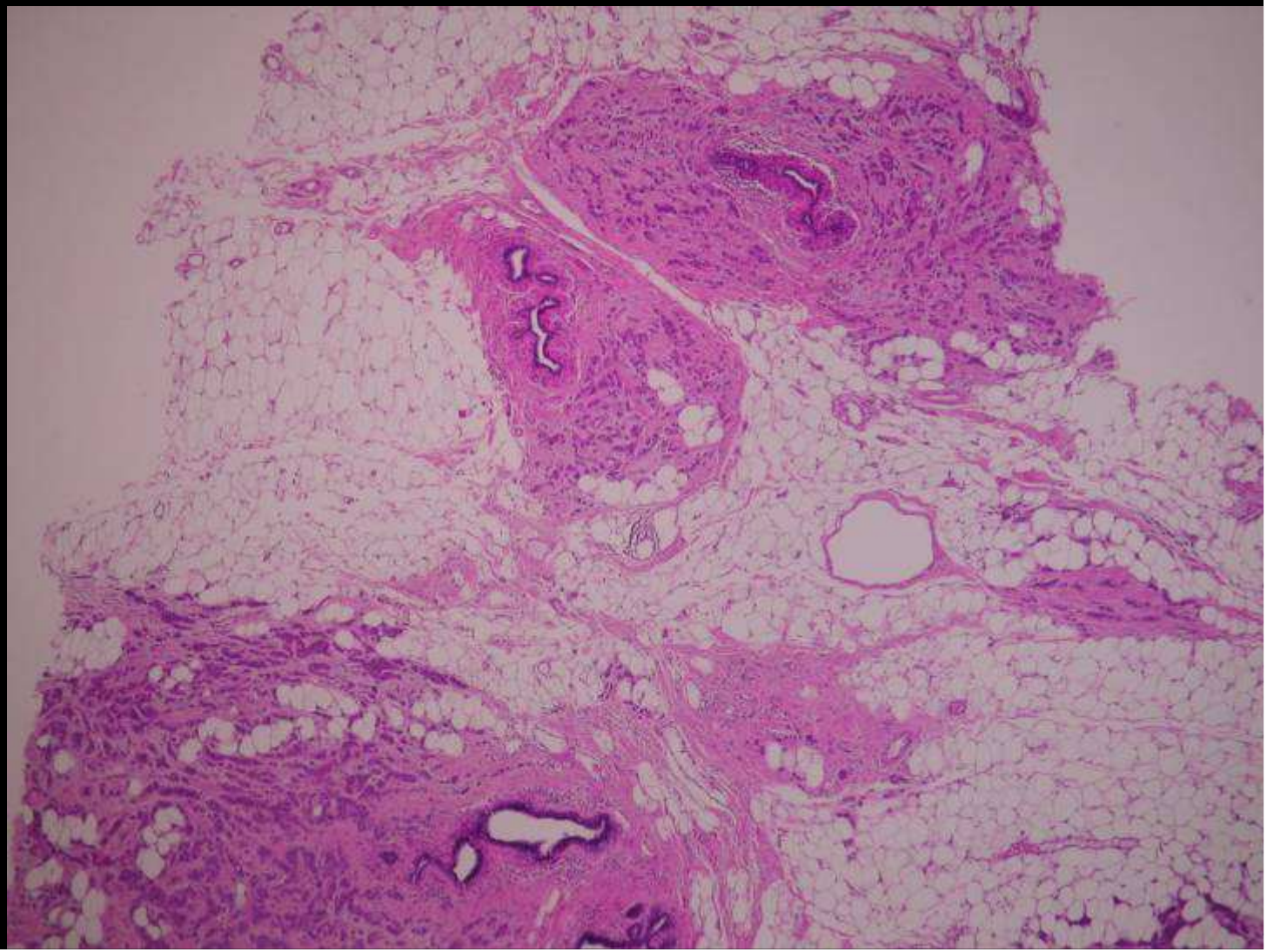
http://ioway.nativeweb.org/images/indianfile.jpg





Invasive lobular carcinoma

More often multifocal and bilateral than other types of breast carcinoma.



Invasive lobular carcinoma

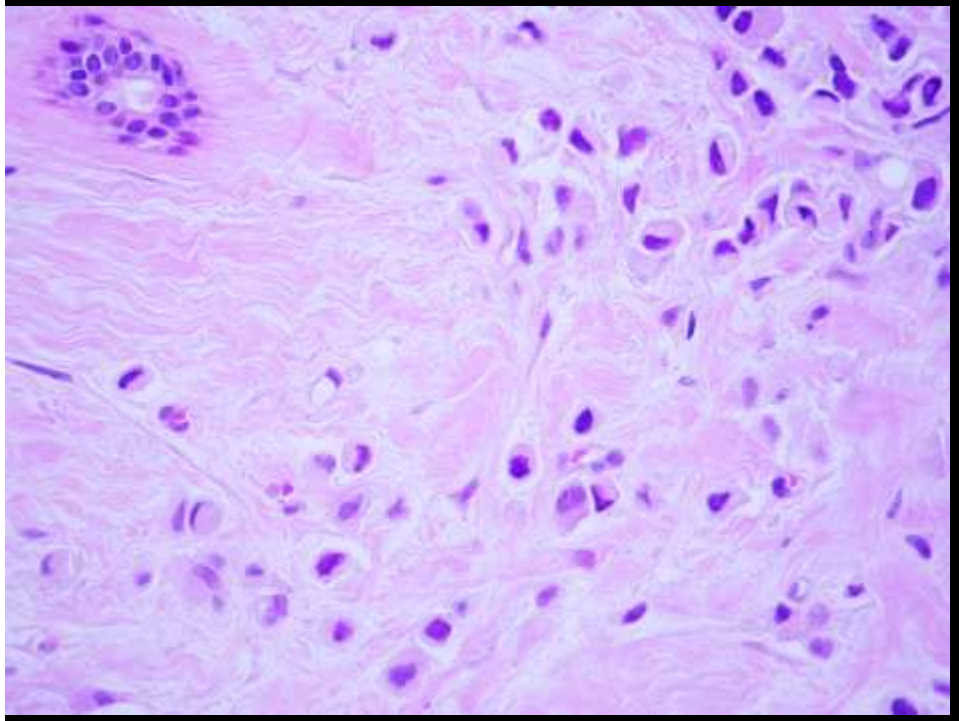
5-10% of invasive carcinomas. Increasing incidence in the last years.

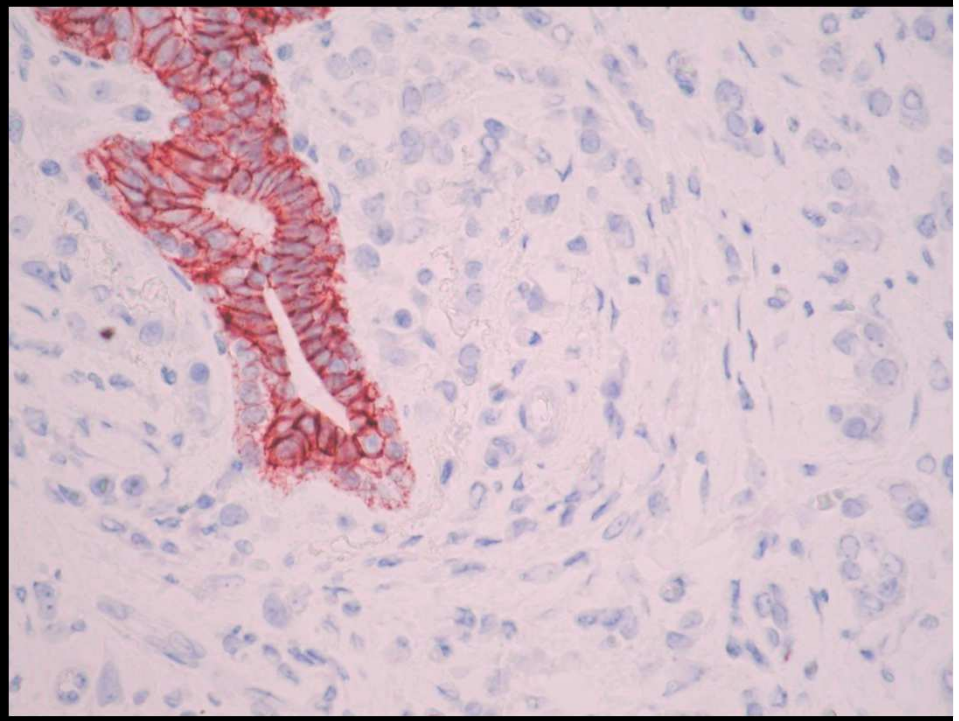
The lack of E-cadherin (silencing of the E-cadherin gene (CDH1-16q22.1 by mutation or methylation) is responsible for the distinct morphological pattern. E-cadherin is a calcium dependent cell-to-cell adhesion molecule.

Tumors can be scirrhous or can have a diffusely infiltrating pattern that is difficult to detect clinically and mammographically. They may remain occult.

Lobular carcinomas have a distant metastatic pattern that differs from that of ductal cancers. They more often metastasize to the meninges, serosal surfaces, ovary, uterus, other viscera and bone marrow.

Invasive lobular carcinoma



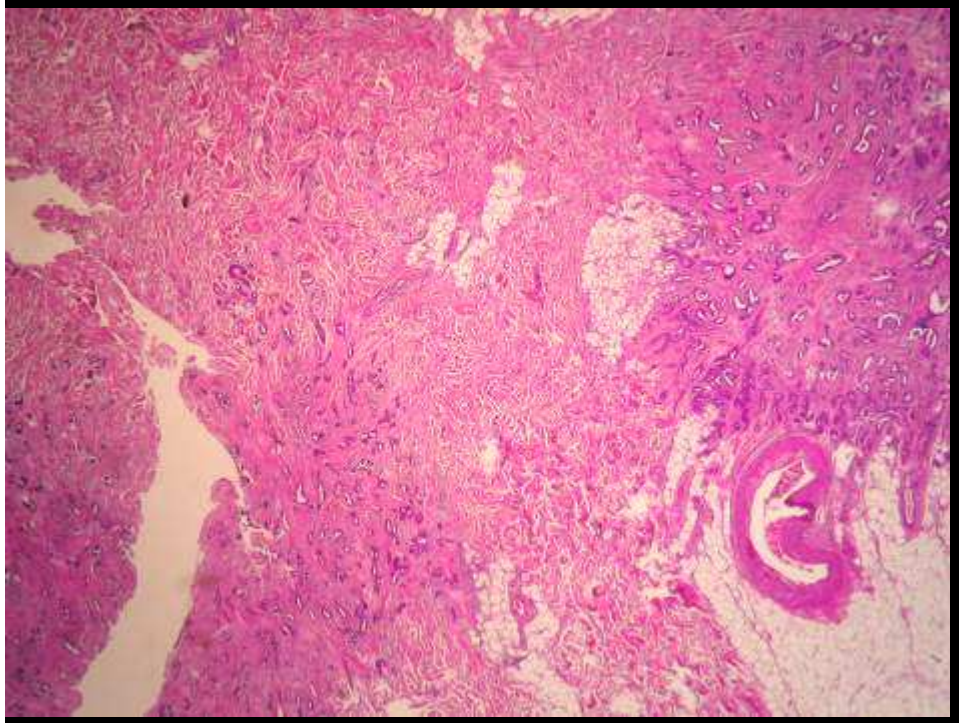


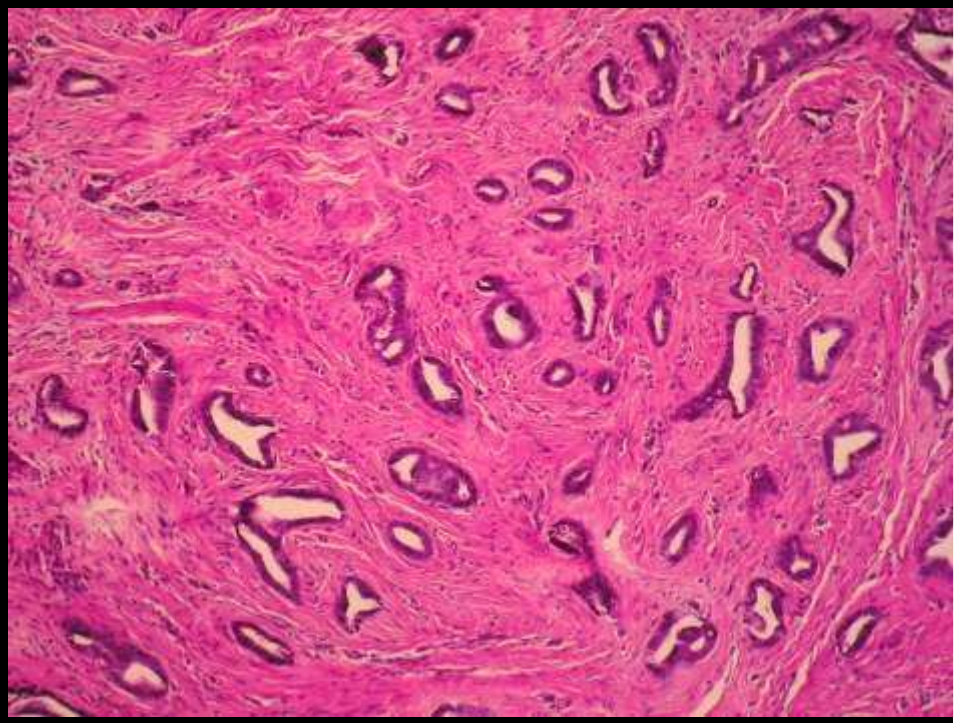
E-cadherin immunostain – no staining of tumor cells, positive membrane staining of normal duct

Tubular (cribriform) carcinoma

- Often less than 1 cm in size
- Detected as mammographic spiculated masses
- Well-formed tubules or cribriform nests with low-grade nuclei and a low mitotic index (by definition a low grade / well differentiated carcinoma)
- This histologic type has the **best prognosis**
- (Typically luminal A)

Tubular carcinoma





Mucinous carcinoma

- Slowly growing
- Most commonly in elderly women

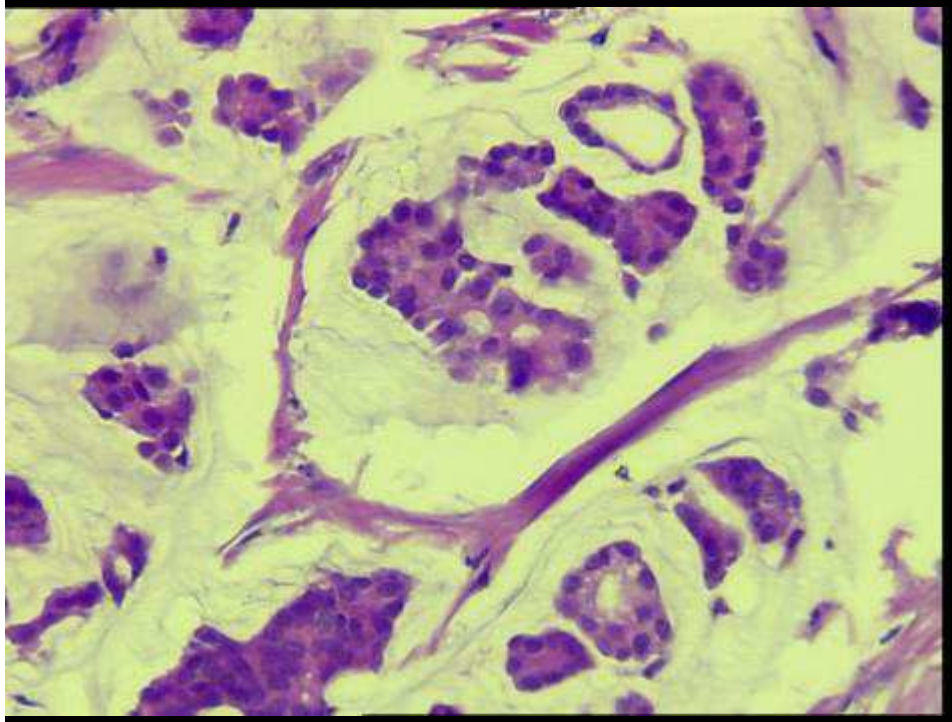
Macroscopy

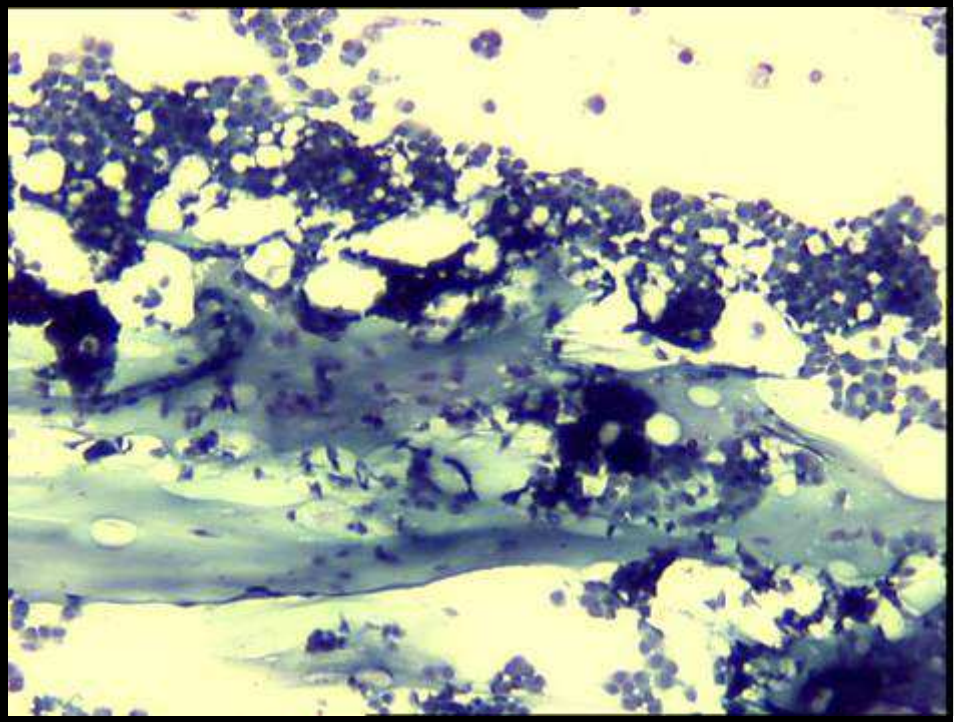
- Often circumscribed
- Soft, gelatinous tumor

Microscopy

- Lakes of mucin, which contains small islands of well differentiated tumor cells

Mucinous carcinoma





Cytology

Carcinoma with medullary features (Medullary carcinoma)

- Occurs in younger women than other forms of breast cancer
- Is more common in women carrying BRCA1, BRCA2 mutations and accounts for 13% of carcinomas in this group

Carcinoma with medullary features (Medullary carcinoma)

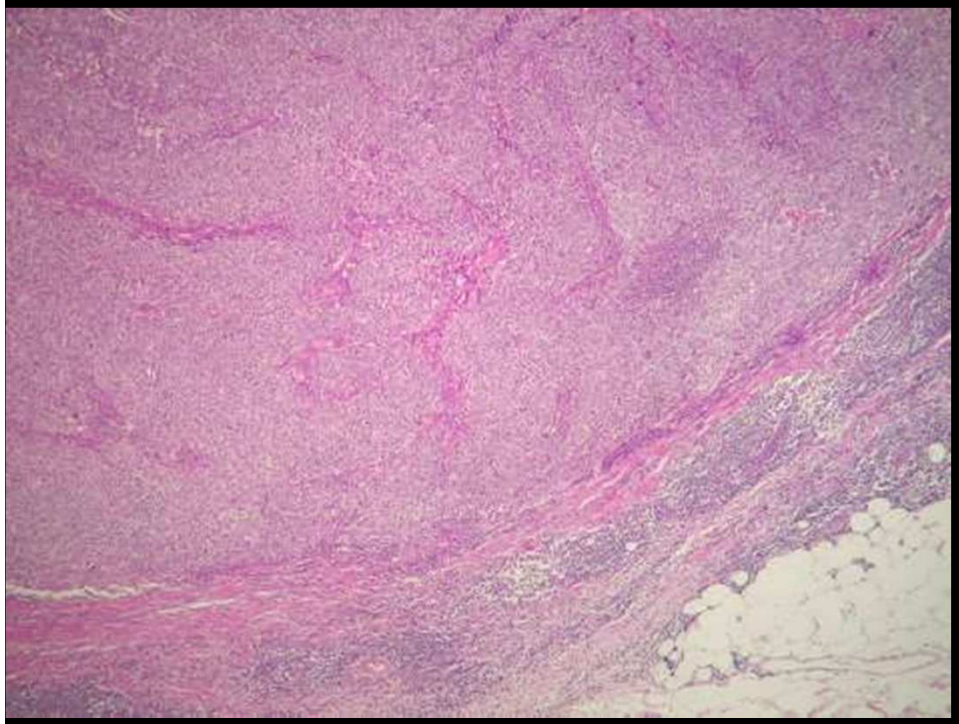
Macroscopy:

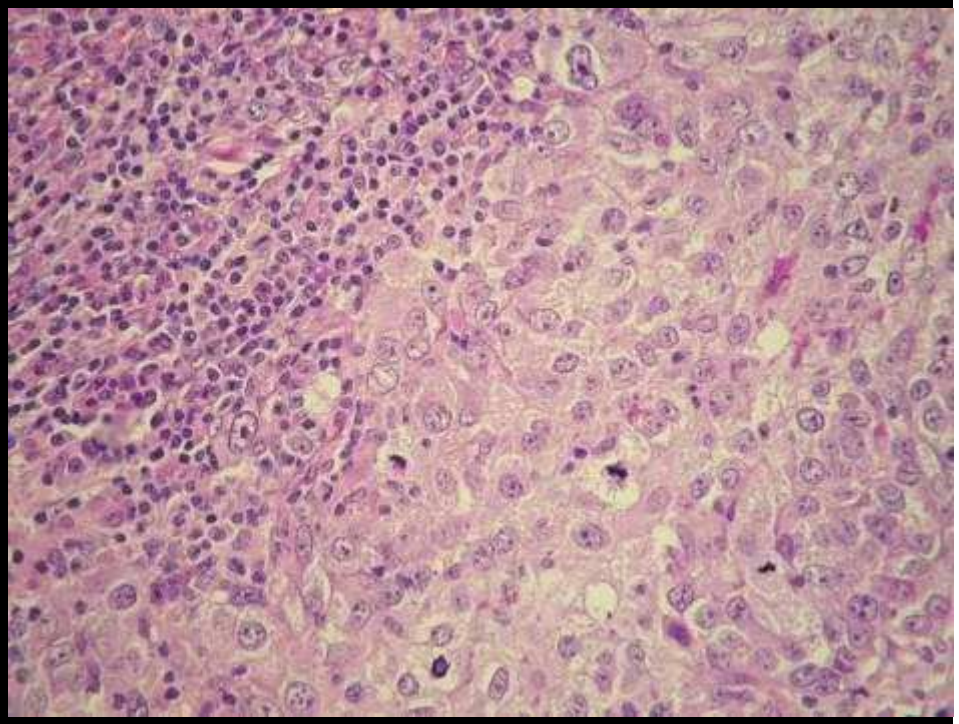
- relatively large, soft, well-circumscribed tumor

Microscopy:

- absence of desmoplasia
- moderately dense lymphocytic infiltrate
- large, pleomorphic tumor cells growing in sheets
- poorly reproducible, features more likely to be linked with BRCA-1 mutations

Carcinoma with medullary features
(Medullary carcinoma)





Breast cancer spread

- To regional lymph nodes (somewhat dependent on the primary tumor site)
  - Axillary lymph nodes (most common; outer quadrant tumors)
  - Internal mammary (parasternal) lymph nodes (less common; more common with inner quadrant tumors)
  - (Intramammary lymph nodes; staged together with axillary LNs)

The sentinel node is defined as a regional lymph node with direct drainage from the primary tumor site.

Breast cancer – prognostic factors

- Prognostic factors: parameters which affect the outcome of the disease (without treatment)

1. Distant metastasis (Stage IV disease). The presence of distant metastases infers the worst prognosis, but patients with single site metastases, especially bone mets can be long term survivors (10-15% 10-y-BCSS).

- Breast cancer spread to distant sites:

  Bones, lung, liver, skin, adrenals…etc (invasive lobular carcinomas have a different pattern; predilection for visceral sites, meninges and serosal surfaces)

Breast cancer – prognostic factors

2. Lymph node metastases (The most important prognostic factor in those without evident distant metastasis) With increasing numbers of involved lymph nodes the prognosis worsens:

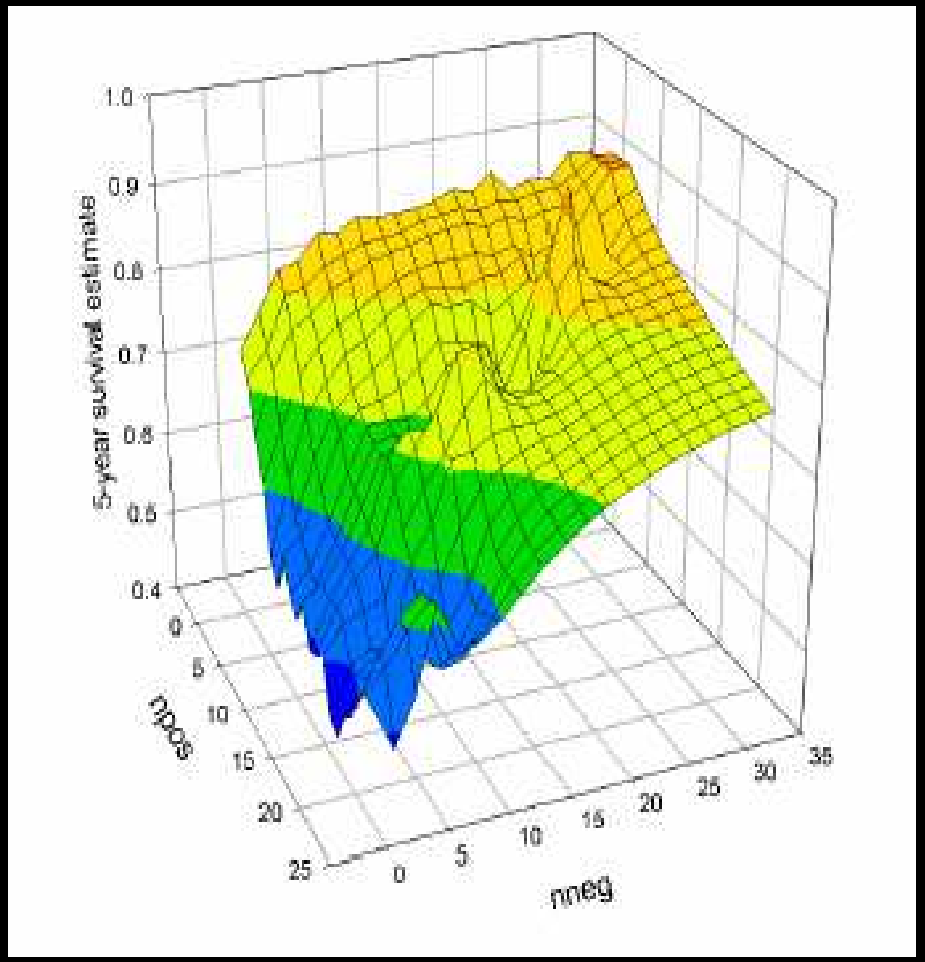
   - Node-negative tumors have 70-80% 10-y-survival
   - Patients with 1-3 positive nodes have 35-40% 10-y-survival
   - Patients with >9 positive nodes have 10-15% 10-y-survival

Valagussa P et al. *Cancer* 1978;41:1170-8.

3D graph of survival estimates as a function of the numbers of positive and negative LNs

- In each stratum of increasing number of positive LNs, the survival improves with increasing number of negative LNs.

Vinh-Hung V, Cserni G, Burzykowski T, et al. Effect of the number of uninvolved nodes on survival in early breast cancer. *Oncol Rep* 2003;10:363-8.



Data from the SEER database
Cases diagnosed between 1988-1997

Breast cancer – prognostic factors (ctd)

3. Tumor size (the larger the tumor, the worse the prognosis)

- Usually cancers are 2-3 cm palpable masses when first diagnosed by palpation and about one third have already metastasized to axillary or other nodes.
- In the era of mammographic screening, breast cancers are discovered earlier; many cases are ≤1.5 cm, only about 20% have metastasized to lymph nodes.

Breast cancer – prognostic factors (ctd)

4. Tumor stage (the first 3 factors are combined in the TNM classification and in the STAGEs of the disease)

TNM7: Primary tumor: (c)T & pT

- T & pT
  - TX: Cannot be assessed (to be minimized) (including R2)
  - T0: No tumor
  - Tis: in situ carcinoma (DCIS) (LCIS) (Paget) – only „pure" Paget's disease (TNM7) (only Paget's disease without tumor – TNM6)
  - T1 (up to and inclusive of 20 mm);
    - pT1mi (pT1mic – TNM6): 1 mm maximum size invasive focus (foci)

    „…rare cases … in the absence of noninvasive disease."
    - pT1a: ≤ 5 mm invasive carcinoma (TNM7 UICC gives definition in cm)
    - pT1b: > 5 mm and ≤ 10 mm invasive carcinoma
    - pT1c: >10 mm and ≤ 20 mm invasive carcinoma
  - T2: >20 mm and ≤ 50 mm invasive carcinoma
  - T3: >50 mm invasive carcinoma
  - T4: direct extension to chest wall (pectoral muscles are not part of it) (T4a) or skin (T4b) [skin edema, ulceration, cutaneous satellite nodules] or both (T4c) or inflammatory carcinoma (at least one 3rd of the skin to be involved) (T4d)

TNM7: Lymph nodes: (c)N

- NX: Cannot be assessed (eg: removed previously) (to be minimized)
- N0 No regional LN metastasis
- N1 Metastasis in **movable** L I-II axillary LN(s)
- N2
  - N2a: Metastasis in axillary LN(s) **fixed** to one another (matted) or to other structures
  - N2b: Metastasis **only** in clinically detected internal mammary LN(s)
- N3
  - N3a: Metastasis in L III axillary / infraclavicular LN(s)
  - N3b: Metastasis in internal mammary **and** axillary LNs
  - N3c: Metastasis in supraclavicular LN(s)

TNM7: Lymph nodes: pN

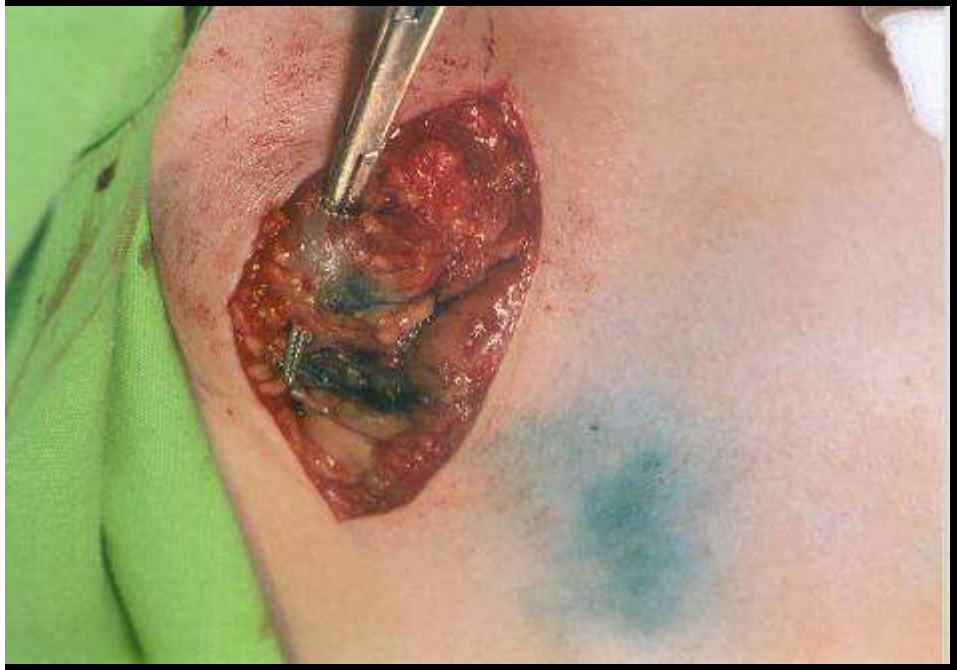
- pNX: Cannot be assessed (eg: removed previously, or not removed)
- pN0: No regional LN metastasis (including isolated tumor cell clusters)
- pN1:
  - pN1mi Micrometastases (>0.2 mm and/or >200 cells, but none greater than 2.0 mm)
  - pN1a Metastasis in 1-3 axillary LN(s), incl at least one >2 mm in greatest dimension
  - pN1b Internal mammary LN(s) with metastasis detected by sentinel LN biopsy but not clinically
  - pN1c pN1a **and** pN1b together
- pN2:
  - pN2a Metastasis in 4-9 axillary LNs, incl at least one >2 mm
  - pN2b Metastasis in *clinically* detected internal mammary LN(s) **only**
- pN3:
  - pN3a Metastasis in ≥10 axillary LNs (at least one >2 mm) ***or*** metastasis in infraclavicular lymph nodes
  - pN3b Metastasis in *clinically* detected internal mammary LN(s) **and** axillary LN(s); or metastasis in >3 axillary LNs **and** in internal mammary LNs with metastasis detected by sentinel LN biopsy but not clinically
  - pN3c Metastasis in supraclavicular LN(s)

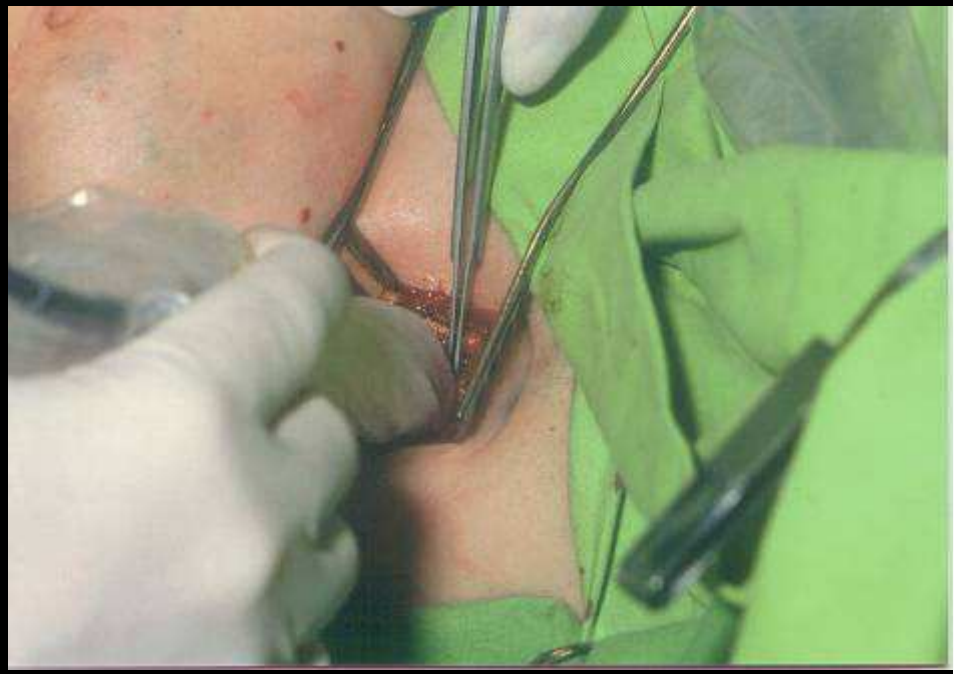
pN0 & isolated tumor cell clusters (ITC)

- pN0 No regional lymph node metastases histologically, no (cytokeratin) immunohistochemistry IHC
- pN0(i-) No regional lymph node metastases histologically, negative IHC
- pN0(i+) Malignant cells in regional lymph node(s) no greater than 0.2 mm or no more than 200 cells in a single cross section (detected by H&E or IHC including ITC)
- pN0(mol-) No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
- pN0(mol+) Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC

Sentinel LN (SLN) biopsy is a functional selection from all of the regional LNs, by the identification of the most likely site(s) of regional metastases

(sn): modifier for cases staged by SLN biopsy only – e.g. pT1c pN1mi(sn) only if less than 6 SNs.





Breast cancer spread (M –pM)

- To distant sites:
  - Mx Not defined / eliminated from TNM7
  - cM0 No distant metastasis. Unless there is evidence for distant metastases by clinical means (cM1) or by biopsy and pathological verification (pM1).
  - pM0 Not valid!
  - cM0(i+) No clinical/radiographic evidence of M1, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow or other non-regional nodal tissue that are ≤ 0.2 mm in a patient without symptoms or signs of metastases
  - M1/pM1 Distant metastasis proven clinically/radiographically and/or histologically (cytology allowed) >0.2 mm

Pulmonary	PUL	Peritoneum	PER
Bone marrow	MAR	Brain	BRA
Osseous	OSS	Adrenals	ADR
Pleura	PLE	Lymph nodes	LYM
Hepatic	HEP	Skin	SKI
		Others	OTH

M dropped from pathology reports, but pM1

Stages of breast cancer TNM7

	N0M0	N1M0	N2M0	N3M0	M1
T0	-	IB* or IIA [1]	IIIA [1]	IIIC [1]	IV
Tis	0	- [2]	-	-	-
T1	IA	IB* or IIA [1]	IIIA	IIIC	IV
T2	IIA	IIB	IIIA	IIIC	IV
T3	IIB	IIIA	IIIA	IIIC	IV
T4	IIIB	IIIB	IIIB	IIIC	IV

1: occult breast cancer; 2: not defied, nonsense; * if pN1mi

ypTNM and reporting regression

- y is added after neoadjuvant therapy.
- Tumor regression (TR)
  - 1. Complete pathological response, either (i) no residual carcinoma or (ii) no residual invasive tumor but DCIS present.
  - 2. Partial response to therapy, either (i) minimal residual disease/near total effect (e.g. < 10% of tumor remaining) or (ii) evidence of response to therapy but with 10–50% of tumor remaining or (iii) > 50% of tumor cellularity remains evident.
  - 3. No evidence of response to therapy.

European guidelines for **quality assurance** in breast cancer screening and diagnosis
Fourth edition Supplements

ypTNM and reporting regression

- Nodal regression (NR)
  - 1. Metastatic disease - & evidence of changes in the LNs -
  - 2. Metastatic disease - & evidence of response/down-staging, e.g. fibrosis +
  - 3. Metastatic disease + & evidence of response, such as nodal fibrosis +
  - 4. Metastatic disease + & evidence of response to therapy -

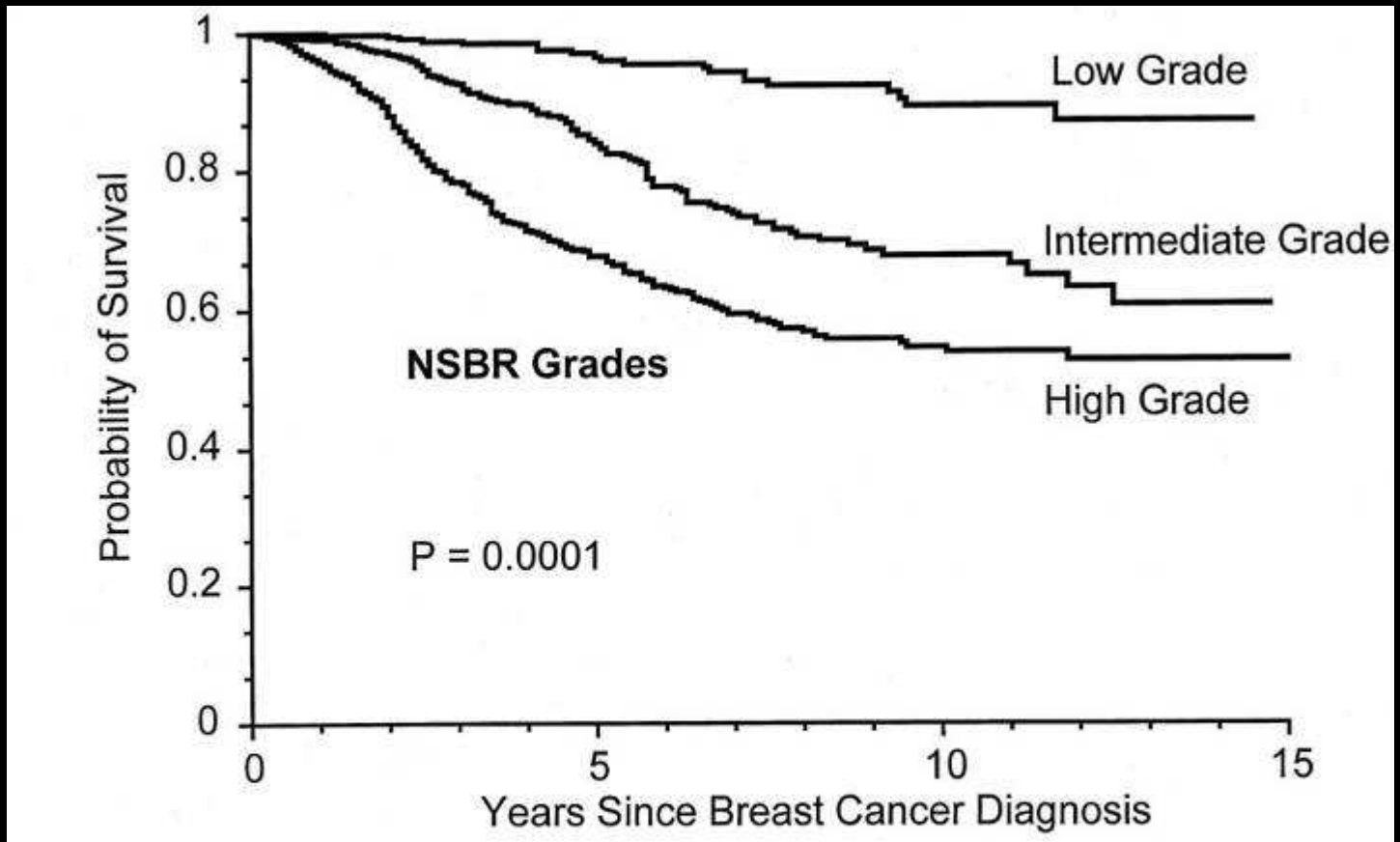
European guidelines for **quality assurance** in breast cancer screening and diagnosis
Fourth edition Supplements

Breast cancer – prognostic factors (ctd)

5. Tumor histologic grade (breast cancers are graded in a 3-tiered system on the basis of their tubule formation, nuclear pleomorphism and mitotic rate all scored from 1 to 3.

grade 1 – (3-5) well differentiated,
grade 2 – (6-7) moderately differentiated,
grade 3 – (8-9) poorly differentiated)

Nottingham TENOVUS study



Grade	Patients at Risk		
Low	381	185	78
Intermediate	661	244	68
High	907	278	84

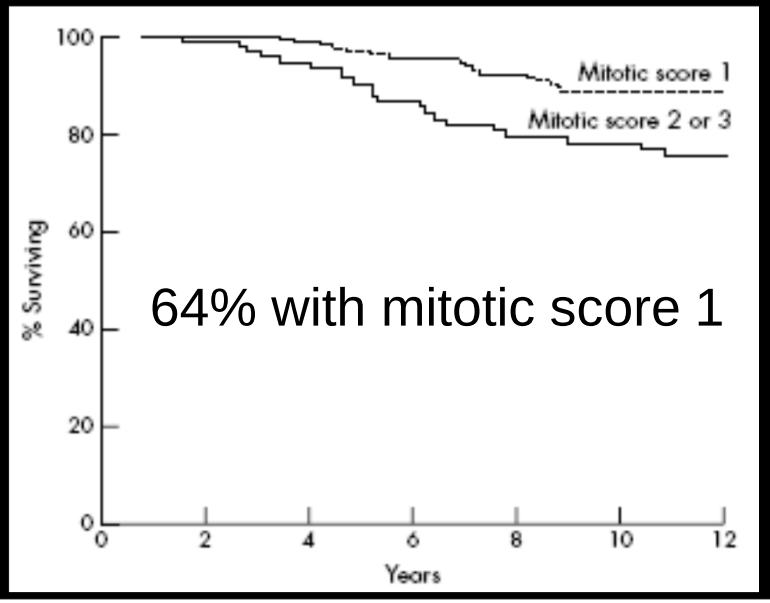
Dalton LW et al. Mod Pathol 2000;13:730-5. cit Elston CW, Ellis IO. Histopathology 1991

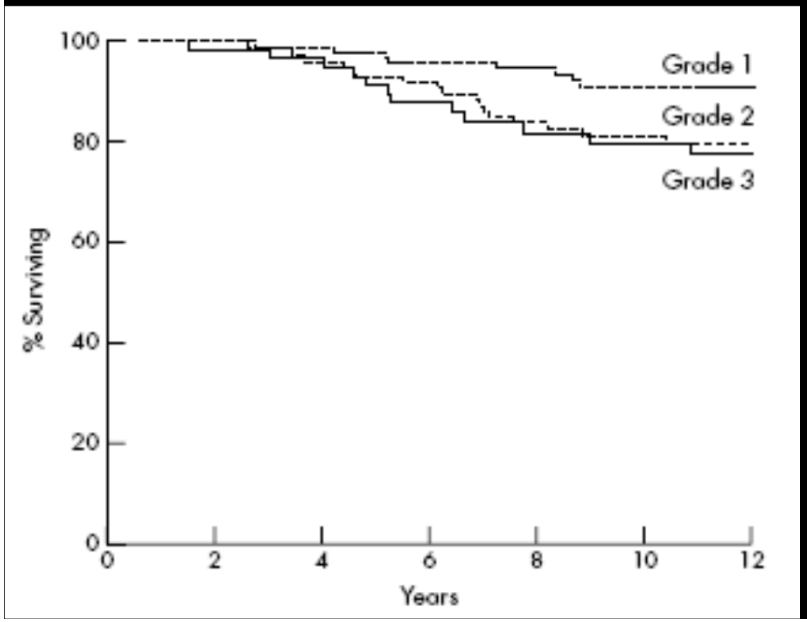
Grade in T1N0M0 BC

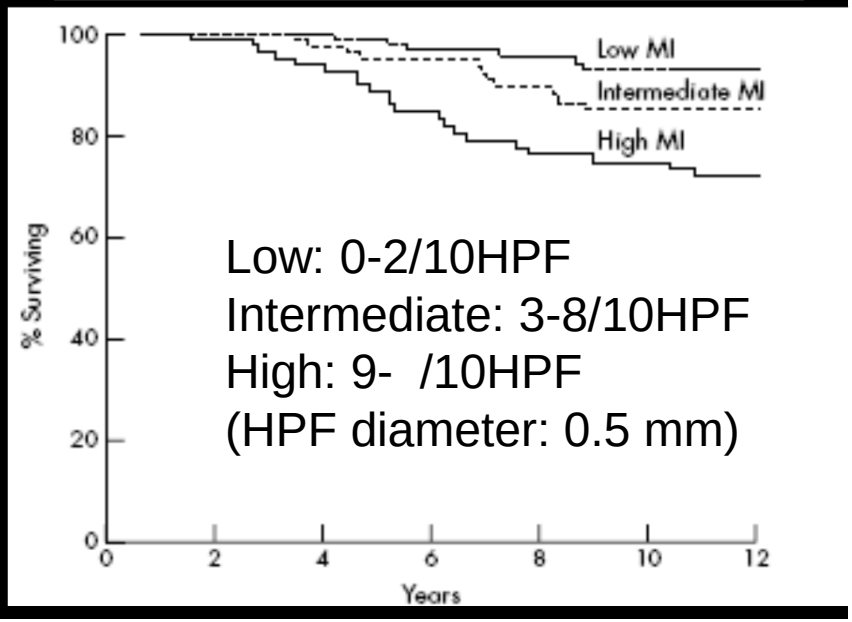
Frkovic Grazio S et al. J Clin Pathol 2002;55:88-92.

270 patients
12.5 years median FU

BC specific survival
is grade dependent.
MI (based on tertile cut offs)
– strongest predictive component

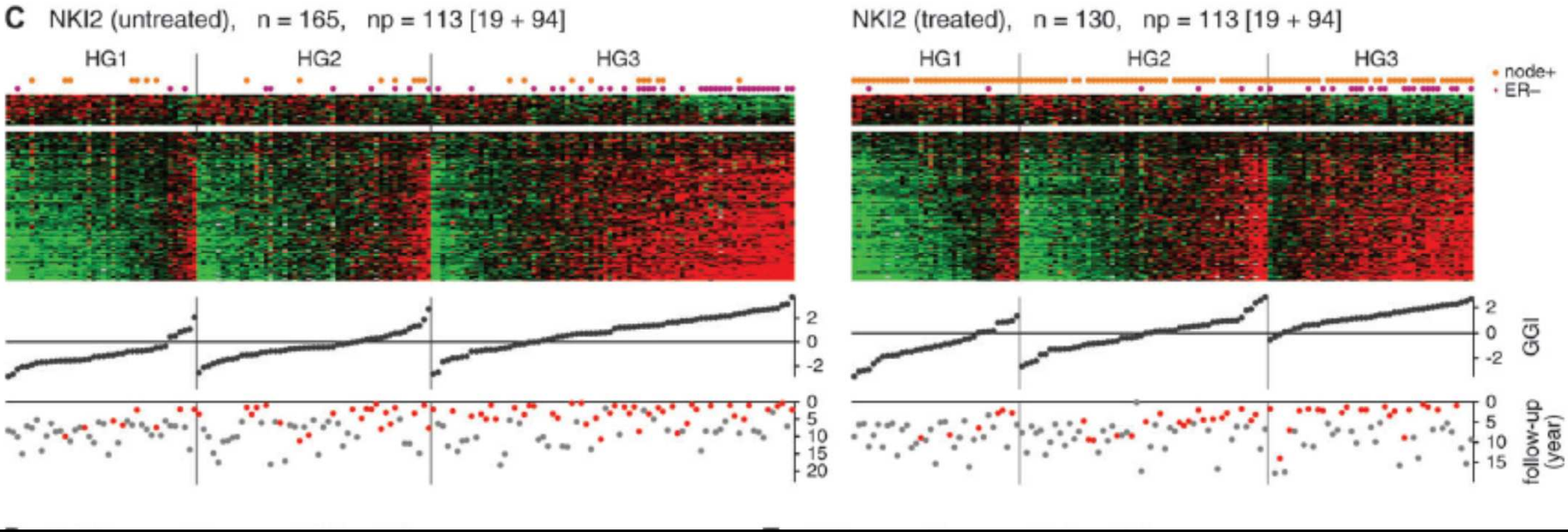






Genomic grade: G2 split into G1 or G3

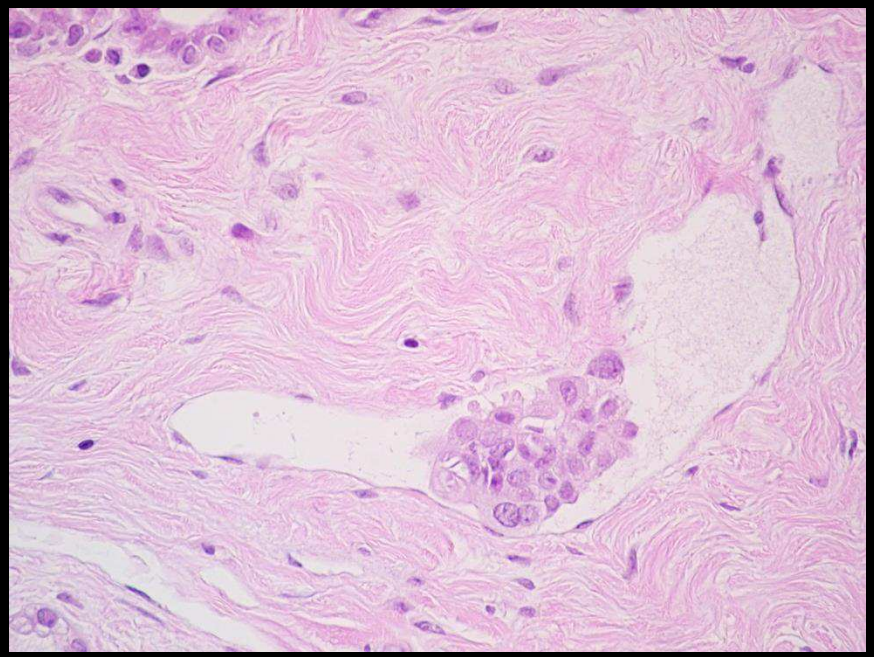
- 62 ER+ tumors: 97 genes (maily related to proliferation) showed differential expressions in G1 vs G3 tumors.
- G2 cases could be subdivided to GG1 vs GG3
- Multivar.: GG, T size, LN status significant predictors of DFS (not ER and not histological G)



Sotiriou C, et al. JNCI 2006;98:262-272.

Breast cancer – prognostic factors (ctd)

6. Lymphatic or vascular / (lympho)vascular invasion; its presence is an adverse sign



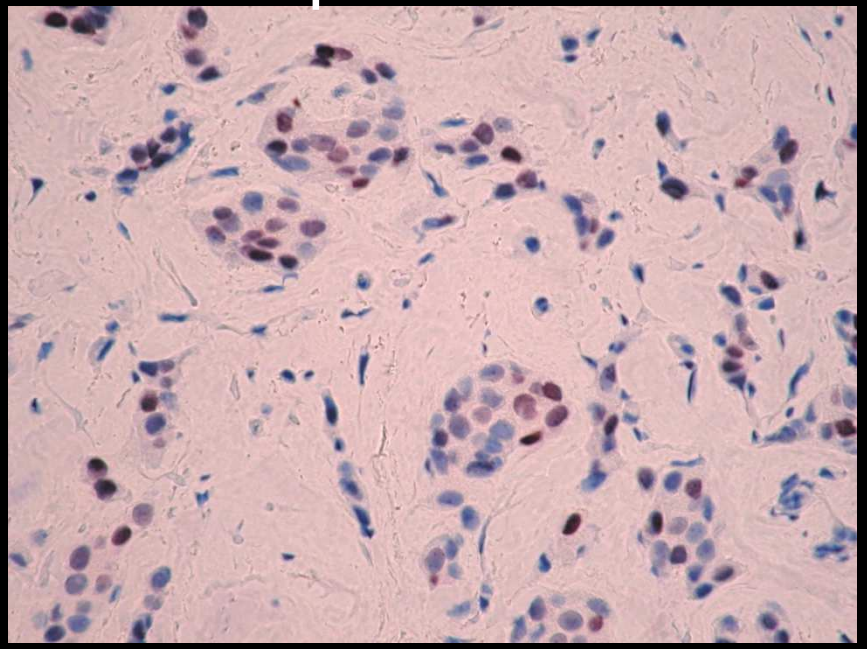
7. Histologic types: tubular, cribriform, mucinous carcinomas are favorable types

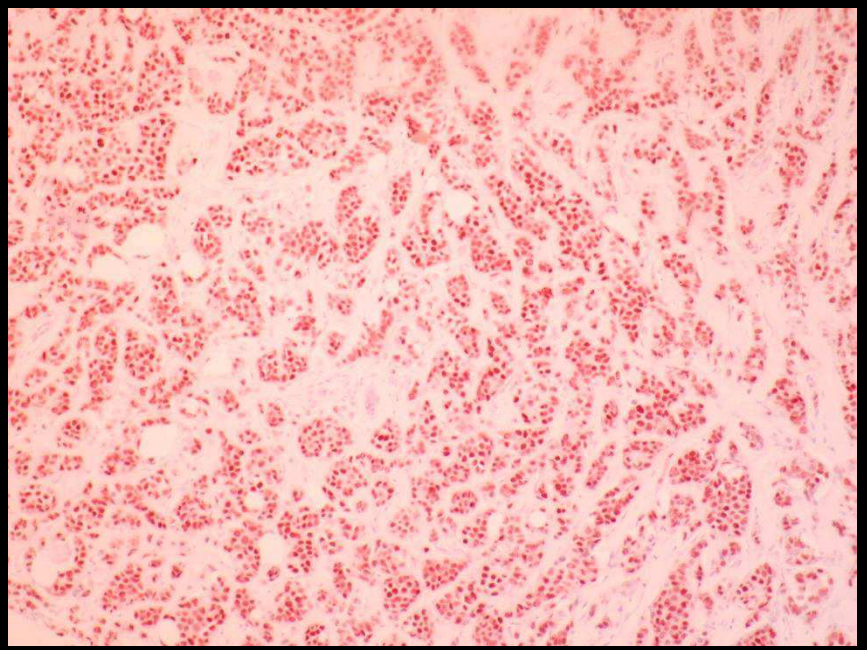
Breast cancer – prognostic factors (ctd)

8. Estrogen and progesterone receptor status: ER and PR positive tumors have better prognosis (GEP: luminal A type has better prognosis) and are likely to react to hormonal treatment (ER and PR status is also a predictive marker – i.e. predicts the responsiveness to a given therapy)

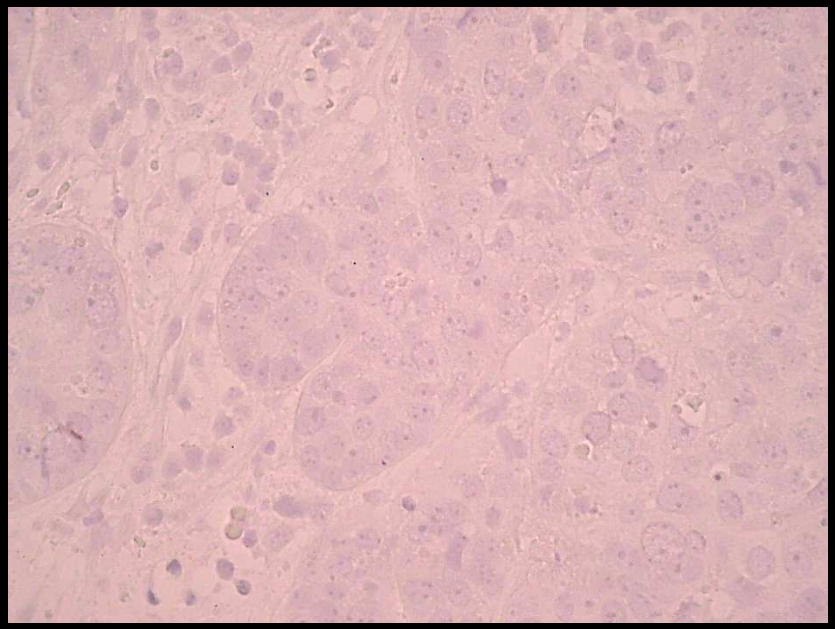
ER

positive





negative



ER: ASCO 2010 recommendations I.

- Pretest conditions: Immediate fixation (10% NBF) for 6-72 (48) hours, slices not thicker than 5 mm.
- Test with validated methods with 1% cut-off value.
  - ER: 6F11, 1D5, SP1, 1D5+ER.2.123;
  - PR: 1294, 1A6, 312.
- Validation, QA (internal, extarnal), Monitoring

Arch Pathol Lab Med 2010 / J Clin Oncol 2010

ASCO 2010 recommendations II.

- Reporting categories
  - Positive (≥1% tumor cell nuclei are immunostained)
  - Negative (<1% tumor cell nuclei are immunostained; generally no staining at all)
  - Uninterpretable (no tumor cell nuclei stain, but internal or external controls do not stain either)

Arch Pathol Lab Med 2010 / J Clin Oncol 2010

Allred scores / quick score

Average intensity:	**Scores**
• Negative	0
• Weak	1
• Medium	2
• Strong	3
Percentage of positive nuclei:	
• None	0
• <1%	1
• 1-10%	2
• 10%-1/3	3
• 1/3-2/3	4
• >2/3	5

The sum of the two component scores gives the overall score. Possible values:0, 2-8. (Endocrine responsiveness can be expected when overall score is >2; i.e. at least 1% of the tumor cell nuclei stain with a validated ER or PR antibody)

Breast cancer – prognostic factors (ctd)

9. HER-2 (c-erb-B2; NEU) status. HER-2 is an oncogen located on chromosome 17q21; it is amplified in 15-30% of breast cancers; the gene amplification is paralleled by protein overexpression. HER-2 positive tumors have worse prognosis. (Also a GEP defined subtype)

The HER-2 status is predictive of the response to targeted therapy against the HER-2 oncoprotein.

HER-2 IHC evaluation

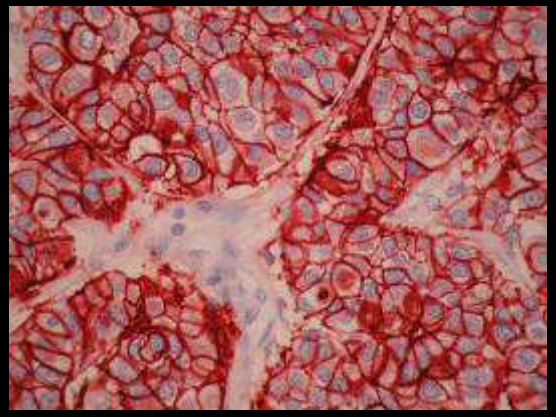
ASCO/CAP 2013 (JCO 2013, APLM 2014)

IHC:

- 3+: Complete, strong membranous staining in >10% of the cells (was >30% between 2007-2013; 3rd change)
- 2+: Incomplete and/or weak or intermediate intensity membranous staining in >10% of the cells, or incomplete strong membranous staining in ≤10% of the cells. (Should be retested by ISH)
- 1+: Incomplete faint/barely visible membranous staining in >10% of the cells.
- 0: No staining or faint/barely visible staining in <10% of the cells

- From the point of view of anti HER-2 targeted treatment 3+ cases are considered positive, 2+ cases are considered equivocal / inconclusive. Cases rated as 1+ or 0 (negative) should be considered negative.

IHC for HER2



Extracellular

Trastuzumab -
4D5 H-MoAb
Reacting with cystein-rich EC domain II

TAB 250 Mouse MoAb
SP3 Rabbit MoAb
4B5 Rabbit MoAb

Transmembrane

Intracellular

CB11 Mouse MoAb
A0485 Polyclonal
Herceptest™ Polyclonal

Lapatinib - Tyr-kinase inhibitor

HER-2 ISH evaluation

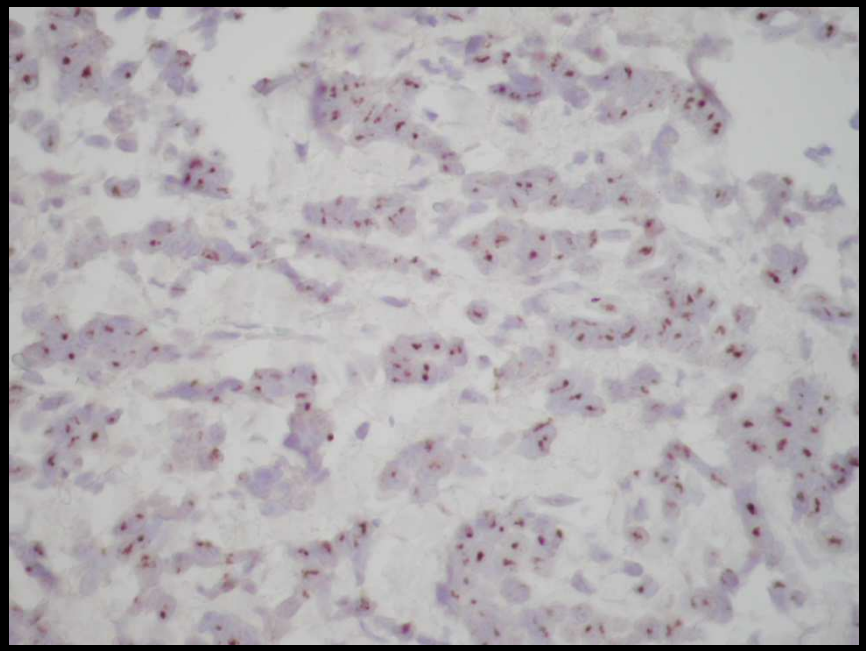
FISH:

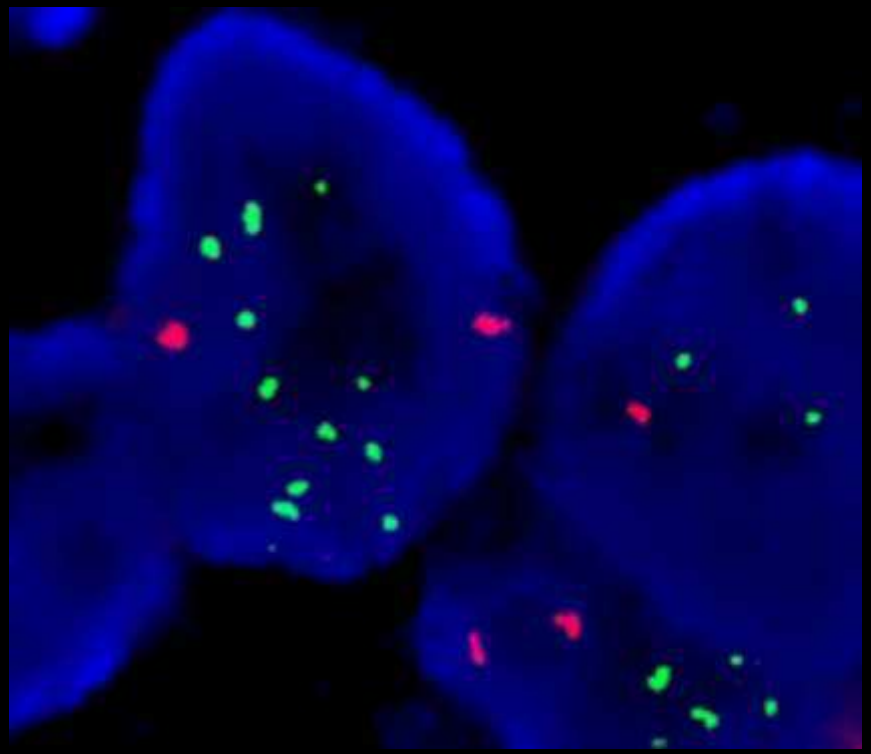
- Positive (amplified): HER2/CEP17 ratio ≥ 2 (independent of HER2 copy numbers) or average HER2 gene copies per nuclei ≥6 in assays lacking internal control (CEP17: centromeric probe for chromosome 17).
- Equivocal / inconclusive: HER2/CEP17 ratio <2 if / or average HER2 gene copies per nuclei ranging between ≥ 4-<6 in assays lacking internal control. (Should be retested)
- Negative: HER2/CEP17 ratio <2 if / or average HER2 gene copies per nuclei <4 in assays lacking internal control.

ASCO Guidelines 2013

CISH – FISH concordance

Multiple studies (with n ≥ 50) show a concordance rate between 90-100%.





Penault-Llorca f et al. Am J Clin Pathol 2010;132:539-48

Breast cancer – prognostic factors (ctd)

10. There are other „traditional” factors with more or less prognostic impact, but they rarely prove to be significant when the former parameters are taken into account

    - DNA content (ploidy; aneuploid tumors have worse outcome)

    - angiogenesis (difficult to quantify; may be targeted by specific therapies)

    - other oncogenes or tumor suppressor genes

    - proliferation (included in the grade as mitotic index)

    - resection margin status (involved margins are important for local recurrence)

Intrinsic subtypes by IHC

- Basal like: ER- HER2- CK5/6+ or HER1+ in 16/21 (76% sensitivity, 100% specificity)

Nielsen TO et al CCR 2004;10:5367-74.

- Luminal A: ER+ and/or PR+, HER2-, Ki67 low (<14%)
- Luminal B: ER+ and/or PR+, HER2+ or Ki67 high (>13%)
- HER2: (ER-PR-HER2+)
- Triple neg: (ER-PR-HER2-)

Hugh J. JCO 2009;27:1168-76.; Cheang MCU et al. JNCI 2009;101: 736-50.

- Luminal A: ER+, HER2-, Ki67 low, PR+>20%

Prat A et al. JCO 2013;31:203-9.

PAM50

- The expression of 50 genes used to delineate the intrinsic subtypes.
- ER+ (5% basal-like, 12% normal-breast-like); ER- (11% were luminal)
- HER2+ (6% basal-like); HER2- (9% HER2 enriched)
- „ER and HER2 status alone are not adequate surrogates for TRUE intrinsic subtype status.”
- PAM50 defined subtypes are prognostic and predictive for pCR after neoadjuvant T&A chemotherapy.

Parker JS, et al. JCO 2009; 27:1160-7.

Original types vs PAM50

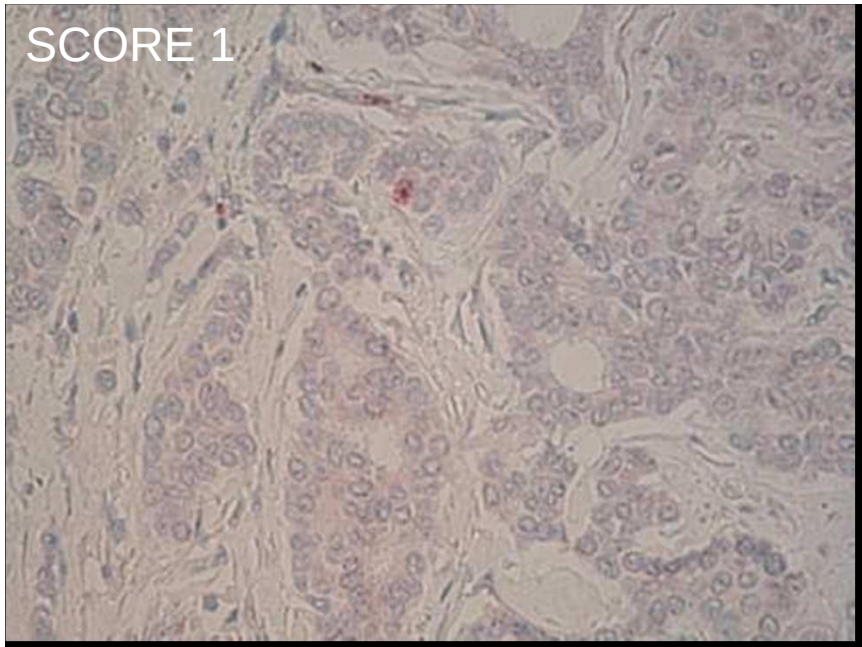
- Basal-like:
  - 19 or 21 genes (Nature 2000) vs 10 genes in PAM50 (JCO 2009); not one overlapping
- HER2 enriched:
  - 11 or 14 genes (Nature 2000) vs 10 genes in PAM50 (JCO 2009); two overlapping
- LUMINAL A+B:
  - 43 or 49 genes (Nature 2000) vs 10+10 genes in PAM50 (JCO 2009); probably only one overlapping (not ER1)

Differences emphasized by Prof. F Moinfar, EGP 2013 Vienna

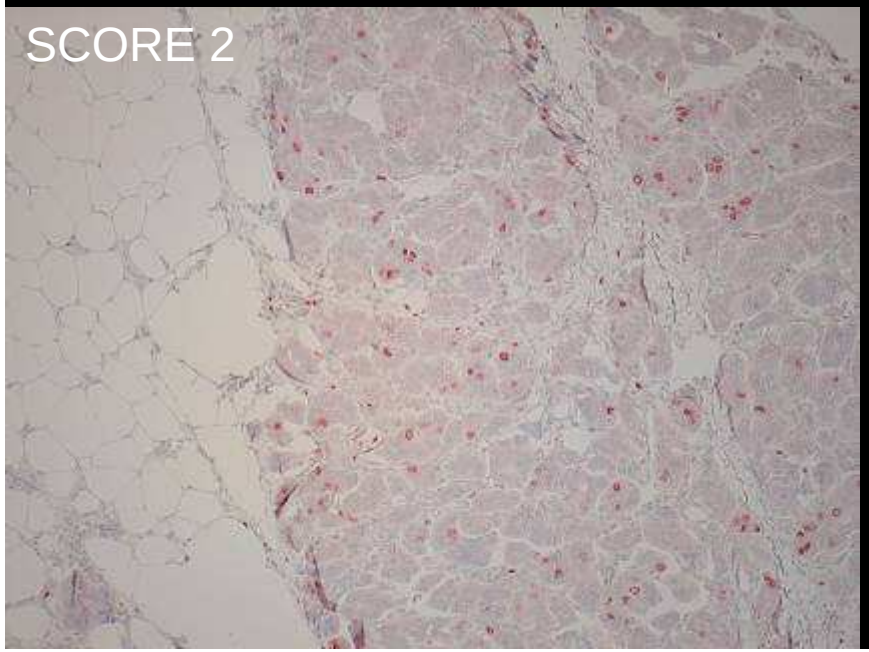
GEP based subtypes

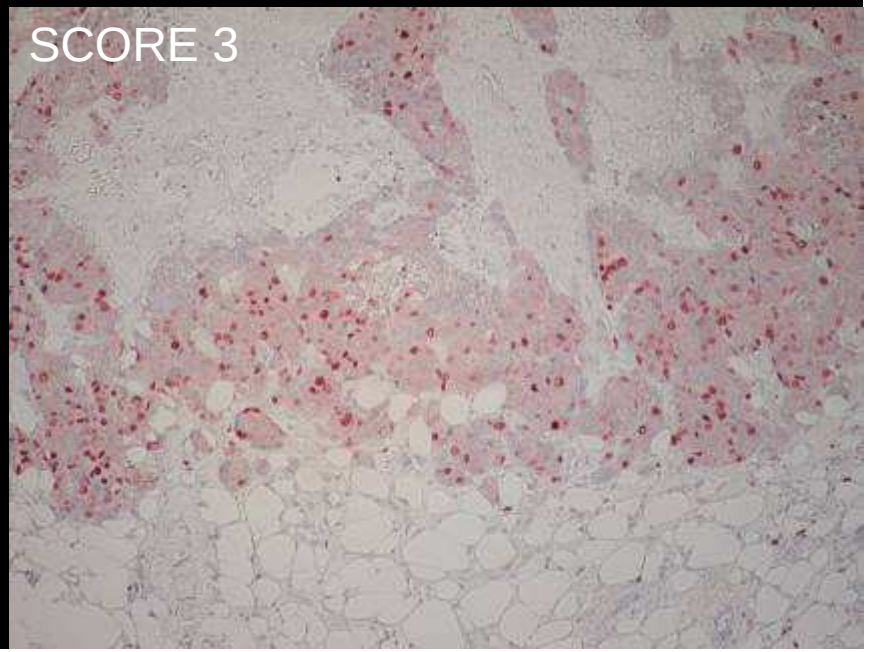
- Luminal C and Normal-breast-like vanished; the latter seems to be a technical artifact – i.e. normal breast.
- New molecular types have emerged: claudin-low, molecular apocrine
- The definitions have changed a number of times - the cases allocated to some subtypes, must have also changed.
- Basal-like is heterogeneous and not a unique type (≠ TN), (incl. some tumors with relatively good prognosis)
- Using ER, PR, HER2, Ki67 to delineate treatment would be less fashionable but more accurate wording or alternatively use PAM50 for identifying the so defined types.

Examples of Ki-67 staining in breast cancers with mitotic score 1-3



Cserni G. 22nd European Congress of Pathology, 2009, Florence





Ki-67 through the cell cycle

- G0: not expressed
- G1 & S: low levels
- G2 & M: high levels
- Sharp decrease in anaphase and telophase

- Ki67+ cells may undergo mitosis or apoptosis

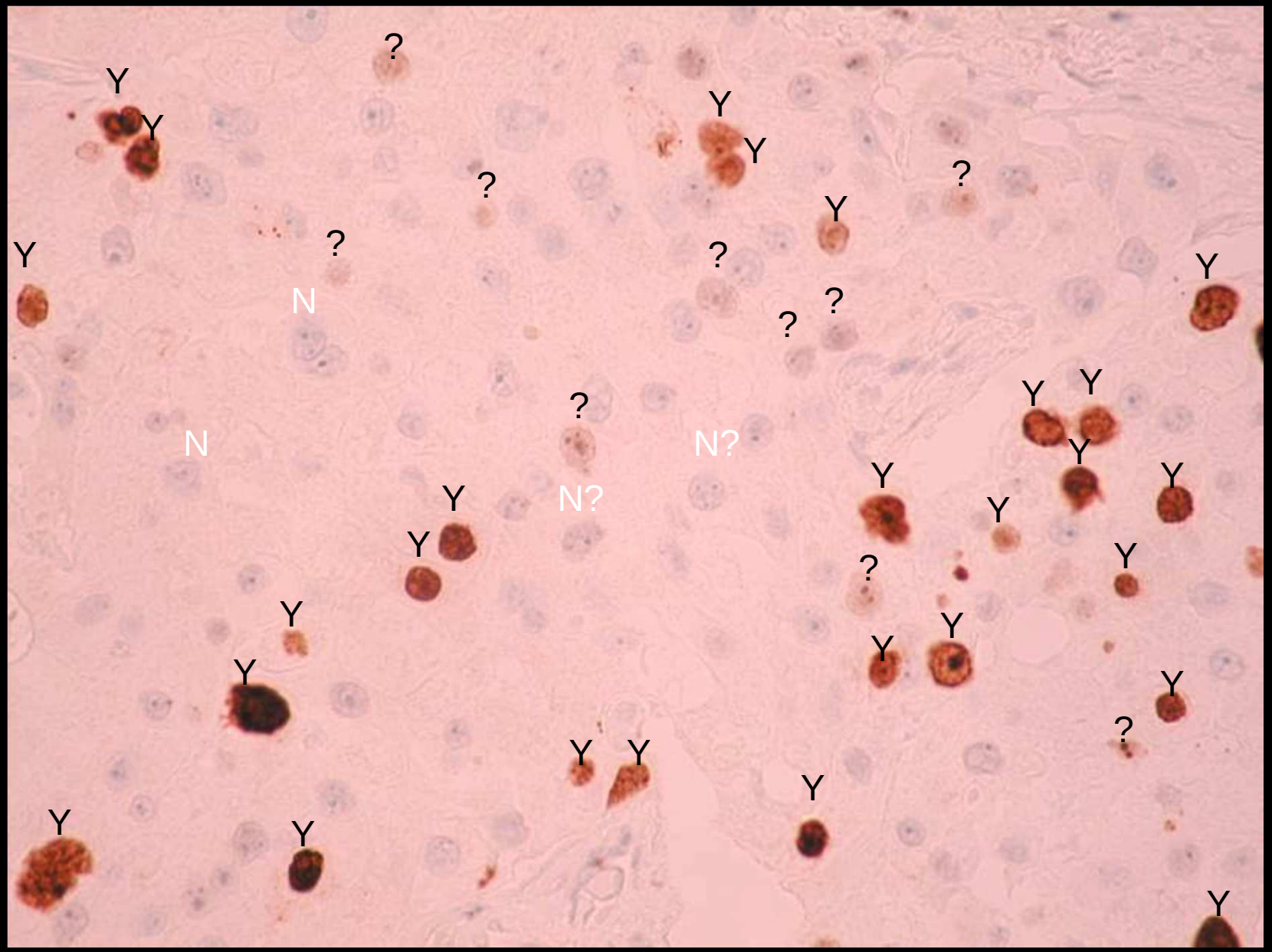
Yerushalmi R, et al. Lancet Oncol 2010;11:174-83.

Pathologists and Ki-67 evaluation

- Estimating the proportion of stained nuclei (not precise)
- Counting several hundred cells (tedious)
- Counting 1000-1500 cells (?)
- Automated counting (non tumoral nuclei?)

In this review: cut-offs for low vs high (or intermediate) 10-40% of nuclei staining.

Yerushalmi R, et al. Lancet Oncol 2010;11:174-83.



(About) 150 cells, 27-37 Ki-67 positive: 18-25% Ki-67 index

Recommendations

Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group

Mitch Dowsett, Torsten O. Nielsen, Roger A'Hern, John Bartlett, R. Charles Coombes, Jack Cuzick, Matthew Ellis, N. Lynn Henry, Judith C. Hugh, Tracy Lively, Lisa McShane, Soon Paik, Frederique Penault-Llorca, Ljudmila Prudkin, Meredith Regan, Janine Salter, Christos Sotiriou, Ian E. Smith, Giuseppe Viale, Jo Anne Zujewski, Daniel F. Hayes

JNCI 2011;103:1656–1664

e.g.: min. 500 cells, 1000 cells…

Homogeneous: 3 randomly selected HPFs

Heterogeneous:

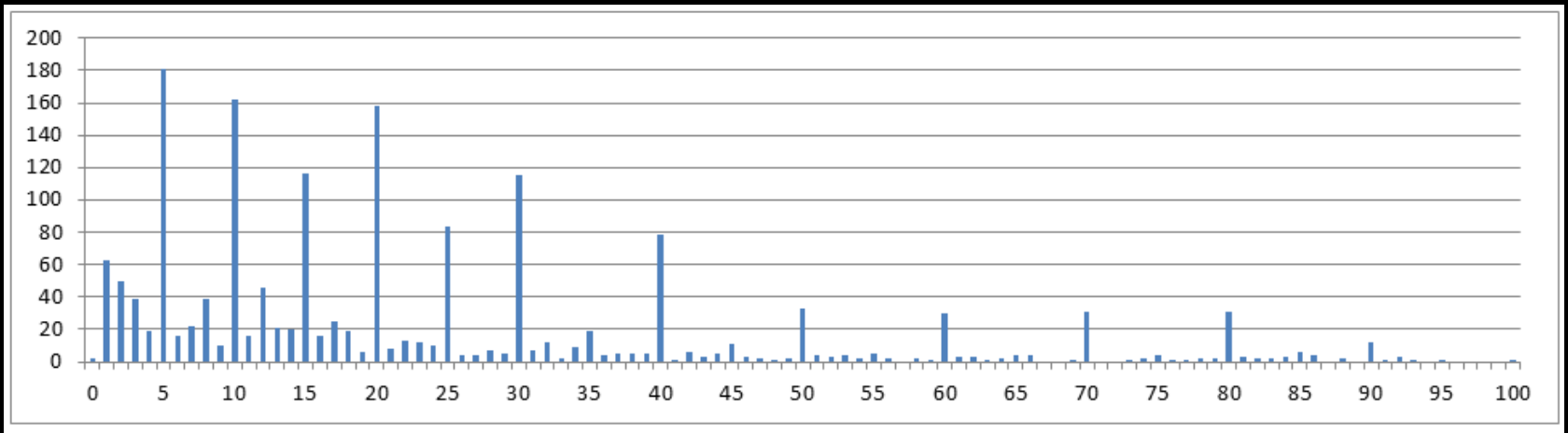
- Edge directed gradient: 3 HPFs there
- Hot spots: ??? Overall average score

Ki67 labelling index (LI) thresholds for considering chemotherapy in ER+ BC

- >30% = high proliferation: YES (16-30% intermediate; ≤15% low) St Gallen 2009
- >13% defining HER2- Luminal B tumors St Gallen 2011
- ≥20% = high proliferation for Luminal B tumors St Gallen 2013
- St Gallen 2015?

Ki67 LI distribution pattern

(n = 1709 BC from 19 institutions)



- The median Ki67 LI was 17% for all tumors and 14% for ER+ HER2- carcinomas.
- Values peaking at …5s and …0s; 13%, 14%, 17% cut-offs are not very realistic.

Cserni G, et al. Breast 2014;23:259-63.

Oncotype Dx

- Prognostic for a subset of breast cancers: ER+, HER2-, (N0, N1mi, N+)
- Predictive of the benefit from specific types of systemic therapy

Special presentations of breast cancer

INFLAMMATORY CARCINOMA

Cancer, clinically presenting as inflammation (peau d'orange sign – resulting from oedema; or frank redness, inflammation)

TNM requires at least third of the breast to be involved.

This is generally associated with dermal lymphatic vessel invasion, although this latter (without the clinical symptoms) is not sufficient for diagnosing inflammatory cancinoma

Poor associated prognosis; this is generally not a surgical disease in this stage – pT4d in the TNM classification

Special presentations of breast cancer

OCCULT CARCINOMA

Cancer presenting as metastasis either to the lymph nodes or to distant sites with no evidence of the primary tumor

Originally, this meant non-palpable tumors with metastases, and such tumors were not so rare.

Now this means non-palpable tumors without imaging (mammographic or ultrasound) evidence. (MRI, PET can be further added to imaging modalities) They are rare; many are of lobular type.

Special presentations of breast cancer

MALE BREAST CANCER

In men carcinomas tend to invade skin and chest wall earlier as there is much less amount of surrounding breast tissue.

Matched by stage, prognosis is believed to be similar in men and women.

There are however some differences in steroid hormone receptor distribution suggesting that male breast cancer might be somewhat different from female breast cancer. Any clinical relevance? (Shaaban AM et al. Breast Cancer Res Treat. 2012; 133(3):949-958)

Other malignancies

- Malignant phyllodes tumors can contain areas of liposarcoma or fibrosarcoma or even chondrosarcoma, osteosarcoma
- Angiosarcoma (can be a consequence of radiotherapy)
- Other sarcomas
- Lymphomas
- Metastases (e.g. melanoma)