

CARCINOMA BREAST

Most common and deadly malignancy of women globally.

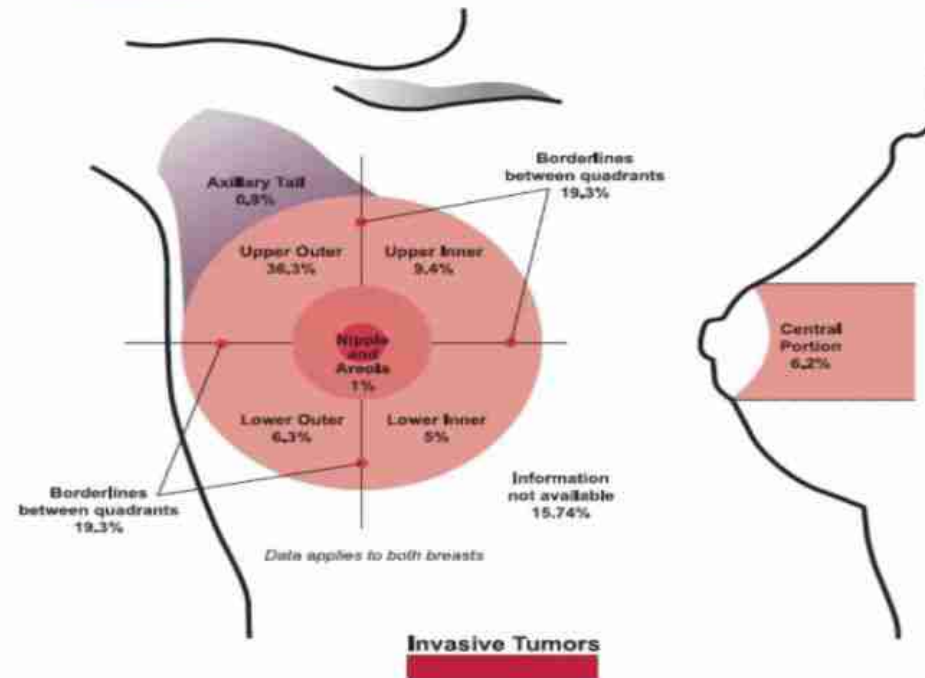
Incidence increases rapidly after 30yrs.

90 % of breast carcinomas arise from –ductal epithelium

10%-arise from lobules.

- Affects **left breast** slightly more than right.
- Bilateral and sequential seen in 4%.
- **Locations of the tumour.**
- **Upper outer quadrant 50%**

Figure 10



RISK FACTORS

- Gender- 99% are female.
- Age
- Lifetime exposure to estrogen
- Germline mutations
- Strong family history
- Personal history of breast cancer
- High breast density
- Environmental and lifestyle factors
 - organochlorine pesticides and certain plastics have estrogenic effects on humans

- Early menarche(age<12yrs)
- Late menopause(>55 yrs)
- Late first pregnancy(>35yrs)
- Nulliparity
- Absence of breastfeeding
- Physical inactivity
- High alcohol consumption

FAMILIAL BREAST CANCER (Germline mutations)

5-10 % associated with specific **inherited mutations(HEREDITARY TYPE)**.

Mutations in *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *STK11*, *PALB2*- high risk and *CHEK2*, *ATM*- moderate risk .

BRCA1 and *BRCA2*= 80-90% of familial breast cancers and 3-6% of all breast cancers.

BRCA1 gene located on chromosome 17q21.

- Mutations in BRCA 2 gene –located in chromosome 13q12.3

Women who carry cancer susceptibility gene develop breast CA at an early age.

Bilateral, & associated with other cancers.

Endogenous estrogen excess

- **Hormonal imbalance** plays a significant role.
- **Long duration of reproductive life-** nulliparity, late age at first child, early menarche, late menopause
- **Functioning tumours of ovary**

Classified into

- those that are confined within ducts and lobules by a basement membrane(**Non invasive**)
- those that have invaded the basement membrane.(**Invasive**)

- Almost all breast malignancies are adenocarcinomas.
- All breast carcinomas arise from cells in the terminal duct lobular unit.

WHO CLASSIFICATION(morphological subtypes)

NON INVASIVE

- 1.Ductal carcinoma in situ (DCIS)
- 2.Lobular carcinoma in situ(LCIS)

INVASIVE (Infiltrating)

- 1.Invasive carcinoma of no special type(typical ductal carcinomas)
- 2.Specific histologic types

a) Lobular carcinoma

b) Carcinomas with medullary pattern

- c) Tubular carcinoma
- d) Papillary carcinoma
- e) Mucinous carcinoma
- f) Apocrine carcinoma
- g) Metaplastic carcinoma
- h) Secretory carcinoma
- i) Inflammatory carcinoma

MOLECULAR CLASSIFICATION(treatment purpose)

- Based on gene expression profiling, invasive breast carcinomas cluster into 3 groups(ER,PR,HER2):

1. Luminal A&B (ER- positive/HER2-negative)

- 50-60% of cases. They usually express PR also.

2. HER2- enriched (HER2 -positive)

- 20% of cancers. Either ER +ve or ER-ve.

3. Basal-like (ER-negative/HER2-negative)

-also PR-ve. 15% of cancers.

Triple negative breast cancers.

INVASIVE CARCINOMA OF NO SPECIAL TYPE

- Majority of invasive breast cancers are **ductal adenocarcinomas**
- Presents as a mass of at least 2-3cm in size-hard, irregular mass with a desmoplastic stromal reaction.

CLINICAL.

Hard palpable mass

Peau d orange-dimpling or retraction of skin due to lymphatic permeation.

Nipple retraction- when tumor involves central portion of skin.

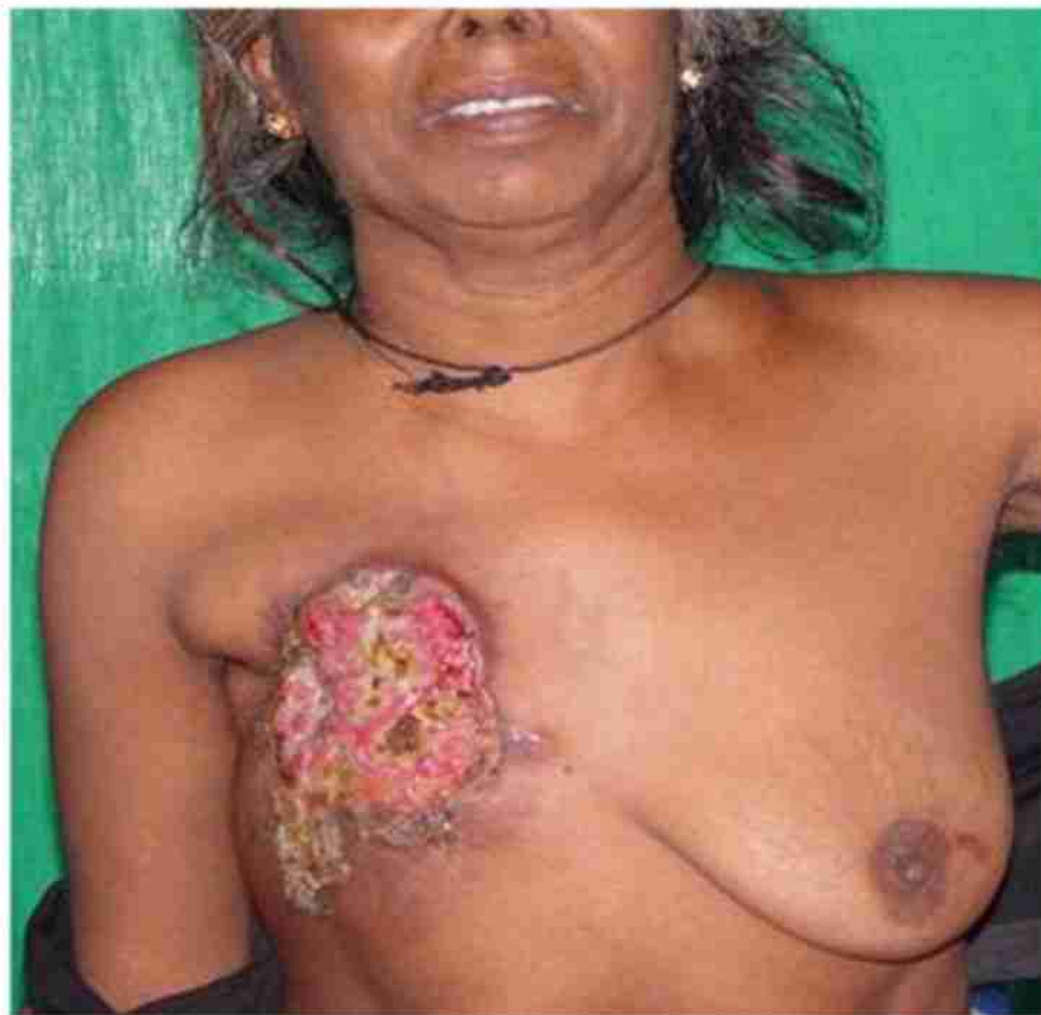
Axillary lymph node metastasis

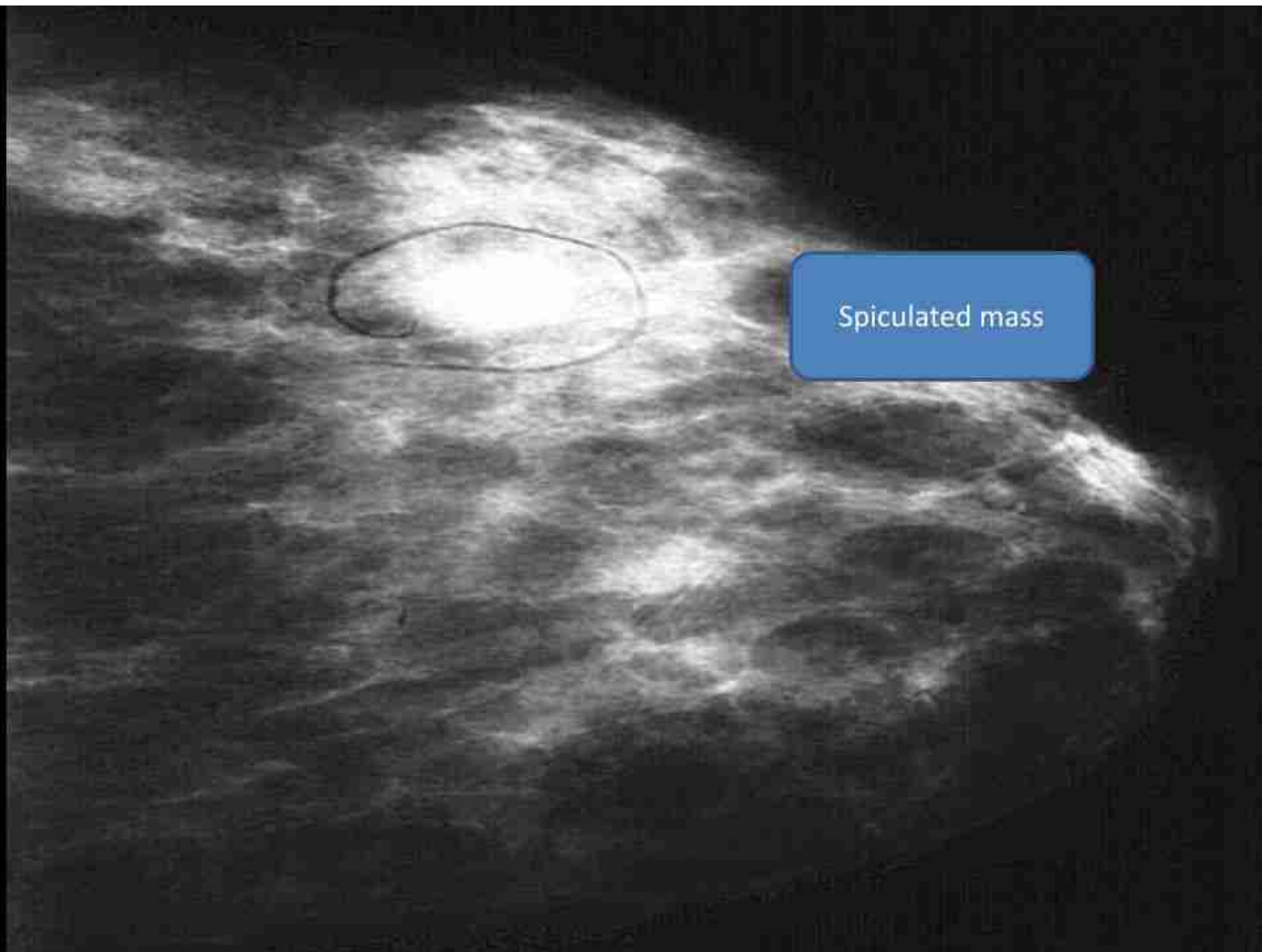
Large carcinomas may invade pectoralis muscle and become **fixed to chest wall**.

DIAGNOSIS

- Imaging- mammography and ultrasound
- Histological sampling- core biopsy or Fine needle aspiration cytology







Spiculated mass



MICROSCOPY

- Malignant cells arranged in different patterns.
- In **groups, cords, sheets and gland** like patterns.
- Amount of stroma-vary.

Scirrhou – abundant fibrous tissue(seen in ductal Ca).

When cutting-grating sound due to small central chalky white desmoplastic stroma and occasional foci of calcification.

- Invasive carcinoma is graded using Nottingham Histologic Score(Bloom Richardson)

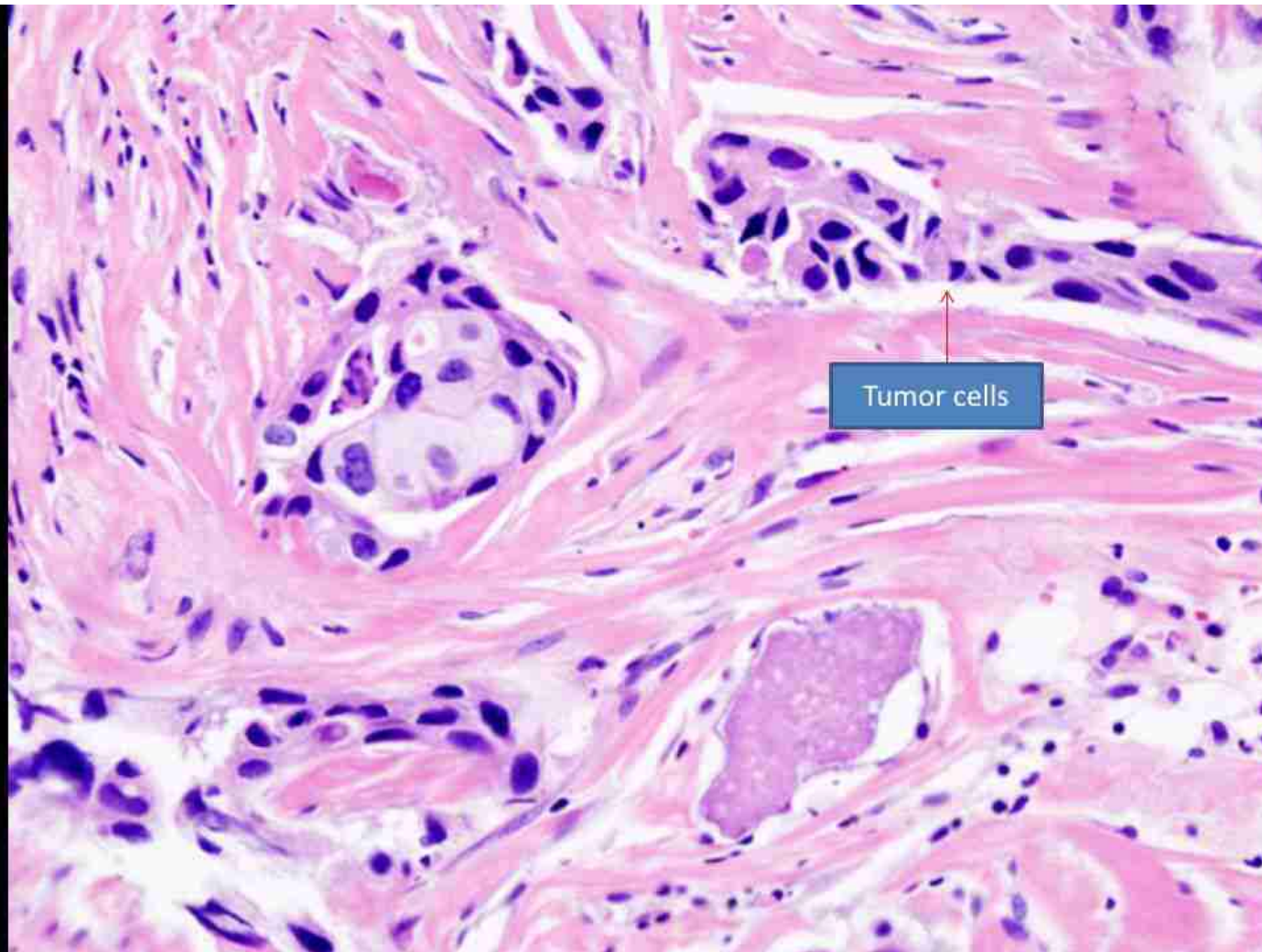
- Tubule formation
- Nuclear pleomorphism
- Mitotic rate

Grade 1- well differentiated,

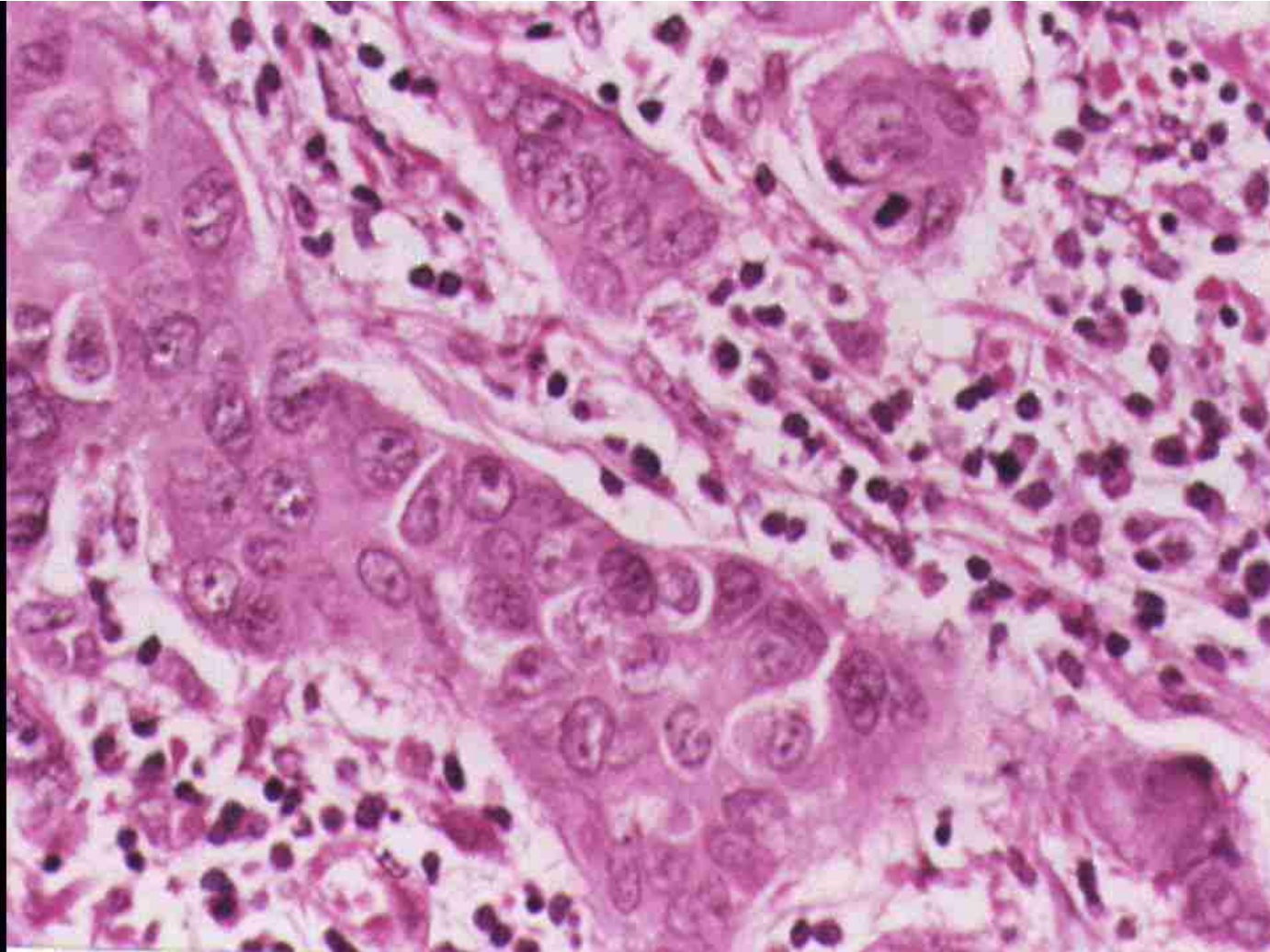
Grade 2- moderately differentiated,

Grade 3- poorly differentiated.

- High- grade tumors- high proliferative rate, tumor necrosis.



Tumor cells

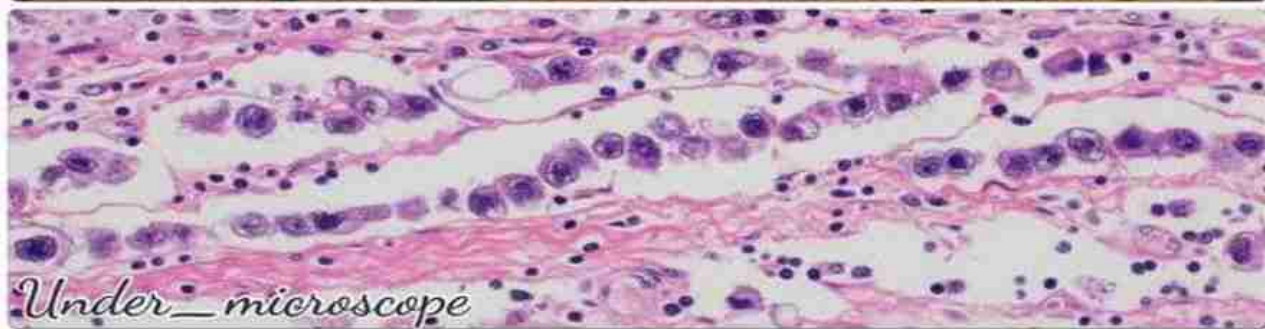
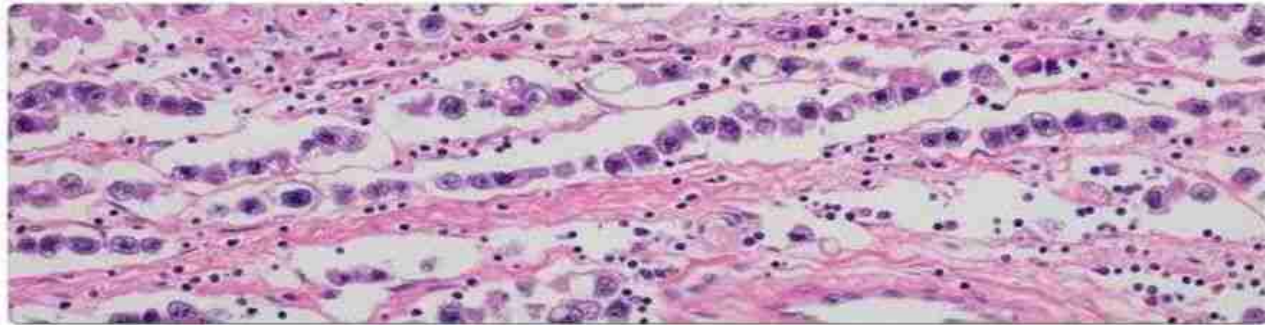


SPECIFIC HISTOLOGIC TYPES

LOBULAR CARCINOMA

- 10 % of invasive carcinoma.
- Biallelic loss of expression of *CDH1*, gene that encodes E-cadherin.
- They are dyscohesive, infiltrate as single cells.
- Sometimes fail to produce desmoplastic response-
difficult to detect by palpation and imaging.
- Distinctive patterns of metastatic spread-
peritoneum, retroperitoneum, leptomeninges, GI tract, ovaries and uterus.

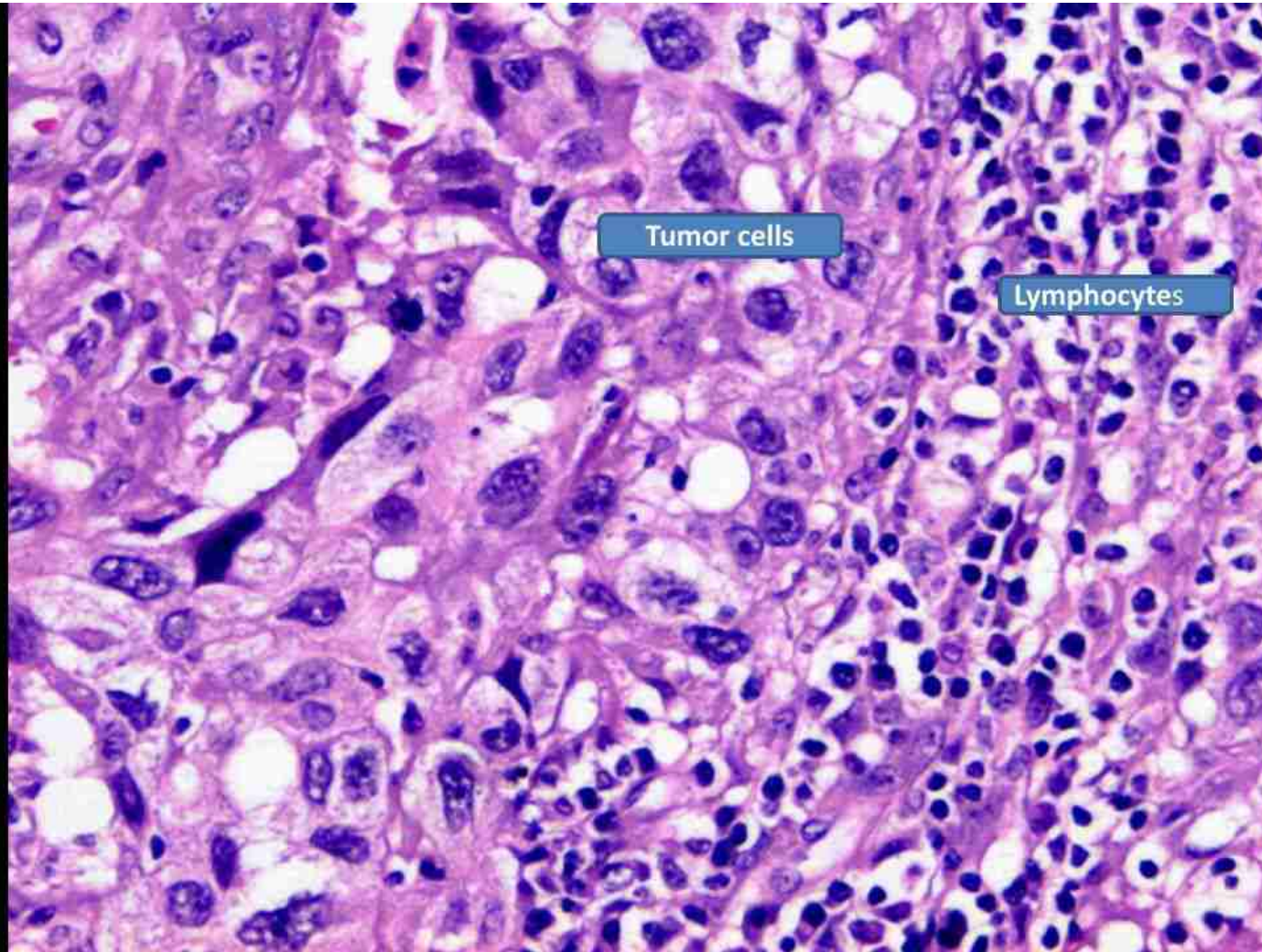
- **Bilateral and multifocal**
- **Micro**
 - Dyscohesive small uniform cells, singly or in columns, one cell wide (INDIAN FILE PATTERN).
 - Minimal desmoplasia



CARCINOMA WITH MEDULLARY PATTERN

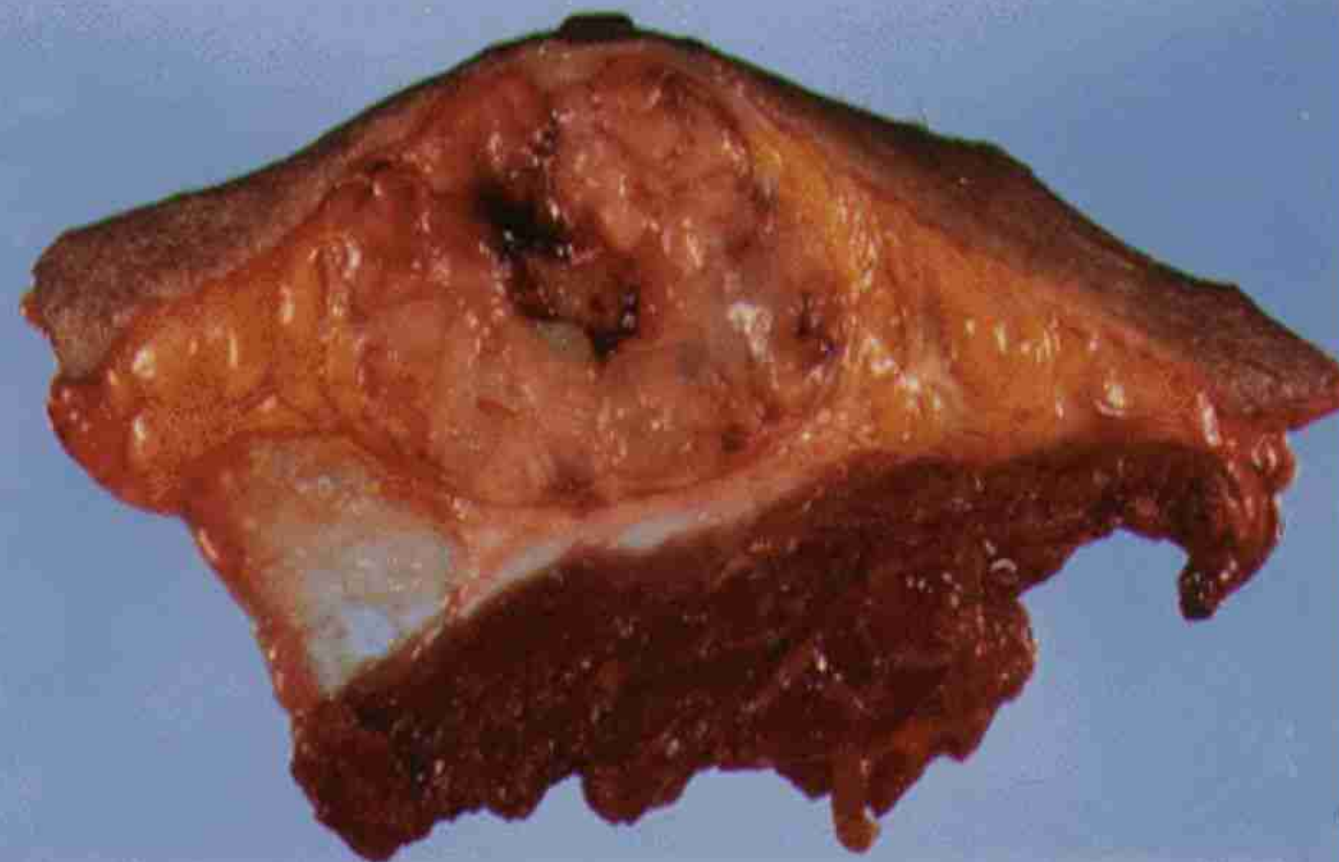
- Very rare
- Softer than other carcinoma due to minimal desmoplasia and often form **well circumscribed mass** with pushing non infiltrative border.
- Large fleshy tumour mass with necrosis and haemorrhage (brain like)
- Solid sheets of large cells with vesicular pleomorphic nuclei , prominent nucleoli and frequent mitosis . Stroma shows moderate to marked lymphoplasmacytic infiltration
- Better prognosis



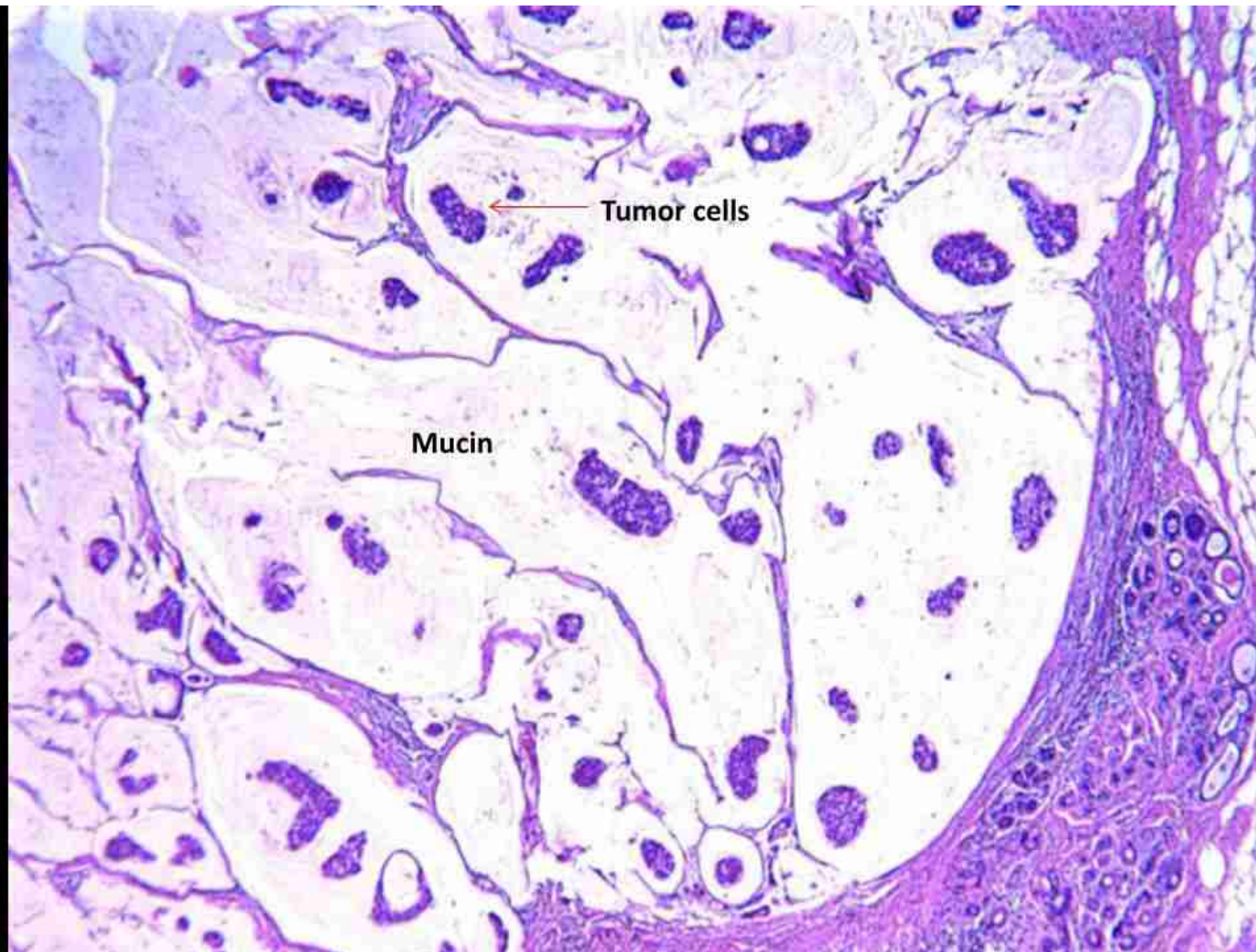


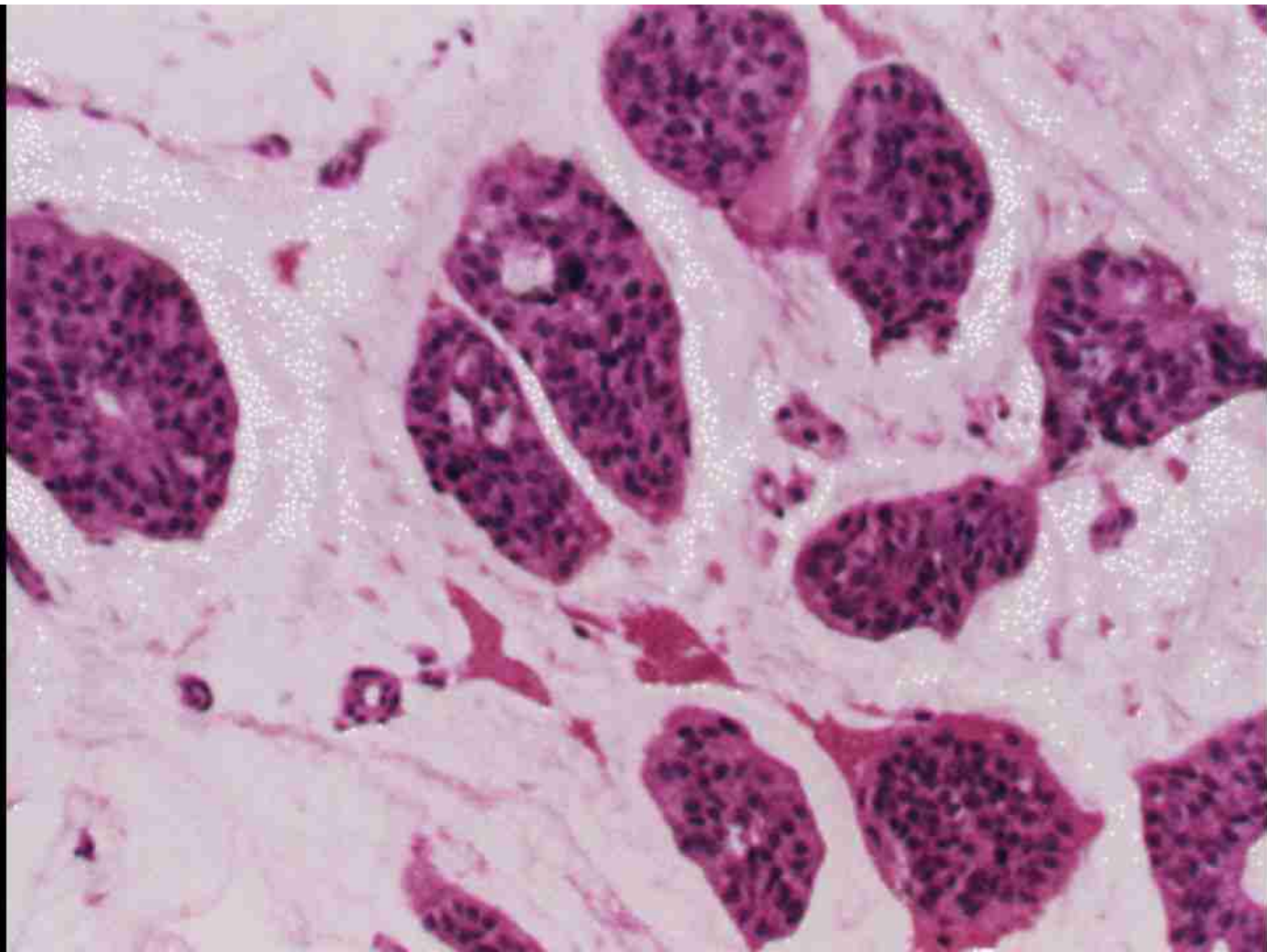
MUCINOUS CARCINOMA (COLLOID CARCINOMA)

- Unusual tumour, occur in older women.
- Extremely soft and gelatinous.
- Borders are pushing or circumscribed
- Small islands and clusters of malignant cells in lakes of mucin.
- good prognosis.



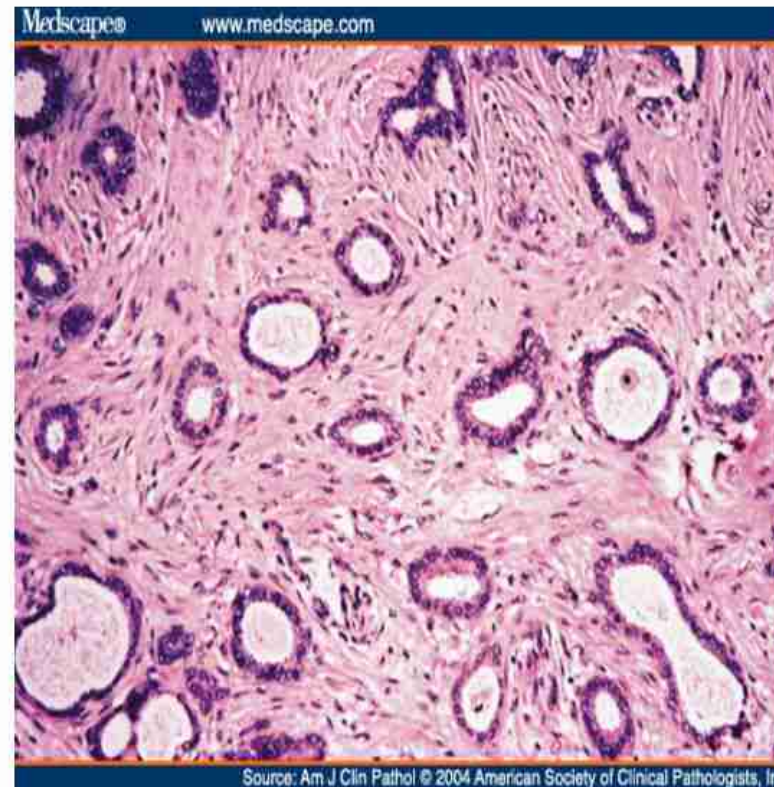
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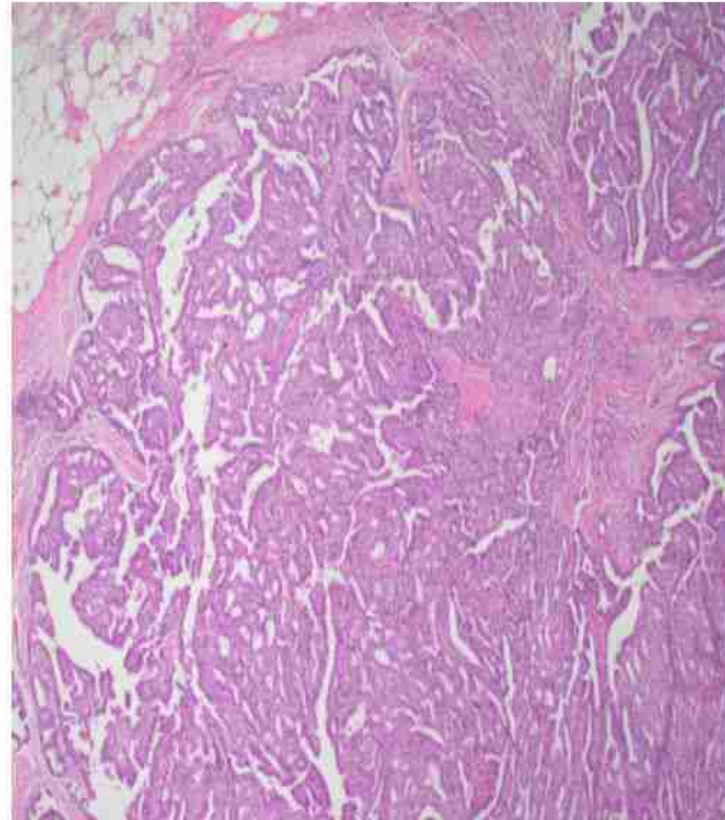
TUBULAR CARCINOMA

- Rare 1-2% .
- Usually small lesions less than 10 mm.
- Exclusively of well formed tubules.
- Better prognosis.



PAPILLARY CARCINOMA

- Rare
- True papillae with fronds of fibrovascular tissue lined by tumor cells.
- Better prognosis



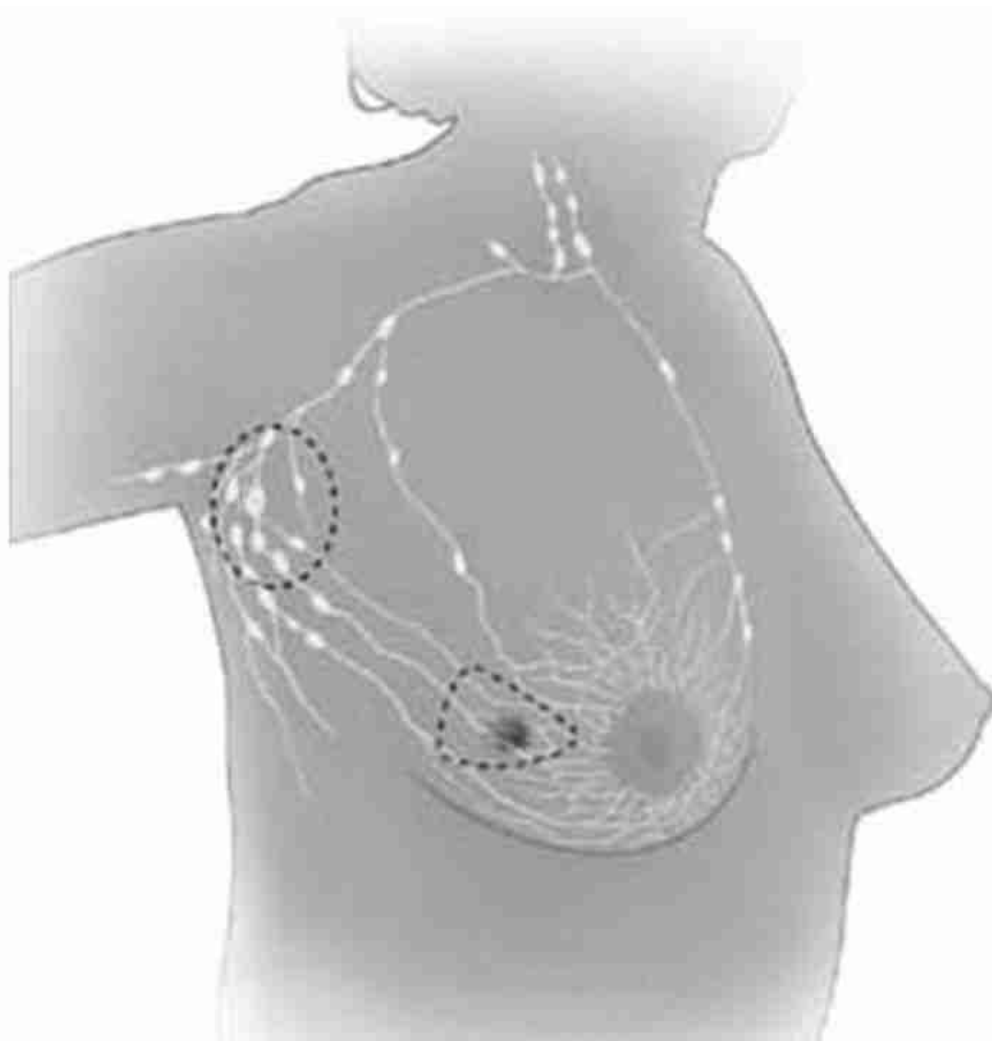
Other very rare types of carcinomas

- **Apocrine carcinoma**- resemble cells that line sweat glands.
- **Secretory carcinoma**- mimics lactating breast.
- **Inflammatory ca**- Clinical entity and not histological type. Extensive invasion of dermal lymphatics with carcinoma cells.
 - Poor prognosis= high grade.
 - breast erythema, swelling, skin thickening

- The edematous skin is tethered to the breast by Cooper ligaments and mimics the surface of an orange peel- **peau d' orange**.
- 'Inflammatory' is a misnomer= no inflammation is present.
- Underlying carcinoma is diffusely infiltrative and does not form a palpable mass.
- **Metaplastic carcinoma**
 - Matrix producing carcinoma
 - Squamous, cartilaginous, osseous metaplasia.

SPREAD of BREAST CARCINOMA.

- 1.**DIRECT**—Skin and Muscle.
- 2.**LYMPHATICS**-Axillary and other local LNs
- 3.**HAEMATogenous**-Lungs, Bone, Liver, Brain, Adrenals, Pleura.



ASSIGNMENT

- Write down the classification of carcinoma breast.
- Discuss the molecular classification of invasive breast carcinoma.
- Discuss the gross and microscopy of invasive ductal carcinoma.

PROGNOSTIC AND PREDICTIVE FACTORS FOR INVASIVE CARCINOMA

- Outcome for women with breast cancer depends on :
 - biologic features of carcinoma(molecular or histologic type)
 - stage of disease at time of diagnosis
- Distant metastases or inflammatory carcinoma- poor prognosis.

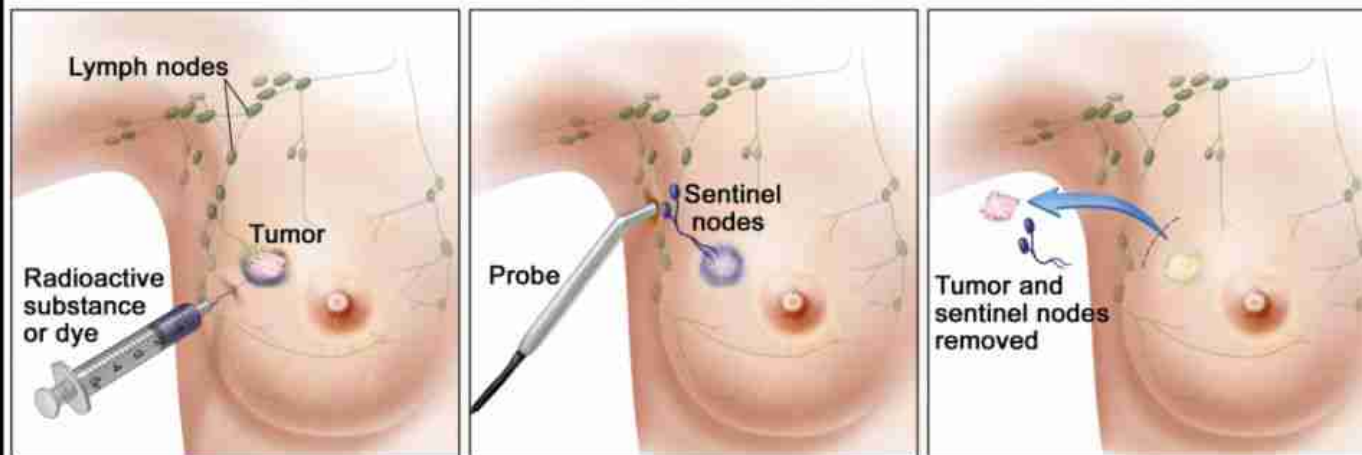
- **Prognostic factors** are important
 - counseling patients about likely outcome of disease.
 - choosing appropriate treatment
 - designing clinical trials
- **Predictive factors**- determine the likely response of a cancer to a specific type of treatment.

- Factors related to tumor biology are both prognostic and predictive- ER and HER2 expression, proliferation index)
- Factors related to tumor extent are prognostic
 - tumor size, LN metastases, distant metastases

- Major prognostic factors are:-

1) Lymph node metastases

- Axillary lymph node status- most important prognostic factor for invasive carcinoma in the absence of distant metastases.
- Lymphatic vessels in breast carcinoma first drain to one or two **sentinel nodes**- identified by radiotracer or colored dyes. **If biopsy of sentinel node is negative for metastases, it is unlikely that other nodes will be involved.**
- **Sentinel node**- the first node in a regional lymphatic basin that receives lymph flow from primary tumor



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2) **Distant metastases**

3) **Tumor size**- risk of axillary LN increases with size of primary tumor(> 2cm= survival drops to 77%).

4) **Locally advanced disease** – Carcinoma invading skin or skeletal muscle.

5) **Lymphovascular invasion** – Tumor cells present within vascular spaces(lymphatics or small capillaries). Strongly associated with lymph node metastases.

Poor prognostic factor.

6) **Inflammatory carcinoma**- extensive invasion of dermal lymphovascular channels. Poor outcome.

7) **Special histologic types**

- Favourable outcome= Tubular, Adenoid cystic, Mucinous, Medullary

8) **Gene expresion profiling**

- Clinical value of these assays- to identify patients with slowly growing, antiestrogen - responsive cancers who can be spared toxicity of chemotherapy.

9) **Response to neoadjuvant chemotherapy-**

Treating patients prior to surgery provides opportunity to observe tumor response to chemotherapy(One third Triple negative and HER2 positive regress completely- **pathologic complete response**).

Those with responsive cancers- better prognosis than nonresponsive cancers.

10) **Histologic grade-** Survival diminishes with higher histologic grade

11) **Expression of ER, PR, HER2-**

Survival highest for high ER and PR with absent HER2.

Lowest for absent ER,PR and HER2.

STAGING

- American Joint Committee on Cancer(AJCC) staging system.
- Includes anatomic staging system and prognostic staging system.
- **Anatomic stage(0 to IV) =**
 - Nature of the disease in breast (T, for tumor)
 - Regional lymph node(N, for nodes)
 - Distant metastases (M, for metastases)
- **Prognostic stage** = biologic features which portend a more or less favourable outcome.

Table 23.6 American Joint Committee on Cancer 8th Edition: Anatomic Stage^a

Stage ^b	T: Primary Cancer (Tumor)	N: Lymph Nodes	M: Distant Metastasis	10-Year Survival (%)
0	Ductal carcinoma in situ	No metastases	Absent	97
I	Invasive carcinoma ≤2 cm	No metastases or only micrometastases	Absent	87
II	Invasive carcinoma >2 cm	1–3 positive LNs	Absent	65
	Invasive carcinoma >5 cm but ≤5 cm	0–3 positive LNs	Absent	
III	Invasive carcinoma >5 cm	Negative or positive LNs	Absent	40
	Any size invasive carcinoma	≥4 positive LNs	Absent	
	Invasive carcinoma with skin or chest wall involvement or inflammatory carcinoma	Negative or positive LNs	Absent	
IV	Any size invasive carcinoma	Negative or positive LNs	Present	5

^aIn the 8th edition, prognostic stages are assigned using T, N, M, grade, ER, PR, and HER2. Pathologic prognostic stage is assigned for patients who undergo surgical excision.

- Pathologic prognostic stage is important for patients who undergo surgical excision prior to other treatment.
- Clinical prognostic stage = patients prior to surgery, patients not eligible for surgery, patients undergoing systemic therapy prior to surgery.

OTHER RARE TUMOURS OF BREAST

STROMAL TUMOURS- Stromal sarcomas

VASCULAR TUMOURS- Angiosarcoma.

LYMPHOID TUMOURS- Malignant lymphoma

PAGET DISEASE OF NIPPLE

- Rare manifestation of breast cancer- 1-4% of cases.
- Unilateral erythematous eruption with a scale crust.
- Pruritis is common. Lesion mistaken for eczema.
- Malignant cells(Paget cells) extend from DCIS within ductal system into nipple skin.
- Paget cells detected by nipple biopsy.
- Palpable mass in 50-60% of women with Paget disease. Women without mass have DCIS.
- Prognosis is based on the underlying carcinoma and not by the presence of Paget disease.



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BREAST DISEASES IN MALES.

GYNECOMASTIA- enlargement of male breast.

Benign lesion. Button-like subareolar enlargement.

Unilateral or bilateral.

Imbalance between estrogens and androgens.

Cirrhosis liver, older males, alcohol, heroin, drugs, testicular neoplasms, Klinefelter syndrome.

CARCINOMA BREAST.

Incidence is 1%.

BRCA2 gene- familial factor

More than 90% are of luminal type.

ASSIGNMENT

- Ennumerate the prognostic factors of carcinoma breast.
- Discuss staging of carcinoma breast.
- Discuss diseases of the male breast.
- What is Paget disease?