An Ideal Histopathology Report in Breast Cancer

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Content in the ppt

1. Pathology of Breast Cancer.
2. Grossing of specimen.
3. Histopathology Report.

The changing role of pathology in breast cancer diagnosis and treatment.

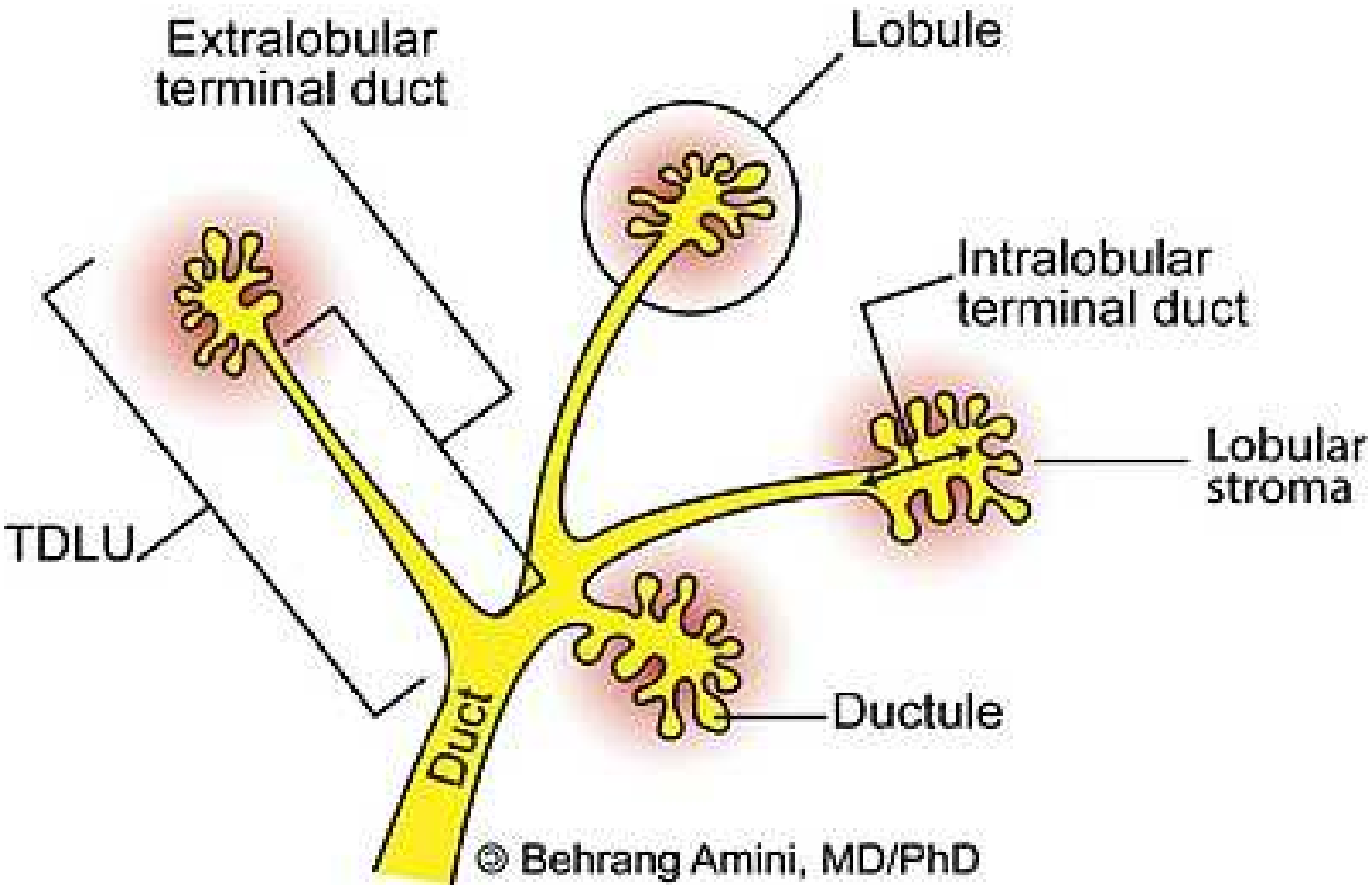
Pathological examination has been the gold standard for diagnosis in cancer and its role has also included the elucidation of etiology, pathogenesis, clinicopathological correlation, and prognostication.

The advent of newer technologies and the realization that breast cancer is heterogeneous has shifted the focus to prognostication, with increased attention being paid to the identification of morphological features and immunohistochemical markers of prognostic relevance.

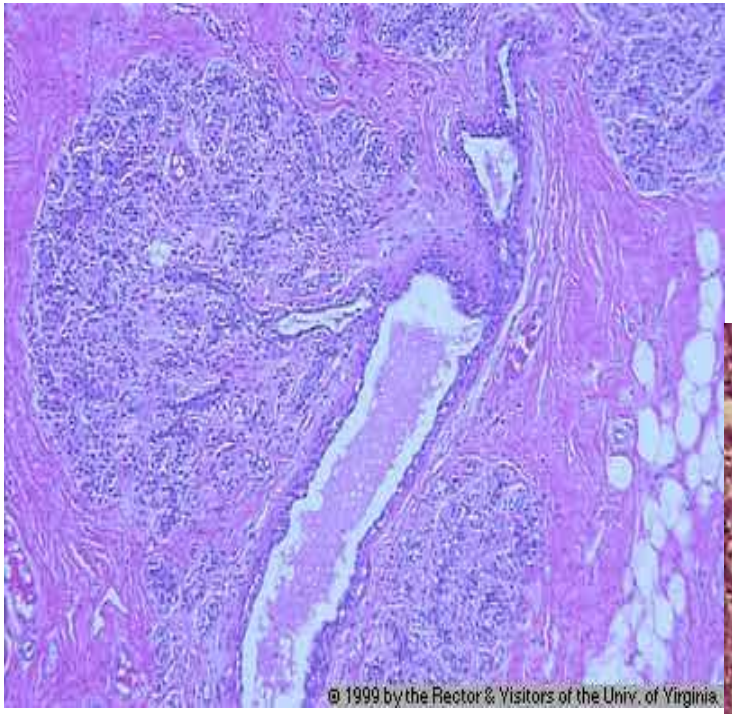
However

Pathologists continue to play their traditional role in diagnosis but, as purveyors of the excised tissue, pathologists now have the additional role of identifying biomarkers responsive to therapeutic manipulation, thus playing an inextricable role as diagnostic oncologists in the management of breast cancer.

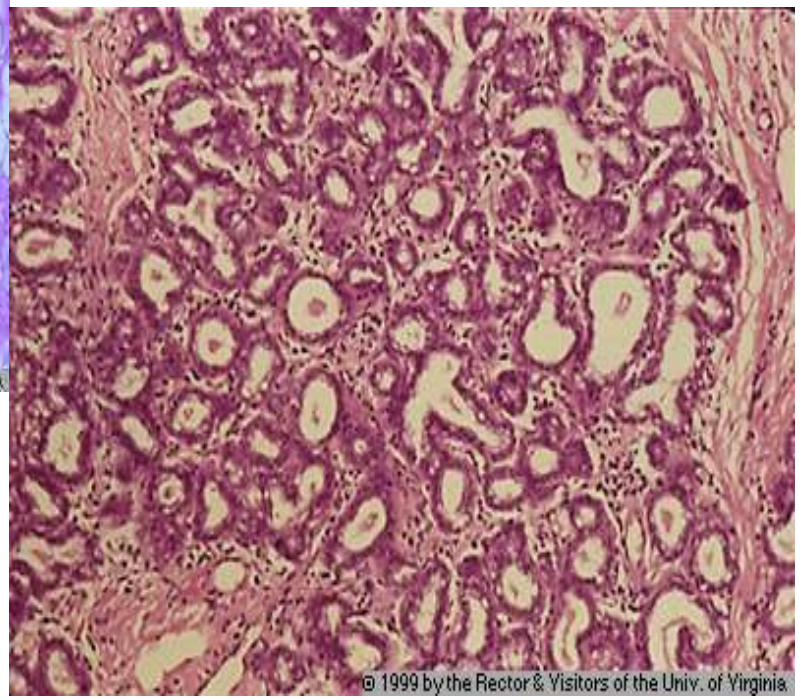
Path biology. 2011;78(2):99-114. doi: 10.1159/000292644. Epub 2011 Jun 14



Ductal System in Breast

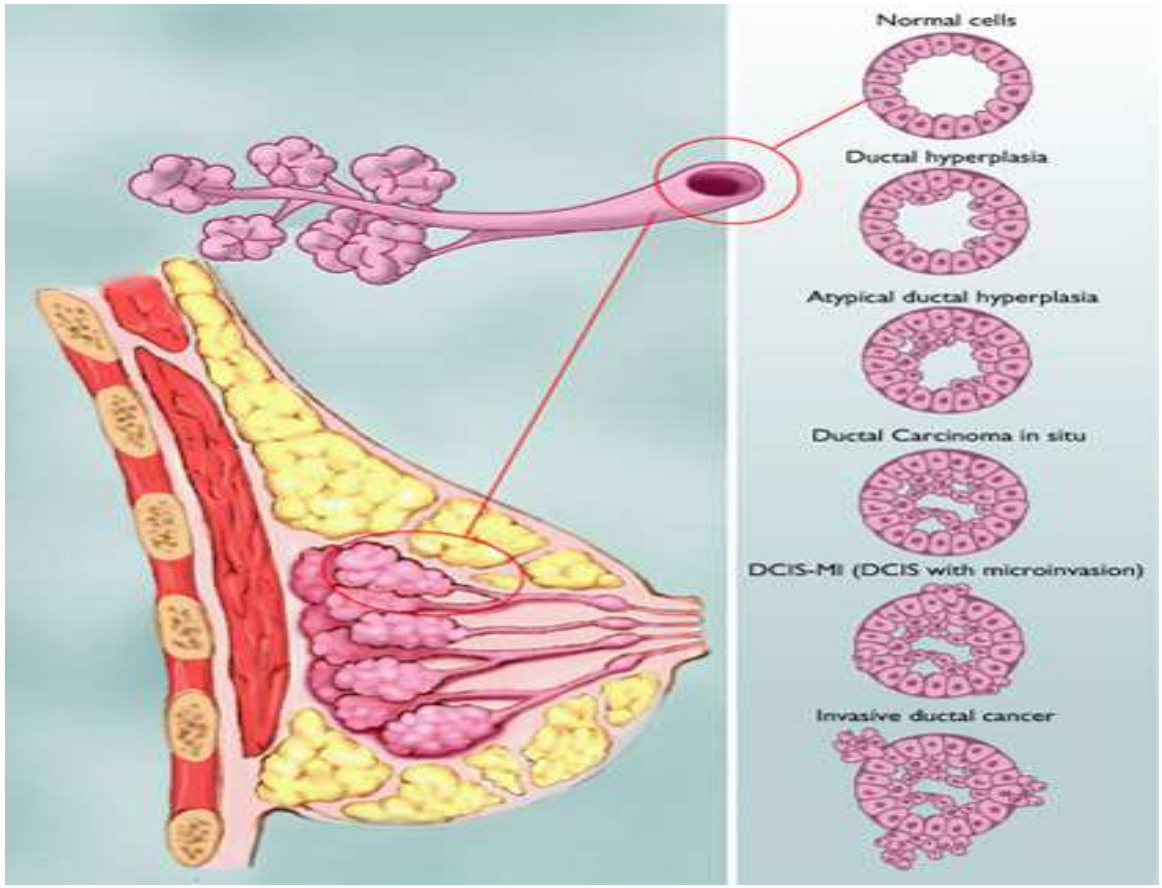


Interlobular ducts leading to TDLUs



TDLU. High power view showing the two-cell layer epithelium

Morphological progression



In-situ carcinoma`

Ca. at site of origin confined by basement membrane.

It is Curable when excised completely.

However

BM is discontinuous

Occasional extension of cells across BM.

DCIS &LCIS

Mammography

Incidental findings

As mass -DCIS

Paget's disease of Nipple-DCIS

DCIS &LCIS- not an anatomic classification

DCIS	LCIS
• A cytoarchitectural pattern of growth wherein tumour cell are relatively large &cohesive&appear to grow predominantly within larger ducts. • A lesion arising within a duct as a result of "unfolding of TDLU"	• A cytoarchitectural pattern of growth wherein tumour cell are relatively small,dyscohesiveand appear to grow predominantly within lobules or TDLU. • The lobular architecture is retained.

In-situ Ca.

- Ductal carcinoma in situ (DCIS accounting for about 15% of all new breast cancer cases in the U.S(most common)
- A heterogenous gr.eachhaving differentprognostic significance.Unilateral regional.

- LCIS is much less common (accounting for only about 4,200 cases annually in the United States) slightly less risk of invasive cancer than DCIS. (>20yrs.)Also called lobular intraepithelial neoplasia, most subsequent breast cancers are ductal rather than lobular.
- LCIS typically includes multiple lesions and is frequently bilateral.
- It is usually discovered as an incidental finding from breast biopsy; there are rarely clinical or mammographic signs.

Histologic Classification of DCIS

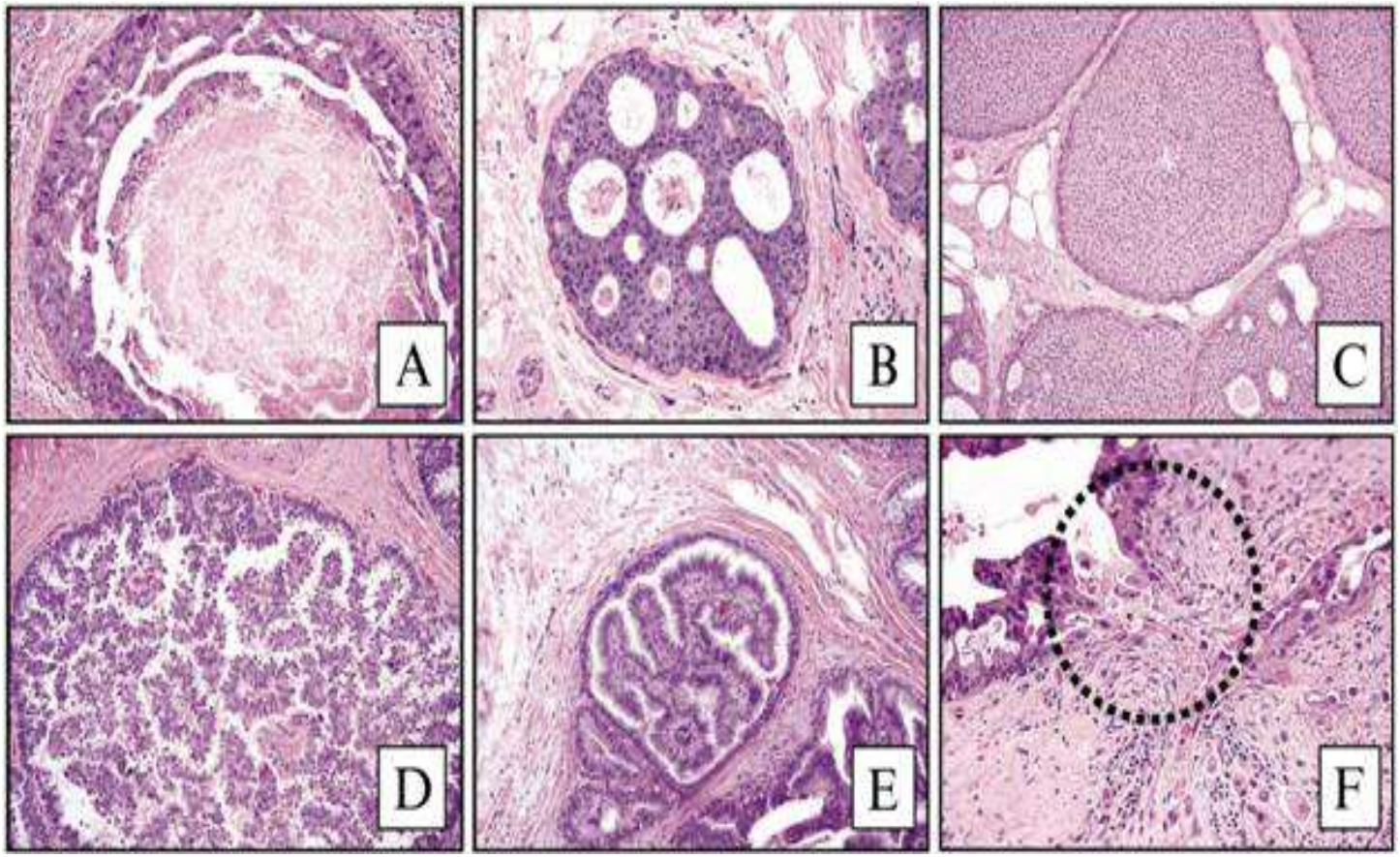
Feature	Low Grade (Well Differentiated)	Intermediate Grade (Moderately Differentiated)	High Grade (Poorly Differentiated)
Defining			
Nuclei (size variation)	Monomorphic (usually small)	Intermediate	Pleomorphic (usually large)
Chromatin	Fine granular, even	Fine to coarse	Coarse, clumped
Nucleoli	Insignificant or absent	Evident, rarely multiple	Prominent, often multiple
Mitoses	Rare	May be present but not numerous	Often present, may be numerous
Polarization	Prominent throughout	Present, not prominent	Absent or focal
Not Defining			
Comedo necrosis	Absent or minimal	Variable	Usually prominent, but not necessary
Calcification	Psammoma-like, rarely amorphous	Psammoma-like or amorphous	Usually amorphous
Growth patterns	Clinging, micropapillary, cribriform, and rarely solid	All patterns	Solid, clinging or pseudomicropapillary, and cribriform

- Low gr DCIS usually more localized
- Incidental, mammographic rather than palpable
- Positive –NSE
- Negative-Cerb2protein
- Risk for invasive ca-10-11old, 25%in 10yrs.

- High gr DCIS can be very extensive.
- Aneuploid, negative receptors, c-erb oncoprotein, p53overexpresion, metallothreonin expression. Often areas suggestive or equivocal of micrometastasis, occasional finding of LN-mets without apparent invasion.

Size,Morphology,Margin

Comedo cribriform solid



micropapillary Fern-like invasion

DCIS

Extensive intraduct component (EIC)

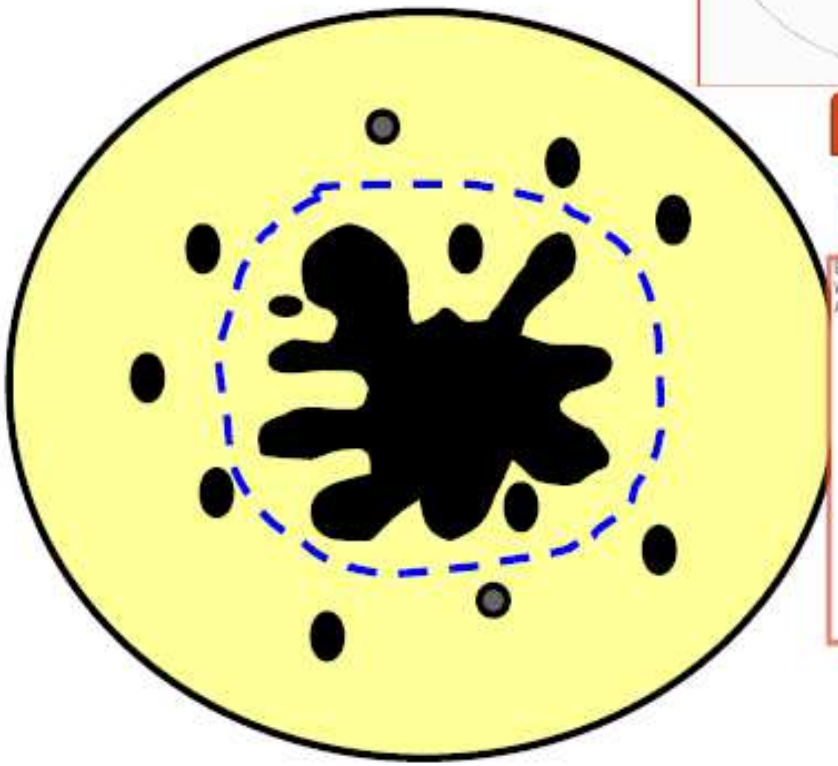
Schnitt & Connolly – Ca 1984 53,1049

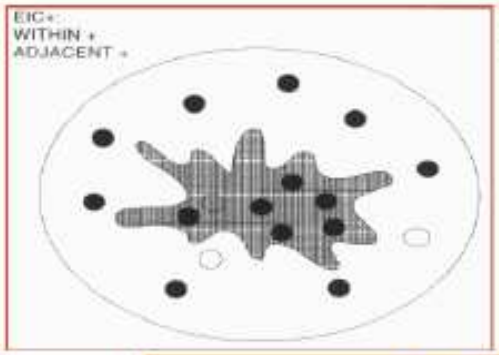
- Presence of intraduct carcinoma comprising greater than 25% of area encompassed by the infiltrating tumor or intraduct carcinoma in grossly normal breast tissue adjacent to invasive tumor – extent not specific

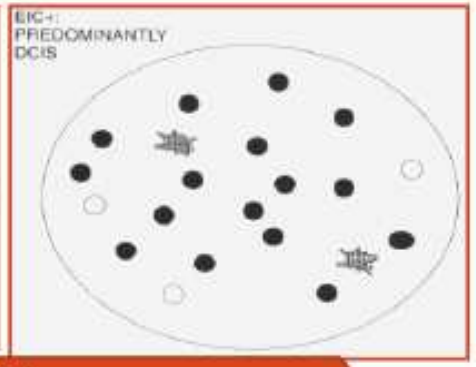
- Young age and EIC have been shown to be associated with increased local recurrence in BCT. *Int J Radiat Oncol Biol Phys* 1998;40:851– 858. *J Clin Oncol* 1990;8:591–598. Int J Radiat Oncol Biol Phys. 2003:15:979

- An EIC histology associated with an elevated risk of residual tumor irrespective of age and may undermine the predictive utility of margin status. Int J Rad Oncol Biol physic 1999;45:885

EIC

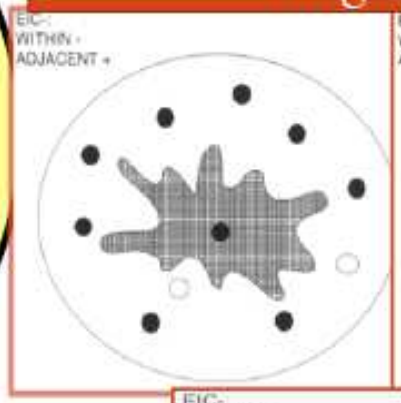


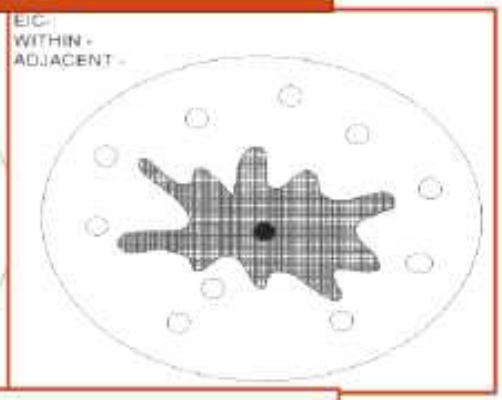


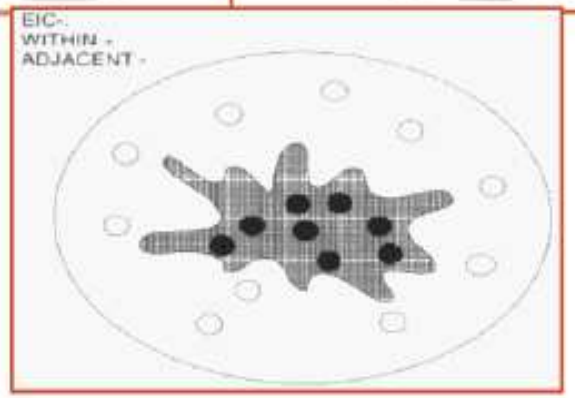


Positive

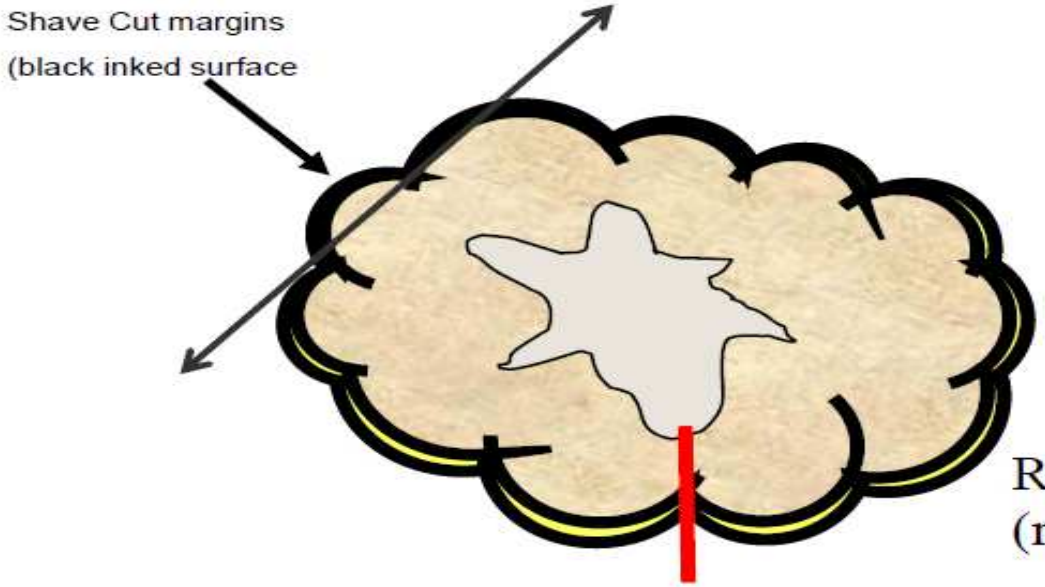
Negative







How to assess the margins



- Specimen must be oriented
- Sample six surfaces
- Type of margin must be specified by pathologist during grossing
- Embedding must be proper

Margins in lumpectomy

- It is always better to take the margins (radial or shave, as required) in the following order:

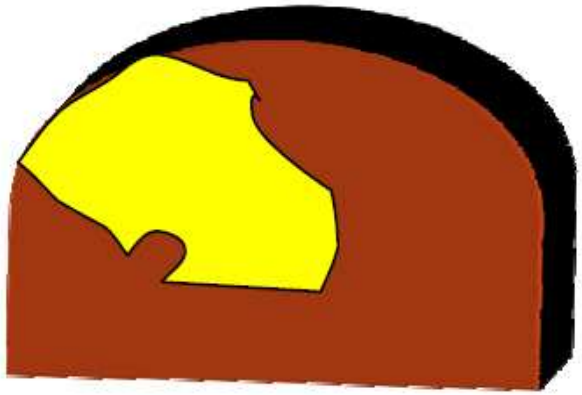
S---Superior, I---Inferior, M---Medial, L---Lateral, A---Anterior (skin if present), P---Posterior. Remember the mnemonic **SIMLAP.**

- **Please remember that margin assessment is actually just a sampling and is not 100% accurate. The more extensively a margin is sampled the more chances of finding a positive margin.**

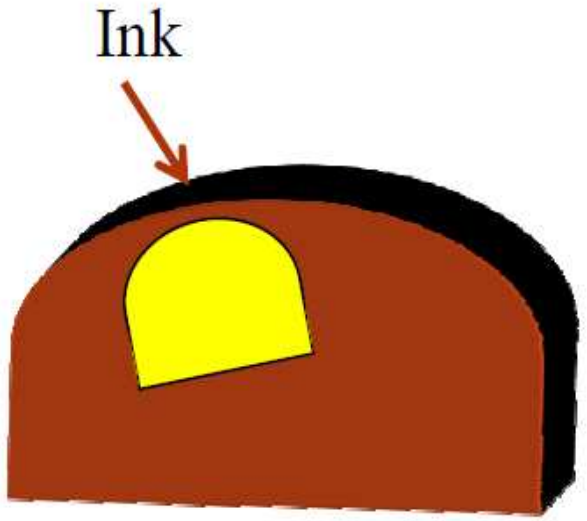
Definition of + margin

Schnitt et al - Cancer 1994,74:1746

RADIAL

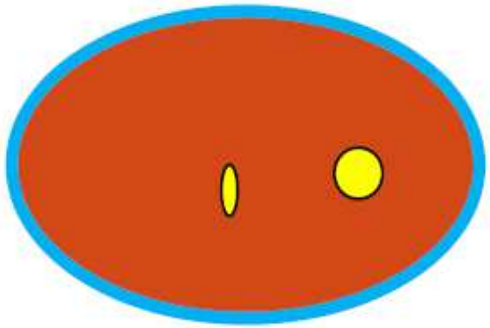


Positive margin – tumor transects ink surface

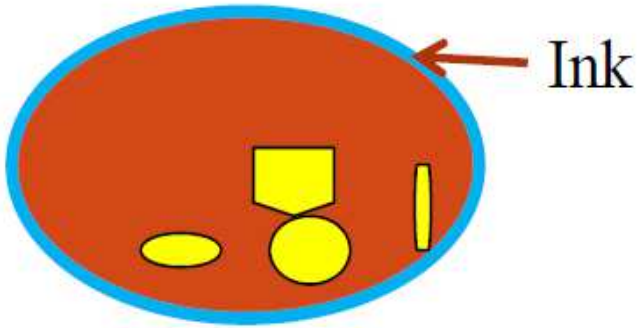


Close margin – Tumor reaches close to but does not transect ink

SHAVE



Focal positive for tumor or DCIS- if ½



Gross positive for tumor or DCIS- if >/=3

Invasive Carcinoma

Invasive duct ca-NOS-majority

Special type(<30%)

Mixed.(33%)

What is 10% and 90%

- **Special Types**

  Tubular ca, cribriform ca medullary ca, ILC, mucin ca, papillary ca, secretor metaplastic ca, adenoid cystic carcinoma

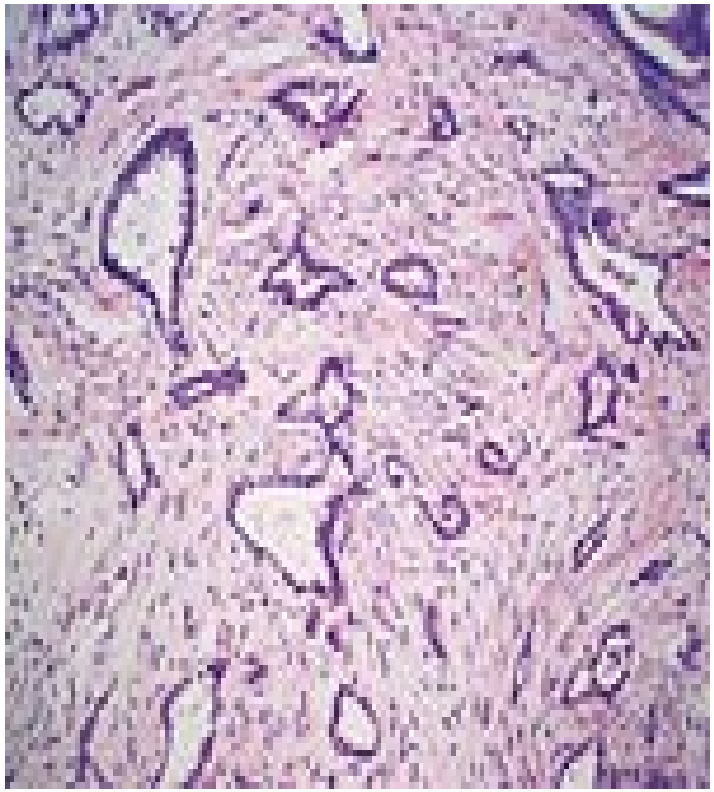
- **Miscellaneous or variant presentation**

  Lipid cell ca and variants, small cell ca, IDC with granulomatous reaction, Anaplastic variantof pagets, Ca with chorio ca. diff. Neuroendocrine diff. with myoepithelail/myofibroblastic diff, etc.

HISTOLOGIC TYPES OF INVASIVE BREAST CANCER IN FOUR LARGE SERIES BEFORE THE WIDESPREAD USE OF MAMMOGRAPHIC SCREENING

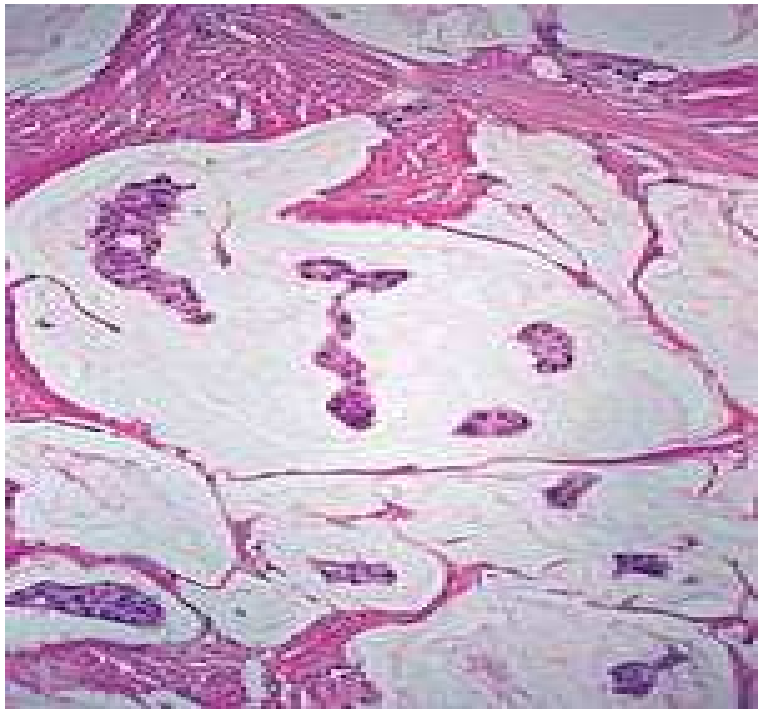
Study	No. of Cancers	Histologic Type							
		Ductal[a] (%)	Lobular (%)	Medullary (%)	Mucinous (%)	Tubular (%)	Tubular Mixed (%)	Mixed (%)	Other (%)
Fisher and colleagues (119)	1,000	53	5	6	2	1	—	32	—
Rosen (120)	857	75	10	9	2	2	—	—	—
Ellis and colleagues (122)	1,547	49	16	3	1	2	14	14	2
Page and Anderson (121)	Not stated	70	10	5	2	3	2		8

[a]In some series, designated *not otherwise specified (NOS)* or *no special type (NST)*.

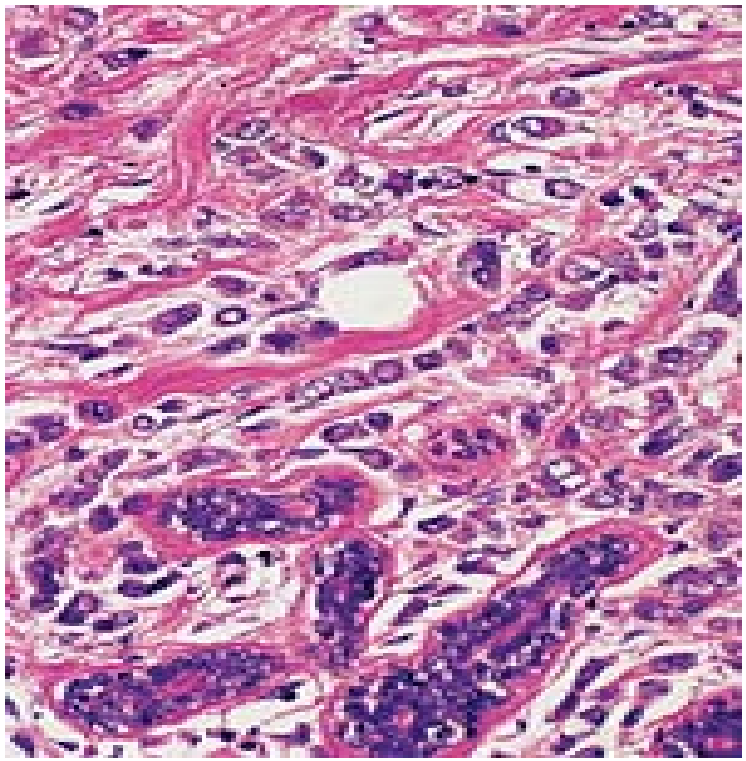


Tubular carcinoma of breast. The angulated shape of the glands and the cellular stroma are characteristic of this lesion,composed of cells with low-grade nuclei, comprise at least 90% of the carcinoma.

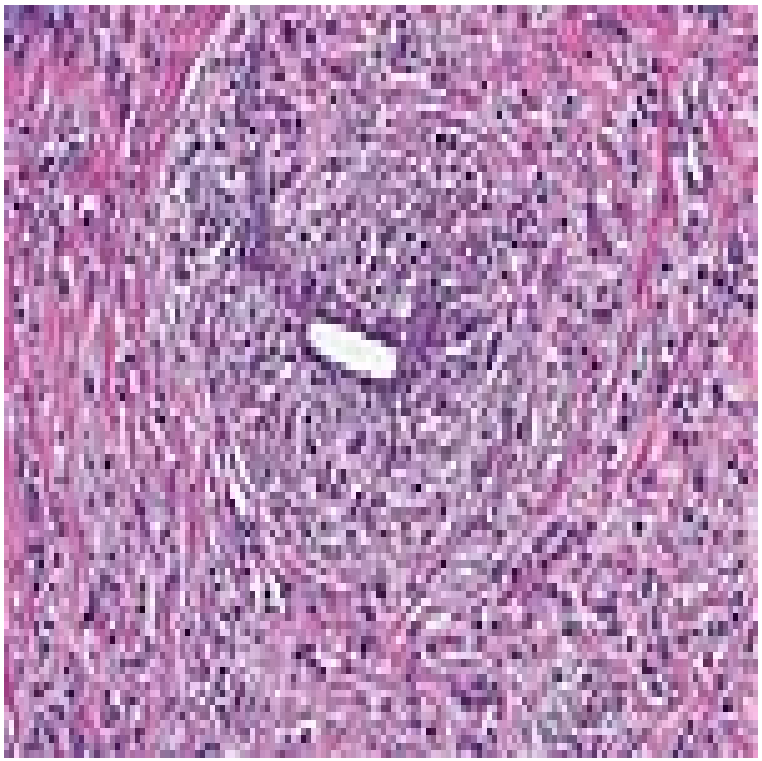
well diff.(gr-1 tm.),good prognosis.
Typically ER/PR+ve, Her2neu –ve, diplid,low proliferative rate,no p53 overexpression



Mucinous carcinoma of the breast. Clusters of well-differentiated tumor cells are seen floating in a sea of mucin.

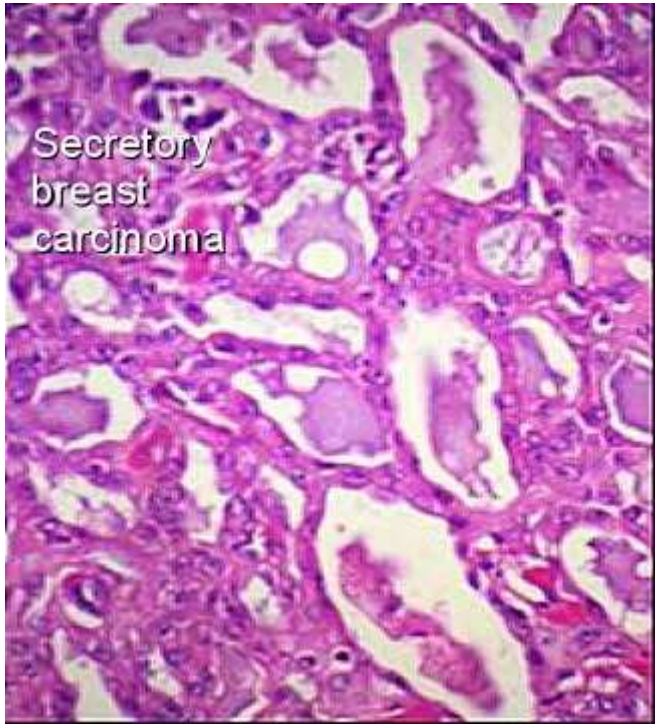


Invasive lobular carcinoma. The tumor cells are small and uniform with round nuclei and grow in an Indian file fashion.

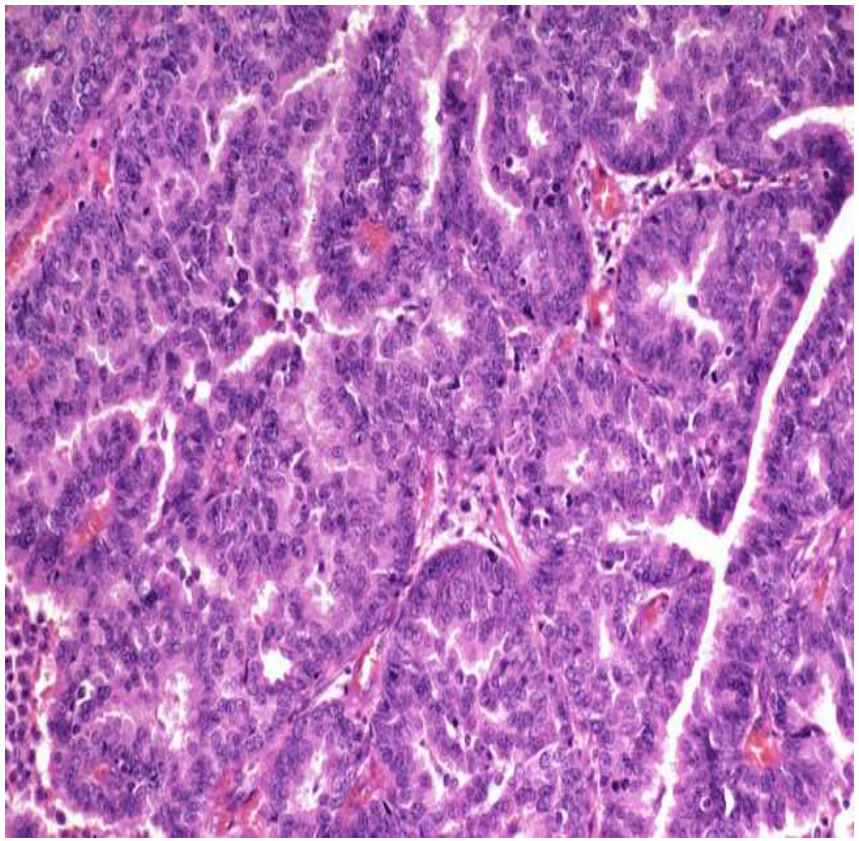


Typical target-like growth of tumor cells around an uninvolved duct in invasive lobular carcinoma

- Secretory breast carcinoma is a slow growing breast cancer which is actually more common in younger patients, and was in fact originally termed 'juvenile' breast cancer.
- It is called secretory carcinoma because of the abundant secretion of mucin within the tumor. It is one of the rarest types of breast carcinomas, accounting for less than 1% of all breast cancers. Average age of presentation is estimated at around 25 years. associated with a better prognosis.
- However, secretory breast carcinoma is prone to metastasis and local recurrence so must be treated aggressively.



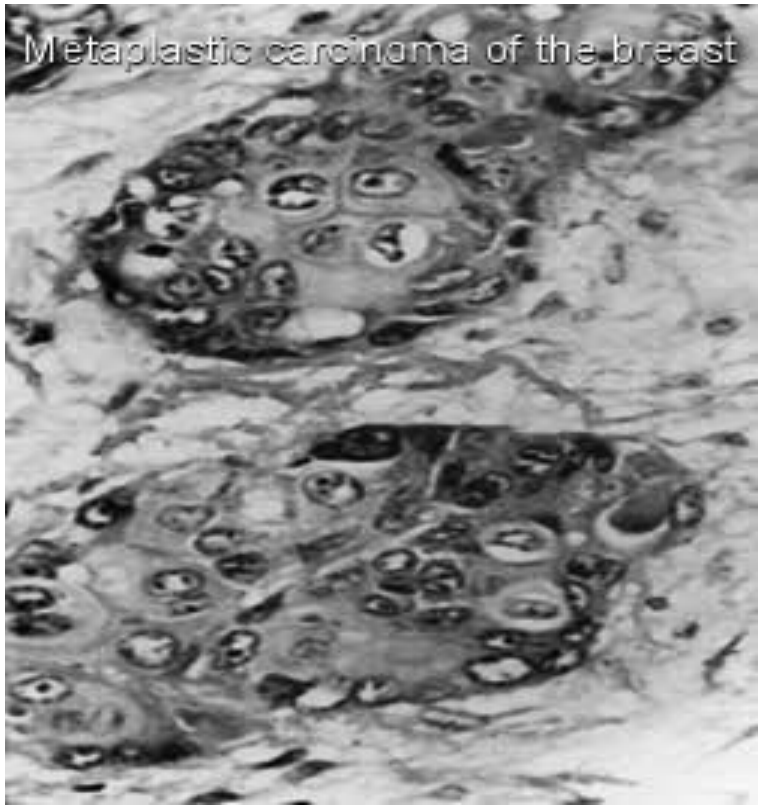
Papillary ca.

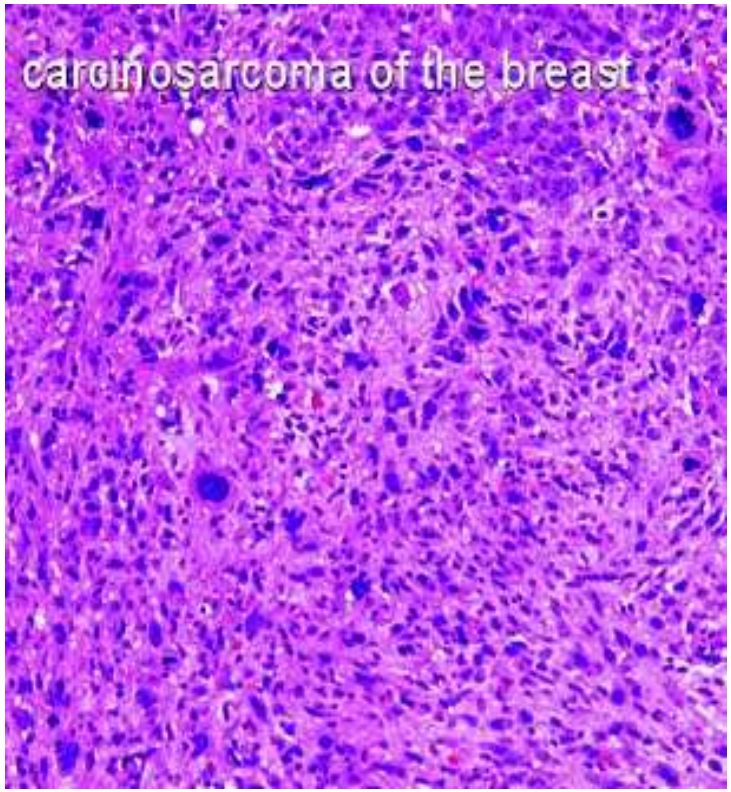


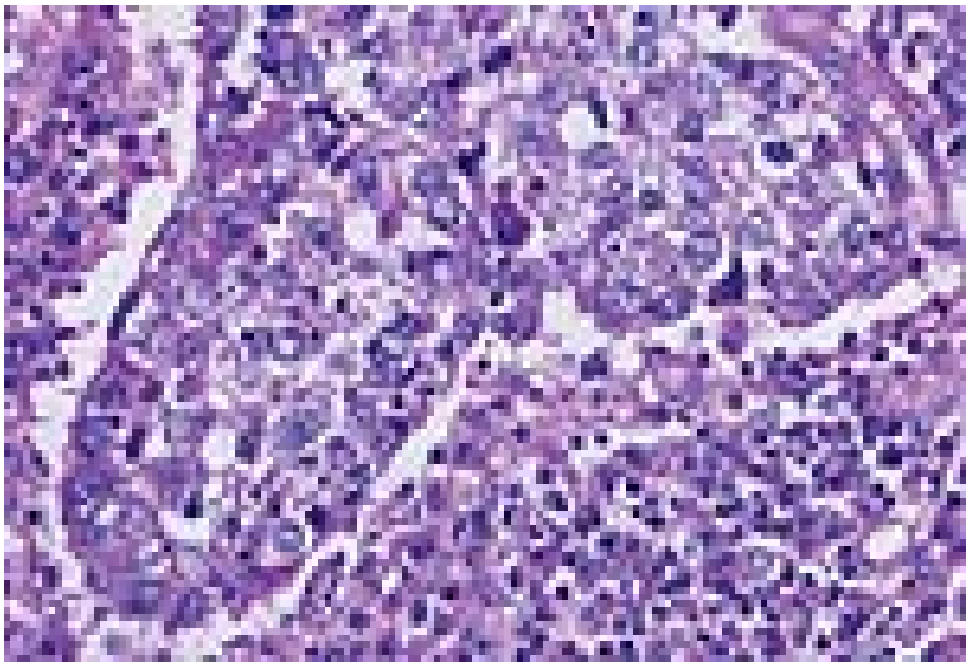
Intracystic papillary carcinoma, high power. In contrast to papillomas, the epithelial cells in papillary carcinoma grow in a more haphazard fashion showing uneven stratification and loss of polarity. Myoepithelial cells are absent.

Metaplastic breast carcinoma (MBC) is a rare form of breast cancer in which there is a mixture of malignant mesenchymal and epithelial elements. Metaplastic breast cancers are really quite rare, accounting for only about 0.02% of all breast cancers. Metaplastic breast carcinoma is an aggressive cancer, and tends to present at a more advanced stage and has a high propensity for local recurrence.

Metaplastic ca







Medullary carcinoma. The large tumor cells grow in a "syncytial" fashion and are sharply separated from the surrounding stroma, which is heavily infiltrated by lymphocytes and plasma cells.

Medullary/ Atypical medullary

(All the following features)

Predominant syncytial growth pattern(>75%)

(Other typical features)

circumscribed margin both gross and micros.

Marked/moderate lymphoplasmacytiv stromal reaction

Pleomorphic nuclei with high mitotic rate

Absence of tubule formation

No in situ component

(Features of typical medullary but no more than two atypical features)

Predominant syncytial growth pattern(>75%)must be present

Atypical features :

Focal areas of infiltration at tumour margins.

Absent or mild lymphoplasmacytic infiltration, or at margin only.

Uniform nuclei with infrequent mitosis.

Focal areas of tubule formation.

In situ ca present

Prognosis is variable in different series ?variability ?interobserver or ? molecularheterogenety

Biological markers in med. ca reflect aggressive histologic features.
ER/PR –ve, Her2neu+ve, mostly aneuploid,p53 over expression.
Common in women with mutation in the breast ca susceptibility gene BRCA-1.

Tumour Size

Easily, quickly and cheaply determined prognostic parameter.

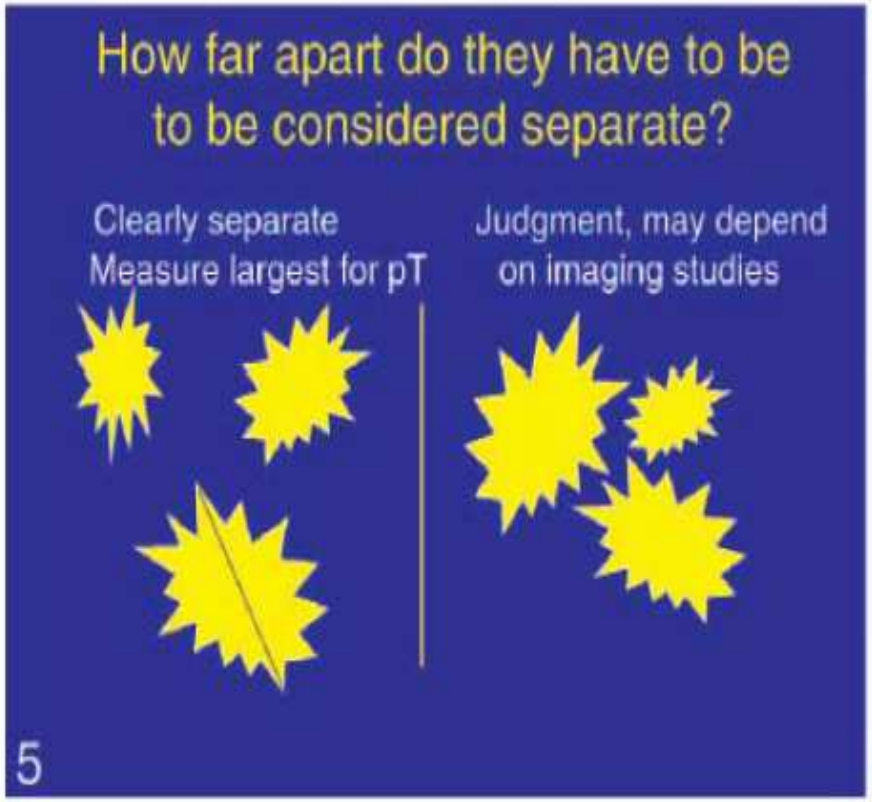
Good correlation with incidence of nodal mets, and with survival rate.

One of the strongest predictor of dissemination and rate of relapse in node negative breast ca.

Microscopically determined size has greater prognostic significance that includes both in situ and invasive.

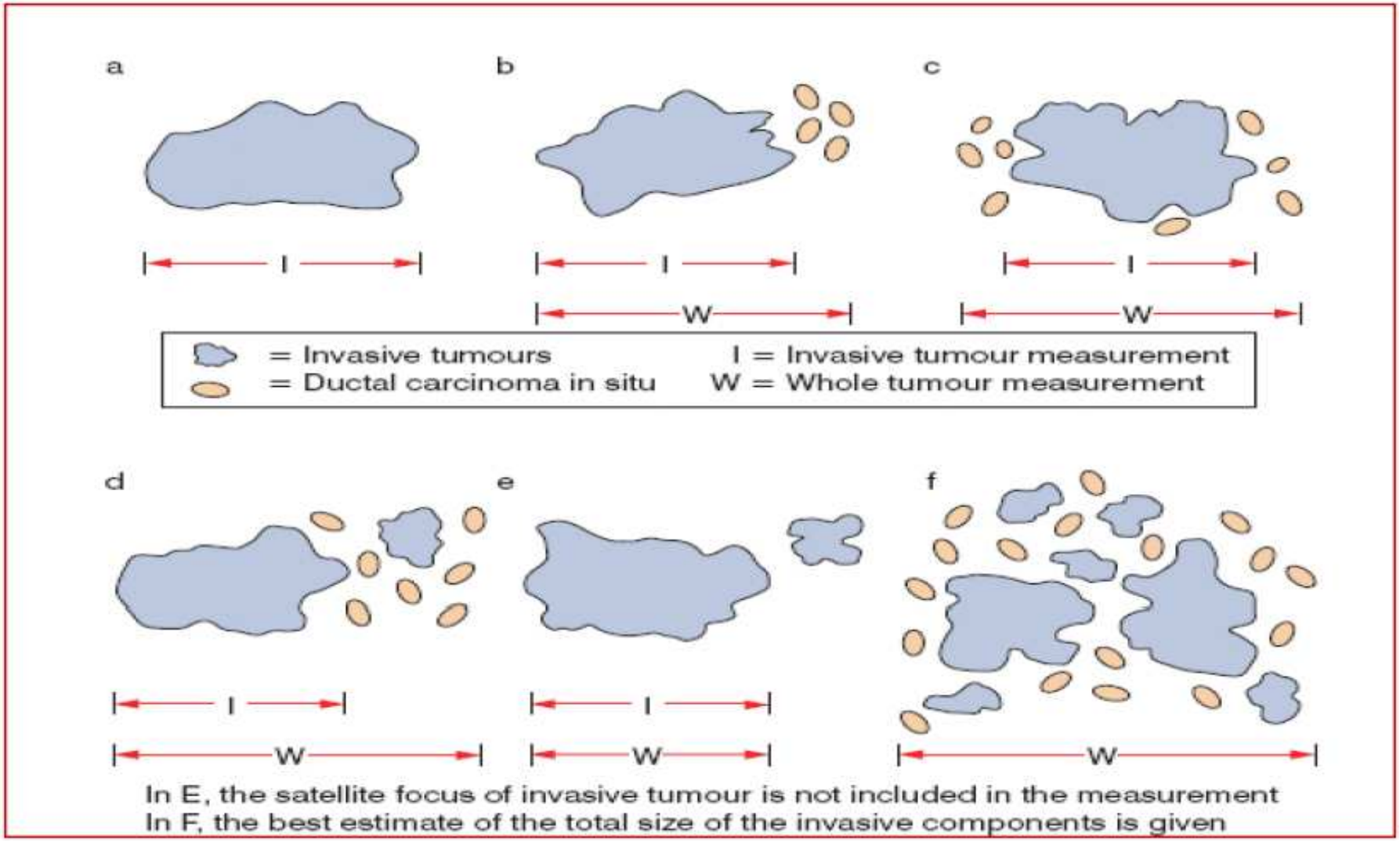
Size is one of two criteria for definition of minimal breast ca.Minimal breast ca-All in situ and invasive ca 1cmor less.

Tumor size



Arch Pathol Lab Med. 2006;130:287–291

Tumor size measurement



Rosen et al followed 111 pts. with tm. 1cm or less with MRM for 10 yrs.

75%- alive with no evidence of disease.

4%- with recurrent ca.

6%-died of the disease.

15%- died of other causes.

Grading of Breast Cancer

- Histological grade provides important prognostic and management information
- The internationally accepted system is that defined by Elston and Ellis modification of Bloom and Richardson
- Assess by evaluating acinar formation, nuclear size/pleomorphism and mitotic activity
- Although originally designed for grading NST tumours it is recommended that it is applied to all cancers
- An attempt should be made to grade the pre-operative core biopsy as there is acceptable concordance with excision grade

Scoring system

Each element evaluated is given a score of 1 - 3

Acinar/tubule formation is assessed over the whole tumour and is a low/medium power assessment

Nuclear evaluation is of the worst area

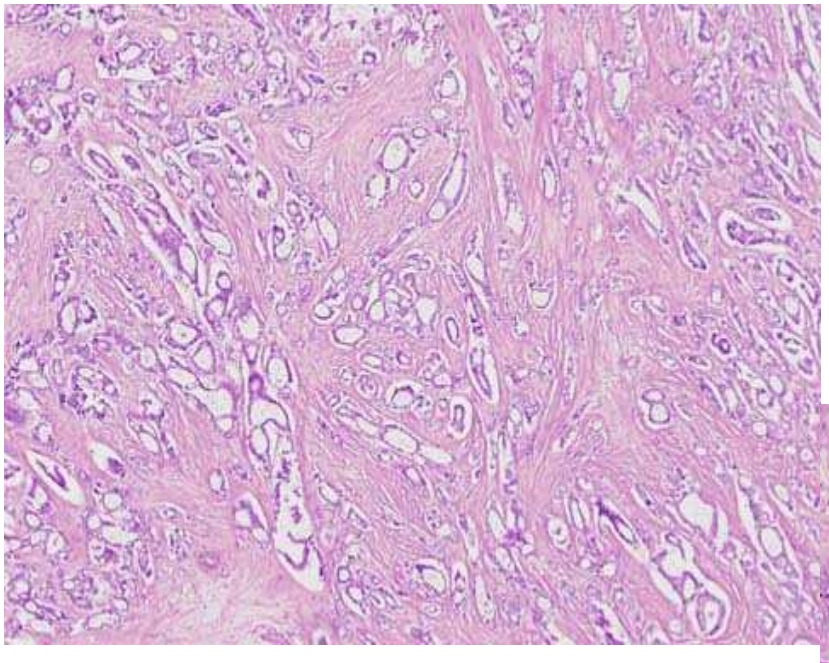
Mitotic count is also in the most mitotic area.

HISTOLOGIC GRADING

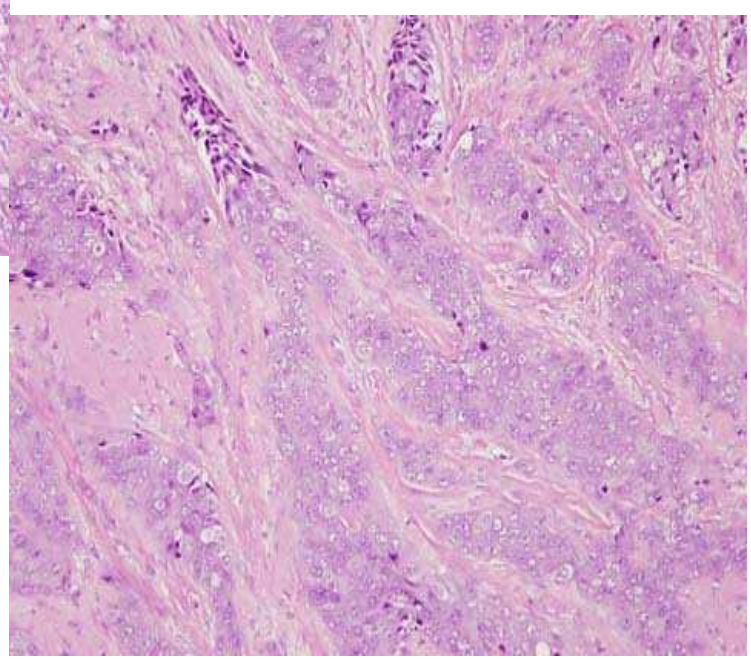
Feature	Score
Tubule formation (extent within tumor)	
>75%	1
10%–75%	2
<10%	3
Nuclear pleomorphism	
Small, regular, uniform	1
Moderate variation in shape and size	2
Marked variation in shape and size	3
Mitotic count per 10 hpf (dependent on microscopic field area)	
Field diameter 0.59-mm diameter/0.274-mm^2 area	
0–9	1
10–19	2
>20	3
Field diameter 0.44-mm diameter/0.152-mm^2 area	
0–5	1
6–10	2
>11	3

Total score: 3–5, grade 1, well differentiated; 6–7, grade 2, moderately differentiated; 8–9, grade 3, poorly differentiated.
hpf, high-power field.

Examples of Tubule Formation

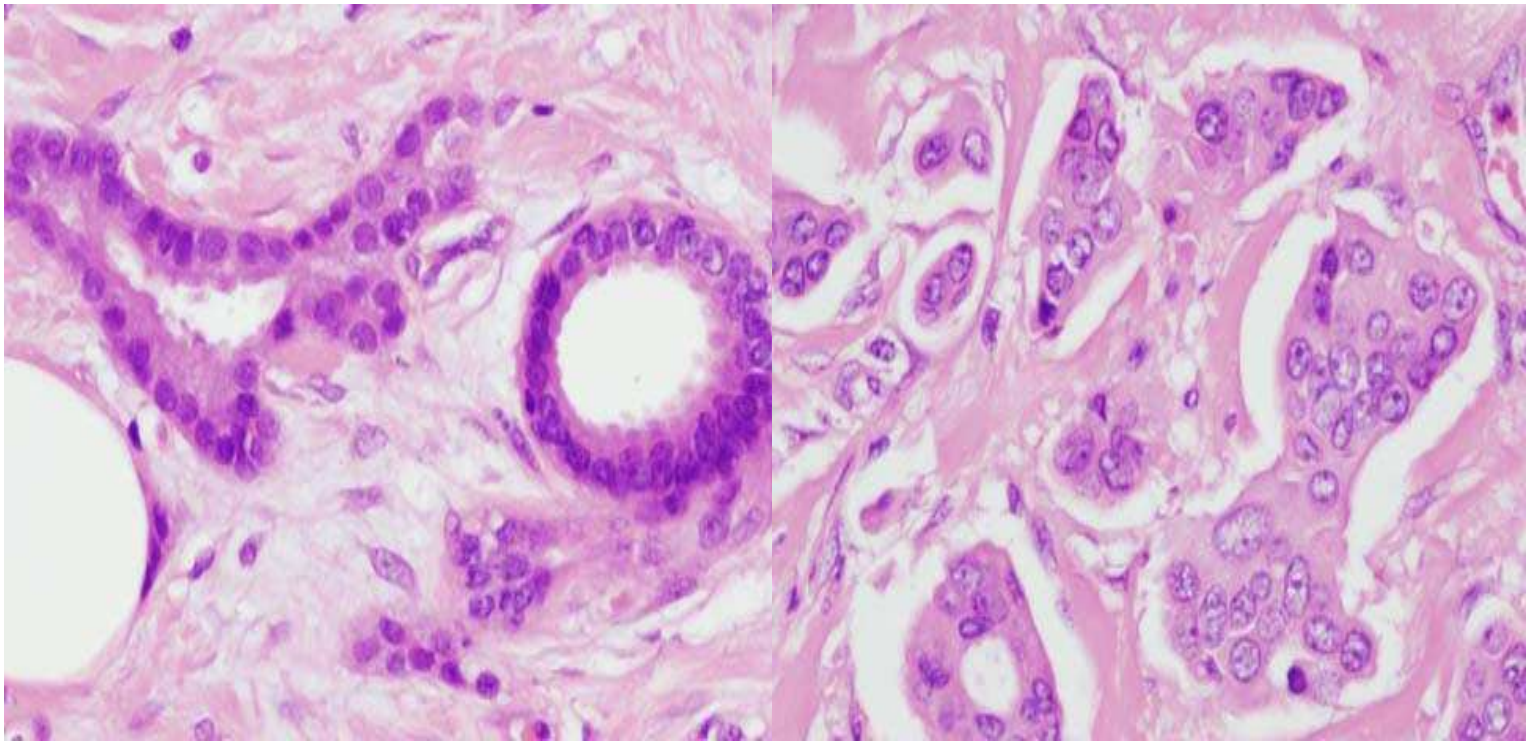


<<Tubule score = 1 (>75% tubules)



Tubule score = 3 (< 10% tubules)>>

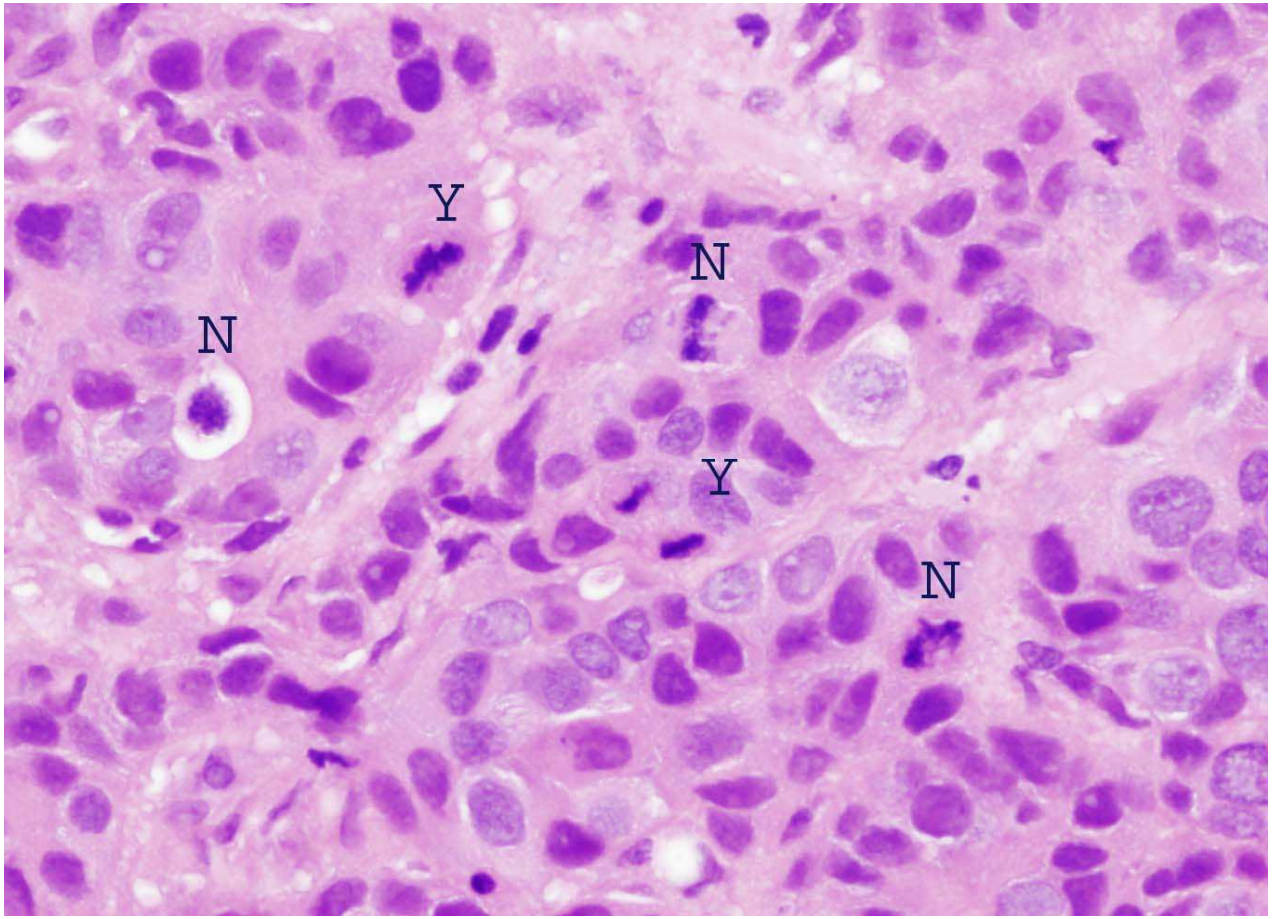
Examples of the three *nuclear* grades



Nuclear score = 1

Score 3 nuclei

Examples of mitoses (Y) and not mitoses (N)



Lymphatic/vascular invasion

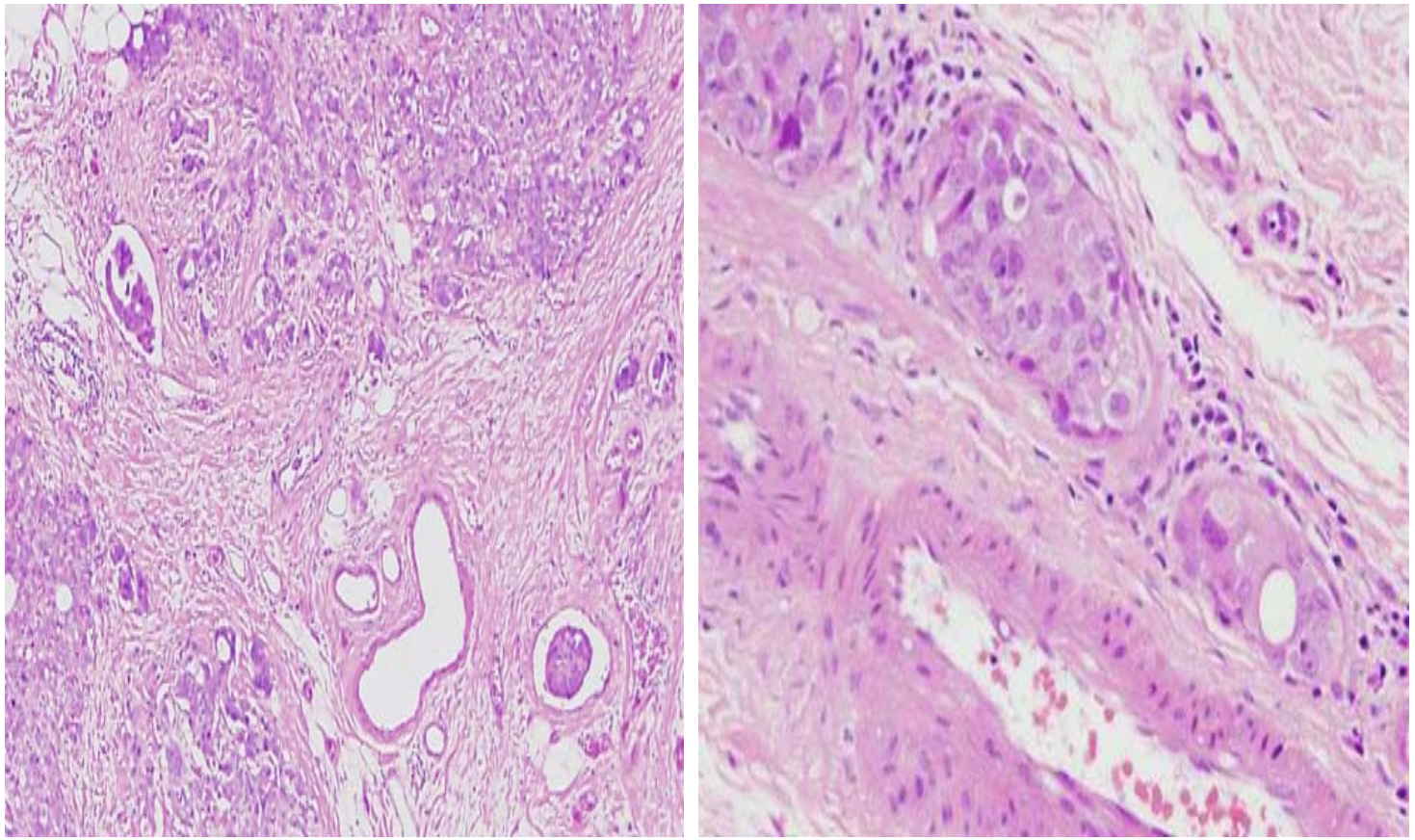
Best assessed around periphery of tumour.

Difficulty distinguishing from shrinkage artefact in section - not to overdiagnose!

Lymphatics tend to accompany small veins arteries and nerves - if seen improves confidence in diagnosis

Tumour in vessels tends to be 'stuck' to the sides and may be accompanied by red cells

An independent prognostic factor so not to diagnose just because the nodes are positive!!



Nodal metastases

- Identification of nodal metastatic disease is the most important task facing the pathologist examining an operative lymph node specimen in a case of breast cancer
- Microscopic assesment should include the size of the largest metastasis, extra nodal extension & invasion of adjacent lymphatics if present
- Node metastases are subclassified into - replacement type, micrometastases and isolated tumour cells (ITCs)according to TNM 6

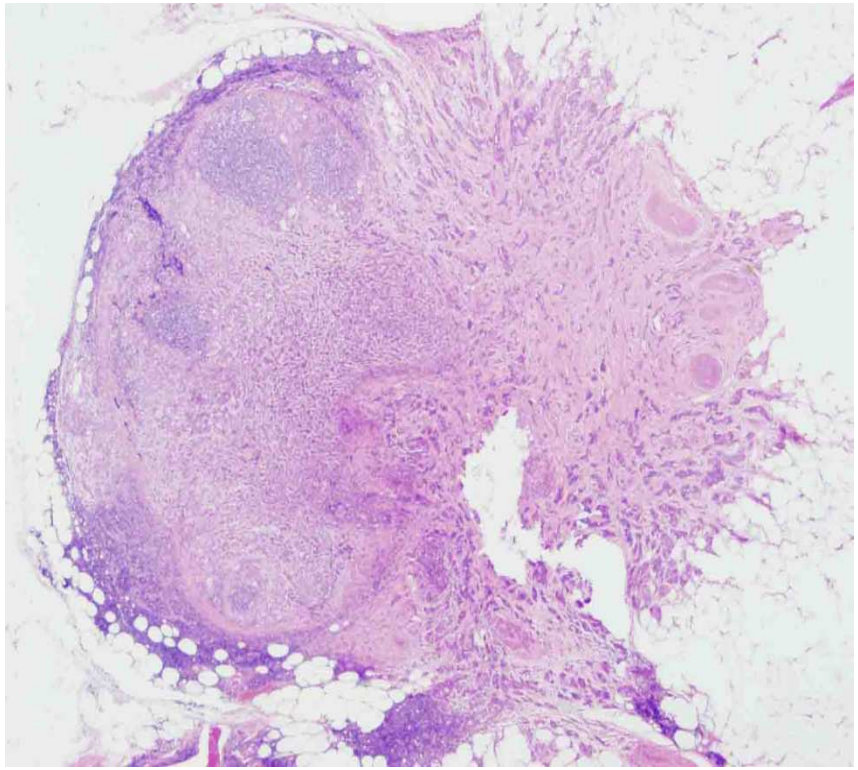
Sub classification of nodal metastases (TNM6)

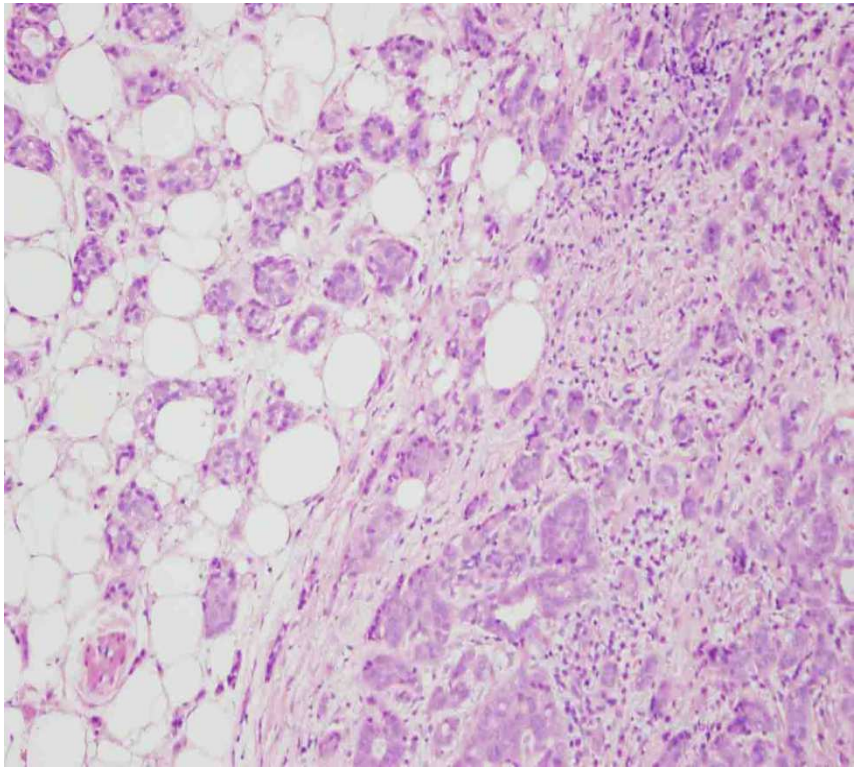
Replacement metastases > 2mm

Micro metastases 0.2mm-2mm

isolated tumour cells < 0.2mm

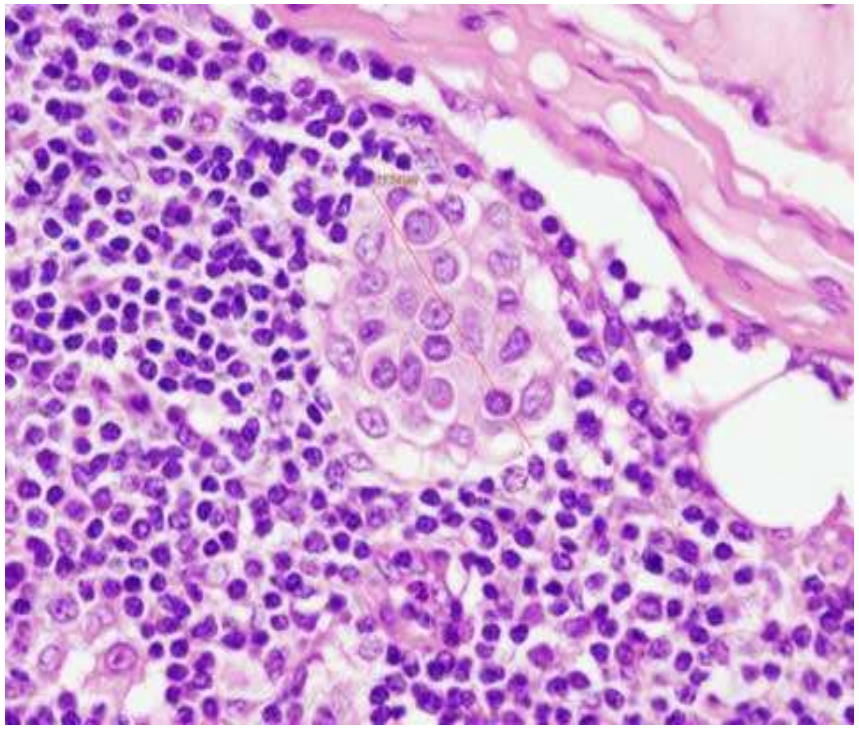
Replacement metastases in axillary nodes.

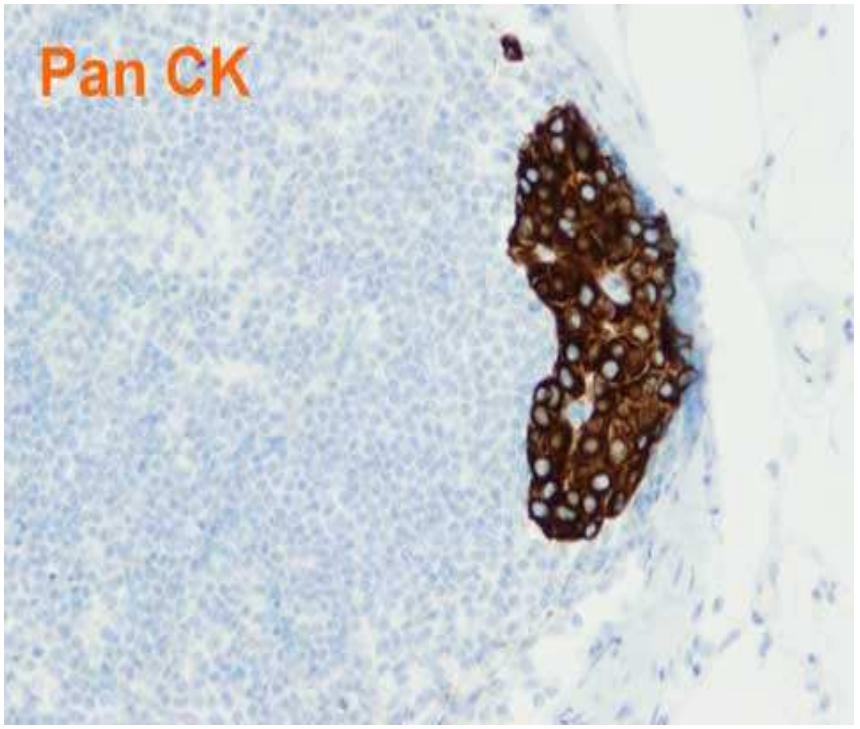




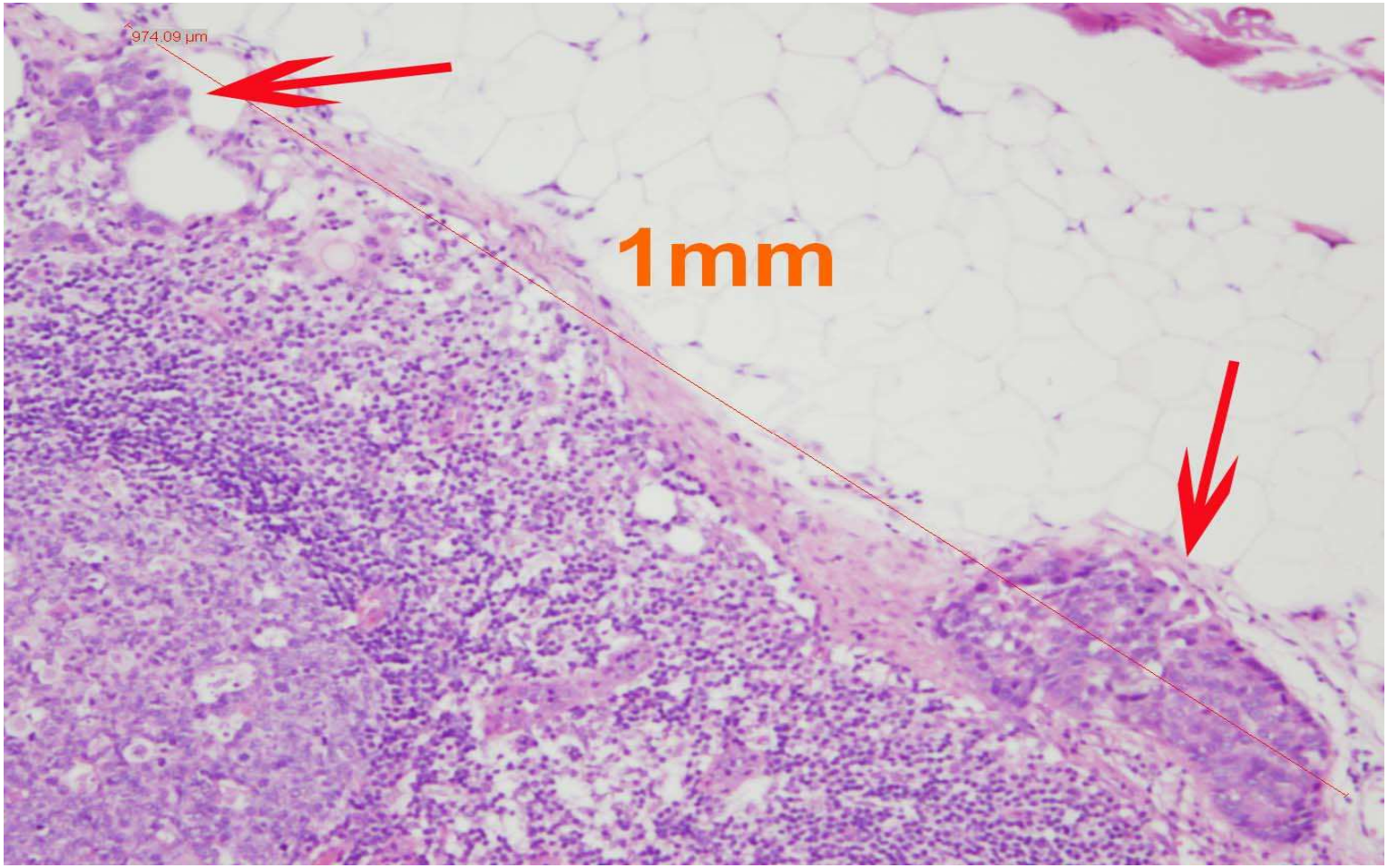
Micrometastases

Micrometastases 0.2mm-2mm





Isolated Tumour Cells and Micrometastases



ER,PR STATUS

- Breast Cancer is a classical hormone dependent tumour. Tamoxifen is the most widely used selective estrogen receptor modulator (SERM) for last 25 years.

- Response to tamoxifen is not uniform irrespective of ER positivity, better in ER + ve PR +ve patients then ER +ve PR –ve patients. ER +ve PR –ve patients also over express HER-2neu (an EGFR). ER +ve patients experience overgrowth of cancer cells rather than suppression with tamoxifen if HER-2 neu is also positive.

- ER, PR, HER-2 neu status is very important in diagnostic work -up.

ERs/PRs bind hormones that exert their effects in the nucleus. Nuclear immunostaining for both receptor proteins can be demonstrated in normal breast.acini, which serve as internal controls for the testing procedure.

One of the effects of estrogen is to induce the PR, and thus the coordinate expression of both hormones in the same cell reflects the fidelity of the ER/PR axis in the cell.

What constitutes positive ER by IHC ?November 1-3, 2000, National Institutes of Health (NIH) Consensus Statement on Adjuvant Therapy for Breast Cancer:

Any positive nuclear ER immunostaining is considered to be a positive result and should be a definitive reason for instituting anti-estrogen therapy for a patient.

ER+ tumour include lobular, tubular, mucinous, and papillary carcinomas, along with ductal carcinomas of good (low) nuclear grade.(Rosen et al)

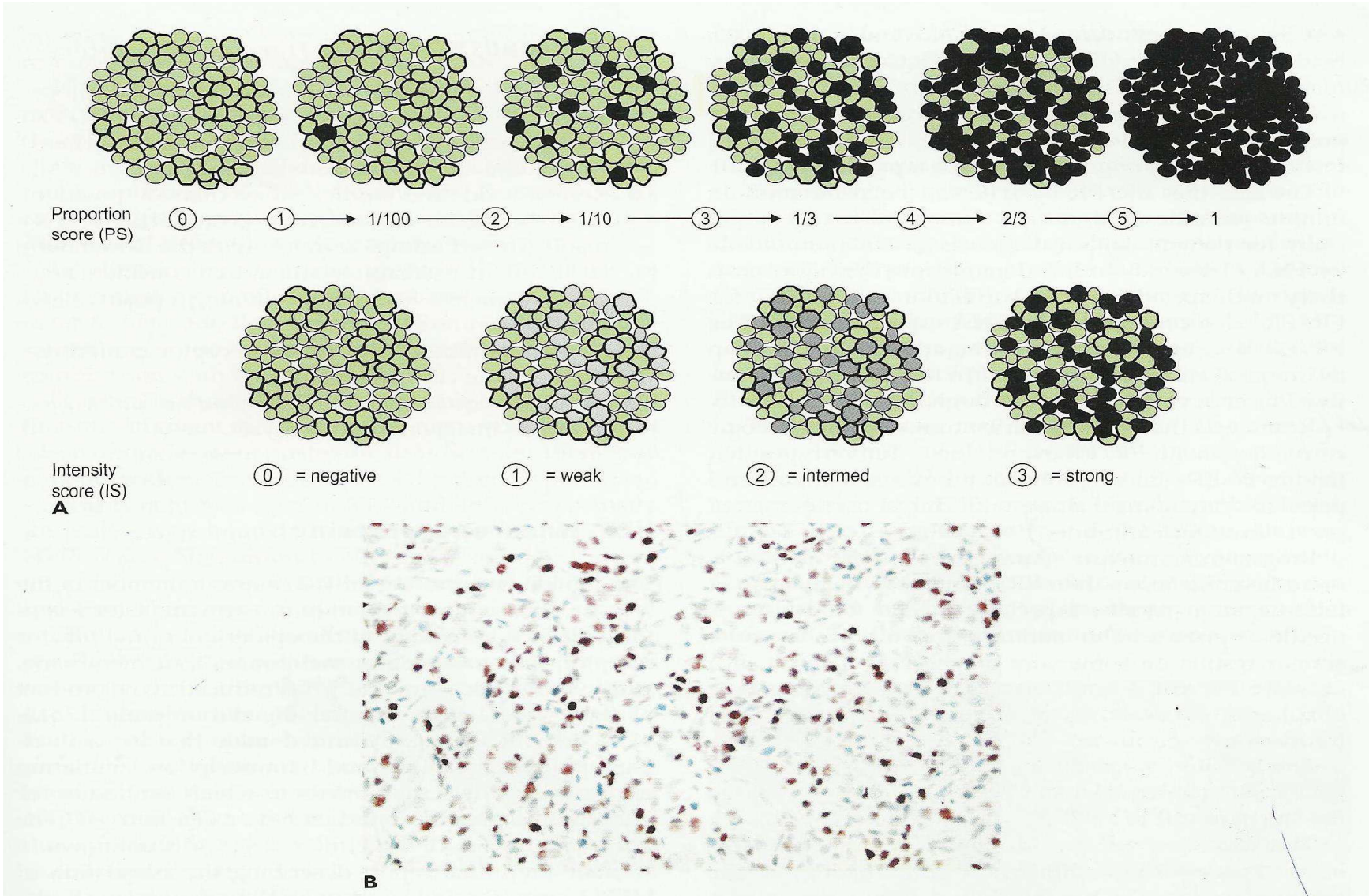


Fig. 17.31 (A,B) The method of incorporating intensity and proportion of nuclear staining for estrogen or progesterone semiquantitation. Add the proportion score (PS) and intensity score (IS) (PS+IS=TS) for the overall value of 0 to 8. (From Harvey, et al. 1999.)

HER -2/neu oncoprotein

The 185 kD oncoprotein HER-2/neu is a member of the tyrosine kinase receptor family, is a growth factor receptor with 50% homology to the epidermal growth factor receptor, and has surface membrane, transmembrane, and cytoplasmic domains, a product of the *c-erb-B2* gene located on chromosome 17q12- 21.32.

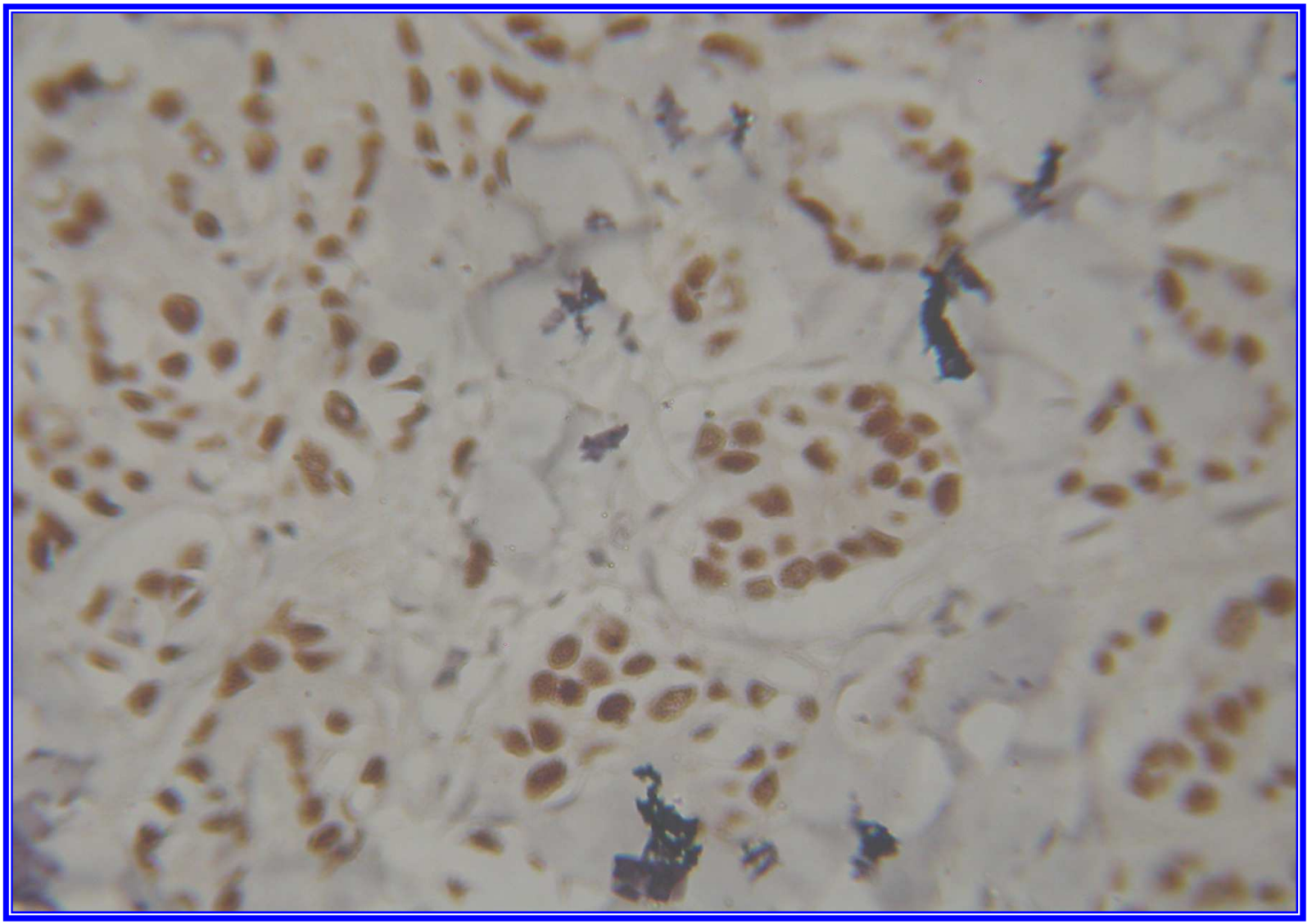
HER-2/neu overexpression in lymph node negative patients has a weaker association with prognosis. The results for lymph node-positive disease seems to be clear cut, with the vast majority of studies showing a poorer prognosis with overexpression of HER-2 / neu.

The current clinical use for the HER-2/neu status of the breast cancer patient is twofold: (1) as a predictor of response to doxorubicin chemotherapy and (2) to determine which patients would respond to trastuzumab therapy.

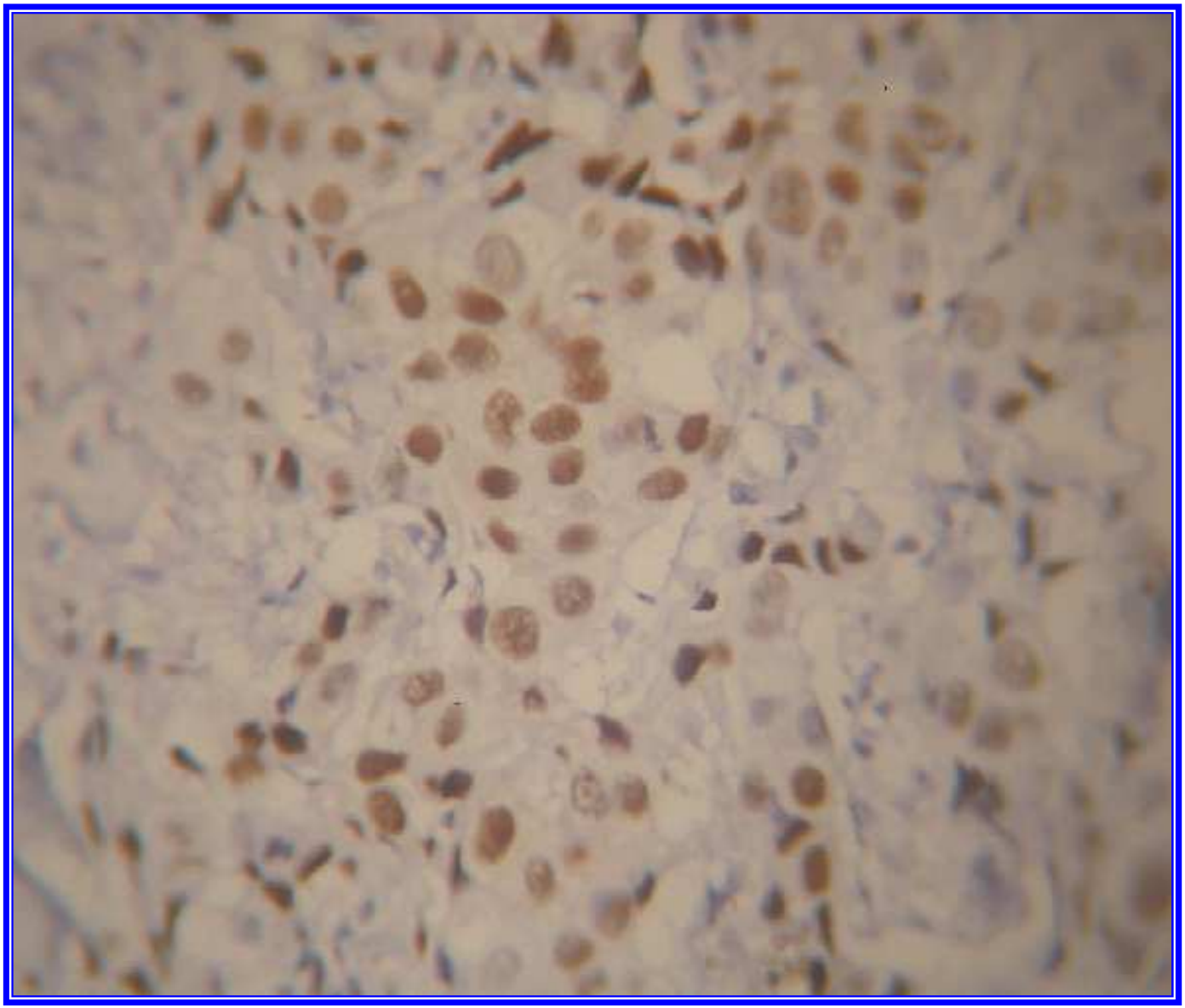
The immunohistochemical method of determining a positive HER-2 test result (oncoprotein over expression) has evolved since the early 1990s as a variety of different antibodies have been studied.

HER-2 neu positivity is identified by strong, diffuse membrane (‘chicken-wire’) stainining.Positive results are interpreted as 3+ score characterized by strong, diffuse, complete staining of more than 10% of tumour cells. All other results - less than 30% of cells staining and often incomplete membrane staining - are interpreted as negative

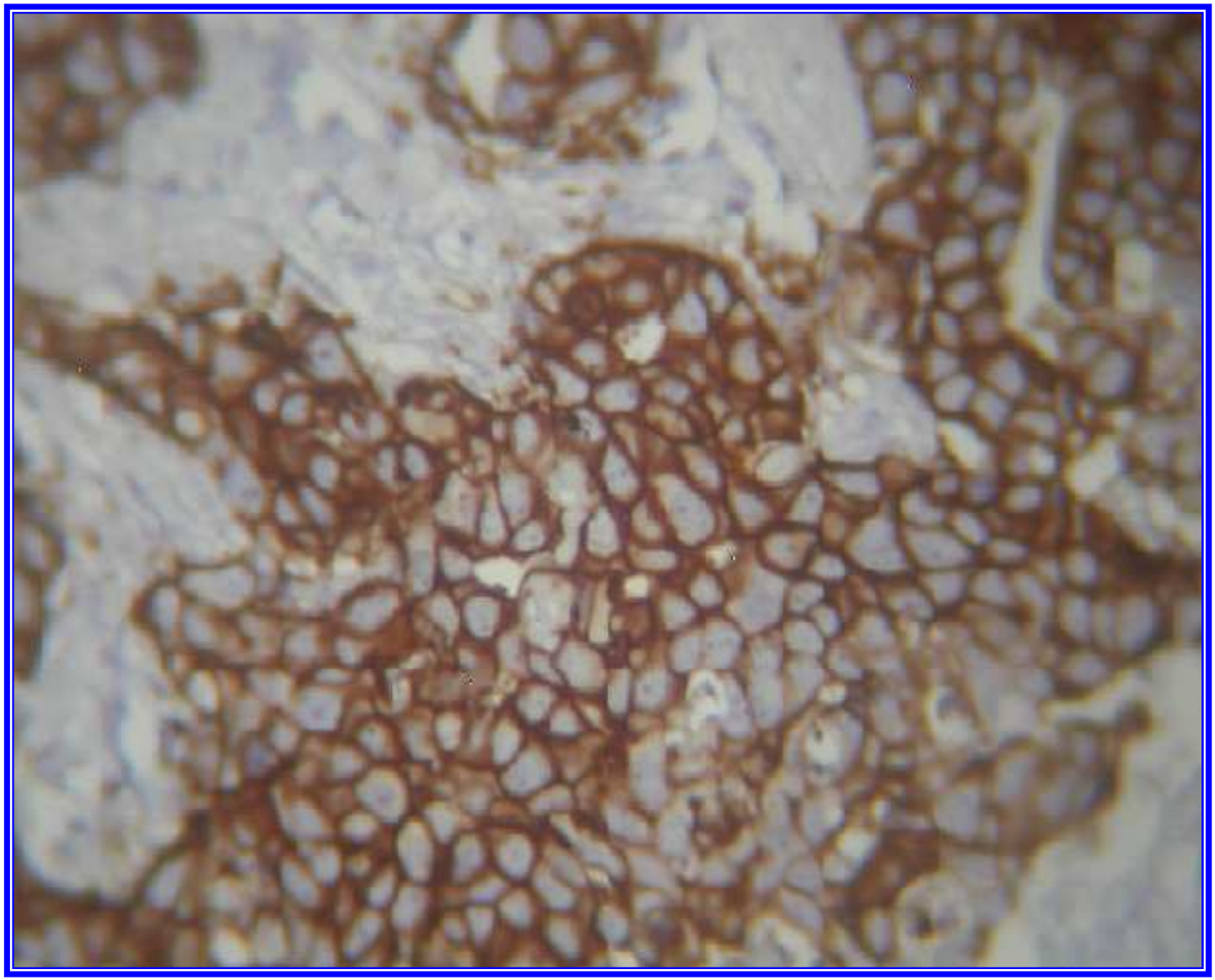
More recently, fluorescence in situ hybridization (FISH) has been advocated as a new gold standard for HER-2 analysis because it has the distinct advantage of detection of gene amplification. There is a better than 90% concordance between the FISH and IHC methods.



ER +ve. IDC



PR +ve, IDC



HER -2 neu +ve.

Diagnosis

- **Open Biopsy and Frozen Section**
- **FNAC**
- **Trucut bx.**

Open Biopsy and Frozen Section:

Open biopsies from breast lesions are usually of excisional type when the tumor measures 2.5 cm or less and of incisional type for larger neoplasms. Performance of an open biopsy followed by frozen section and mastectomy if the diagnosis is carcinoma has been the standard approach for breast nodules for decades.

Much has changed in recent years :

1.the wish to discuss with the patient the therapeutic options

2. a delay of days or weeks between biopsy and mastectomy does not affect prognosis;

3.the increasing alternative use of needle core biopsy and fine needle aspiration biopsy; and

4. the fact that an increasingly large number of cases involve small non-palpable lesions. Indeed, the need for performing this time-honored procedure has been increasingly questioned, one of the most powerful reasons

5.being that the final interpretation of the lesion may become difficult or even impossible if the entire specimen has been frozen.

The following recommendations have been made depending on the settings

- **A palpable mass, over 1 cm size, provides ample tissue for frozen section, permanent section, and hormone receptors. Therefore, not much harm results from doing the frozen section even if the medical indication is questionable.**
- **A non-palpable mass identified on a mammogram is often less than 1.0 cm in diameter. This *should not* be submitted for frozen section. If it turns out to be an invasive carcinoma, hormone receptor determinations can be done immunohistochemically on the paraffin-embedded material.**
- **A biopsy carried out only for calcifications without a mass *should not* be frozen. Instead it should be examined by specimen radiography.**
- **It should be added here that intraoperative cytologic examination can be very useful .**
- **Finally, frozen sections have been used effectively in evaluating re-excision lumpectomy margins.**

FNAC

A pre operative diagnosis ,that offers several advantages.

1) **The definitive treatment can be planned in advance with the informed consent of the patient.**
2) **If cancer is confirmed, staging investigations (bone scan , liver scan etc.) can be done preoperatively.**
3) **Many benign conditions can be confidently diagnosed by FNB combined with radiological imaging, and surgery avoided.**
4) **Immediate diagnosis relieves the patients anxiety and save time.**
5) **The need for frozen section diagnosis is reduced.**
6) **Hospital facilities can be more economically used if the extent of surgery is known beforehand.**

Core-Needle Breast Biopsy ,provides material for cytoarchitectural diagnosis along with both in-situ and invasive ca.

Core-needle biopsy uses a hollow-core needle, ranging in size from 11 to 16 gauge, to remove one or more pieces of breast tissue.

The operator either aims the needle directly to the area of a palpable lesion (freehand biopsy) or uses an imaging technique to localize the target lesion. The imaging techniques include stereotactic radiography, ultrasound, and magnetic resonance imaging (MRI). Techniques to extract the biopsy specimen include automated gun and vacuum assistance.

There is no consensus on which of these techniques is preferable for attaining the highest accuracy and lowest rate of harm for core-needle breast biopsies.

Sensitivity ranges from 86%(free hand)to 98% (guided)

Type of ca. again varies, depends on palpable or nonpalpable ca.

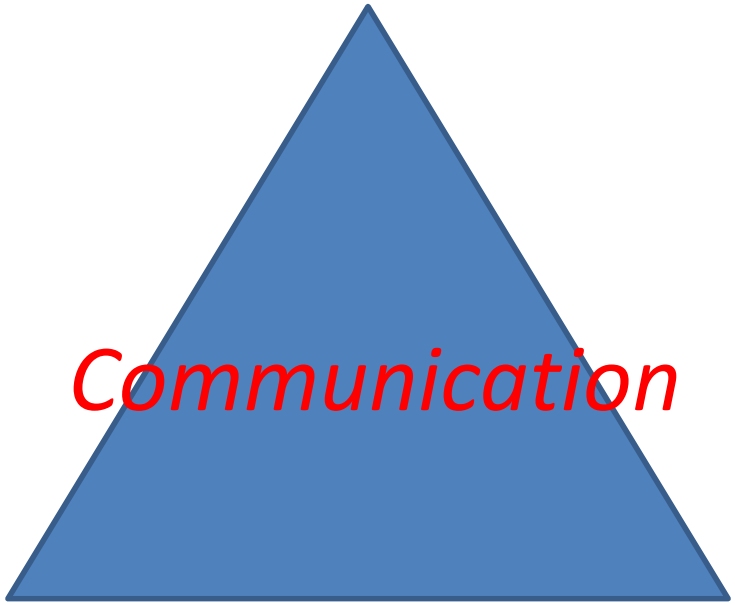
Misclassification of Biopsy Results

About 13-36 percent of core-needle breast biopsy specimens diagnosed as DCIS will be found to have invasive breast cancer on subsequent surgical biopsy.

About 22-44 percent of core-needle breast biopsy specimens diagnosed as ADH will be found to have in situ or invasive breast cancer on subsequent surgical biopsy.

Histopathology Report

Management of Cancer Patient



Surgeon

Specimen

Histopathologist

Surgical Pathology

Specimen

Fixation, Grossing,Processing

Tissue Section,Stained by H&E Stain

Now HP-Slide is ready

Fixation

- 10% neutral buffered formalin (NBF)
- pH maintained at 7.2-7.4
- Fixative with volume at least twice that of the specimen size
- Fixation not less than 6 hour and not more than 72 hour
- Underfixation--- false negativeER
- Overfixaion--- false positive Her2 neu

Rationale

To provide accurate information for tumor staging , relevant margins and assessment of treatment response (in neoadjuvant chemotherapy cases), breast grossing has never been more dependent on clinicopathologic correlation [1-4]

Annals of Diagnostic Pathology 15 (2011) 291–301

CONTENTS OF GROSSING

- Types of surgery
- Specimen orientation by surgeon
- Appropriate transport of specimen
- Receiving of specimen in histopathology lab in ideal fixative
- Re-Orientation and inking by pathologist
- Overnight fixation
- Sectioning of specimen
- Processing
- H&E staining & IHC staining
- Observe under microscope
- Final Reporting

Types of specimen

- Lumpectomy
- Mastectomy – modified radical /simple/radical
- Mammolocalisation
- Microdochectomy

Message points

For lumpectomy most important –

- Negative Margins ensure complete excision(avoid re excision)
- Take sections from adjacent breast with tumor to asses Extensive Intraduct component. EIC + and Margin + patients need re-excision
- Tumor size and nodal status determine need for adjuvant therapy

For Mastectomy

- Tumor size, nodal status, important
- Skin or nipple areola involvement documents advanced stage
- Base is the only relevant margin

For mammographic localization –

- Size of lesion and margins are important
- Mammoguided grossing is important

Final histopathology report

- Grossing – tumour size & nodes
- Tumour type
- Tumour grade
- EIC
- Margins
- Lympho vascular emboli
- Nodes- total no., number of positive nodes, size of largest positive nodes, perinodal extension.
- ER/PR
- cerb2


THANKS