CARCINOMA OF BREAST

DR. SAURAV

Normal Breast
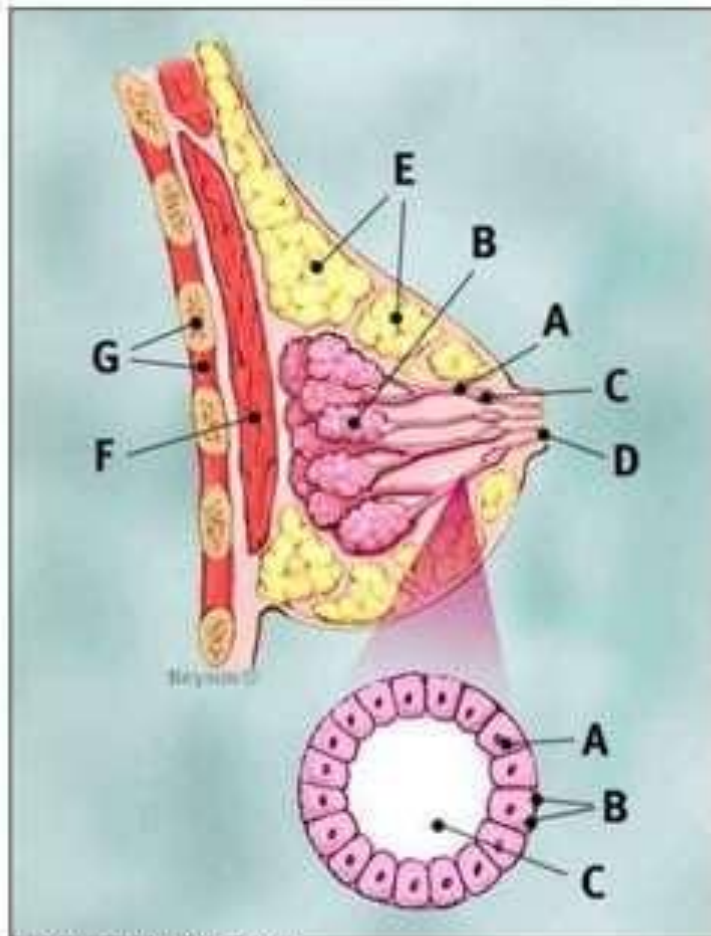

Illustration © Mary K. Bryson
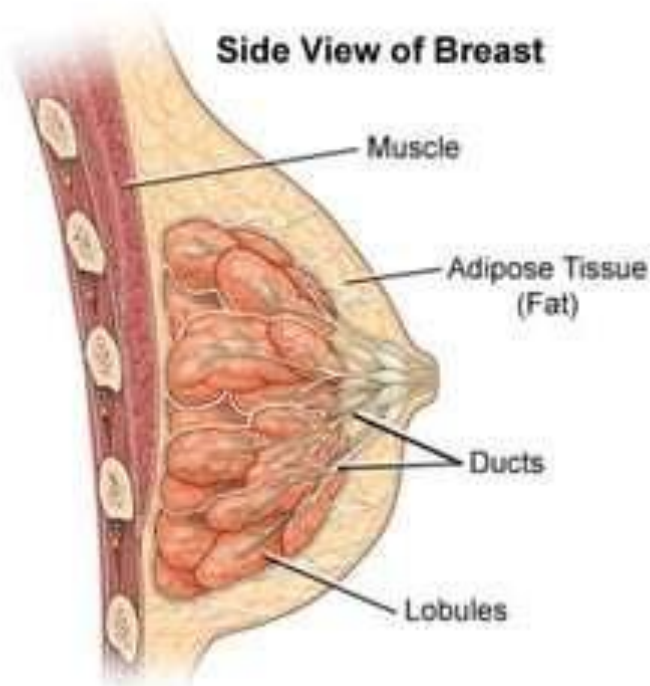
Breast profile	
A	ducts
B	lobules
C	dilated section of duct to hold milk
D	nipple
E	fat
F	pectoralis major muscle
G	chest wall/rib cage

Enlargement	
A	normal duct cells
B	basement membrane (duct wall)
C	lumen (center of duct)

Female Breast Anatomy

Side View of Breast

Muscle

Adipose Tissue (Fat)

Ducts

Lobules

- Breasts consist mainly of fatty tissue interspersed with connective tissue

- There are also less conspicuous parts
  - lobes
  - ducts
  - lymph nodes

Breast Gland

Breast Anatomy
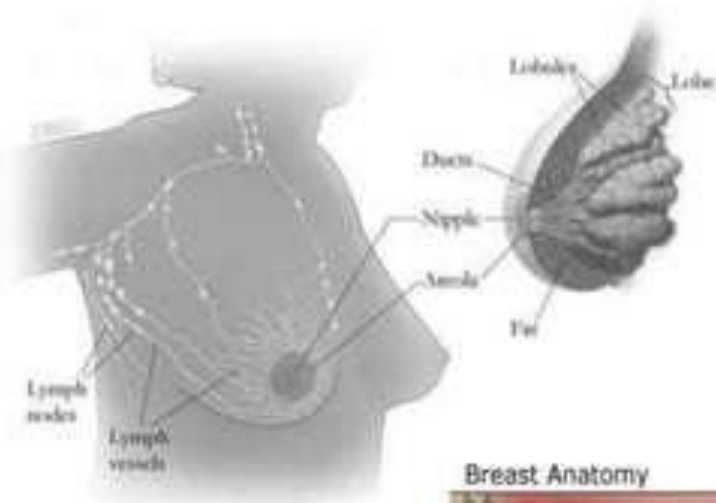
- Each breast has 15 to 20 sections (lobes)

- Inside each lobe are many smaller structures called lobules

- At the end of each lobule are tiny sacs (bulbs) that can produce milk

Breast Cancer

- The most common form of cancer among women
- The second most common cause of cancer related mortality
- 1 of 8 women (12.2%)
- One third of women with breast cancer die from breast cancer

Epidemiology

➢ Incidence rates are highest in North America, Australia and Western Europe; intermediate in South America, the Caribbean and Eastern Europe and lowest in China, Japan and India.

➢ Over the years there has been decline in breast cancer mortality rates due to early detection by screening and more effective treatment modalities.

Risk factors

◆ Age

➢ Incidence of breast cancer increases with age. More than 80 % of breast cancer cases occur in women over 50 .

➢ Uncommon before age 25 years; incidence increases to the time of menopause and then slows

◆ **Family**

➢ Approx 10% of breast cancer is due to inherited genetic predisposition

➢ A woman whose mother or sister has had breast cancer is at ↑relative risk 2 to 3 times compared to other women

◆ Family

➢ At least two genes that predispose to breast cancer have been identified— *BRCA 1* and *BRCA 2*

➢ Mutations in these tumour-suppressor genes also predispose affected women to ovarian cancer

◆ Benign Breast Disease

➤ Certain types of benign breast disease like
- – Hyperplasia - 1.5 to 2 fold
- – Atypical hyperplasia- 4 to 5 fold

◆ History of Other Cancer

➤ A history of cancer in the other breast or a history of ovarian or endometrial cancer

◆ Hormonal Factors

➢ $\uparrow$ levels of estrogen $\uparrow$ risk:

➢ Early age at menarche

➢ Late age at menopause

➢ Nulliparity

➢ Late age at first child-birth

➢ Obesity

◆Environmental Factors

➢ High fat intake

➢ Excess alcohol consumption

➢ Ionizing radiation

Etiology

➢ The etiology of breast cancer in most women is unknown.

➢ Most likely due to a combination of risk factors i.e. genetic, hormonal and environmental factors .

Hereditary breast cancer

- Genes are as follows;

  -BRCA1 or BRCA2 are now believed to be responsible for 30% to 50% of **hereditary breast cancer**, ovarian cancer or both in families with a history of these cancers.

  - About 90% of BRCA1 carriers will develop breast cancer in whole lifetime.

  -These mutations can be passed down to the daughter by either mother or the father.

- Other defective genes that contribute to breast cancer include:

  BRCA3

  p53 (Li-Fraumeni syndrome)

  CHEK2 (Variant of Li-fraumeni)

  PTEN (Cowden syndrome)

  LKBI/STK11 (Peutz-Jeghers syndrome)

  ATM (ataxia telengiectasia)

Sporadic breast cancer

- Over-exposure to estrogen

  Because growth of breast tissue is highly sensitive to estrogens, the more a women is exposed to estrogen over her lifetime,the higher the risk for breast cancer.

- Hormone exposure increases the number of potential target cells by stimulating breast growth. It also drives cycles of proliferation that can cause DNA damage.

- Majority occur in post menopausal women and are ER positive.

Signs and Symptoms

Most common: lump or thickening in breast. Often painless

Lump in breast or underarm area

Change in size or shape of breast

Nipple changes

Discharge or bleeding from the nipple

Discharge or bleeding

Crusting

Redness or pitting of skin over the breast, like the skin of an orange

Inversion

Change in size or contours of breast

Change in color or appearance of areola

18

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Classification of carcinoma of breast

- 95% of breast malignancies are adenocarcinomas which are divided into in situ and invasive carcinomas.

- Carcinoma in situ- it is a neoplastic proliferation that is limited to ducts and lobules by the basement membrane.

- Invasive carcinoma- infiltrating cancer that has penetrated through the basement membrane into stroma.

Histological types

- In situ
  - Ductal carcinoma in situ (DCIS)
  - Lobular carcinoma in situ (LCIS)
- Invasive
  - Infiltrating ductal carcinoma
  - Tubular/ cribriform carcinoma
  - Medullary carcinoma
  - Mucinous/ colloid carcinoma
  - Papillary carcinoma
  - Metaplasic carcinoma

Relative risk of developing invasive cancer

❖ No Increased Risk (1%)

➢ Mastitis

➢ Fat necrosis

➢ Mammary duct ectasia

➢ Non-proliferative
   ("fibrocystic") disease

➢ Fibroadenoma without complex features

❖ Slightly ↑ Risk
= ↑ Risk 1.5-2 Times

➢ Moderate/florid hyperplasia
➢ Sclerosing adenosis
➢ Fibroadenoma (complex)
➢ Duct papilloma

❖ Moderately ↑Risk
  = ↑Risk 4-5 Times

➢ Atypical ductal hyperplasia
➢ Atypical lobular hyperplasia

Carcinoma in situ = 8-10%

    lobular carcinoma in situ

    ductal carcinoma in situ

Invasive ductal carcinomas, No special type(NST)

- Clinical presentation-

➢ Hard, irregular palpable lump

➢ *Peau d'orange* (lymphatic obstruction + thickening/dimpling of the skin)

➢ *Paget's disease of the nipple* (ulceration/inflammation due to intraductal spread to the nipple)

- Tethering of the skin

- Retraction of the nipple

- Axillary mass (spread to regional lymph nodes)

- Distant mets (lung, brain, bone)

morphology

- Gross examination

  Characterised by a irregular , hard to firm mass. Produces a grating sound while cutting.

  Small, central foci of chalky- white elastotic stroma and occasionally small foci of calcification can be seen.

- Histology

➢ well differentiated carcinomas show prominent tubule formation and small round nuclei.

➢ moderately differentiated carcinomas may have tubules but solid clusters or single infiltrating cells may also be seen.

➢ poorly differentiated cancers often invade as ragged nests or solid sheets of cells with enlarged irregular nuclei.
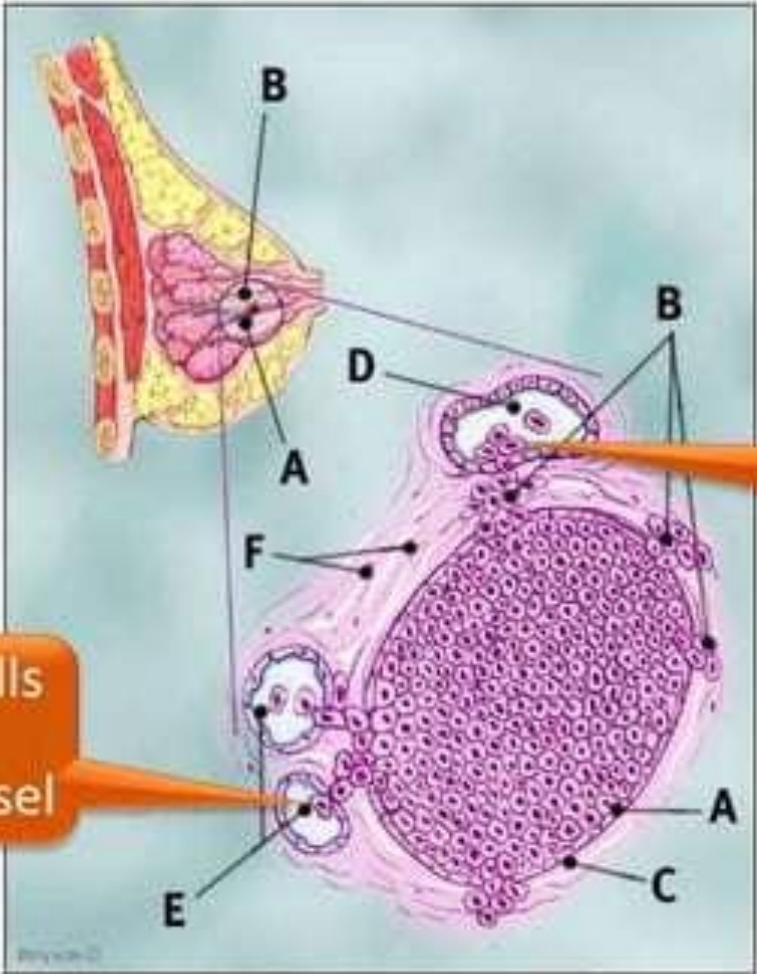
Invasive ductal carcinoma(IDC)
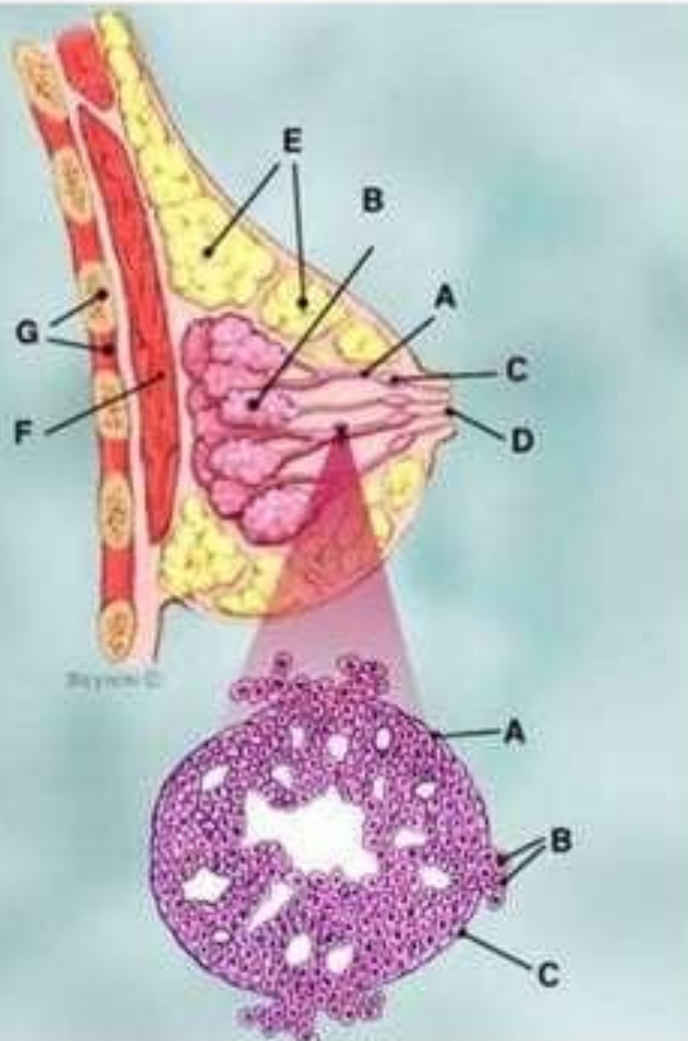
- A. Breast Duct System
- B. Lobules
- C. Breast Duct System
- D. Nipple
- E. Fat
- F. Chest Muscle
- G. Ribs

- A. Cells lining duct
- B. Cancer cells, breaking through the basement membrane
- C. Basement membrane
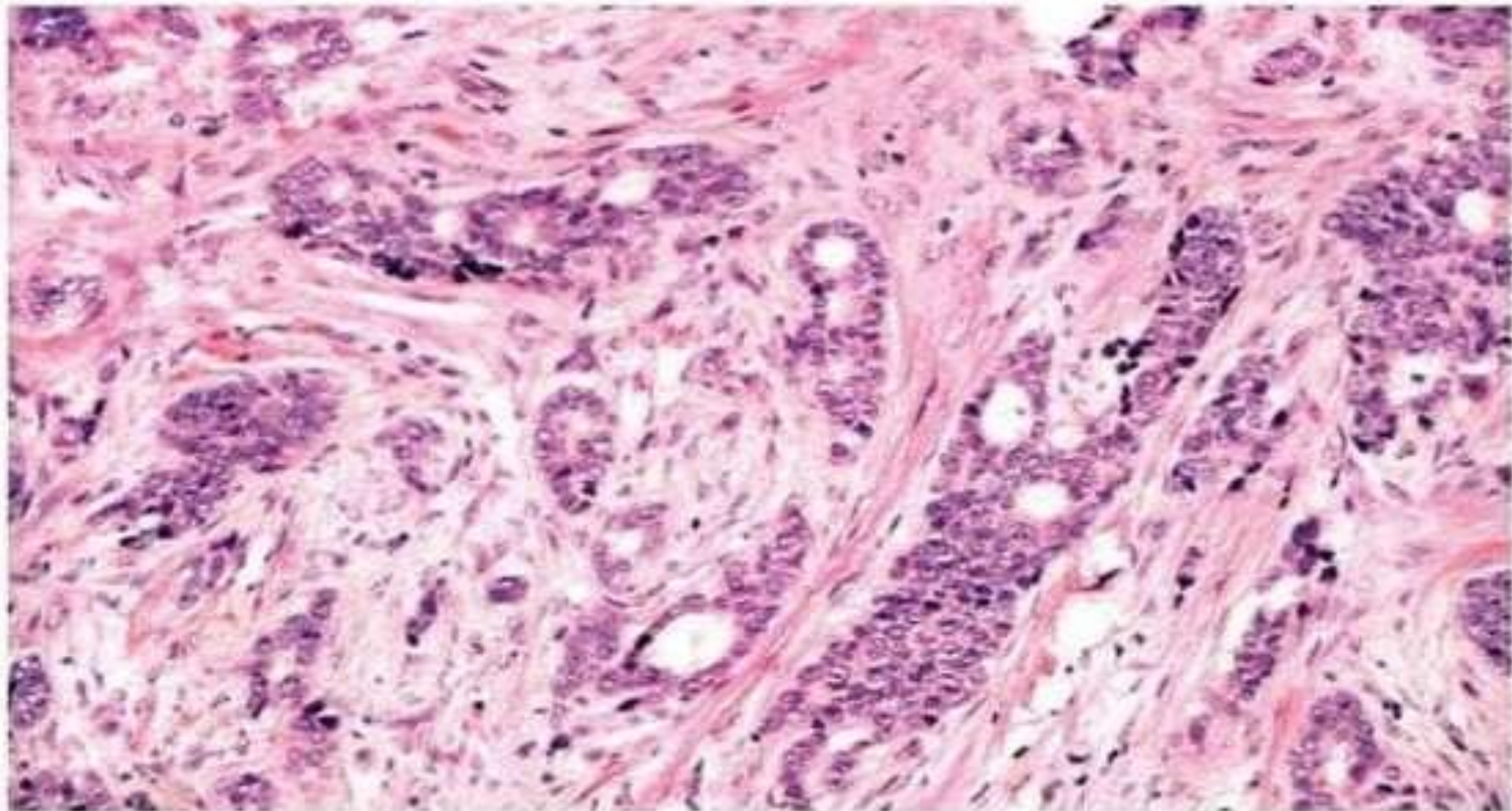
Cancer Can also Invade Lymph or Blood Vessels

Cancer cells invade lymph duct

Cancer cells invade blood vessel

Illustration © Mary K. Bryson

30

Gross specimen of ductal carcinoma.

Infiltrating ductal carcinoma NST

Patterns of gene expression in NST

1. Luminal A – 40 to 50% of NST cancers
   ER positive and HER2/neu negative.

2. Luminal B – 15 to 20% of NST
   ER positive , higher proliferation rate and HER2/neu expression. Referred as triple positive.

3. Normal breast like - 6 to 10% of NST
   well differentiated ER positive , HER2/neu negative cancers

4. Basal-like – 13 to 25% of NST cancers

ER, PR, HER2/neu Negative

expression of myoepithelial cell markers like basal keratins, P-cadherin or laminin

5. HER2/neu Positive- 7 to 12%

ER negative but overexpression of HER2/neu protein.

Invasive lobular carcinoma

➢ Much less common than IDC

➢ Can present with similar features like palpable mass or mammographic density with irregular borders.

➢ More likely to be *bilateral* and/or *multicentric* (multiple lesions within the same breast

morphology

- Hallmark is presence of dyscohesive inflitrating tumor cells.

- Arranged in single file or in loose clusters or sheets . Tubule formation is absent.

- Signet-ring cells containing intracytoplasmic mucin droplet are seen.
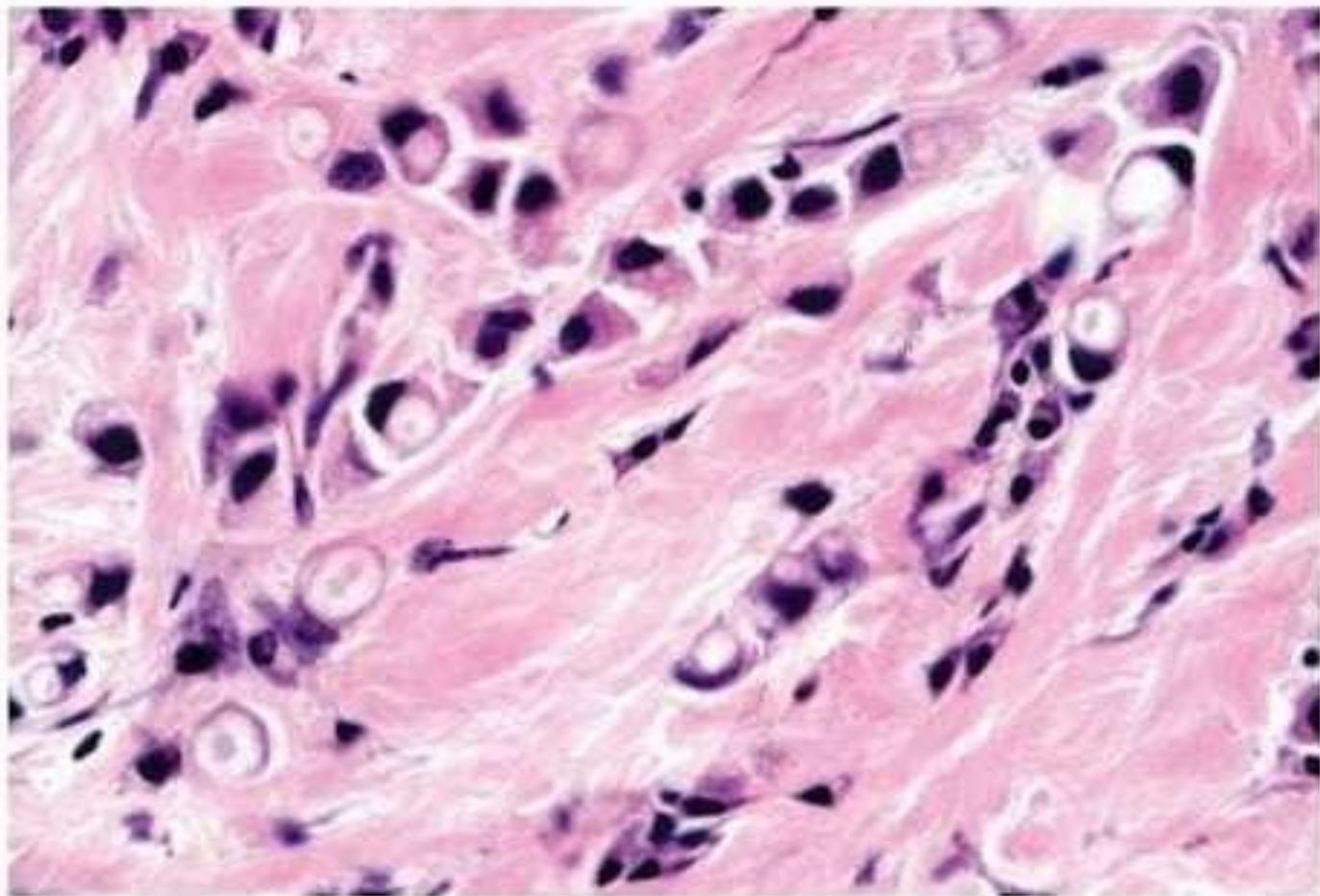
Invasive lobular carcinoma, signet ring variant

- Grading-

  well differentiated and moderately differentiated lobular carcinomas are usually diploid, ER positive and associated with LCIS

  Poorly differentiated cancers are generally aneuploid , lack hormone receptors and may overexpress HER2/neu.

- Lobular carcinomas are characterised by loss of E-cadherin, a cell adhesion molecule that functions as a tumor suppressor.

- Metastasize more frequently to CSF, serosal surfaces and pelvic organs

Invasive lobular carcinoma(ILC)
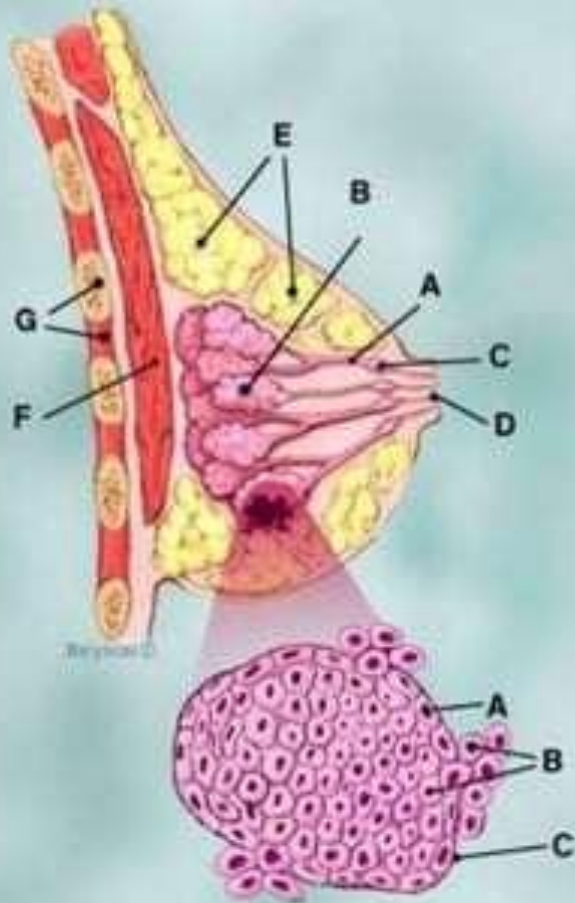
- A. Breast Duct System
- B. Lobules
- C. Breast Duct System
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- E. Fat
- F. Chest Muscle
- G. Ribs

- A. Cells lining lobule
- B. Cancer cells, breaking through the basement membrane.
- C. Basement membrane
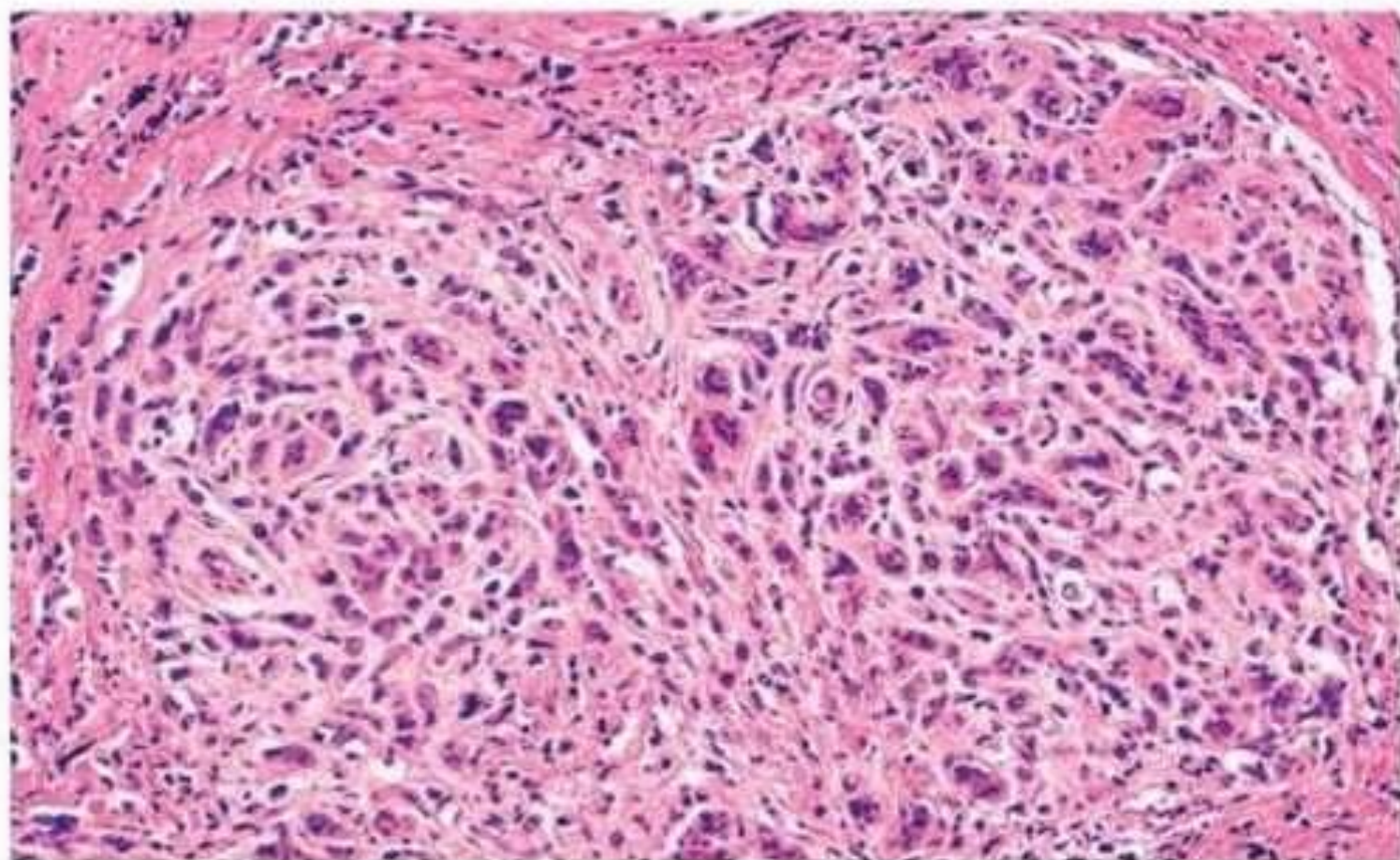
Infiltrating lobular carcinoma

Medullary carcinomas

- Most common in women in 6th decade presenting as a well- circumsribed mass with rapid growth.

- 4%

- Originates in large ducts.

- Commonly, the lesion is positioned deep within the breast and mobile.

Morphology

- Tumor is soft , fleshy and well- circumscibed mass.

- Histologically –

✓ Solid syncytium like sheets of large cells with pleomorphic nuclei and prominent nucleoi.

✓ Frequent mitotic figures

✓ Moderate to marked lymphoplasmacytic infiltrate in and around the tumor
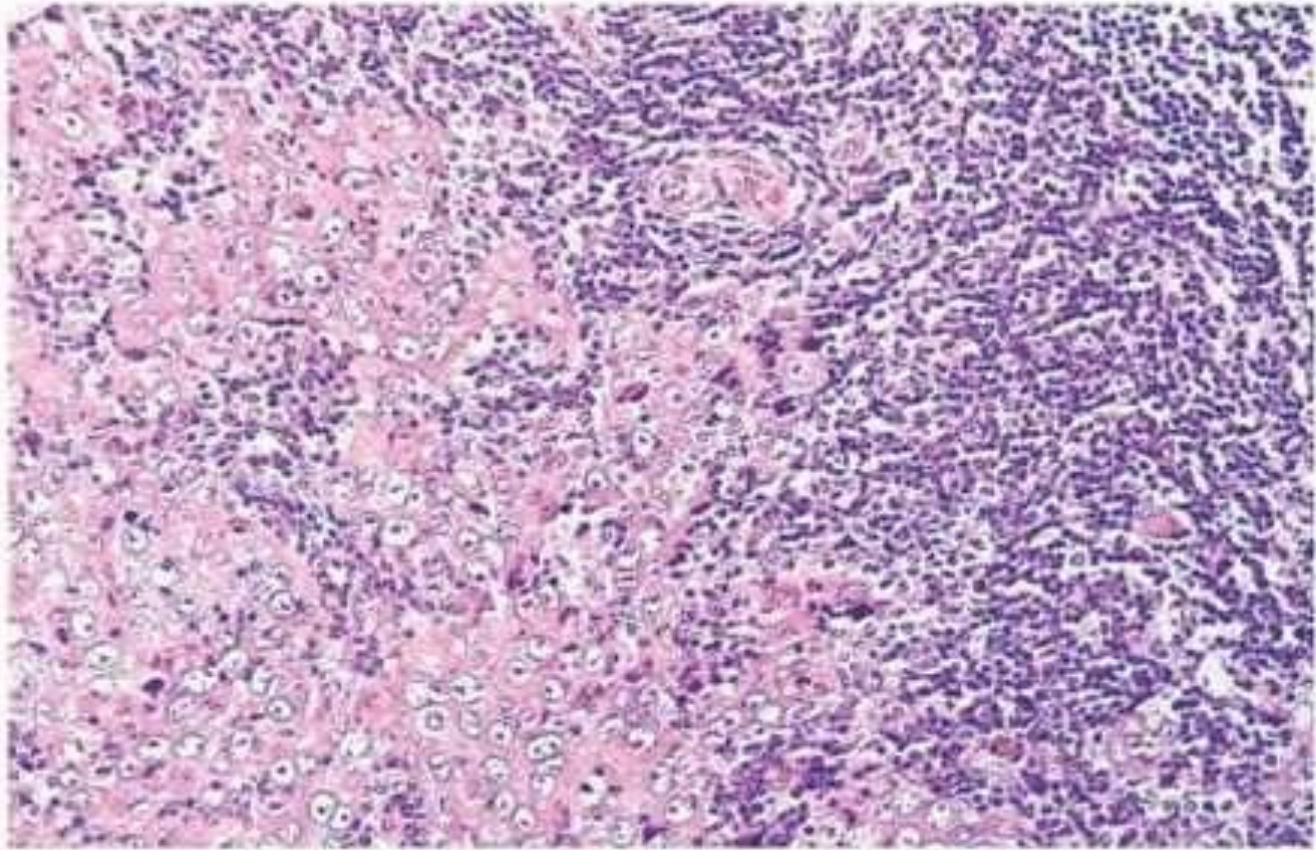
Medullary carcinoma.

- Diagnosis of this lesion denotes a better 5-year survival than pure invasive ductal or lobular carcinoma.

- They have a basal-like gene expression profile

Mucinous (colloid) carcinomas

- This adenocarcinoma of ductal origin constitutes approximately 2% of all breast cancers

- Typically presents as a bulky, mucinous (colloid) tumor that is largely confined to the elderly population.

- Tends to grow slowly over years.

morphology

- Tumor is soft or rubbery

- Borders are circumscribed

- Tumor cells are arranged in clusters and small islands of cells within large lakes of mucin.
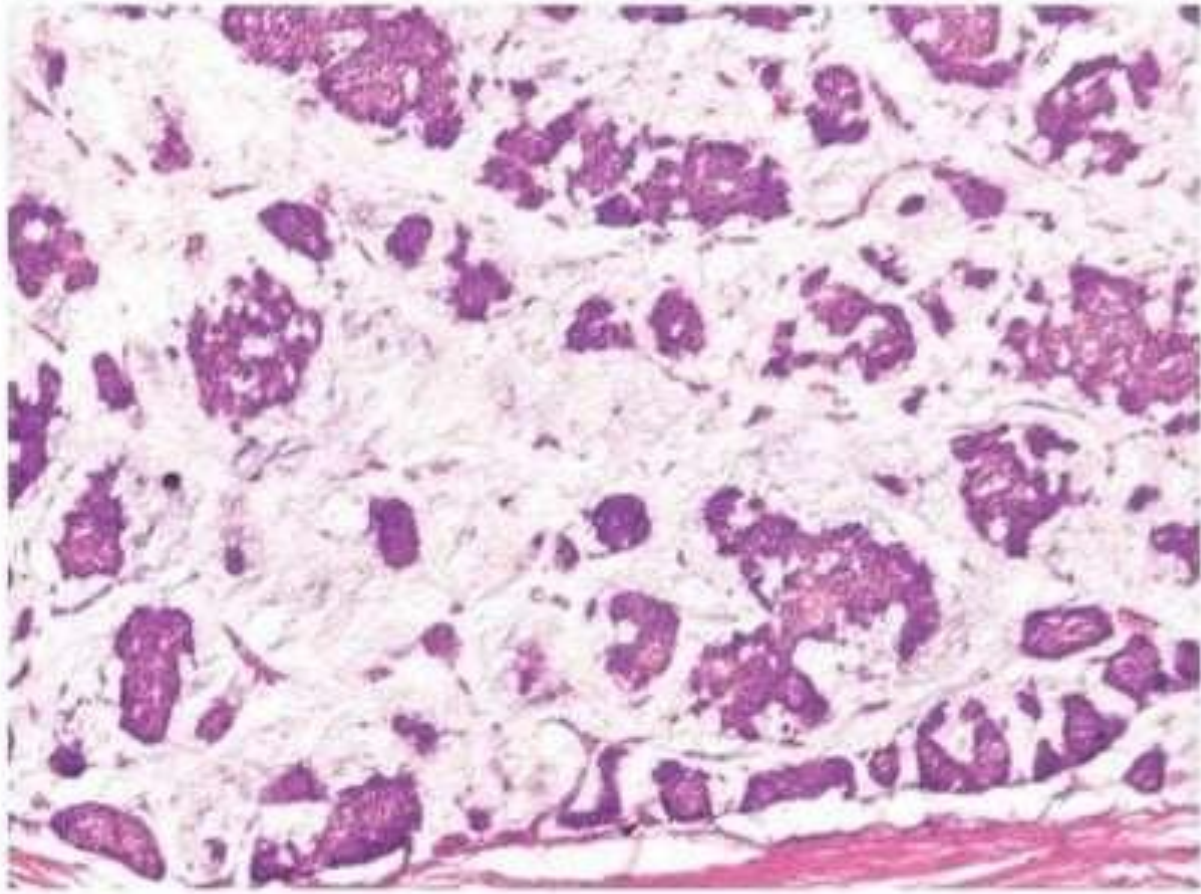
Mucinous carcinoma.

- Mucinous cancers are usually diploid, well to moderately differentiated and ER positive.
- Lymph node metastasis rare
- Overall prognosis is slightly better than NST carcinomas.

Tubular carcinoma

- This lesion is a well-differantiated variant of breast carcinoma with an incidence of approximately 2 percent.

- Most commonly, is diagnosed in the perimenapousal or early menopausal population.

morphology

- Tumor consists of well formed tubules.

- Myoepithelial cell layer is absent placing cells in direct contact with the stroma

- Typical apocrine snouts and calcification may be present.

- Frequently associated with atypical lobular hyperplasia or LCIS.
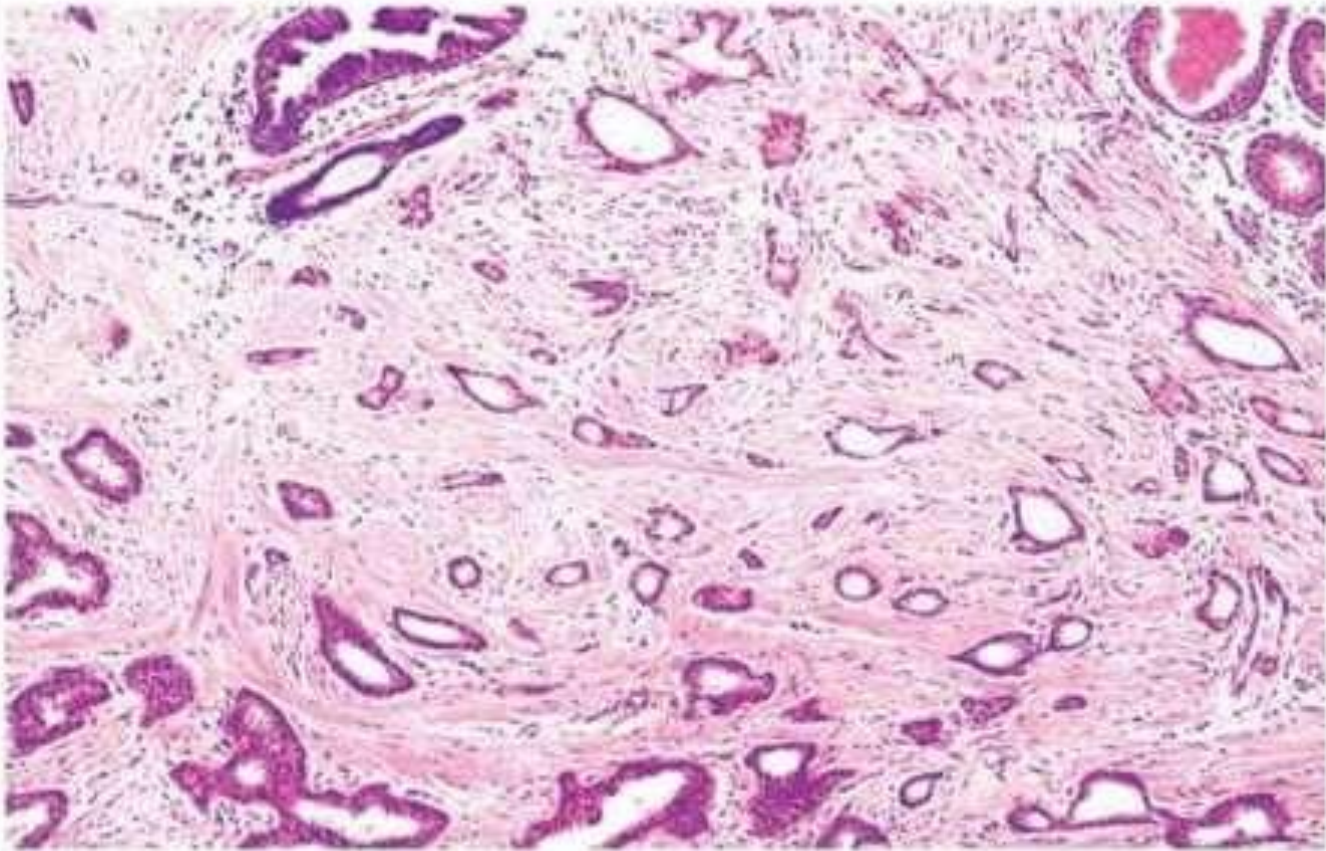
Tubular carcinoma

- Majority of tubular carcinomas are diploid, ER positive and HER2/neu negative.

- Excellent prognosis.

Invasive Papillary carcinoma

- Papillary cacinoma and micropapillary accounts for less than 1% of all invasive carcinomas

- generally presents in the 7th decade.

- Typically, papillary or micropapillary cancer is small and commonly seen in DCIS.

- Invasive papillary are ER positive with favourable prognosis while micropapillary are ER +ve and HER2/neu −ve.

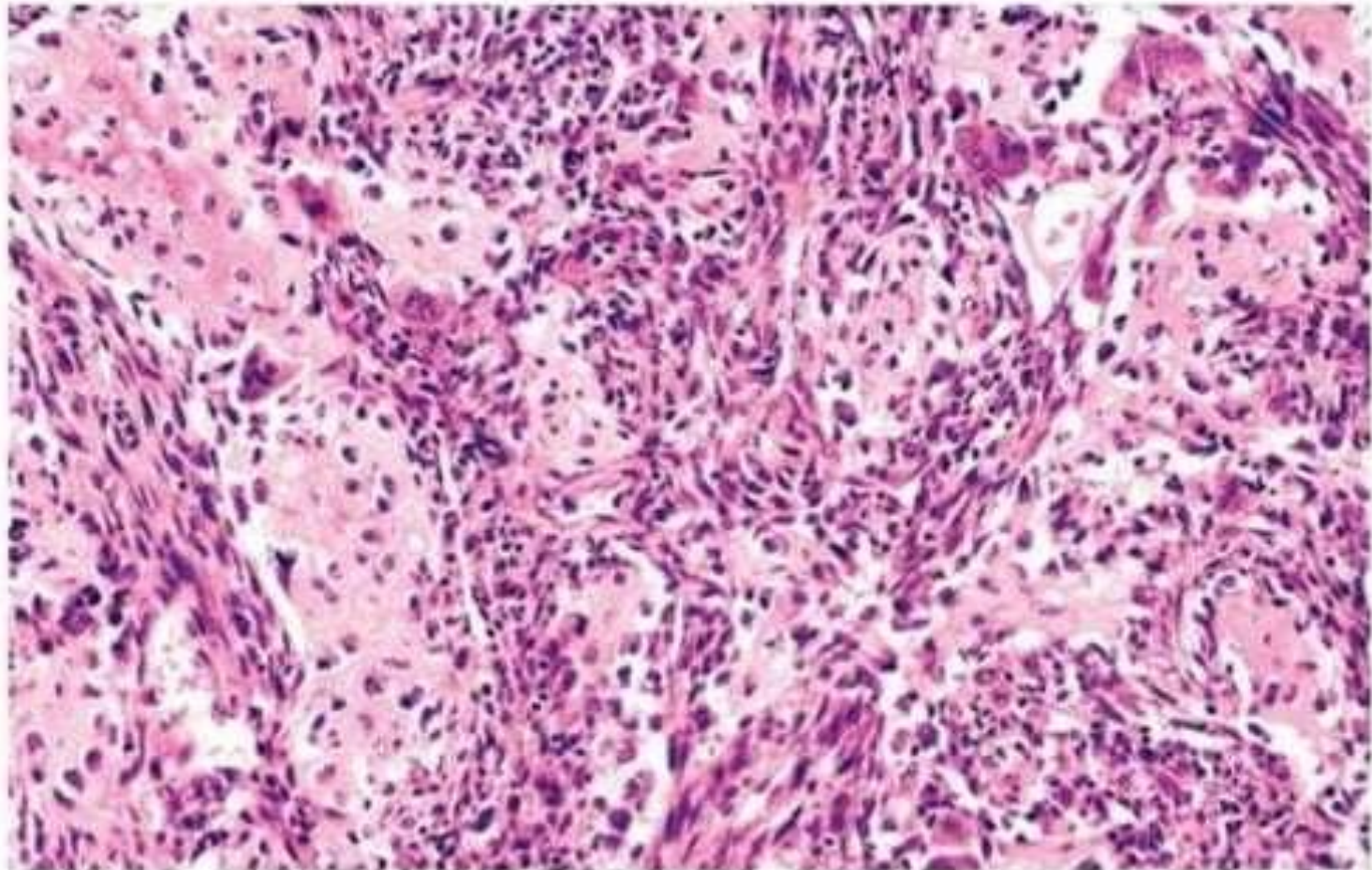- Lymph node metastasis very common and prognosis is poor.
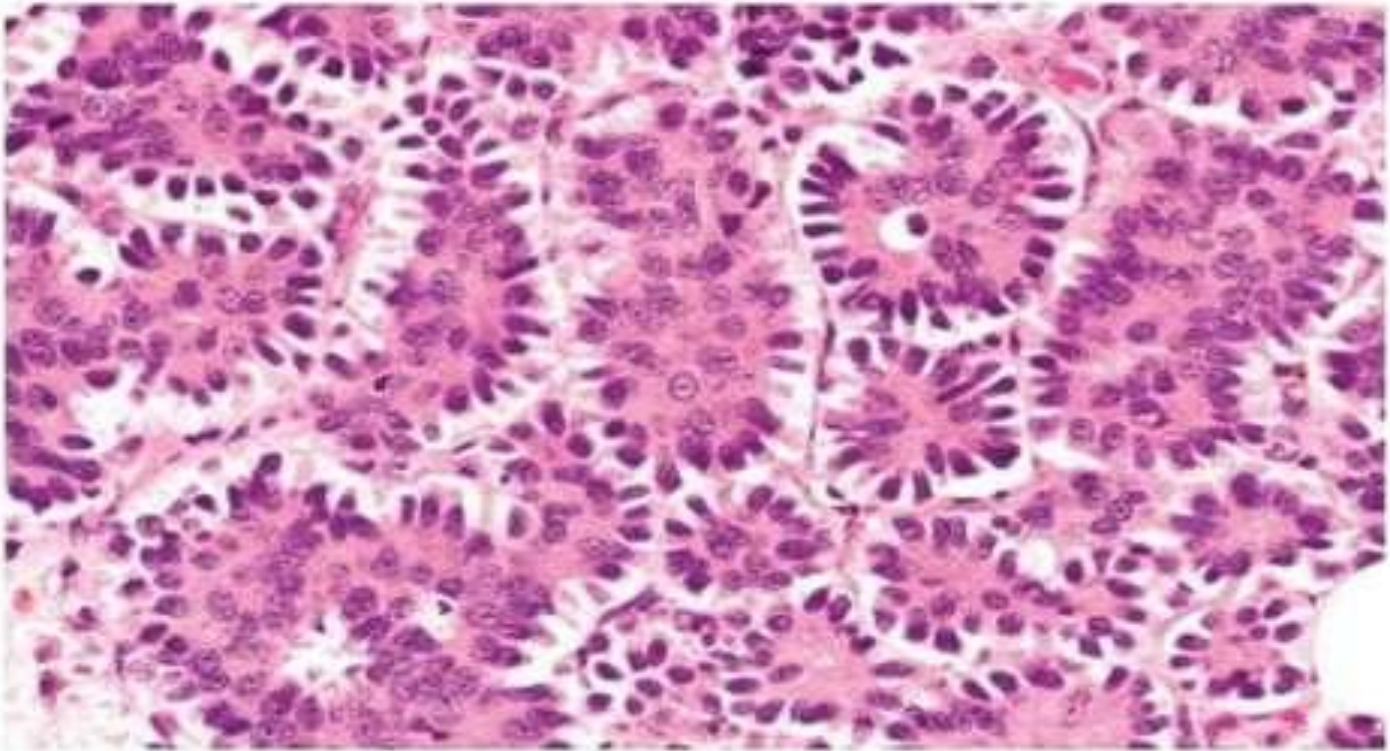
Invasive micropapillary carcinoma

Metaplastic carcinomas

- Rare tumors- less than 1% of all cases.
- Types-

    matrix producing carcinomas

    squamous cell carcinomas

  They are triple negative but often express myoepithelial proteins.

  Poor prognosis.

Metaplastic carcinoma

Inflammatory carcinoma

- 1.5 to 3% of all cancers

- Clincal features : erythema, peau d'orange, and skin thickening due to dermal lymphatic involvement with or without the presence of a palpable mass

- Typically the skin over the lesion is warm, diffusely scaly, and indurated with ridging

- It may present with the characteristics of a cellulits.

- Diagnosis : biosy of skin, subcutaneous tissue, and parenchyma

- This disease progresses rapidly and prognosis is poor.

Diagnosis

- Early detection of breast cancer significantly reduces the risk of death
- 20-49 ages ⟶ physical examination by a health professional every 1 to 2 years.
- 50 and over ⟶ should be examined annualy
- Women should perform self examination every month.

imaging techniques

- Breast sonography
  - Superior in dense breast, young age
- Mammography
  - Superior in loose(fatty) breast, elder.

  Others

- Schintomammography
- Doppler ultrasonography
- Breast MR

Biopsy

- A definitive diagnosis of breast cancer can be made only by a biopsy.

- When a lump can be felt and is suspicious for cancer on mammography:
    - ✓ FNAC
    - ✓ Excisional biopsy
    - ✓ İncisional biopsy
    - ✓ Core biopsy
    - ✓ Radioguided biopsy (for occult lumps)

Staging of Breast Cancer

- **The American Joint Committee on Cancer (AJCC) has designated staging by TNM**

- T= tumor size

- N = lymph node involvement

- M = metastasis

TNM

- Tx ⟶ No evidence of primary tumor
- Tis ⟶ Carcinoma in situ
- T1 ⟶ Tumor 2cm or <
- T2 ⟶ 2 to 5 cm
- T3 ⟶ T> 5cm
- T4a ⟶ extension to chest wall
- T4b ⟶ edema (including peau d'orange), ulceration of skin, satellite nodules
- T4c ⟶ T4a + T4b
- T4d ⟶ Inflammatory carcinoma

Regional lymph nodes

- N0 → no regional lymph node met.
- N1 → Movable ipsilateral axillary lymph node.
- N2 → Fixed ipsilateral axillary lymph n. or internal mammary lymph nodes
- N3 → -ipsilateral supraclavicular lymph node.

    -Fixed ipsilateral axillary lymph n. and İnternal mammary lymph nodes

    -İpsilateral infraclavicular lymph node.

Distant metastasis

- M0 - no distant metastasis
- M1 - distant metastasis

Stage 1

- **Tumor ≤ 2.0 cm in greatest dimension**
- **No nodal involvement (N0)**
- **No metastases (M0)**
- **5-year survival- 87%**

Stage II

- **Tumor > 2.0 ≤ 5 cm**
  or
- **Ipsilateral axillary**
- **lymph node (N1)**
- **No Metastasis (M0)**
- **5-year survival- 75%**

Stage III

- **Tumor > 5 cm (T3)**

- **or ipsilateral axillary lymph nodes fixed to each other or other structures (N2)**

- **involvement of ipsilateral internal mammary nodes (N3)**

- **Inflammatory carcinoma (T4d)**

- **5-year survival- 46%**

Stage IV (Metastatic breast cancer)

- **Any T**
- **Any N**
- **Metastasis (M1)**
- **5-year survival- 13%**

Prognosis of breast carcinomas

- Major prognostic factors
  - ✓ Tumor Size
  - ✓ lymph nodes status
  - ✓ Nuclear grade
  - ✓ Age
  - ✓ The location of the tumor its spread

- Minor prognostic factors

✓ *Histologic Subtypes*
✓ *Tumour Grade*
✓ *Hormone Receptors: ER, PR*
✓ *HER2/neu*
✓ *Lymphovascular invasion*
✓ *Proliferative rate*
✓ *DNA content*
✓ *Response to neoadjuvant therapy*
✓ *Gene expression profiling*
✓ *Molecular Markers*
    Includes c-erb-B2, c-myc and p53