BREAST CANCER

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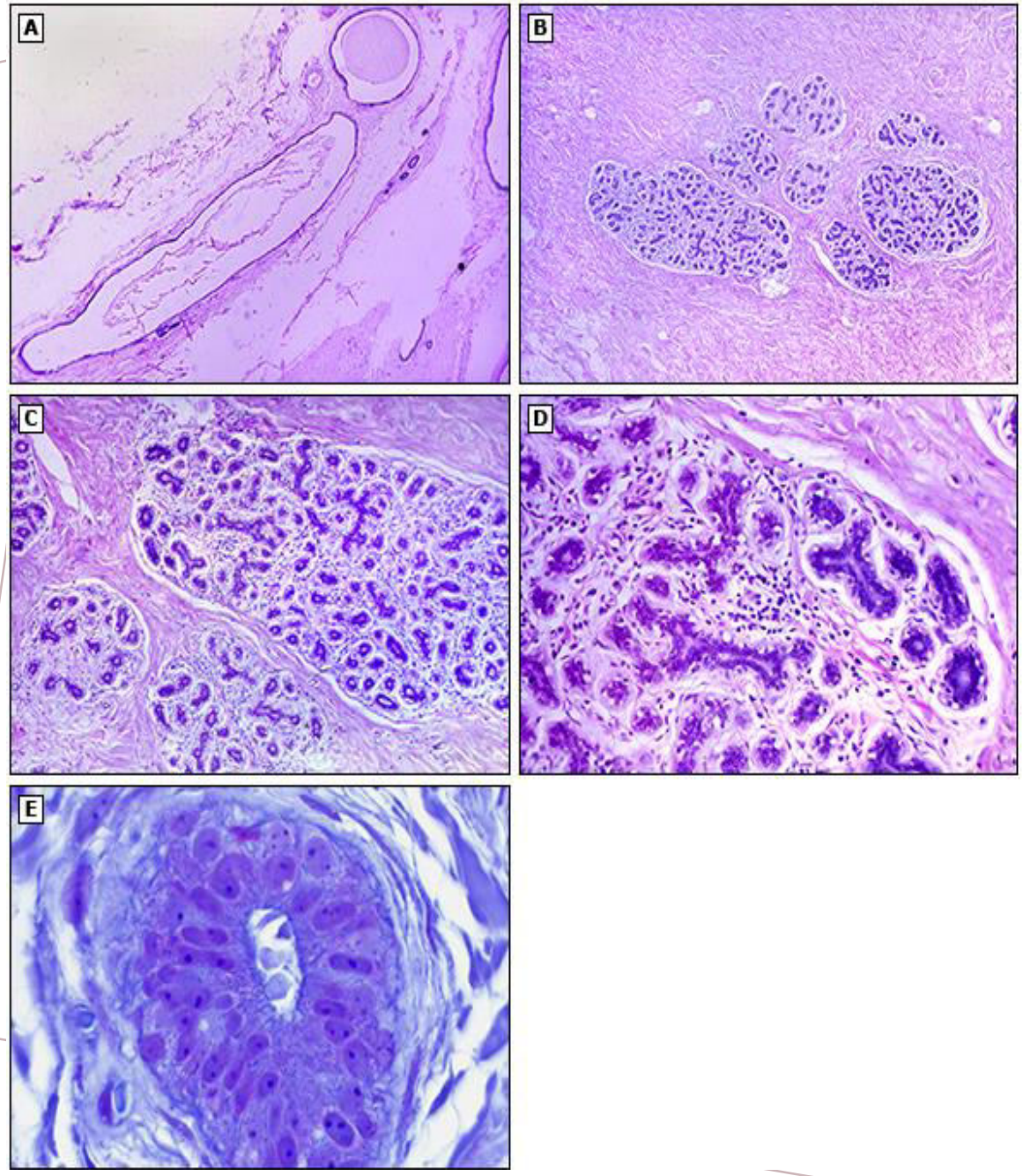
HISTOLOGY

- Microscopically, the breast tissue is comprised of epithelial and mesenchymal elements. The epithelial portion comprises secretory parts called acini that connect to a series of ducts that increase in diameter as they approach the nipple.

HISTOLOGY

- The terminal ductal lobular unit (TDLU) is the functional and structural unit of the breast.
- The TDLU comprises the distal smallest ducts (terminal duct) and the acini attached to them . The epithelial elements of the TDLU, the acini and terminal duct, are embedded in the intralobular stroma



(A) Major duct at low magnification
(B) Several TDLU at low magnification
(C) Sharp interphase between dense extralobular connective tissue and each TDLU
(D) Loose intralobular stroma investing ductules
(E) Single duct cut transversely revealing an inner layer of secretory cells with abundant mitochndria and an outer sparse cell layer of myoepithelium with sparse cytoplasm

HISTOLOGY

- Under the light microscope, the two cell layers are clearly discernable, with the columnar or cuboidal larger and taller cells lining the luminal aspect of the duct and acini with an outer cell layer composed of the smaller myoepithelial cell layer, which lies between the epithelial cell layer and the basal lamina.
- The myoepithelial cell layer is continuous and lies parallel to the long axis of the duct system.
- The contractile properties of the myoepithelial cells contribute to the flow of milk during lactation.

HISTOLOGY

- Appreciation of the two-cell-type layer is critical in distinguishing benign from malignant processes:

-For example, in sclerosing adenosis and nipple adenomas, which are benign lesions, the two-cell layer is evident by routine histologic examination or immunohistochemical stains to detect the presence of the myoepithelial cell layer .

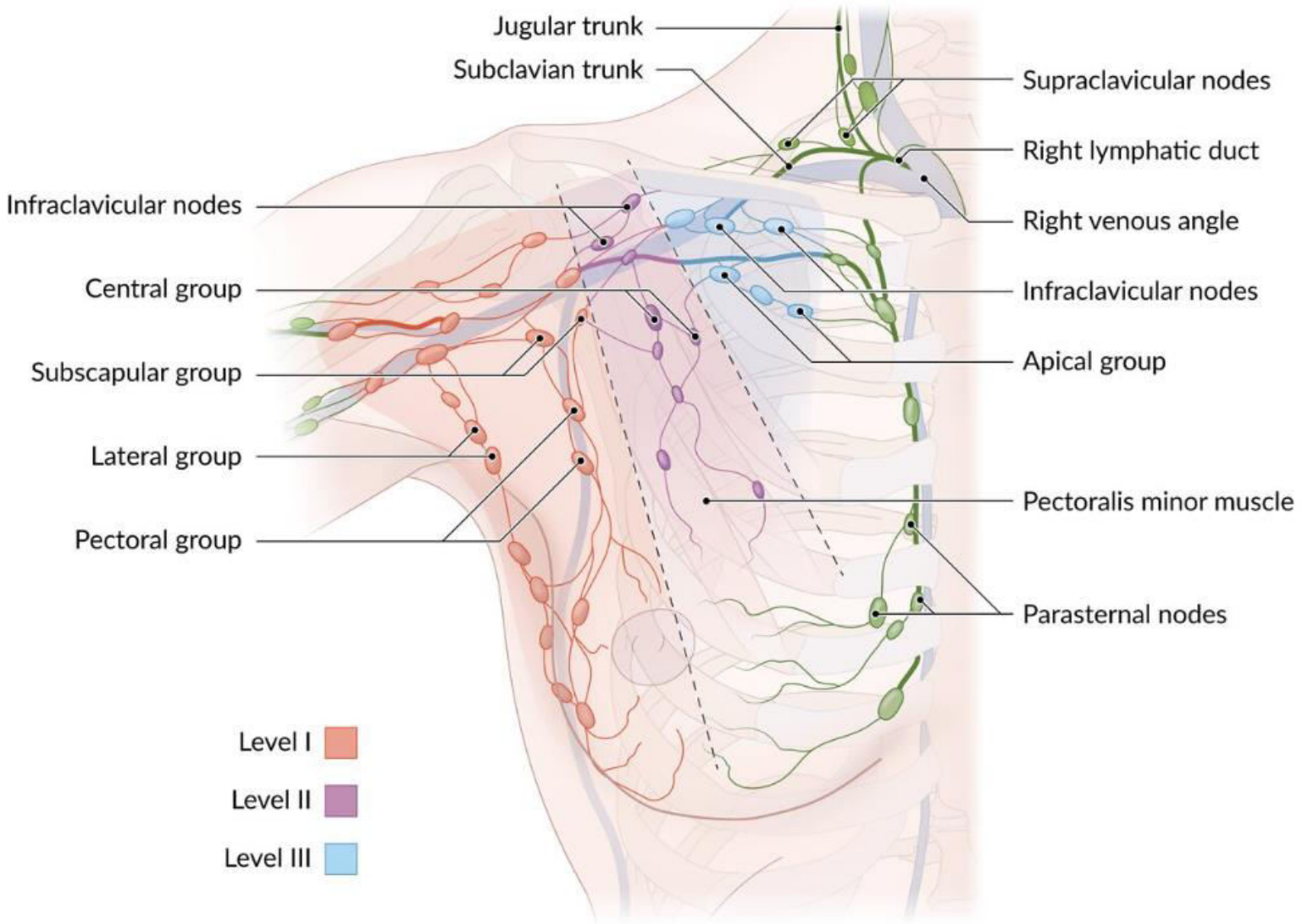
-By contrast, in well-differentiated malignancies like tubular carcinoma, the myoepithelial cell layer is lost around invasive glands and confirms the malignant nature of these lesions.

BLOOD SUPPLY

- The main blood supply of the breast is derived from the internal mammary artery. Approximately one-third of the blood supply (mainly to the upper outer quadrant) is provided by the lateral thoracic arteries.

Lymphatic drainage

- Lymph nodes of the breastLymphatics of the breast drain into three groups:
- 1. Axillary group, further divided into three levels
  - Level I: lateral to the lateral border of the pectoralis minor
  - Level II: behind the pectoralis minor
  - Level III: medial to the medial border of the pectoralis minor
- 2. Parasternal (internal thoracic) group
- 3. Posterior intercostal group Efferent lymphatics travel to the supraclavicular nodes and terminate in the thoracic duct (on the left; not shown here) or the right lymphatic duct


Jugular trunk
Subclavian trunk
Supraclavicular nodes
Right lymphatic duct
Right venous angle
Infraclavicular nodes
Central group
Subscapular group
Lateral group
Pectoral group
Infraclavicular nodes
Apical group
Pectoralis minor muscle
Parasternal nodes
Level I
Level II
Level III

EPIDEMIOLOGY OF BREAST CANCER

- Breast cancer is the most commonly diagnosed cancer type, accounting for 1 in 8 cancer diagnoses worldwide.

- In 2020, there were about 2.3 million new cases of breast cancer globally and about 685 000 deaths from this disease, with large geographical variations observed between countries and world regions.

CLINICAL PRESENTATION

- Typically, small tumors are asymptomatic and usually discovered during screening.

- Symptomatic or palpable tumors are generally present in advanced stage.

CLINICAL PRESENTATION

- Abnormality in a screening test, e.g., mammogram. (**Most common presentation**).
- Changes in breast size and/or shape; asymmetric breasts
- Palpable mass
- Presenting signs: Redness, edema, and pitting of the hair follicles.
- Nipple changes: inversion
- Pain: although most painful masses are benign, a small fraction of cancers cause pain.
- Inflammation: most often caused by infections that occur during lactation and it is rare to be caused by malignancy (an important mimic of inflammation is inflammatory breast carcinoma).
- Axillary lymphadenopathy

Most commonly, individuals with breast cancer develop clinical symptoms in later stages of disease :

- Early stages.
- Locally advanced disease.
- Progressive disease.
- Signs of metastatic disease.

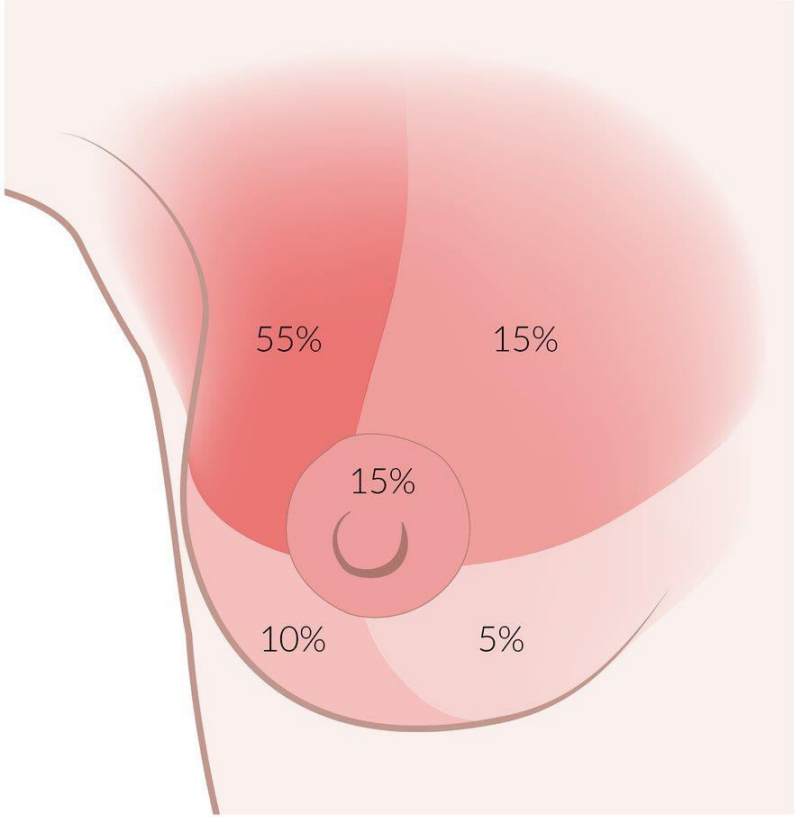
EARLY STAGES

In early stages, affected individuals may notice a palpable mass with the following characteristics:

- Typically single, non-tender, and firm.

- Poorly defined margins.

- Most commonly located in the upper outer quadrant (~ 55%).



<u>Breast cancer incidence by location:</u>

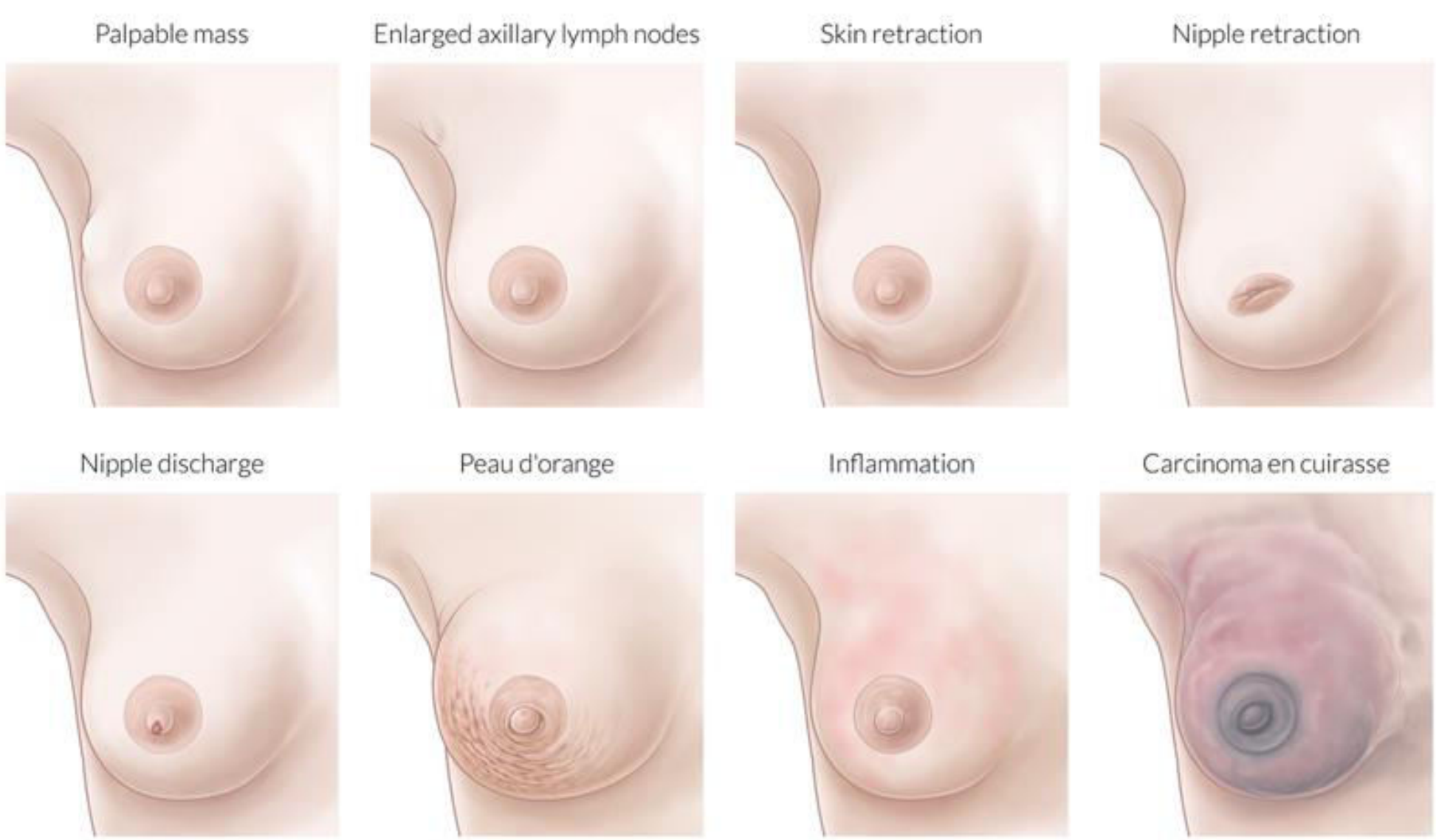
~ 55%: upper outer quadrant
~ 10–15%: upper inner quadrant
~ 10–15%: nipple
~ 10–15%: lower outer quadrant
~ 5%: lower inner quadrant

LOCALLY ADVANCED DISEASE

Locally advanced disease is characterized by a number of changes affecting the appearance of the breast. These include:

- **Morphology** : changes in size and/or shape → asymmetric breasts (Potential findings should always be compared to the contralateral breast).
- **Skin** :
- Retractions or dimpling
- Peau d'orange

- **Nipple**
- Inversion
- Blood-tinged discharge



Local findings in Breast cancer

PROGRESSIVE DISEASE

- Ulcerations

- Edema of the arm

- Paget disease of the nipple

SIGNS OF METASTATIC DISEASE

Lymphatic spread

-Lymphadenopathy

-Non-tender, firm, enlarged lymph nodes (> 1 cm in size), that are fixed to the skin or surrounding tissue.

-Most commonly the axillary nodes and, in later stages, the supraclavicular and/or infraclavicular nodes.

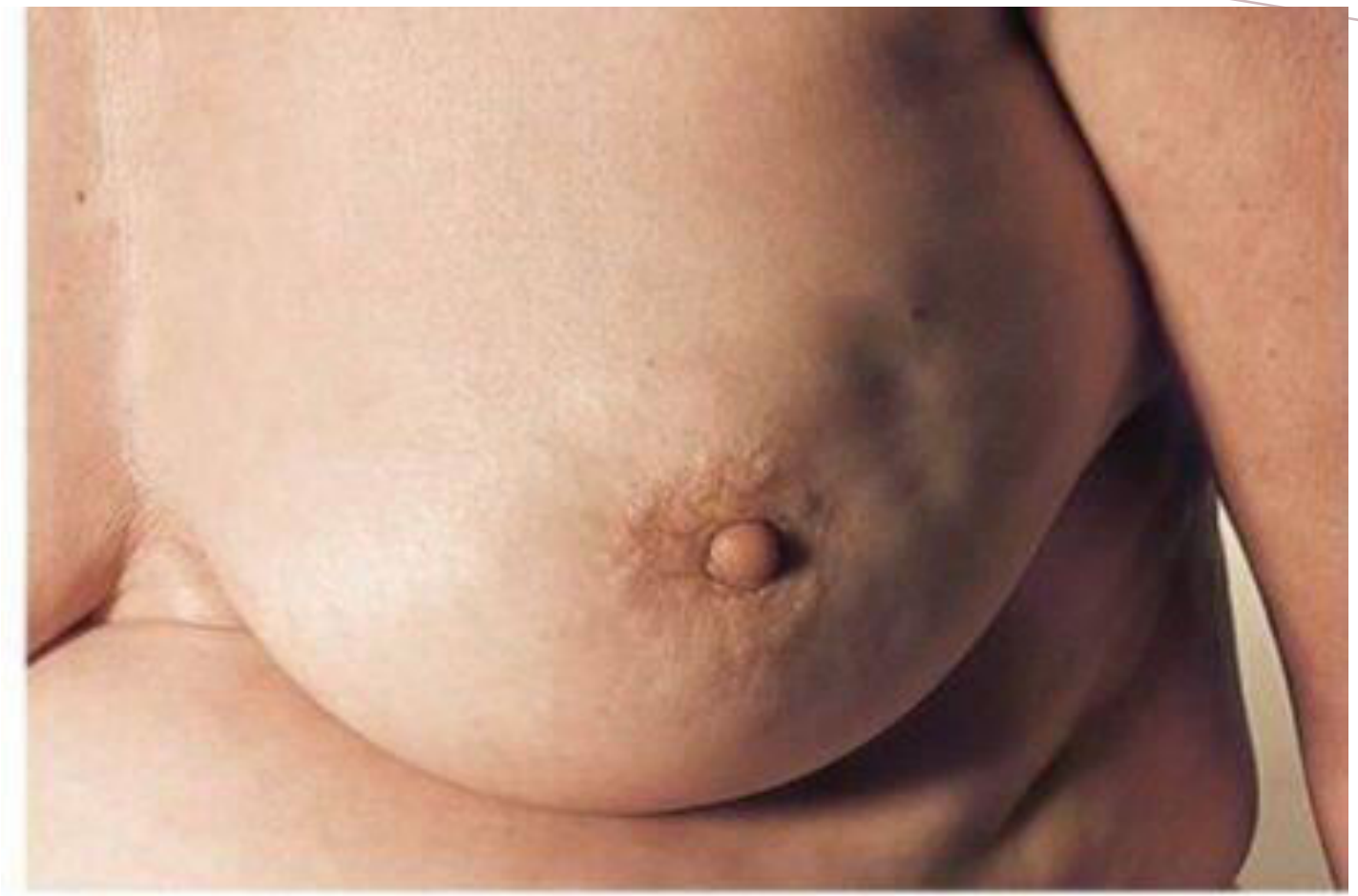
Hematogenous spread

Bone metastasis (Bone pain, Pathologic fractures, Spinal compression).

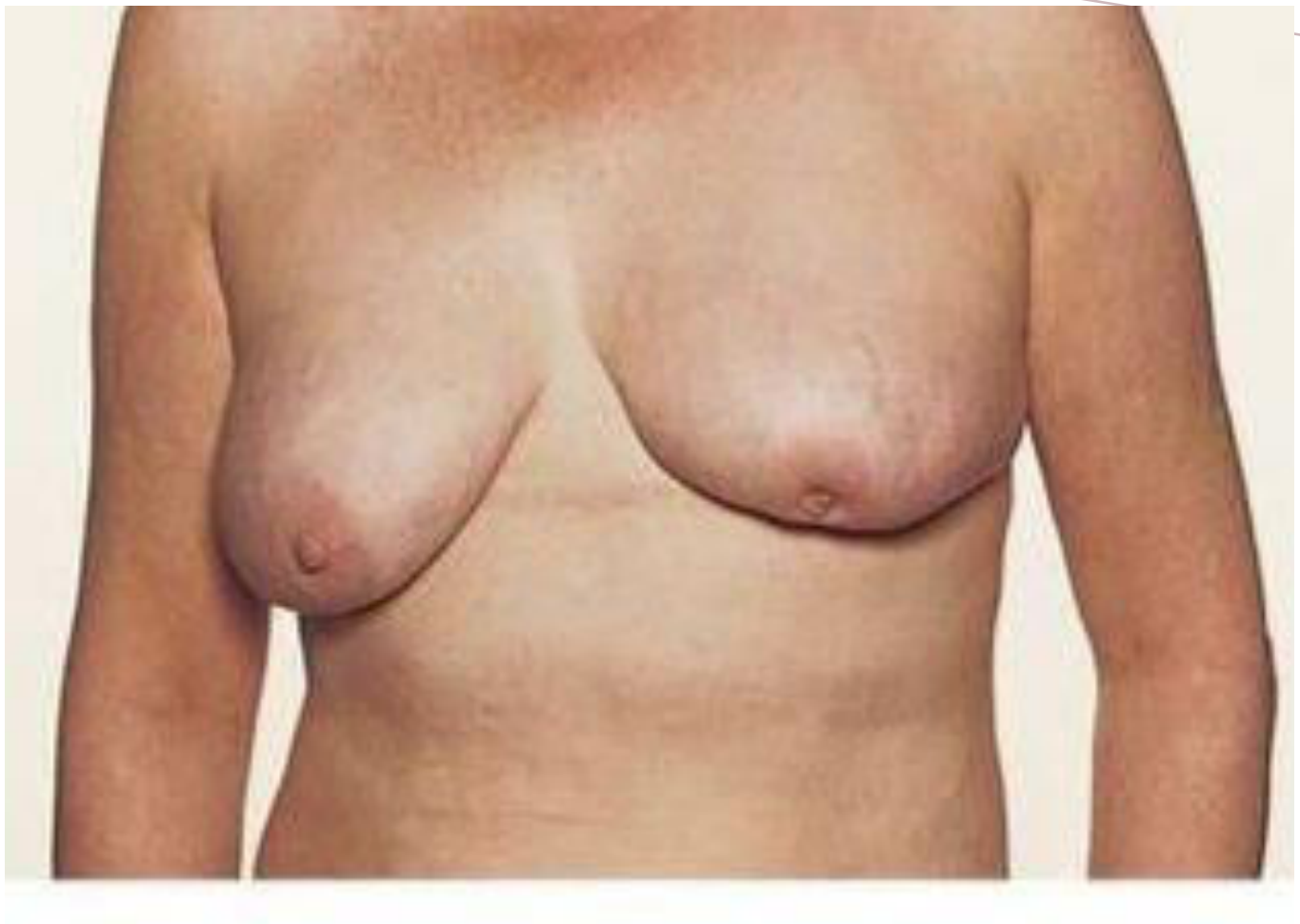
Liver metastasis (Abdominal pain, distention, Nausea, Jaundice).

Lung metastasis (Cough, Hemoptysis, Dyspnea, Chest pain).

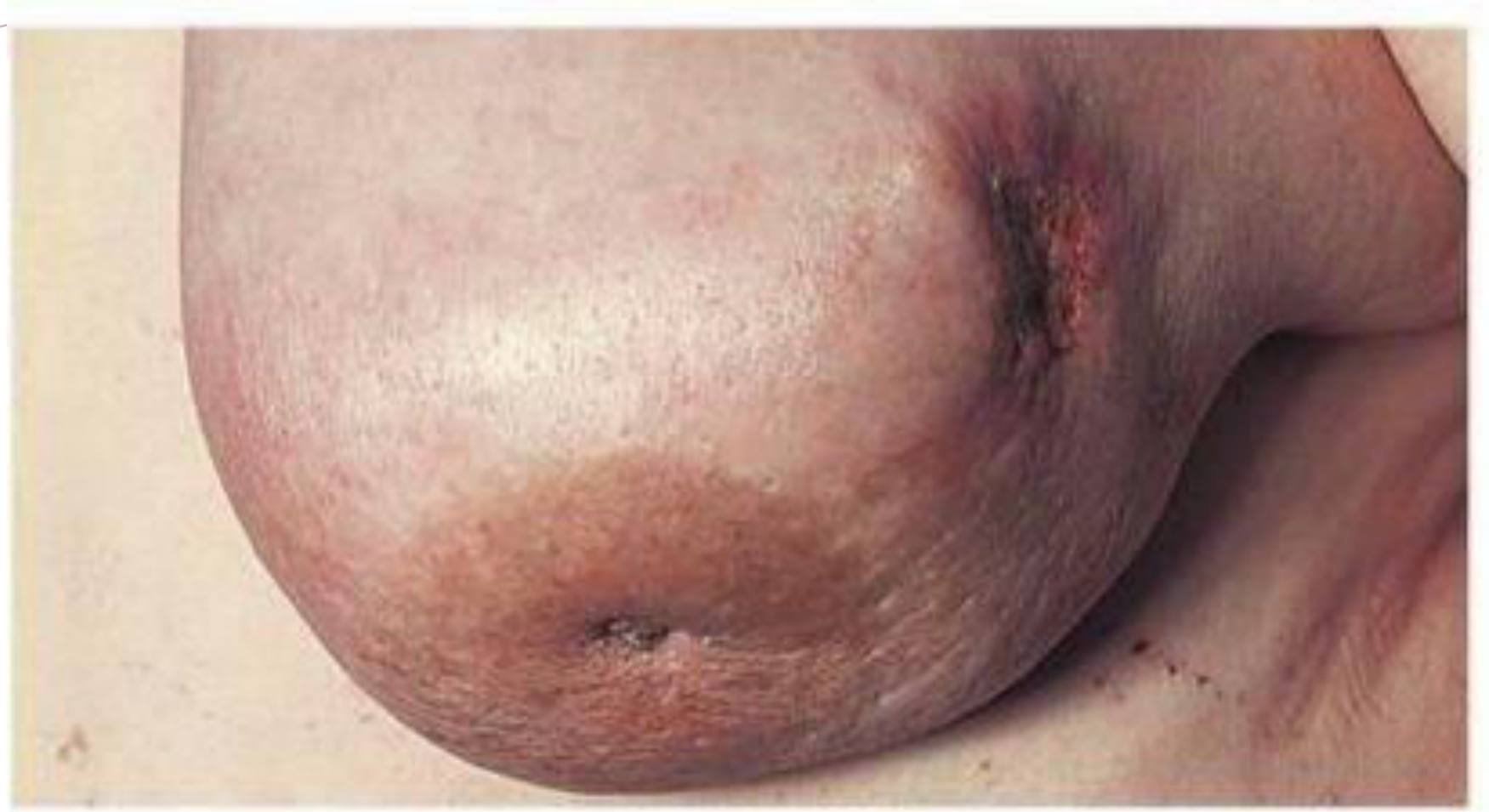
Brain metastasis (Headaches, Seizures, Cognitive deficits, focal neurological deficits).



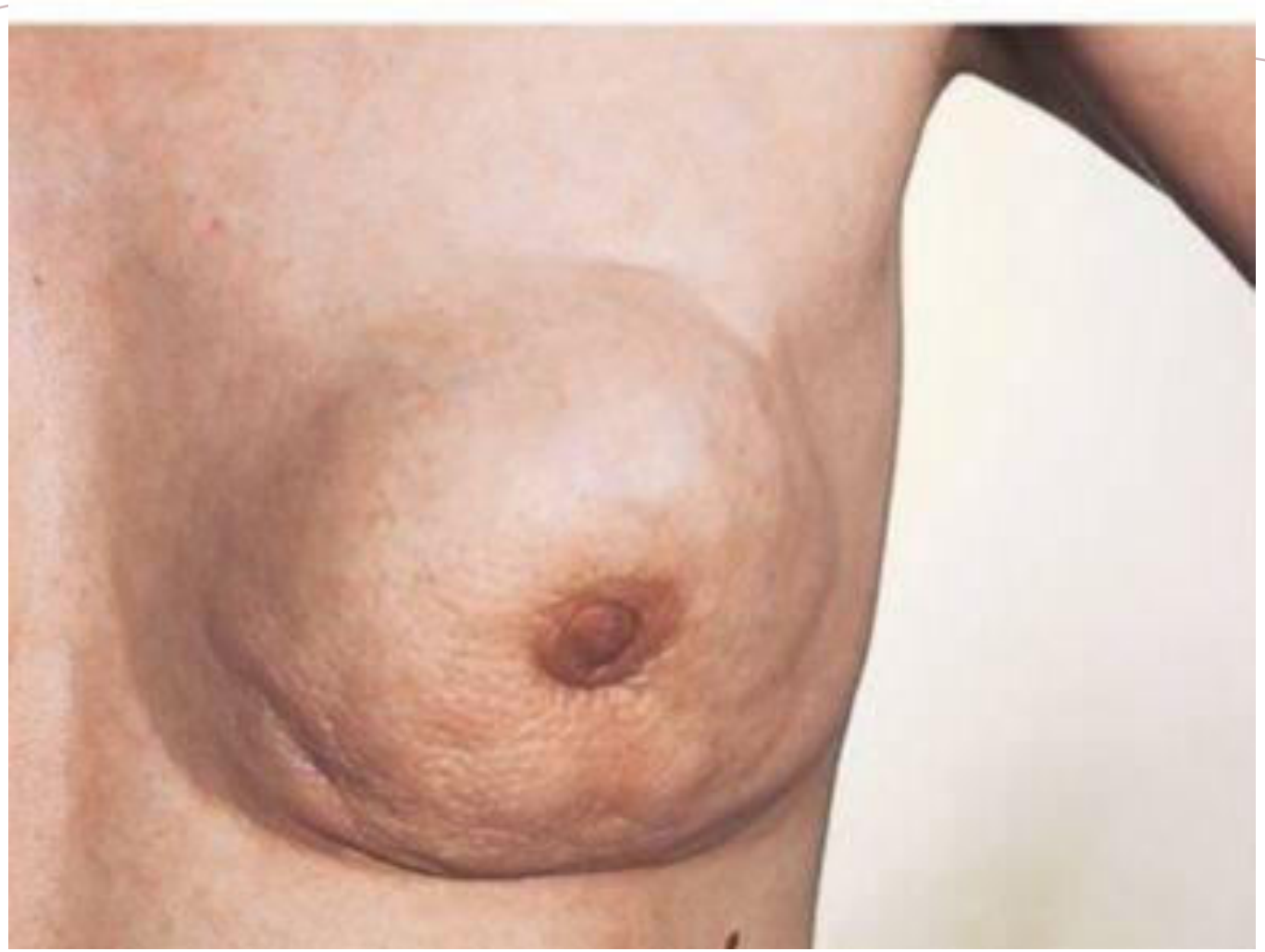
Retraction, deviation and displacement of the nipple. Puckering and tethering of the skin. Visible axillary lymphadenopathy.



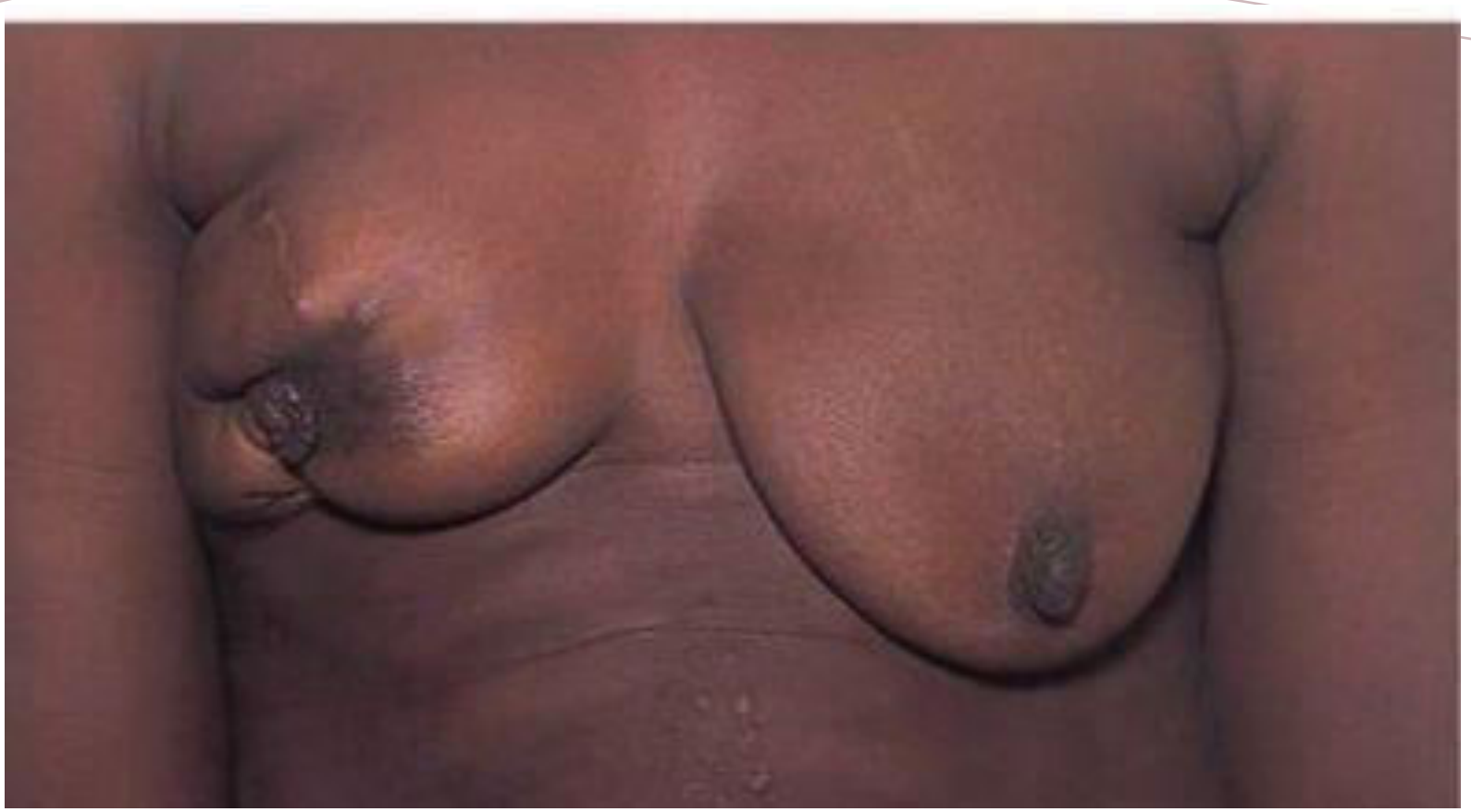
Retraction and displacement. The left nipple has been pulled into the breast (retraction) and pulled upwards (displacement) by the underlying carcinoma



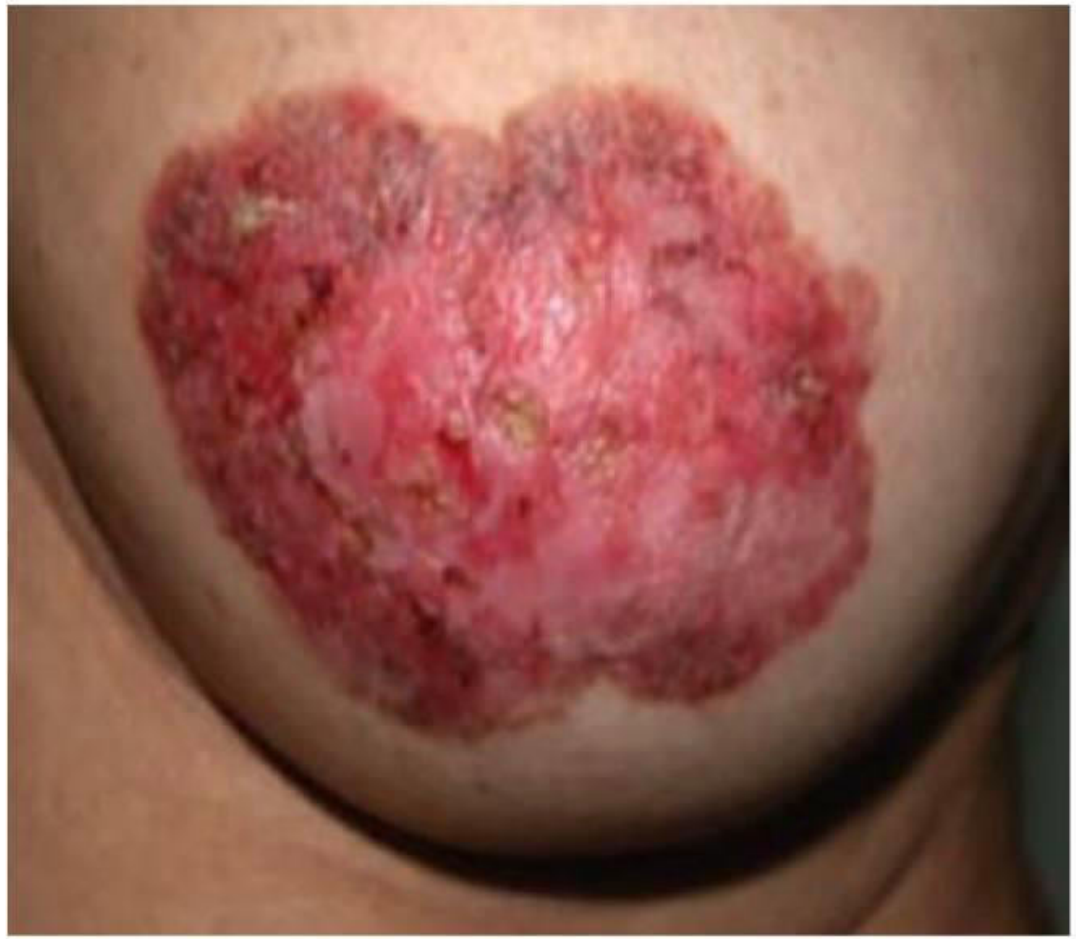
Retraction and peau d'orange. This carcinoma has invaded the skin and ulcerated. The skin of the lower part of the breast is oedematous and looks like the skin of an orange.



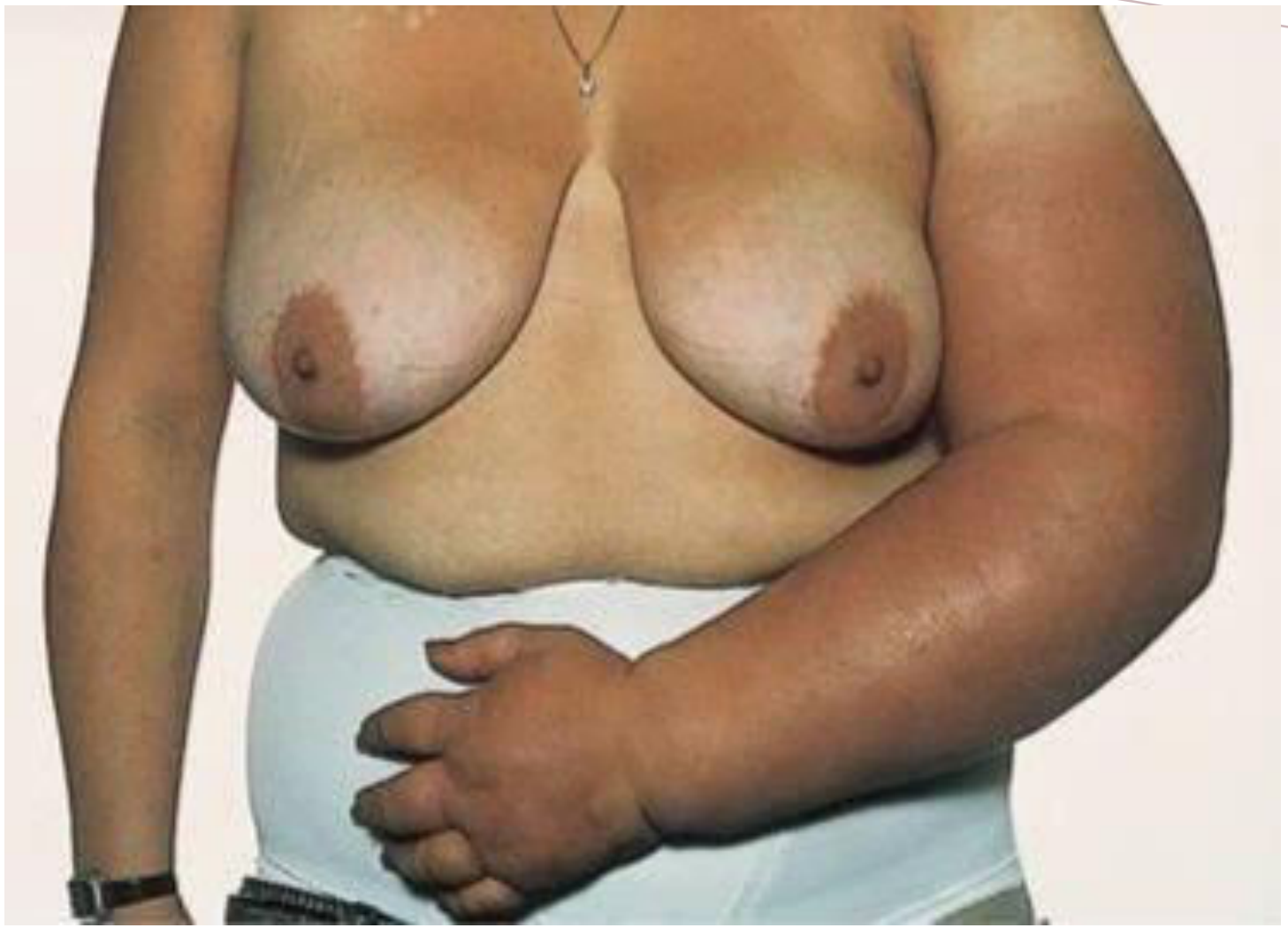
Fixation to the skin and the underlying muscle



Destruction. The right nipple and areola have been invaded and destroyed by the underlying carcinoma



Paget disease of the breast : nipple ulceration and erythema (eczematous patches on nipple)



Secondary lymphoedema of the left arm caused by metastases in the lymph glands

RISK FACTORS

NON MODIFIABLE RISK FACTORS

- Personal history BC / OC
- Female Gender
- Age
- Race
- Menstrual history
- Family history of BC / OC
- Breast density
- Radiation exposure
- Reproductive history
- Genetic factors

MODIFIABLE RISK FACTORS

- Obesity
- Breast feeding
- HRT
- Alcohol consumption
- OCP
- Exercise
- Smoking
- Nulliparity

RISK FACTORS

Gender

Breast cancer occurs 100 times more frequently in women than in men.

Age

The risk of breast cancer increases with older age : Birth to death – 12.9 % (1 in 8 women)

Genetic Factors (BRCA 1 / 2 mutations)

- BRCA1 and BRCA2 : BRCA are tumor suppressor genes that code for a DNA repair protein.
- Autosomal-dominant mutation
- Associated with an increased risk for breast cancer and ovarian cancer
- BRCA-positive women develop breast cancer earlier than women without the mutation.
- **positive status** will develop **invasive breast cancer before the age of 70**:
  - An estimated 55–60% in BRCA1-positive women & 45% in BRCA2-positive women.
- Men with breast cancer are often positive for BRCA2.

RISK FACTORS

Family history

- The risk associated with a positive family history of breast cancer is strongly affected by:
  1. **NUMBER** of female first-degree relatives with and without cancer,

     One 1st degree member >>> 2 times higher

     Two 1st degree relative >>> 3 times higher

     Three or more 1st degree relatives >>> 4 times higher

  2. **AGE** when they were diagnosed

     first-degree relative was diagnosed before age 30 the patient have a **three-fold higher risk**

     but if the affected relative was diagnosed after age 60, risk is only **1.5-fold higher**

Personal history of breast cancer

A personal history of either invasive or in situ breast cancer increases the risk of developing an **invasive breast cancer in the contralateral breast**.

RISK FACTORS

Bone Mineral Density (BMD)

- women with higher BMD have a higher breast cancer risk.
- Bone contains Estrogen receptor and is highly sensitive to circulating estrogen levels

Benign Breast Disease

- proliferative lesions (especially those with histologic atypia) are associated with an increased risk of breast cancer.

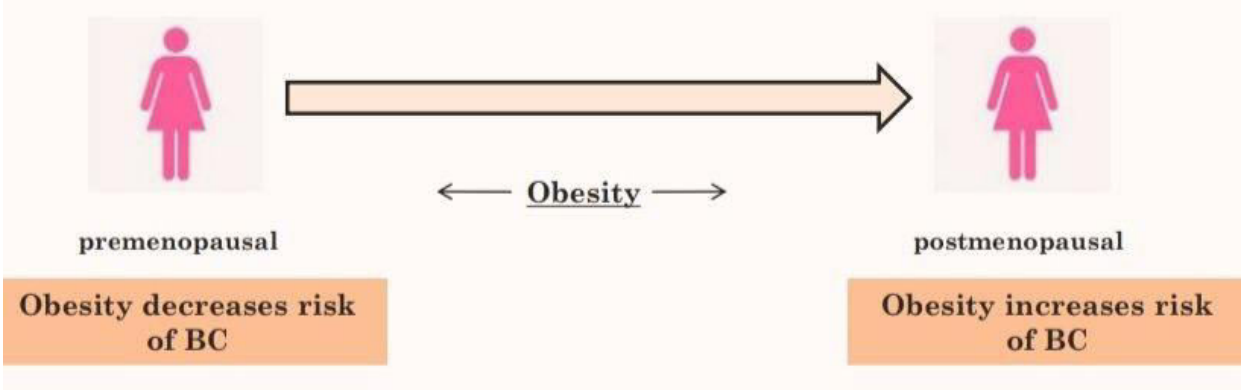
RISK FACTORS

Obesity

- **Premenopausal women** –increased BMI is associated with a **lower** risk of breast cancer

- **Postmenopausal women** –
    1. A higher BMI
    2. and/or perimenopausal weight gain
    3. or normal BMI a higher body-fat percentage

  ➔ have been consistently associated with a **higher** risk of breast cancer (mediated by higher estrogen levels resulting from the peripheral conversion of estrogen precursors (from adipose tissue) to estrogen)



HORMONAL FACTORS

A- Higher endogenous estrogen levels

associated with **higher** breast cancer risk in both postmenopausal and premenopausal women.

B- Menopausal hormone therapy

Combined estrogen/progesterone replacement in women with intact uterus has been shown to **increase** risk of subsequent ER-positive breast cancer.

- women with prior hysterectomy, single-agent estrogen replacement has **not** increased the risk of breast cancer.

C- Contraceptives

Breast cancer risk is **temporarily increased** with current or recent use of combined OCP, but this association disappeared within 2-5 years of discontinuation.

- (OCPr) oral contraceptives pills (ER-positive breast cancer) estrogen receptor-positive bre

REPRODUCTIVE FACTORS

A- Earlier menarche or later menopause

Early age at menarche & later age at menopause is associated with a **higher** breast cancer risk.

- Women with menarche at or after 15 years of age were **less** likely to develop hormone receptor-positive breast cancer compared with women who experienced menarche before the age of 13 years.

B- Nulliparity

Nulliparous women are at **higher** risk for breast cancer compared with parous women.

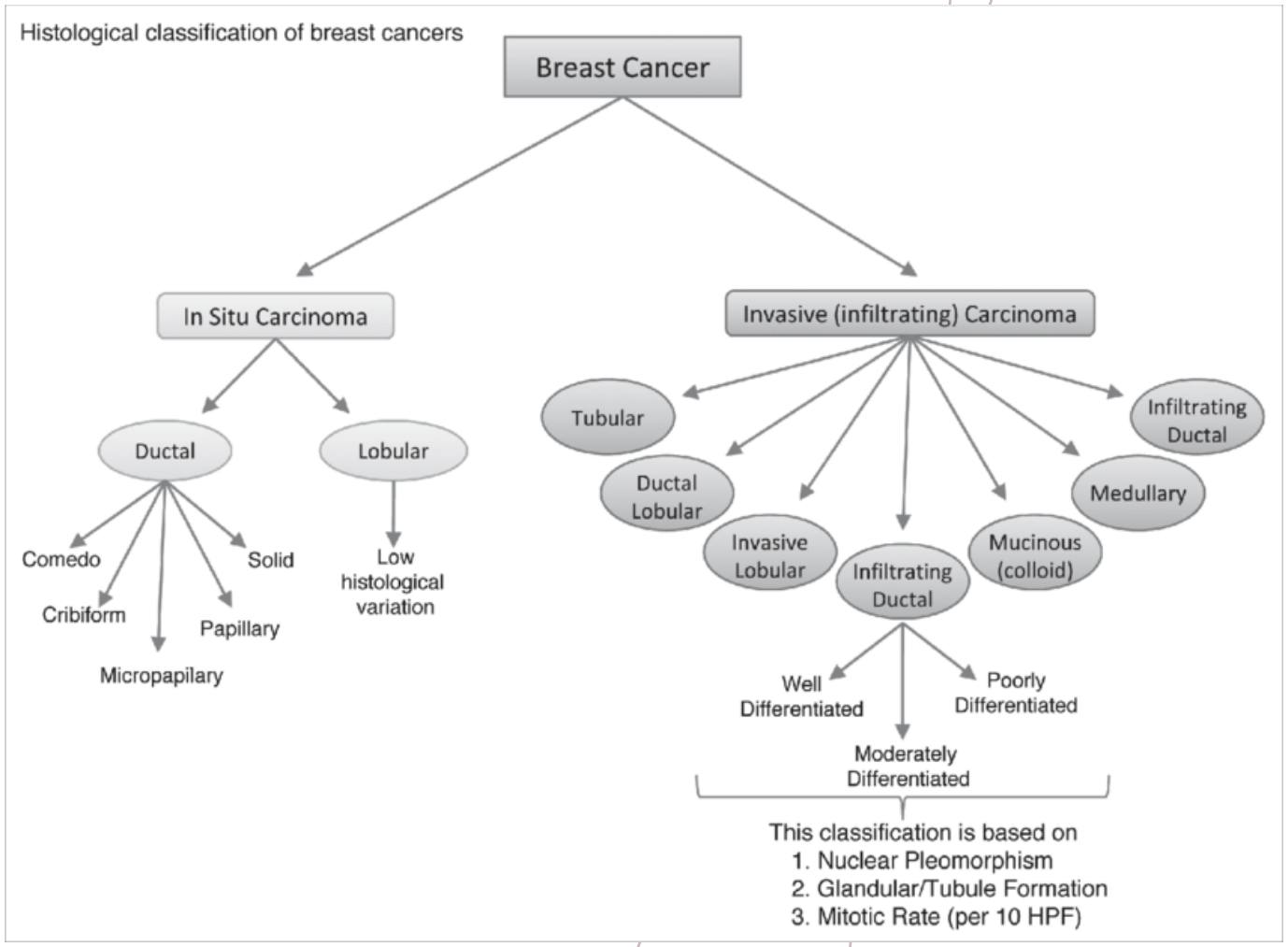
C- PREGNANCY

Women with first child before 20 years of age have a 50% **reduced** lifetime risk of breast cancer compared to women who have not had children

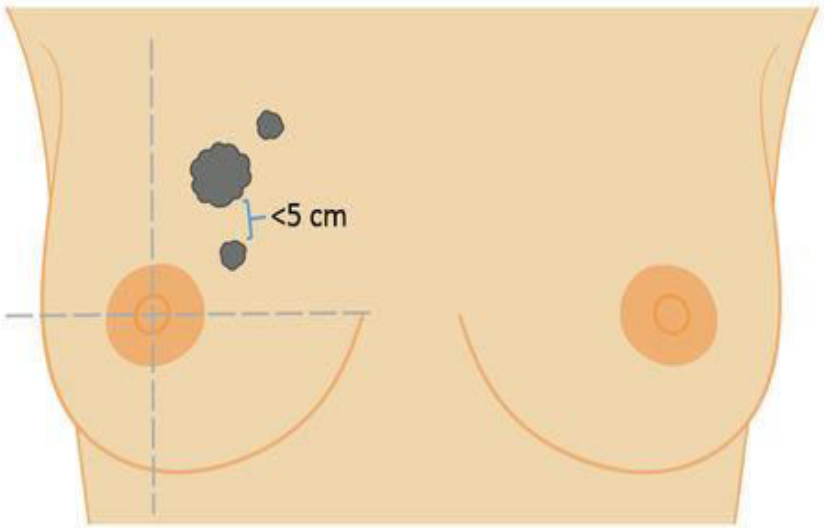
Women who have their first child after 35 years of age remain at **higher** risk of breast cancer compared to women have not had children

HISTOPATHOLOGY OF BREAST CANCER

- Cancer cells are in situ or invasive depending on whether or not they invade through the basement membrane.

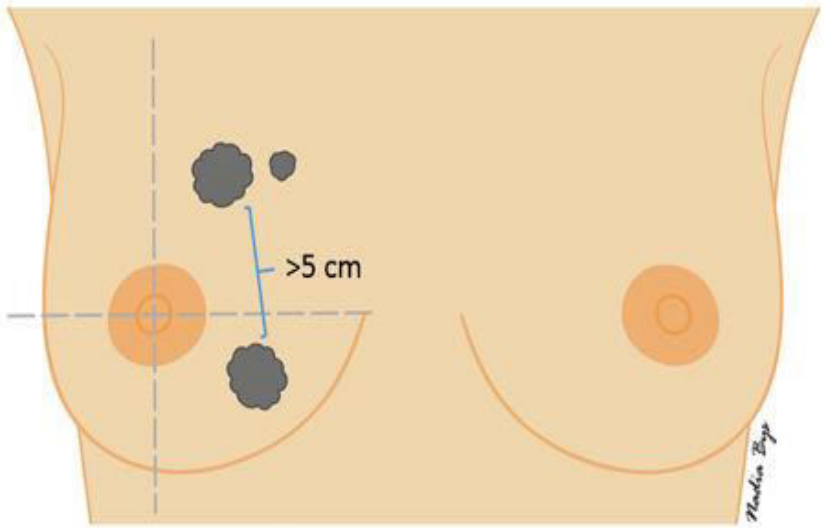


MULTIFOCALITY VS MULTICENTRICITY



Multifocal disease

Multifocal breast cancer is defined as the presence of two or more tumor foci within a single quadrant of the same breast or tumor foci within 5 cm of each other.



Multicentric disease

Multicentric breast cancer is defined as the presence of two or more tumor foci within different quadrants of the same breast or tumor foci separated by more than 5 cm

IN SITU CARCINOMA
(NON-INVASIVE)

- is preinvasive cancer that has not breached the epithelial basement membrane.
- In situ carcinoma may be ductal (DCIS) or lobular (LCIS).

DUCTAL CARCINOMA IN SITU (DCIS)

- ✓ premalignant condition
- ✓ the cells have taken on a malignant phenotype
- ✓ but invasion through the basement membrane has not yet taken place (proliferation of malignant ductal epithelial cells completely contained within breast ducts)
- ~ 25% of all newly diagnosed breast cancers
- multicentricity for DCIS is reported to be 40% - 80%

- The average estimate of untreated DCIS to develop invasive carcinoma is between 25%–70%.
- The invasive cancers are observed in the ipsilateral breast, usually in the same quadrant as the DCIS that was originally detected

Mammogram: Microcalcifications is the most common finding
  - But that DCIS typically does not produce a mass. In contrast to invasive breast cancer, which often forms a palpable lump or mass in the breast tissue

MRI is The gold standard

TRANSITION OF DCIS

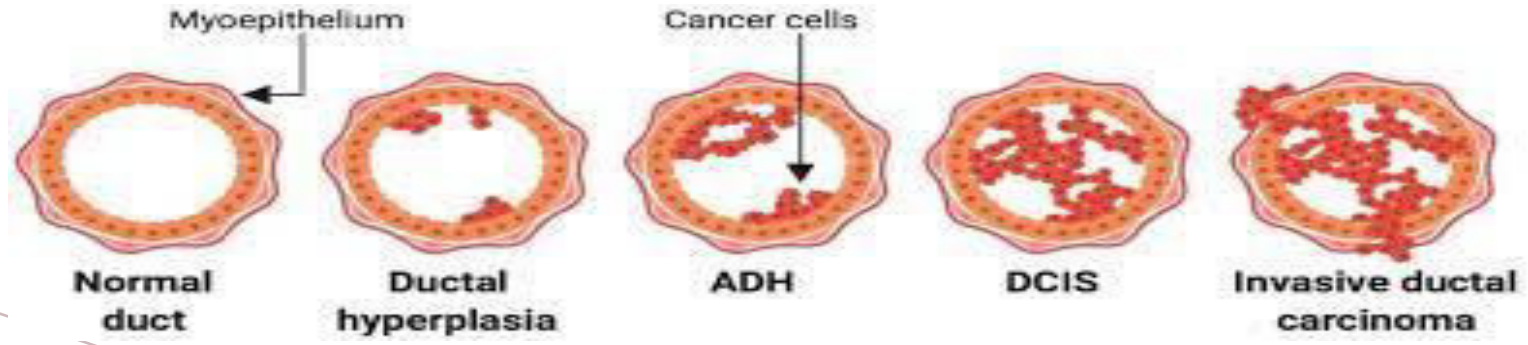
- Normal cells

- Ductal hyperplasia or **"overgrowth"** means that too many cells are present.

- Atypical ductal hyperplasia means that there are **too many cells (hyperplasia)** and they are **starting to take on an abnormal appearance (atypical or "not typical").**

- Ductal carcinoma in situ (DCIS) means that there are **too many cells** and they **have the features of cancer**, but **they are still confined to the inside the duct**. (**DCIS is stage 0 breast cancer**.)

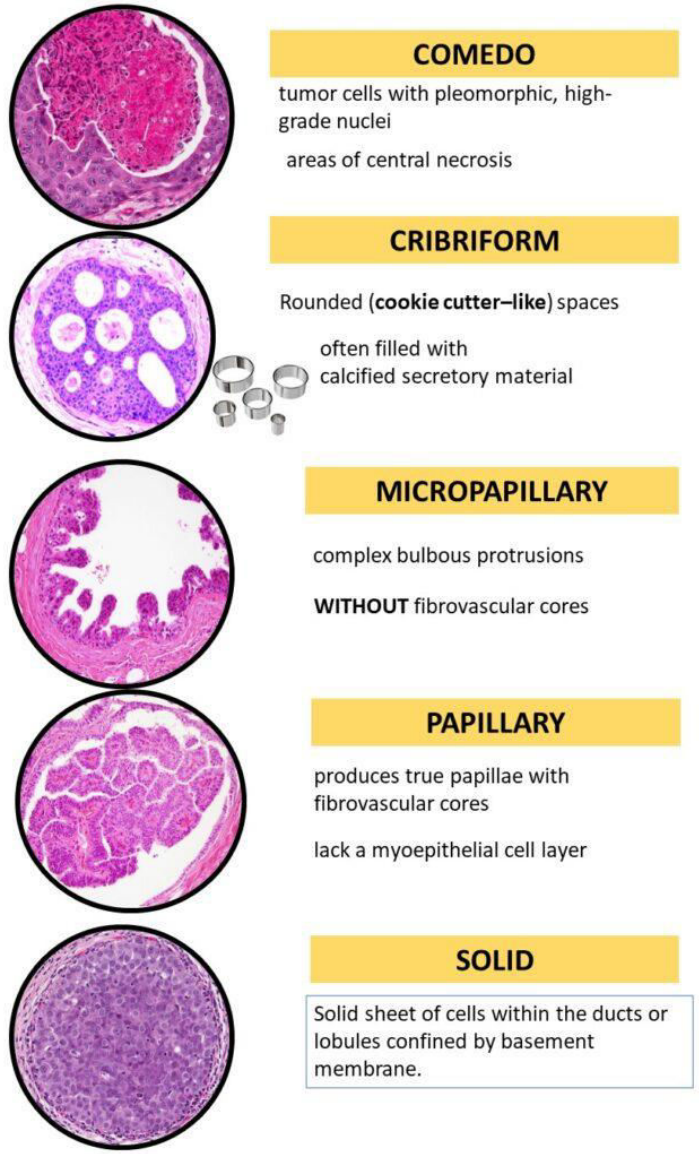
- Invasive ductal cancer (IDC) means that the cancer cells have broken beyond the breast duct. the most common type of breast cancer. IDC can be diagnosed at any stage from I-IV.



HISTOLOGICALLY THERE ARE MANY TYPES OF DCIS DEPENDING ON THE ARCHITECTURAL PATTERN.

A. **COMEDO :** tumor cells with pleomorphic, high-grade nuclei with central necrosis

B. **Non COMEDO:**
   1. **CRIBRIFORM**: Rounded (cookie cutter–like) spaces, and often filled with calcified secretory material
   2. **MICROPAPILLARY:** Seen as complex bulbous protrusions WITHOUT fibrovascular cores
   3. **PAPILLARY:** produces true papillae with fibrovascular cores AND lack myoepithelial layer
   4. **SOLID:** Solid sheet of cells within the ducts or lobules confined by basement membrane.
   5. **MIXED:** Mixture of two or more patternss above.



- Ductal carcinoma in situ carries a high risk for the development of breast cancer in the area of the breast in which it occurs, the risk being **proportional to the grade of ductal carcinoma in situ**.

Grade	Cells morphology	Nuclei	Mitoses
High-grade DCIS	Large, pleomorphic cells	Nuclei more than 2.5 red blood cells in diameter. Nucleoli often multiple prominent	frequent
Intermediate-grade DCIS	This is diagnosed when the lesion cannot be assigned to the high or low nuclear Grade. Nuclei show moderate pleomorphism, less than that seen in the high-grade cell disease but lack the monotony and regularity of size and spacing of the low-grade form		
Low-grade DCIS	Spaced small, regular cells	Round monotonous nuclei, typically 1.5 - 2 red blood cells in diameter. Nucleoli are typically not prominent	Mitoses are sparse and chromatin is usually finely dispersed

LOBULAR CARCINOMA IN SITU(LCIS)

- ✓ originates from the terminal duct lobular units and develops only in the female breast.
- ✓ It is characterized by distention and distortion of the terminal duct lobular units by cells that are large but maintain a normal nuclear to cytoplasmic ratio.
- ✓ Cytoplasmic mucoid globules are a distinctive cellular feature.

- may be observed in breast tissues that contain microcalcifications, but the calcifications associated with LCIS typically occur in adjacent tissues (unique to LCIS)
- 1–5% of all newly diagnosed breast cancers.
- The average age at diagnosis is 45 years.
- LCIS has a distinct racial predilection, occurring 12 times more frequently in white women than in African-American women.
- risk of development of breast cancer: DCIS > LCIS
- Multicentricity occurs in 60% - 90% of women with LCIS.
- LCIS may be classic LCIS or pleomorphic LCIS

INVASIVE BREAST CARCINOMA

FOOTE AND STEWART ORIGINALLY PROPOSED THE FOLLOWING CLASSIFICATION FOR INVASIVE BREAST CANCER

Paget's disease of the nipple	Invasive ductal carcinoma—Adenocarcinoma with productive fibrosis (scirrhous, simplex, NST), 80%	Medullary carcinoma, 4%	Mucinous (colloid) carcinoma, 2%
Papillary carcinoma, 2%	Tubular carcinoma, 2%	Invasive lobular carcinoma, 10%	Rare cancers (adenoid cystic, squamous cell, apocrine)

INVASIVE DUCTAL CARCINOMA

- Most invasive ductal carcinomas produce a **desmoplastic response**, which **replaces normal breast fat** (resulting in a mammographic density) and eventually leads to the appearance of a **hard, palpable irregular mass**.
- This cancer occurs most frequently in perimenopausal or postmenopausal women in the 5^{th} to 6^{th} decades of life as a **solitary, firm mass**.
- poorly defined margins
- its cut surfaces show a central stellate configuration with chalky white or yellow streaks extending into surrounding breast tissues
- Pathological features of invasive ductal breast cancer:
    1. Disorganized, small, duct-like glandular cells with stromal invasion (desmoplastic stroma)
    2. Fibrosis of surrounding tissue
    3. Microcalcifications

INVASIVE LOBULAR CARCINOMA

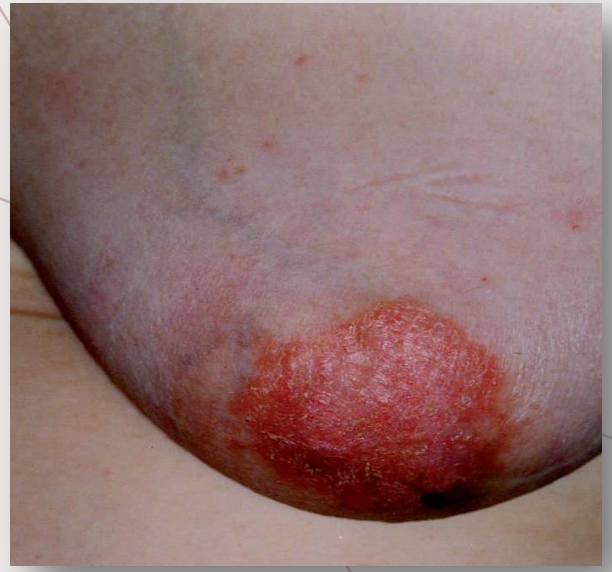
- accounts for 10% of breast cancers.
- The histopathologic features of this cancer include **small cells** with **rounded nuclei**, and **scant cytoplasm**.
- It is frequently **multifocal**, **multicentric**, and **bilateral**
- At presentation, varies from clinically inapparent carcinomas to those that replace the entire breast with a poorly defined mass

INFLAMMATORY BREAST CANCER

- a rare form of **advanced**, **invasive carcinoma**, characterized by **dermal lymphatic invasion** of tumor cells.
- Most commonly a ductal carcinoma.

- Clinical features:
  1. Erythematous and edematous (peau d'orange) skin plaques over a rapidly growing breast mass.
  2. Tenderness, burning sensation, blood-tinged nipple discharge.
  3. Axillary lymphadenopathy.
  4. 25% of patients have metastatic disease at the time of presentation.

PAGET DISEASE OF THE BREAST



- Clinical features:
  1. Erythematous, scaly, or vesicular rash affecting the nipple and areola
  2. Pruritus, burning sensation, nipple retraction.
  3. The lesion eventually ulcerates → blood-tinged nipple discharge

  - *it should be differentiated from eczema.
  - Nipple eczema should be biopsied if there is any doubt about its cause

SCREENING AND DIAGNOSIS OF BREAST CANCER (IMAGING TECHNIQUES)

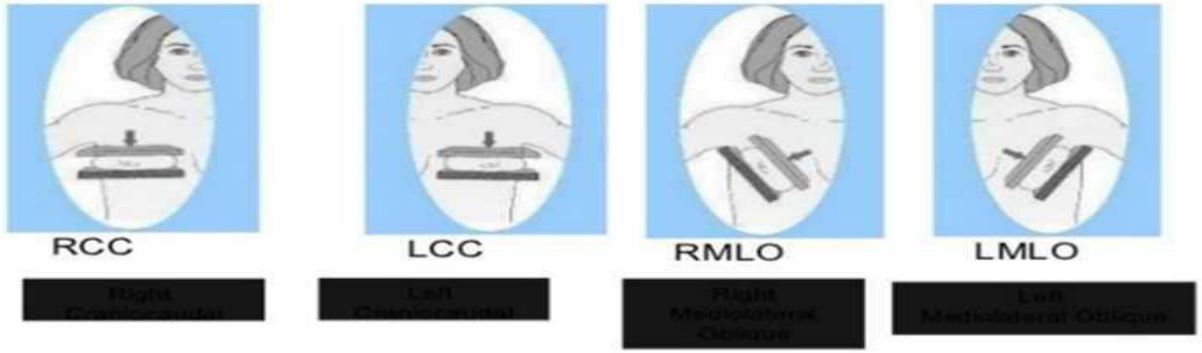
- **MAMMOGRAPHY**: a special type of X-ray create detailed imaging of the breast.
  - ✓ Screening mammography Consists of two images of each breast – Craniocaudal (CC) – Medial-lateral-oblique (MLO).
  - ✓ there is no increased breast cancer risk associated with mammography

- **Breast Ultrasound**
  - ✓ Second only to mammography
  - ✓ US is complementary to mammogram in diagnosis, and it can’t be used alone in screening
  - ✓ Screening ultrasound is not recommended for screening average-risk women

Radiographic views of the breast

Standard views:

- 45° Medio lateral Oblique (MLO view) / Lundgren's view
- Craniocaudal view (CC view)



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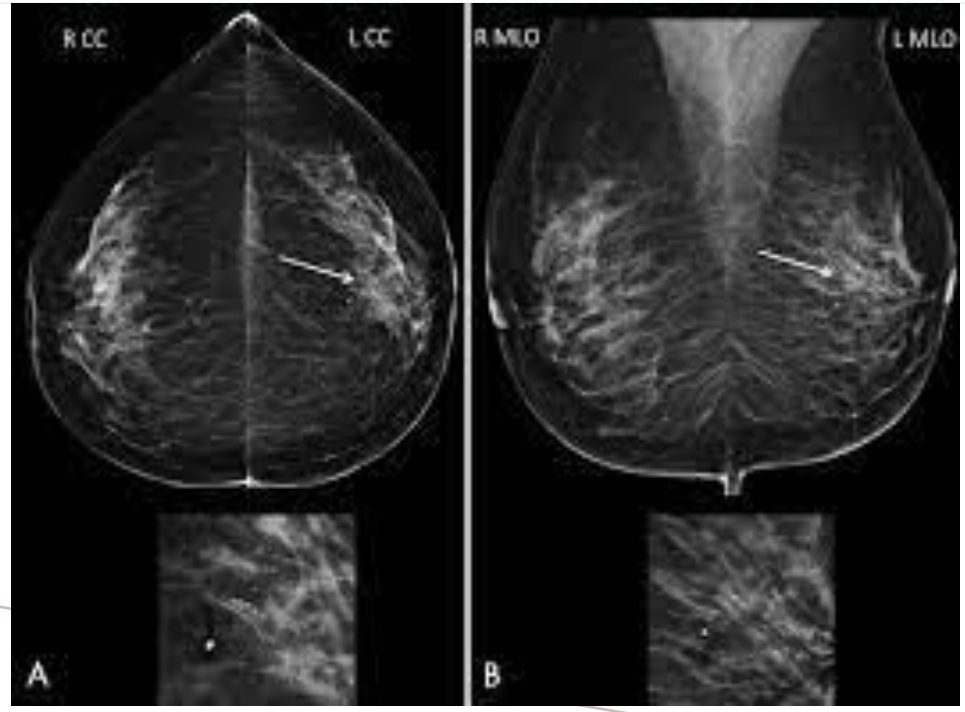
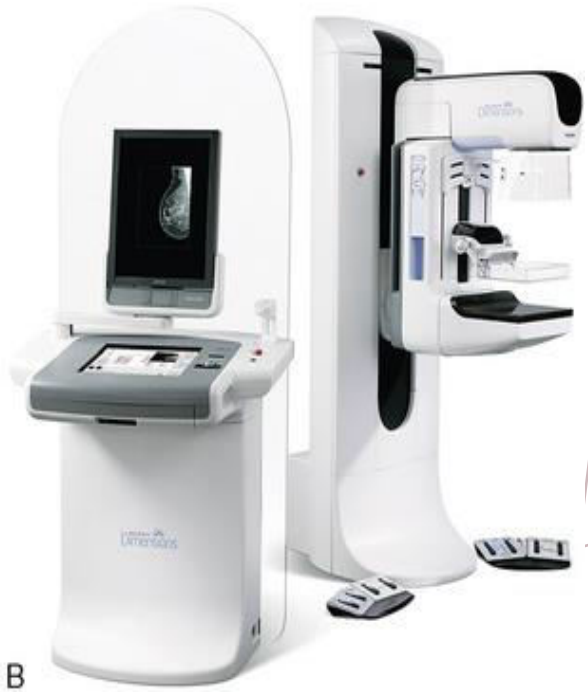
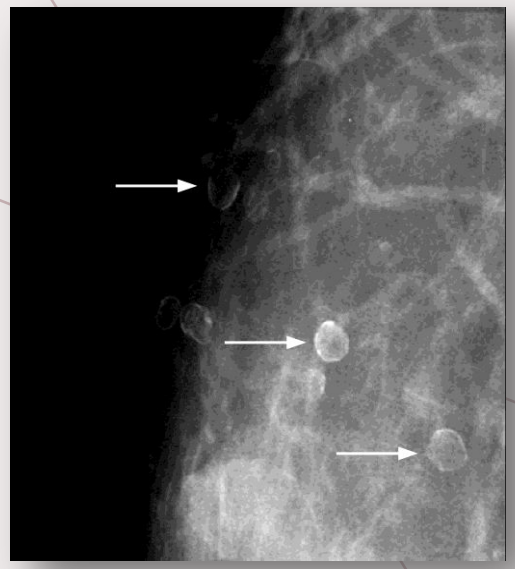
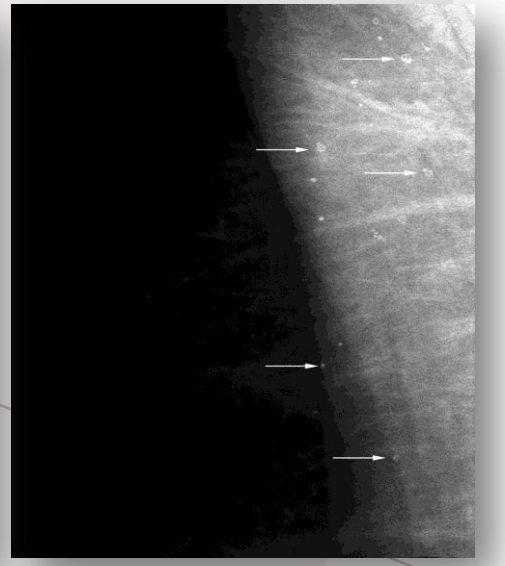




MAMMOGRAPHIC SIGNS OF BENIGN BREAST LESIONS



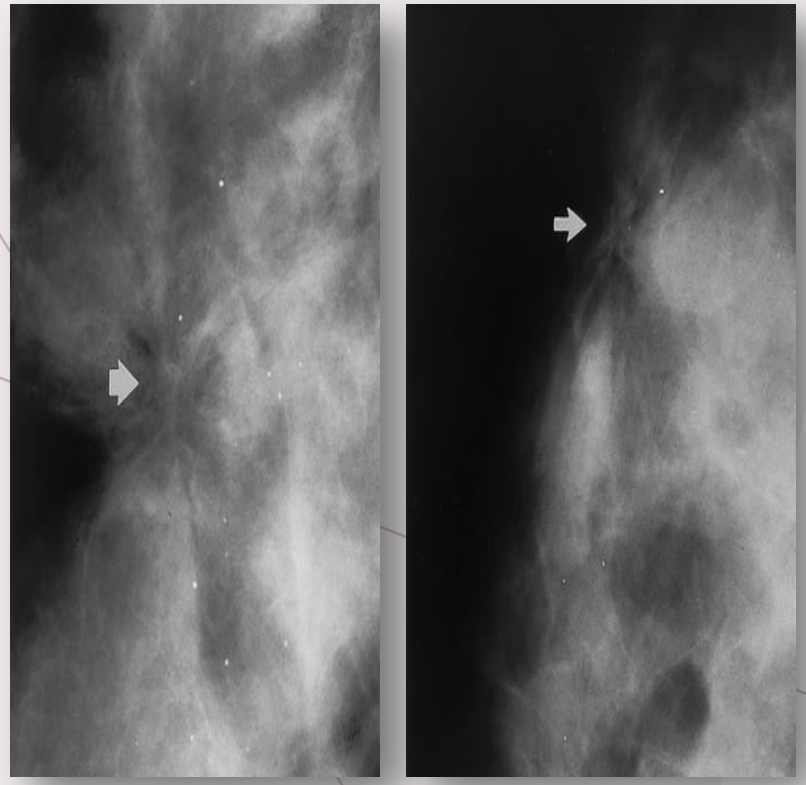


- **Benign masses** tend to be **spherical** with **smooth borders** & if they contain **calcifications** , it is coarser(**macro**) & more **structured-punctate or round** & are of **similar density** than that seen in carcinoma .

BENIGN CALCIFICATIONS:

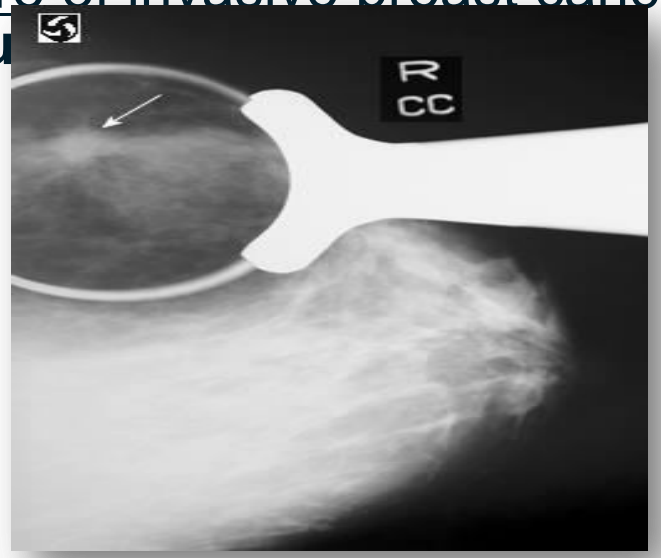
- 1-Skin or dermal calcifications. 2-Vascular calcifications. 3-Lucent-centered calcifications (Fat necrosis). 4- Egg-shell or rim calcifications(Fat necrosis or calcification in cyst wall). 5- Coarse or popcorn calcification(Fibroadenoma). 6-Large rod like calcifications or secretory calcifications. 7- Round or punctate calcification (less than 0.5mm). 8-Milk of calcium. 9-Suture calcification.

MAMMOGRAPHIC SIGNS OF MALIGNANT BREAST LESIONS

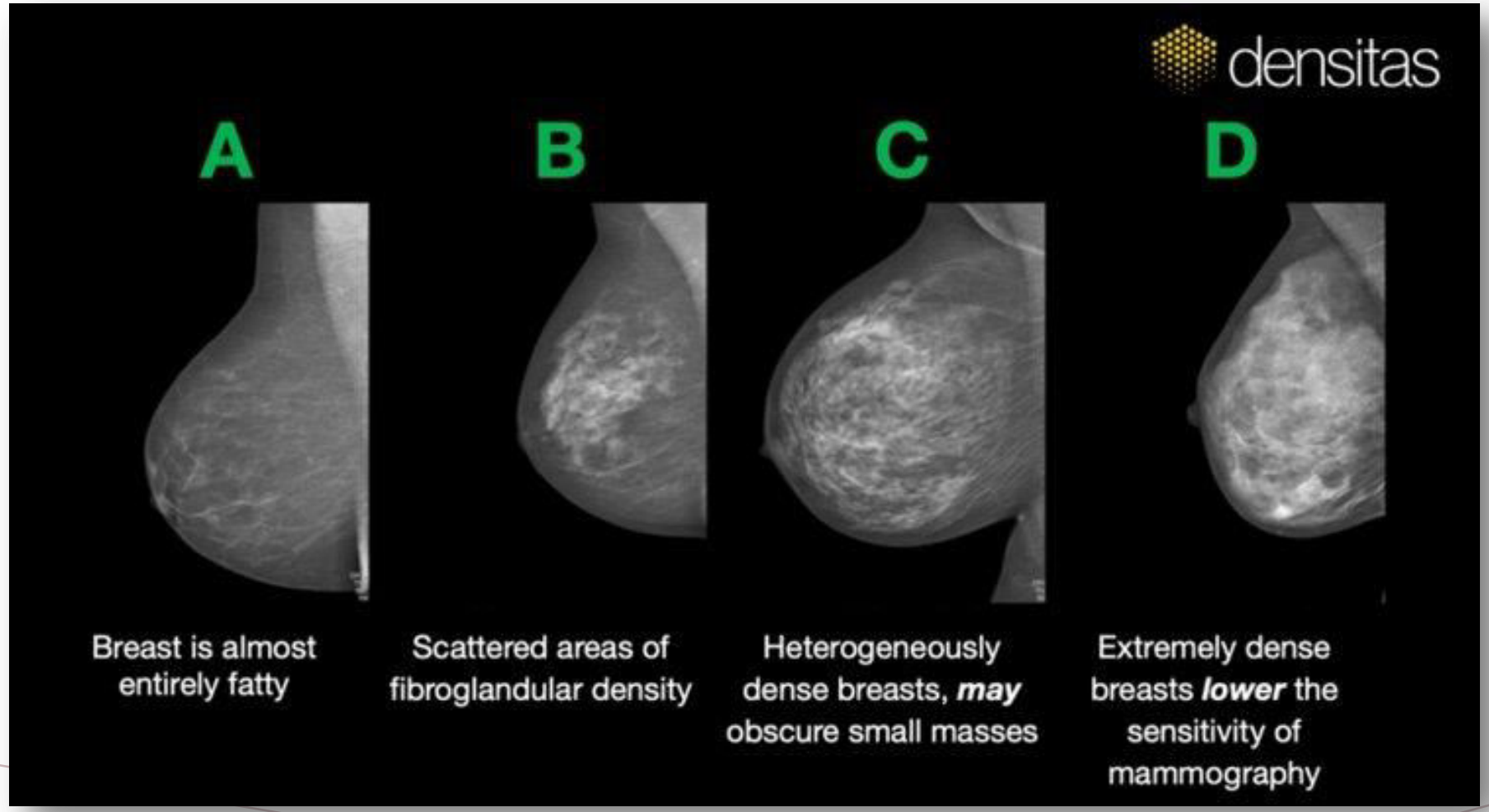


- ✓ Clustered calcifications
- ✓ microcalcifications
- ✓ Spiculated mass (spiky lump)
- ✓ Assymetrical density of breast tissue.
- ✓ Skin thickening
- ✓ Retraction (skin or nipple pulling inwards)
- ✓ Focal distortion (something is pressing on tissue) .

- ❖ The most specific mammographic feature of invasive breast cancer is a **spicu**



The sensitivity of mammography has an inverse relationship with breast density.



MRI

- highly sensitive screening tool for breast cancer, particularly useful when mammography or ultrasound may not provide clear results, such as in younger women with dense breast tissue.
- can lead to false-positive findings, requiring further evaluation through biopsy.
- MRI is often used as a supplement to mammography screening in high-risk groups due to its ability to detect abnormalities regardless of breast density.
- Despite its effectiveness, widespread use of MRI is limited by cost, limited availability, and potential adverse reactions to contrast agents.

WHY SCREEN?

1. Improved outcome by treatment during the asymptomatic period.
2. Significant impact on public health.
3. High prevalence.
4. Early stage disease is

SCREENING VERSUS DIAGNOSTIC TESTS

Screening evaluates a population of ASYMPTOMATIC people at risk for disease

Goals:

- ✓ High sensitivity for disease
- ✓ Low false negative rate
- ✓ Lower specificity acceptable

Diagnostic mammography – Patients with breast signs or symptoms (lump, pain, nipple discharge)

- ✓ Additional specialized mammographic views

DIAGNOSIS OF BREAST CANCER

- -Triple assessment:
  1-Examination:

Inspection/ Palpation/ Axillary nodes examination

- 2-Imaging Techniques
- 3-Breast Biopsy:
  The diagnosis of breast cancer is defined by the presence of malignant epithelial cells.

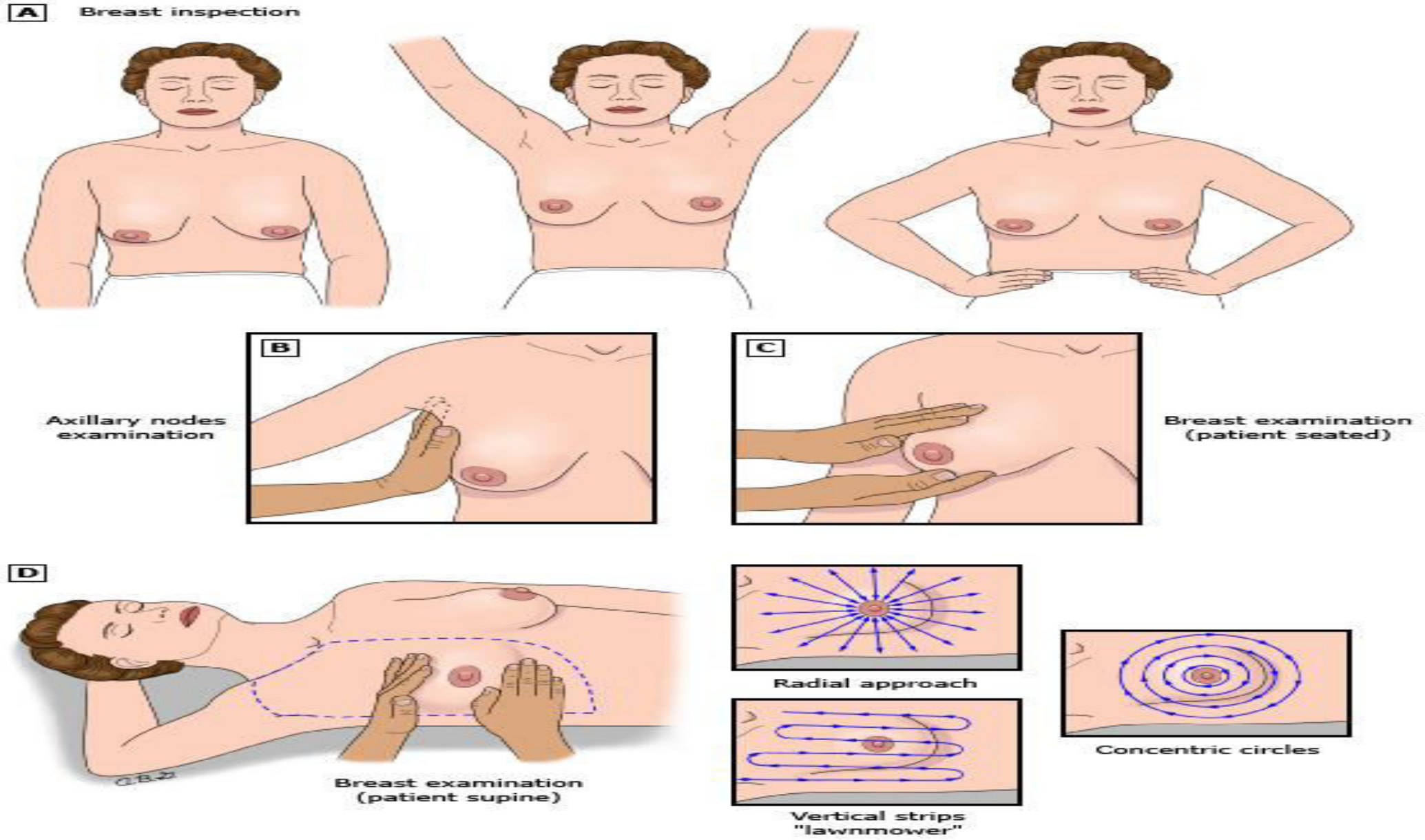
PHYSICAL EXAMINATION

A) INSPECTION: The breast examination is started with the patient in a seated position with her arms relaxed. Breast inspection is aided by patient positioning. The patient is asked to raise her arms over her head so the lower part of the breasts can be inspected for asymmetry, skin changes, and nipple inversion or retraction. The patient then puts her hands on her hips and presses in to contract the pectoral muscles so that any other areas of retraction can be visualized.

B) AXILLARY NODE EXAMINATION: The regional lymph node exam is completed while the patient is still in the sitting position and includes the cervical, supraclavicular, infraclavicular, and axillary nodal basins.

C) BREAST EXAMINATION (Seated position): A bimanual examination of the breasts can be performed while the patient is still in the sitting position. This is especially useful for women with large, pendulous breasts.

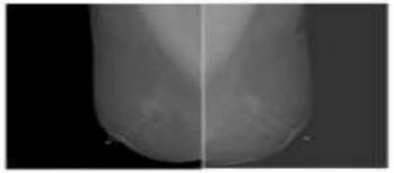
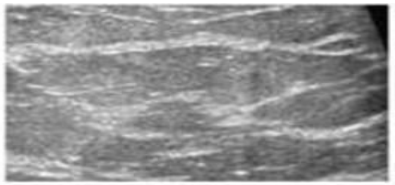
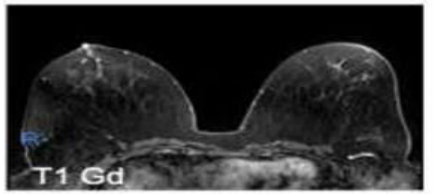
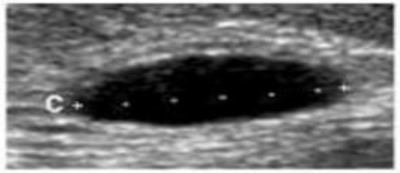
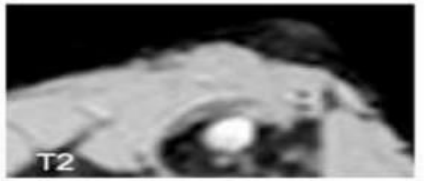
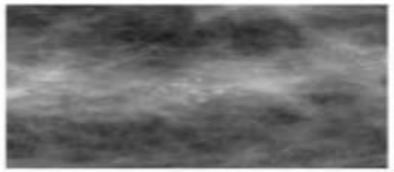
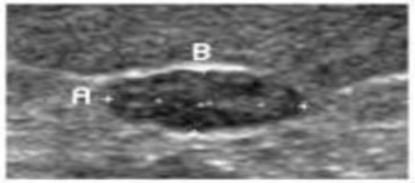
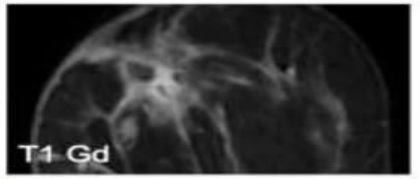
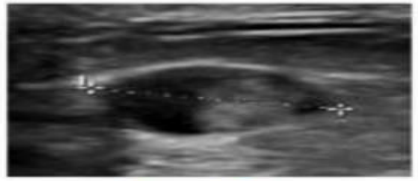
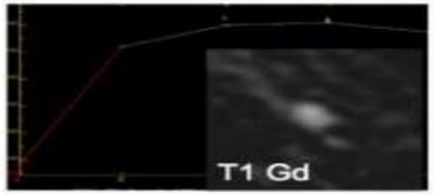
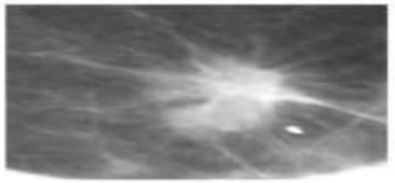
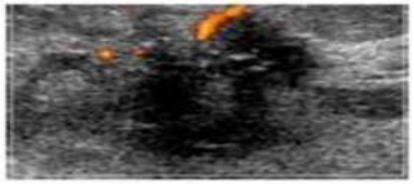
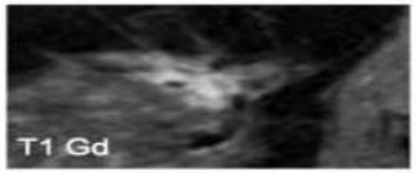
D) BREAST EXAMINATION (Supine position): The breast examination is completed with the patient in a supine position with the ipsilateral arm raised above her head. The area examined should extend from the clavicle superiorly to the rib cage inferiorly and from the sternum medially to the midaxillary line laterally. A systematic approach ensures that the entire breast is examined. This can be accomplished with either concentric circles, a radial approach, or vertical strips, referred to as the "lawnmower" method.

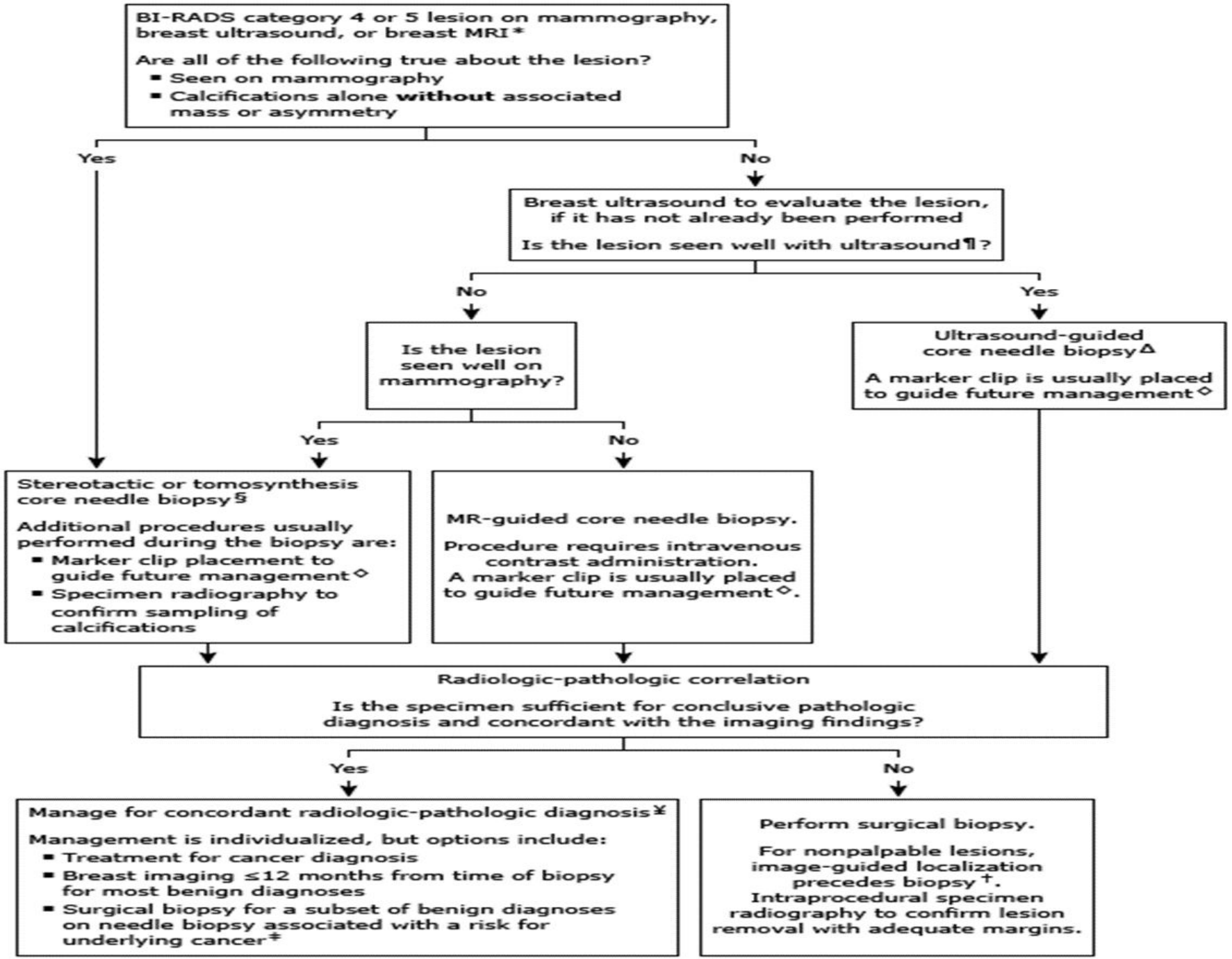

A
Breast inspection
B
Axillary nodes examination
C
Breast examination (patient seated)
D
Breast examination (patient supine)
Radial approach
Concentric circles
Vertical strips "lawnmower"

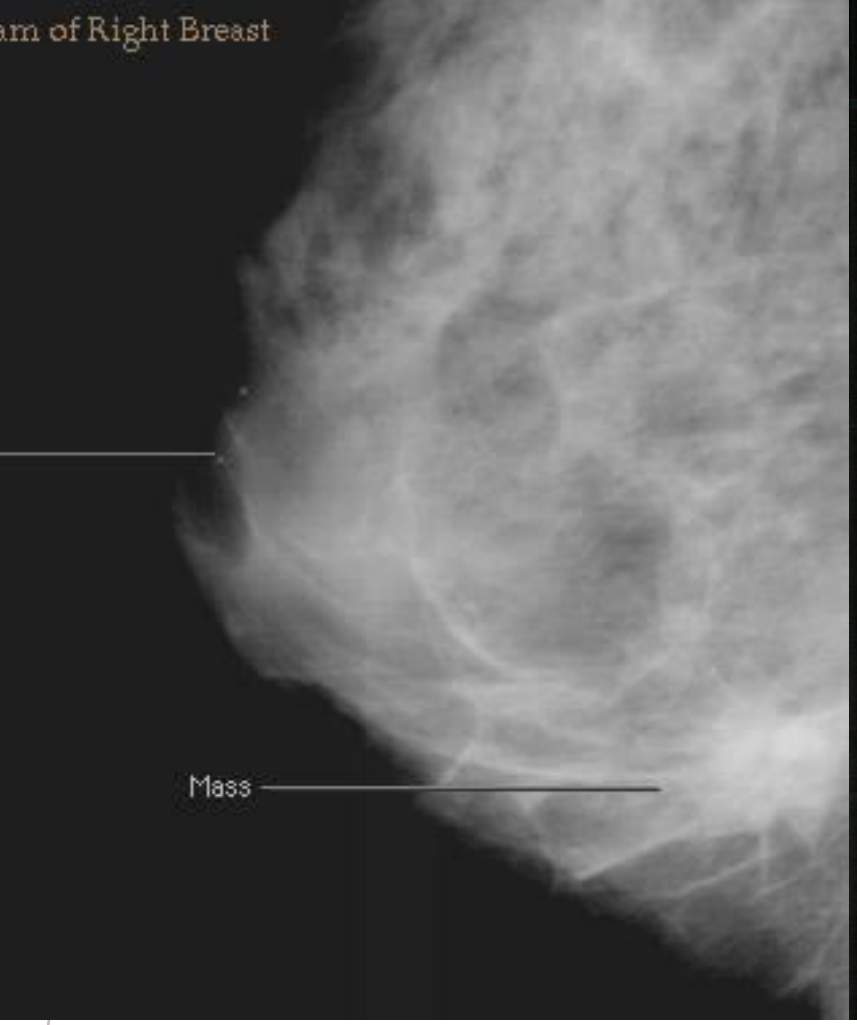
Imaging Techniques
Breast Imaging-Reporting and Data System (BI-RADS) categorization

Assessment	Management	Likelihood of Cancer
Need additional imaging evaluation and/or prior mammograms for comparison	Recall for additional imaging and/or comparison with prior examination(s)	N/A
Category 1: Negative	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 2: Benign	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 3: Probably benign	Short-interval (6-month) follow-up or continued surveillance mammography	>0 but ≤2% likelihood of malignancy

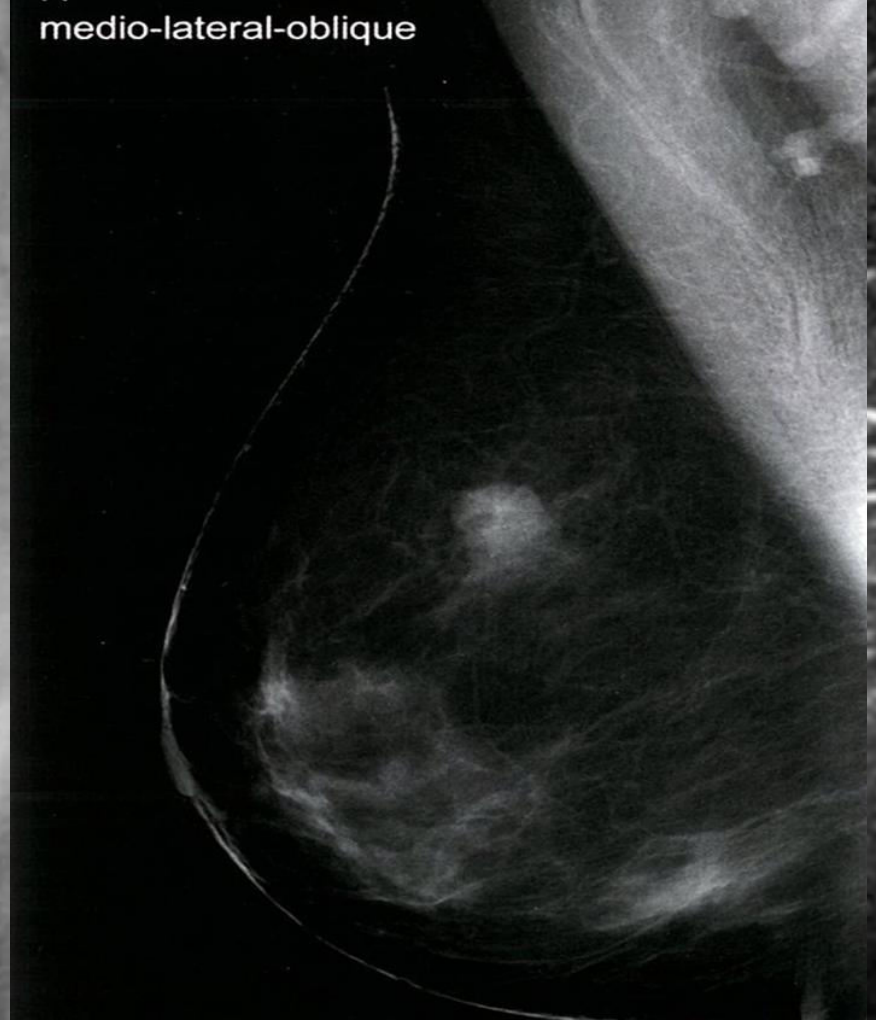
Category 4: Suspicious	Tissue diagnosis*	>2 but <95% likelihood of malignancy
Category 4A: Low suspicion for malignancy		>2 to ≤10% likelihood of malignancy
Category 4B: Moderate suspicion for malignancy		>10 to ≤50% likelihood of malignancy
Category 4C: High suspicion for malignancy		>50 to <95% likelihood of malignancy
Category 5: Highly suggestive of malignancy	Tissue diagnosis*	≥95% likelihood of malignancy
Category 6: Known biopsy-proven malignancy	Surgical excision when clinically appropriate	N/A

BI-RADS Category	A. Mammography	B.Ultrasound	C. MRI	
1				Almost entirely fatty. No abnormality
2				A. Involuting, calcified fibroadenoma B,C. Simple Cyst
3				A. Cluster of punctate calcifications B. Solid mass, most likely fibroadenoma C. Seroma postbiopsy, probable inflamattory changes
4				A. Pleomorphic calcifications B. Complex cyst C. Lobulated solid mass, kinetic curve: type II
5				A,B,C. Spiculated mass

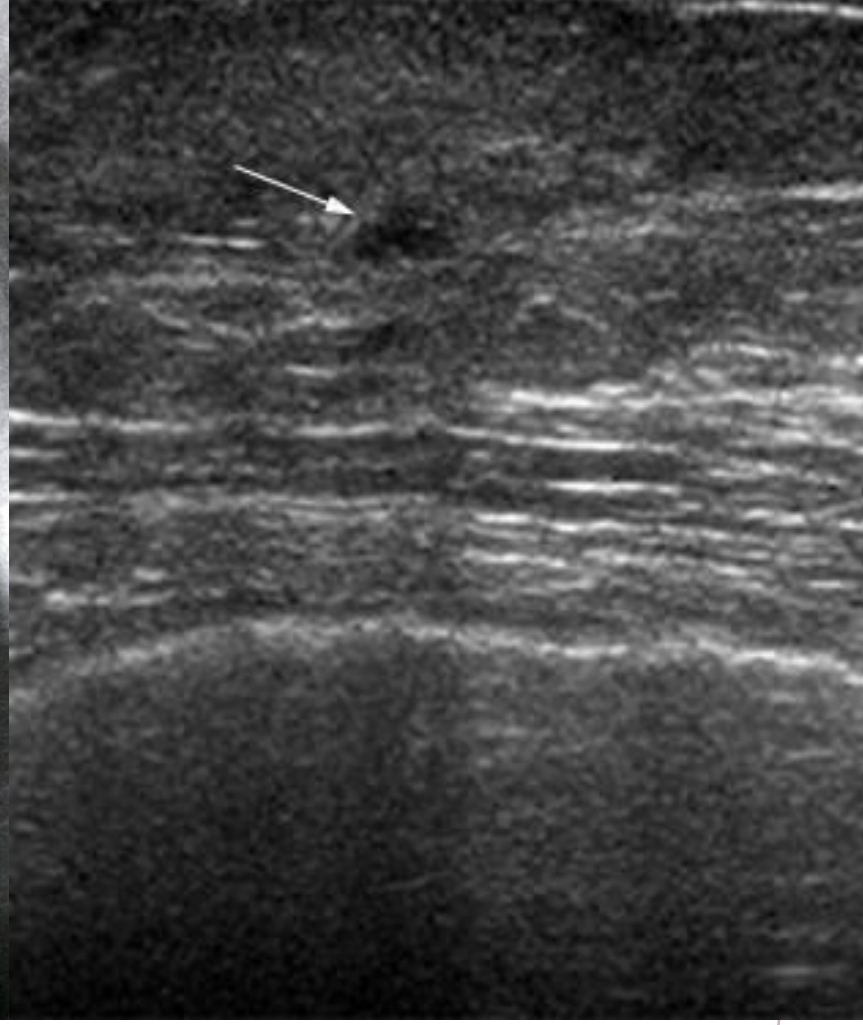

BI-RADS category 4 or 5 lesion on mammography, breast ultrasound, or breast MRI*
Are all of the following true about the lesion?
Seen on mammography
Calcifications alone without associated mass or asymmetry
Yes
No
Breast ultrasound to evaluate the lesion, if it has not already been performed
Is the lesion seen well with ultrasound¶?
No
Yes
Is the lesion seen well on mammography?
Ultrasound-guided core needle biopsyΔ
A marker clip is usually placed to guide future management◇
Yes
No
Stereotactic or tomosynthesis core needle biopsy§
Additional procedures usually performed during the biopsy are:
Marker clip placement to guide future management◇
Specimen radiography to confirm sampling of calcifications
MR-guided core needle biopsy.
Procedure requires intravenous contrast administration.
A marker clip is usually placed to guide future management◇.
Radiologic-pathologic correlation
Is the specimen sufficient for conclusive pathologic diagnosis and concordant with the imaging findings?
Yes
No
Manage for concordant radiologic-pathologic diagnosis¥
Management is individualized, but options include:
Treatment for cancer diagnosis
Breast imaging ≤12 months from time of biopsy for most benign diagnoses
Surgical biopsy for a subset of benign diagnoses on needle biopsy associated with a risk for underlying cancer‡
Perform surgical biopsy.
For nonpalpable lesions, image-guided localization precedes biopsy†.
Intraprocedural specimen radiography to confirm lesion removal with adequate margins.



This is an abnormal mammogram showing a mass, caused by breast cancer.



Mammography of the right breast (mediolateral oblique view).
A poorly defined lesion with radial protrusions is visible (green circular overlay). This finding is consistent with breast cancer



-Ultrasound of early breast cancer.
-Left breast ultrasound demonstrates a hypoechoic nodule with posterior acoustic shadowing that corresponds to the mammographic abnormality.

BREAST BIOPSY

-Breast biopsy methods include core needle biopsy (CNB), fine needle aspiration (FNA), surgical biopsy, and skin punch biopsy.

-AGAIN, The diagnosis of breast cancer is defined by the presence of malignant epithelial cells.

-Based on the prebiopsy imaging, the radiologist makes an assessment of which approach will yield the highest likelihood of success, while considering patient safety and comfort.

-The requirements of subsequent therapy and/or clinical trial (eg, marker clip placement, tissue banking) are additional factors that are included in biopsy planning.

-The choice of imaging guidance depends upon the modality on which the lesion is best visualized and whether it is palpable

Core Needle Biopsy — CNB

-Is preferred as the initial biopsy procedure as it is minimally invasive and still likely to acquire sufficient tissue to adequately sample the intended target.

-preferred tool for assessing a suspicious breast on ultrasound or mammography.

-A small skin incision is made through which the core biopsy needle (typically 9 to 14 gauge [approximately 2.1 mm outer diameter]) is introduced

-CNB is performed under image guidance with either US, x-ray (ie, stereotactic or tomosynthesis), or MRI without and with intravenous contrast.

-However, it is considered as invasive procedure, requires local anesthesia, and is associated with high risk of complications (pain, hematoma) in comparison with FNA.

IMAGE-ASSISSTED CNB

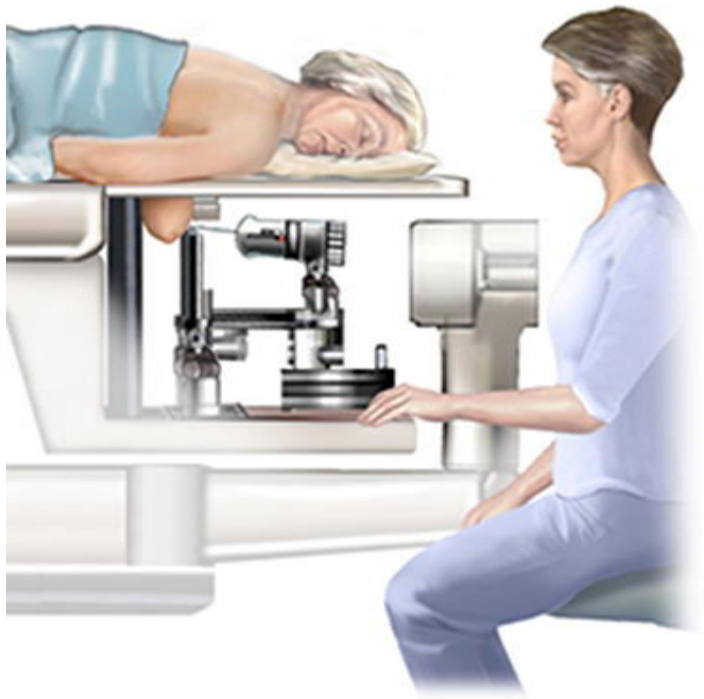
-US guidance - it is preferred if the target lesion is well visualized with this modality, is usually the most tolerated as the patient is lying supine during the procedure and does not require breast compression.

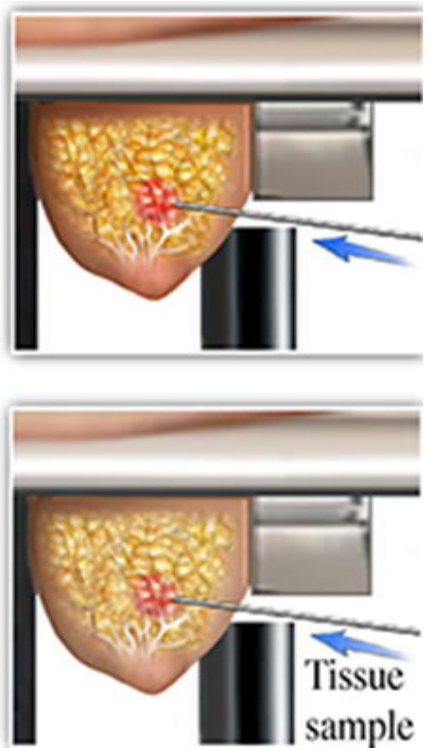
-Stereotactic guidance- For mammographic abnormalities not well visualized on US, stereotactic CNB is performed.

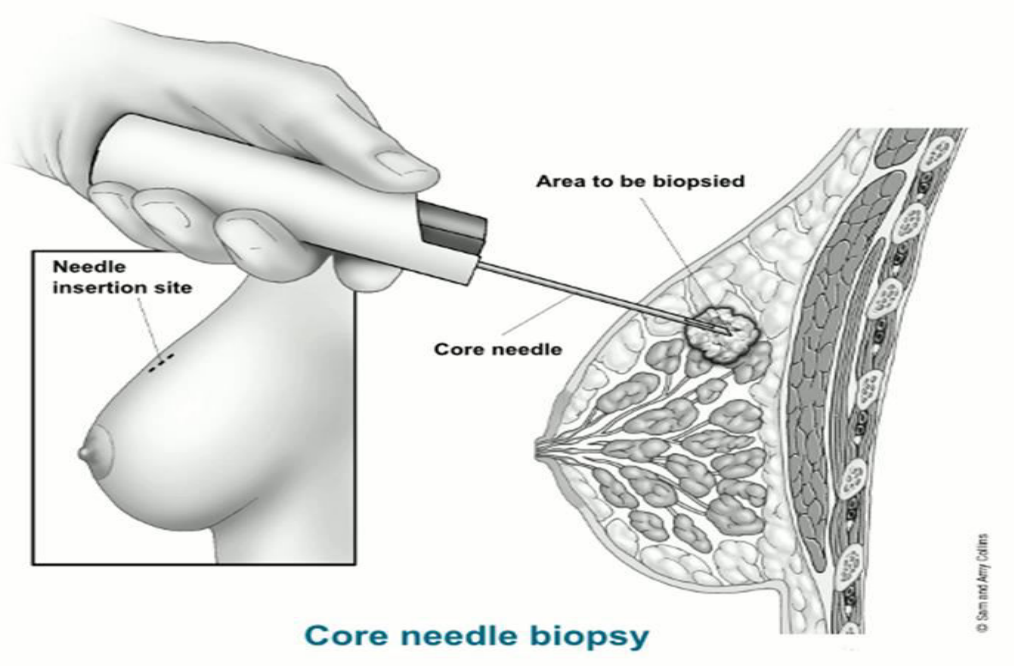
NOTE: While the majority of mammographic lesions can be biopsied using this technique, some lesions (eg, lesions close to the nipple or chest wall, very faint calcifications) are not amenable to this approach.

-Tomosynthesis (3D-Mammography) guidance - For patients with an abnormality seen only on this imaging method, tomosynthesis-guided biopsy is done.

-Magnetic Resonance Imaging guidance– For patients with masses only seen on this method.



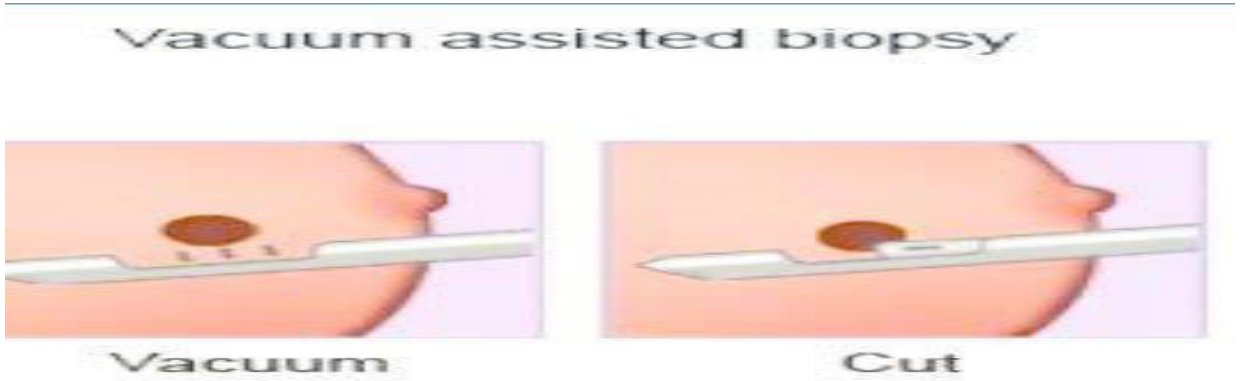

Tissue
sample


Area to be biopsied
Needle
insertion site
Core needle
Core needle biopsy

Vacuum-assisted CNB

-Use of a VAB device increases the volume of tissue that can be obtained quickly and may decrease the false negative rate for tumor detection.

-VAB enables efficient collection of multiple samples in a rotational fashion with a single insertion of the biopsy device

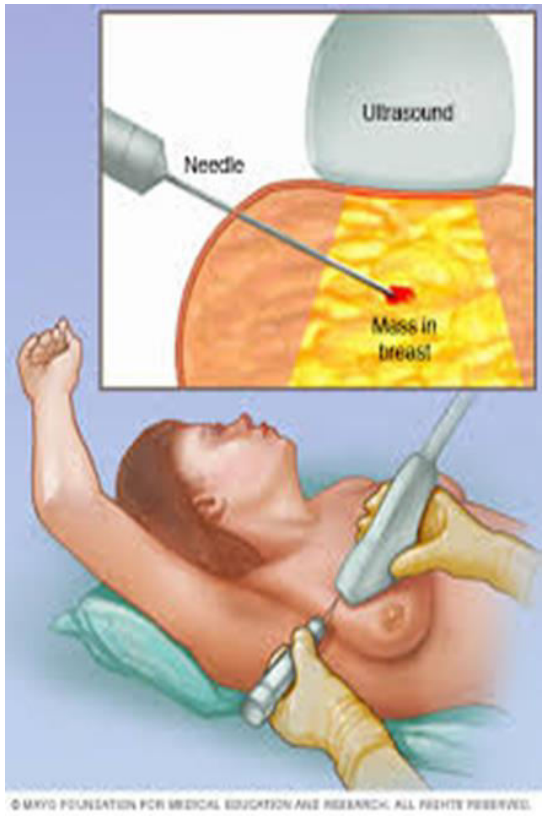


Clip Placement

- A marker clip is placed in the sampled region of the breast at the time of a CNB to mark the biopsy site for subsequent management and follow-up.
- It is done in order:
  - ✓ To document that the lesion has been sampled and that it correlates with the lesion originally detected on mammography or MRI if US guidance was used.
  - ✓ To mark the biopsy site of small lesions that might be completely removed during CNB or are no longer visible following CNB.
  - ✓ To mark the tumor site of patients in whom neoadjuvant therapy is planned

FINE NEEDLE ASPIRATION (FNA)

- FNA, under either palpation or US guidance, is another biopsy option.
- Most useful for masses directly under the skin.
- FNA is considered simple, fast, minimally-invasive, requires no local anesthesia, and is associated with less complications.
- However, because FNA demonstrates higher rates of false negative results and insufficient samples, CNB following FNA is sometimes necessary, especially if cytology indicates there is potential for malignancy.
- FNA biopsy is performed with a 10- or 20-mL syringe and a 21- to 27-gauge needle under palpation or US guidance. The patient is supine, and no breast compression is required.
- While FNA can provide a rapid preliminary diagnosis of cancer, it cannot distinguish between in situ and invasive cancer. In addition, the specimen may not be sufficient for other laboratory analyses (eg, receptor status).



SURGICAL BIOPSY

-Surgical biopsy is not the initial method, unless needle biopsy is not technically feasible. Surgical biopsy more often serves as the secondary method when CNB results are inconclusive or discordant with the imaging findings.

-Surgical biopsy can remove the entire lesion (excisional biopsy) or only a portion of it (incisional biopsy). Whether to perform an incisional or an excisional biopsy depends upon the indications for the biopsy:

-Incisional biopsy is used to confirm a diagnosis when a biopsy is nondiagnostic and the mass is large.

-Excisional biopsy is used in cases where the lesion is in such a location that it is not amenable to CNB or where the result of a CNB is atypical or nondiagnostic/indeterminate, is discordant with imaging results, or yields benign but high-risk lesions.

-Surigcal biopsy is also required for cysts that do not completely resolve after aspiration, indicating that there may be a residual mass, and size increase of a mass or suspicious changes are seen on follow-up imaging after a CNB with benign results.

-This method requires general anesthesia, is considered the most invasive, and is associated with the highest risk of complications (Surgical site infection, bleeding) in comparison with FNA & CNB.

-Skin punch biopsy A small skin biopsy using a punch biopsy device can differentiate between benign and malignant skin changes. Punch biopsy may be needed if there is concern for Paget disease, skin involvement with invasive breast cancer, inflammatory breast cancer, or skin recurrence of breast cancer

WHAT'S NEXT?

- If cancer is identified, **hormone receptor status is determined.**
- **Breast cancer receptor testing** — Newly diagnosed breast cancers must be tested for estrogen (ER) and progesterone (PR) receptor expression and for overexpression of human epidermal growth factor 2 (HER2) receptors. **This information is critical for both prognostic and therapeutic purposes**.

➢ patients who are ER and/or PR positive are candidates for endocrine therapy as neoadjuvant or adjuvant treatment.

- Analysis involves immunohistochemical staining.
- 80% of breast cancers are positive for overexpression of at least one hormone receptor
- HER2-positive breast cancer can be treated with therapeutic receptor inhibition, which can help to slow cancerous growth and decrease cancer mass. "Trastuzumab"

TUMOR MARKERS

- CEA
- CA 15-3
- CA 27-29

Tumor markers can not be used to detect breast cancer because they lack sensitivity and specificity. In newly diagnosed breast cancer, however, they can be used for monitoring therapeutic success (e.g., the response to systemic therapy or success of surgical tumor removal).

STAGING OF BREAST CANCER

The TNM staging system

This system takes into account:

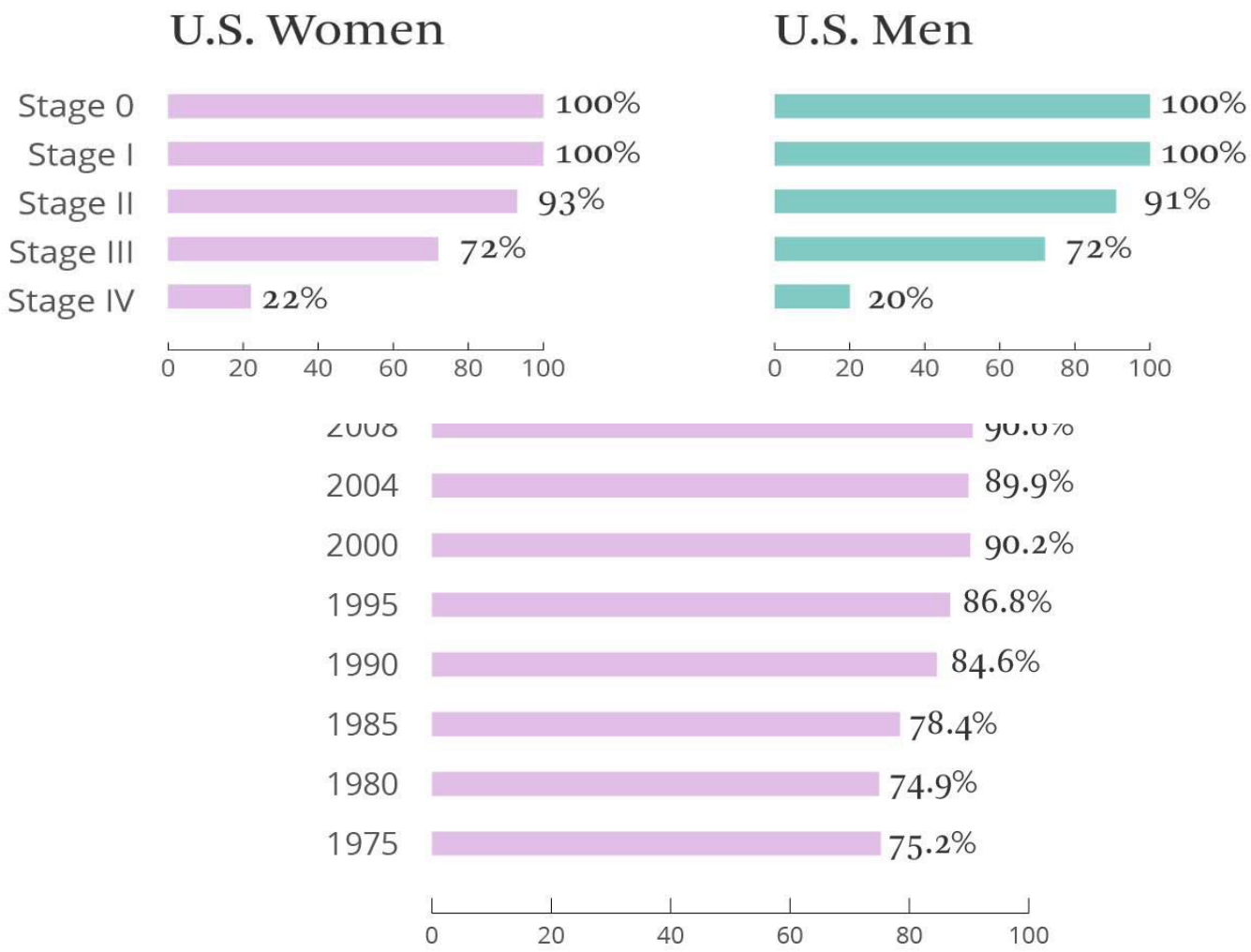
- The tumor size and spread (T),
- Whether the cancer has spread to lymph nodes (N)
- Whether it has spread to distant organs (M) for metastasis

- **Stage 0** cancer means that the cancer is limited to the inside of the milk duct and is a non-invasive cancer. Stage 0 breast tumors include ductal carcinoma in situ (DCIS). **Lobular carcinoma in situ (LCIS) used to be categorized as Stage 0 but this has been changed, because it is not cancer, but does indicate a higher risk of breast cancer**.
- **Stage I**: These breast cancers are still relatively small and either have not spread to the lymph nodes or have only a tiny area of cancer spread in the sentinel lymph node (the first lymph node to which cancer is likely to spread).
- **Stage II**: These breast cancers are larger than stage I cancers and/or have spread to a few nearby lymph nodes.
- **Stage III**: These tumors are larger or are growing into nearby tissues (the skin over the breast or the muscle underneath), or they have spread to many nearby lymph nodes.
- **Stage IV**: cancers have spread beyond the breast and nearby lymph nodes to other parts of the body. Treatment for stage IV breast cancer is usually a systemic (drug) therapy.
- **Recurrent breast cancer** : Cancer is called recurrent when it comes back after treatment. Recurrence can be local (in the same breast or in the surgery scar), regional (in nearby lymph nodes), or in a distant area.

PROGNOSIS & SURVIVAL RATES

- **According to stages we know the survival rates of breast cancer.**
- Estimated five year survival rates:
- stage I: ~87%
- stage II: ~75%
- stage III: ~46%
- stage IV: ~13%

5-Year Survival Rate



THERAPEUTIC GUIDELINES FOR BREAST CANCER

- Nonmetastatic breast cancer is broadly considered in two categories:
  - **Early stage** – This includes patients with stage I, IIA, or a subset of stage IIB disease (T2N1).
  - **Locally advanced** – This includes a subset of patients with stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease.

EARLY-STAGE BREAST CANCER TREATMENT

- In general, patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) to the breast and regional nodes with or without radiation therapy (RT).
- Following definitive local treatment, adjuvant systemic therapy may be offered, based on various primary tumor characteristics such as tumor size, grade…

1) **Breast-conserving therapy:**

Breast-conserving therapy (BCT) is comprised of breast-conserving surgery (BCS; i.e., lumpectomy) plus Radiotherapy (RT).

Successful BCT requires complete surgical removal of the tumor (with negative surgical margins) followed by moderate-dose RT to eradicate any residual disease.

- Criteria that **preclude** BCT are as follows:
  - Multicentric disease
  - Large tumor size in relation to breast
  - Presence of diffuse malignant-appearing calcifications on imaging (ie, mammogram or magnetic resonance imaging [MRI])
  - Prior history of chest RT (eg, mantle radiation for Hodgkin disease)
  - Pregnancy
  - Persistently positive margins despite attempts at re-excision
- **The most reported side effects of BCT:**
  - Pain or tenderness or a "tugging" sensation in the breast
  - Temporary swelling
  - Hard scar tissue that forms in the surgical site
  - Change in the shape of the breast Nerve (neuropathic) pain (sometimes described as burning or shooting pain) in the chest wall, armpit, and/or arm that doesn't go away over time.
  - This can also happen in mastectomy patients and is called post-mastectomy pain syndrome or PMPS.

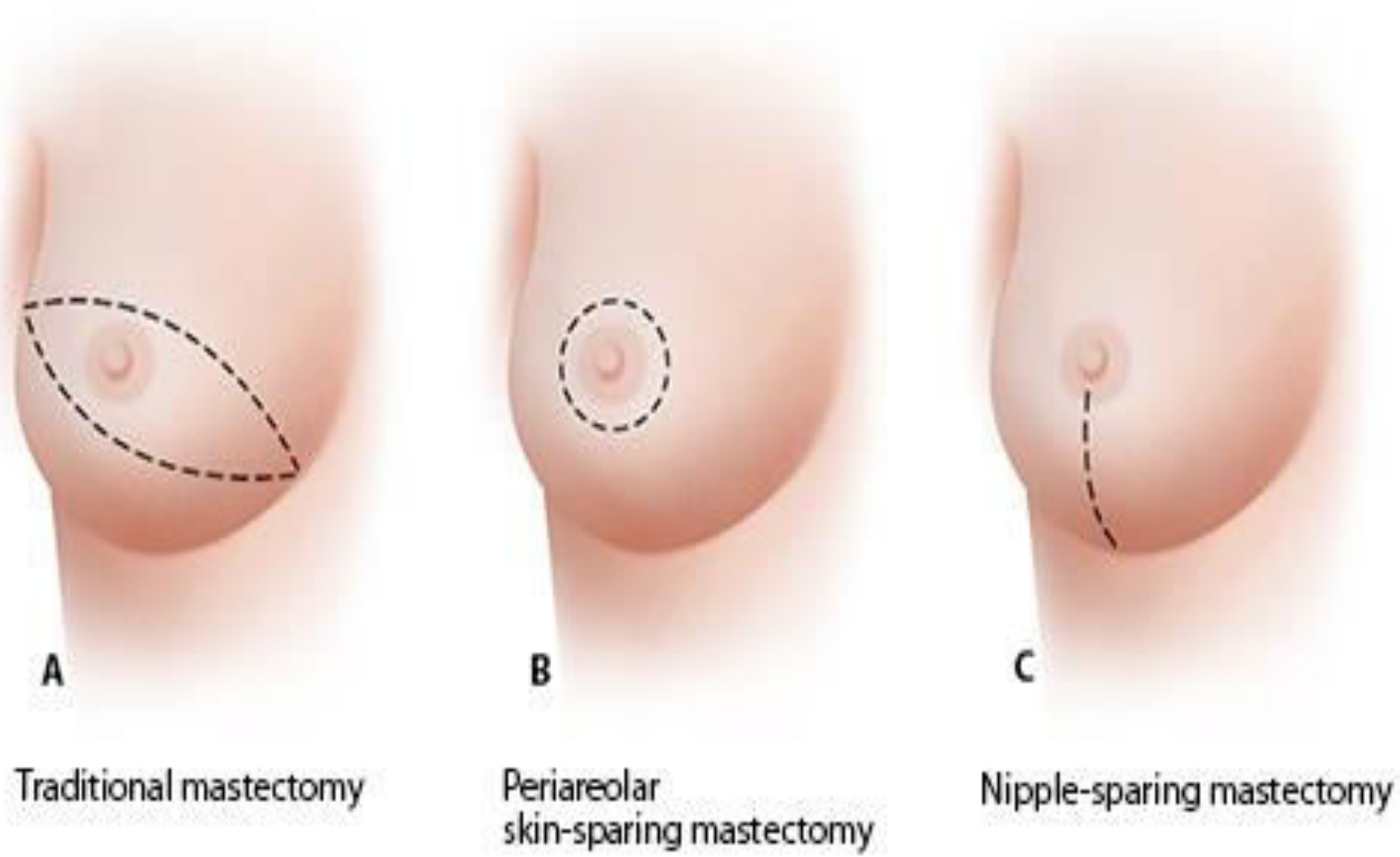
2) MASTECTOMY

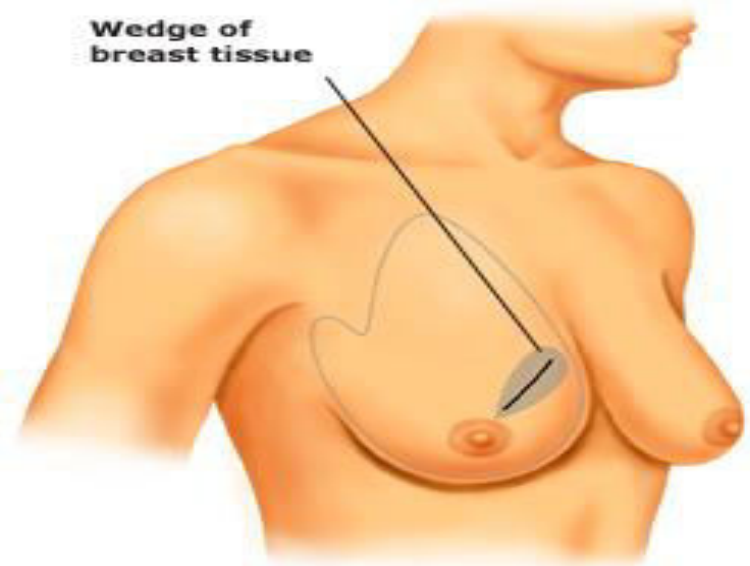
- A surgery in which the entire breast is removed, including all the breast tissue and sometimes other nearby tissues. It's often done when a woman cannot be treated with breast-conserving surgery (lumpectomy), which spares most of the breast.
- Women at very high risk of getting a second cancer sometimes have a double mastectomy, the removal of both breasts.
- **Indications of mastectomy:**
  - recurrence tumor post BCS
  - Multiple tumor in the same breast
  - Having a larger tumor (greater than 5 cm)
  - Have a genetic factor such as a BRCA mutation, which might increase your chance of a second cancer
  - Have a serious connective tissue disease such as scleroderma or lupus, which may make you especially sensitive to the side effects of radiation therapy
  - Have inflammatory breast cancer

CHOICE OF MASTECTOMY

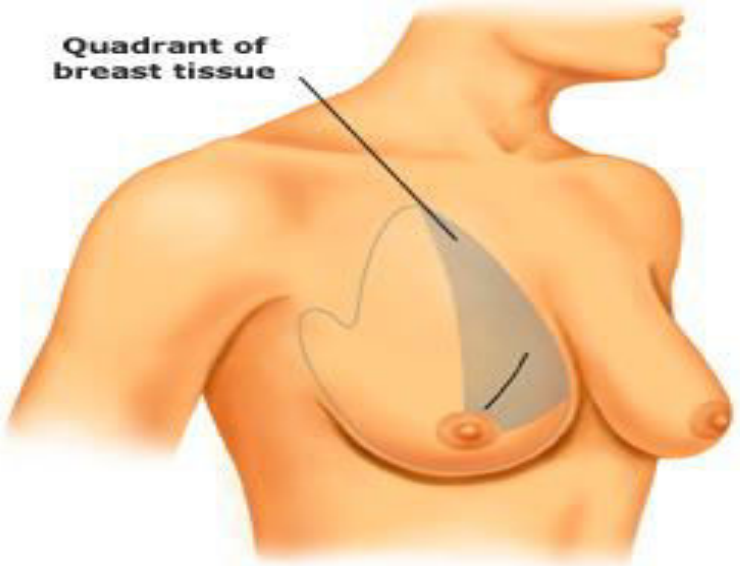
- **Delayed or no reconstruction:**
  - **Simple (or total) mastectomy;** in this procedure, the surgeon removes the entire breast, including the nipple, areola, and skin. Some underarm lymph nodes may or may not be removed depending on the situation. Most women, if they are hospitalized, can go home the next day.
  - **Modified Radical Mastectomy (MRM);** An MRM is a complete removal of the breast and the underlying fascia of the pectoralis major muscle, along with the level I and II axillary lymph nodes. Several randomized trials have documented equivalent survival rates with MRM compared with radical mastectomy, with less morbidity.
- **Immediate reconstruction:**
  - **Skin-sparing mastectomy;** most of the skin over the breast is left intact. Only the breast tissue, nipple and areola are removed.
  - **Nipple-areolar-sparing mastectomy;** it differs from other mastectomy techniques in that it preserves the dermis and epidermis of the nipple but removes the major ducts from within the nipple lumen, whereas other techniques remove the NAC. If the nipple cannot be preserved, there is also an option of removing the nipple and preserving the areola (areolar-sparing mastectomy), which can also preserve the cosmetic outcome, particularly in women who do not have a sizable nipple

- **Radical mastectomy** — Radical mastectomy is rarely used in modern breast surgery. A radical (Halsted) mastectomy consists of en bloc removal of the breast, the overlying skin, the pectoralis major and minor muscles, and the entire axillary contents (level I, II, and III nodes). This extensive resection was originally proposed to provide a better chance of disease control than lumpectomy alone and was the standard of care for treating breast cancer for many years, largely in an era where systemic therapy was unavailable. However, despite improved local control, the curative potential of this operation remained limited

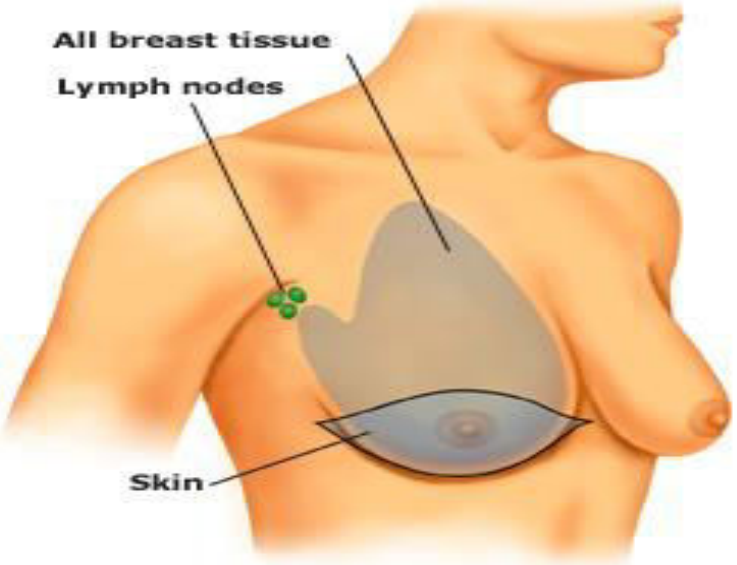

A
B
C
Traditional mastectomy
Periareolar
skin-sparing mastectomy
Nipple-sparing mastectomy



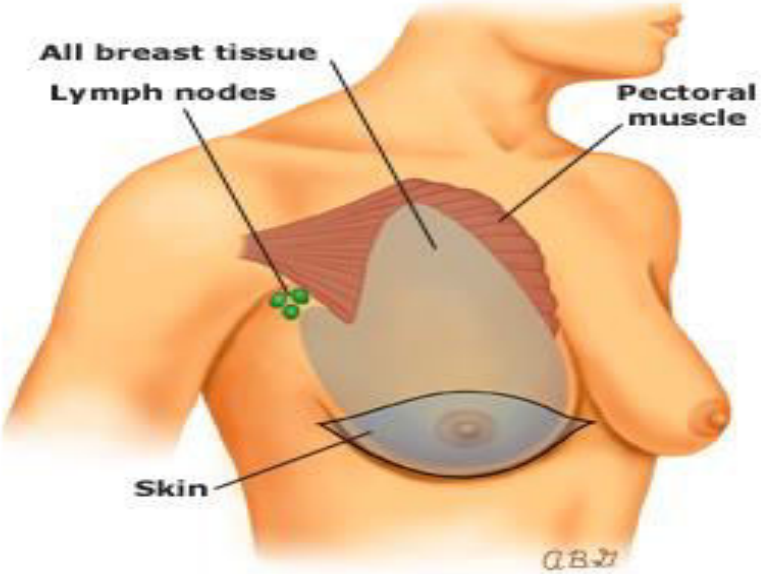
Partial mastectomy/lumpectomy



Quadrantectomy



Modified radical mastectomy



Radical mastectomy

LYMPH NODE SURGERY FOR BREAST CANCER

- **Sentinel lymph node biopsy (SLNB)**

-The surgeon finds and removes the first lymph node(s) to which a tumor is likely to spread The surgeon injects a radioactive blue dye into the tumor (do breast massage for 15 minutes, up to 3 SLN are required to asses the status of axillary nodes, if positive we do LN dissection.

- **Targeted axillary dissection**

-TAD is an axillary staging technique that removes any biopsy-proven positive axillary nodes, which are marked with a clip or tattoo prior to neoadjuvant chemotherapy, in addition to SLNB. TAD is an adaptation of axillary sampling that targets removal of positive nodes while minimizing morbidity

- **Axillary lymph node dissection (ALND)**

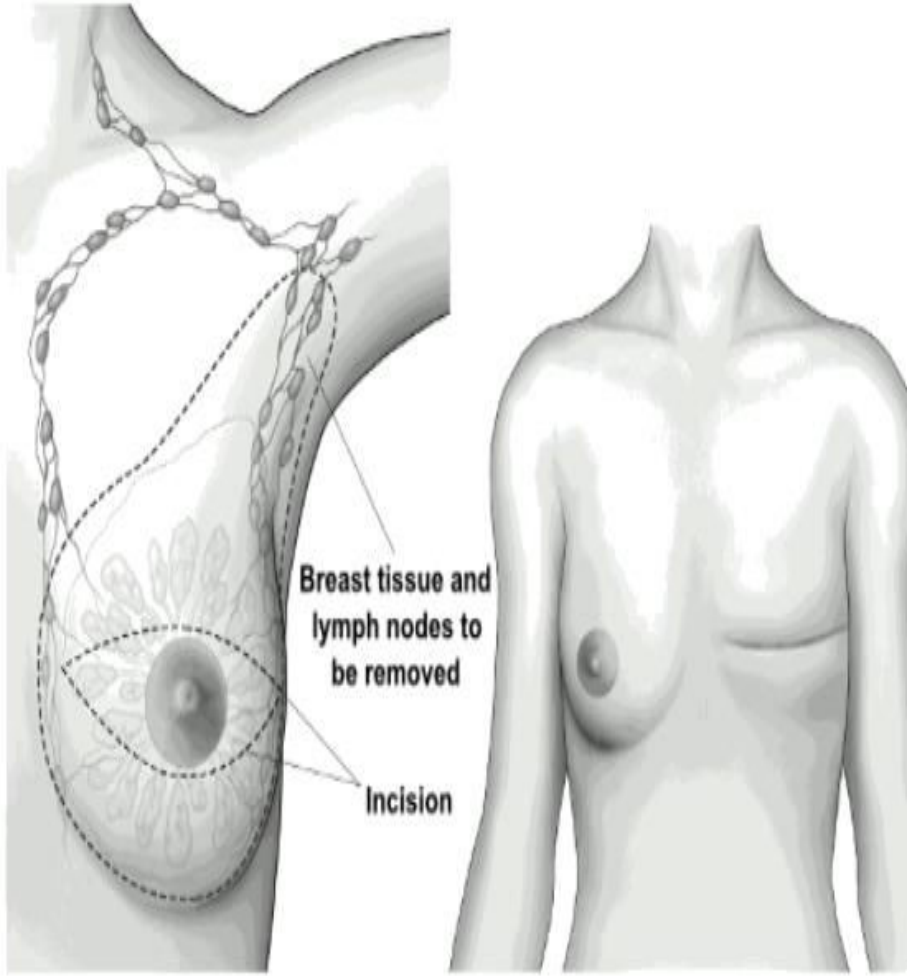
-About 10 to 40 lymph nodes are removed. Usually done at the same time as the mastectomy or breast-conserving surgery

❖ **Side effects of lymphatic dissection:**

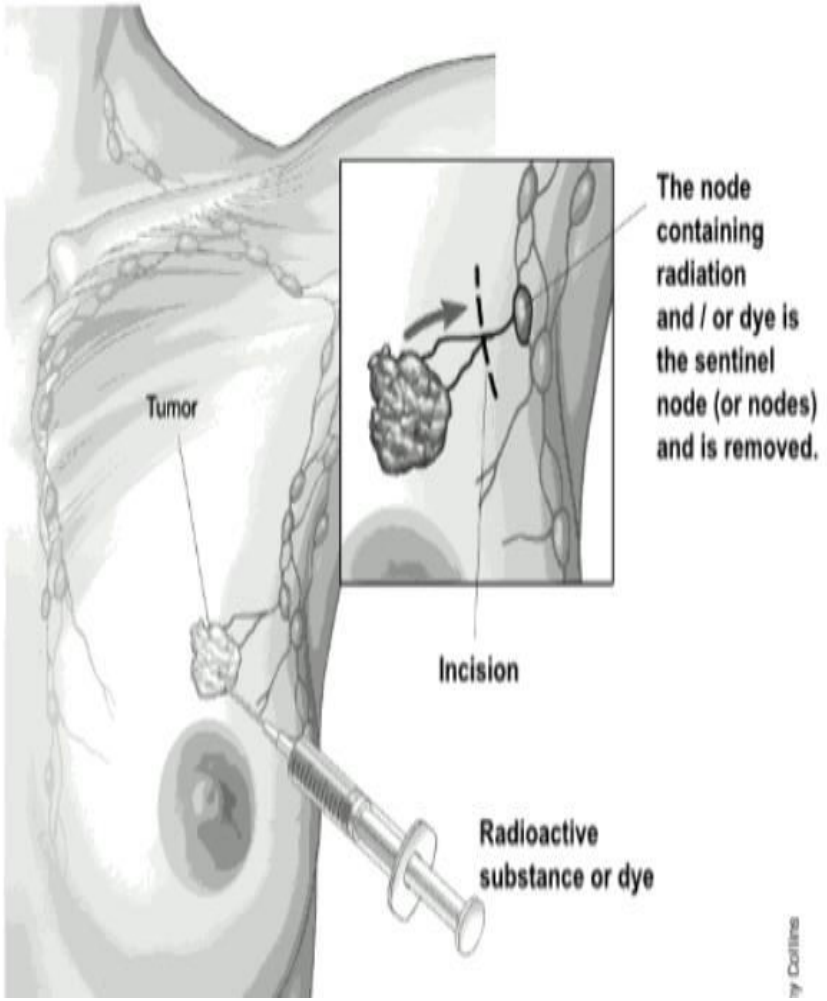
-Lymphedema; this is less common after (SLNB) than (ALND).

-Limited arm and shoulder movement is more common after ALND than SLNB

-Numbness of the skin on the upper arm


Breast tissue and
lymph nodes to
be removed
Incision

ALND


Tumor
The node
containing
radiation
and / or dye is
the sentinel
node (or nodes)
and is removed.
Incision
Radioactive
substance or dye

SLNB

COMPLICATIONS OF AXILLARY LN DISSECTION

Acute	Chronic
Hematoma	Chronic pain > 2weeks
Seroma	Lymphedema
Limited arm movement	Paresthesia
Pain	

LOCALLY-ADVANCED BREAST CANCER TREATMENT

- Locally advanced breast cancer is best managed with multimodality therapy employing systemic and locoregional therapy.

1) **Neoadjuvant systemic therapy**

Most patients with locally advanced breast cancer, and some with earlier-stage disease (particularly if triple negative or human epidermal growth factor receptor 2 [HER2] positive), are treated with neoadjuvant systemic therapy.

The goal of treatment is to induce a tumor response before surgery and enable breast conservation.

- **The approach in selecting treatment in neoadjuvant therapy is outlined as follows:**

- For most patients with hormone receptor-positive disease receiving neoadjuvant therapy, we offer chemotherapy rather than neoadjuvant endocrine therapy. **Chemotherapy is associated with higher response rates in a shorter time**..
- For patients with HER2-positive breast cancer, a HER2-directed agent (eg, **trastuzumab** with or without **pertuzumab**) should be added to the chemotherapy regimen.
- For patients with hormone receptor-negative, HER2-negative disease, neoadjuvant therapy consists of chemotherapy, with the addition of immunotherapy for some patients with high-risk disease.

2) Surgical approach after neoadjuvant treatment

- All patients should undergo surgery following neoadjuvant systemic therapy, even if they have a complete clinical and/or radiological response..
- In selecting the type of surgery for primary tumor, the choice between breast conservation and mastectomy after neoadjuvant treatment is dependent on the treatment response and patient characteristics (eg, breast size in relation to residual tumor size). Similar criteria used in the treatment of early-stage breast cancer are applied.
- Most patients require a surgical evaluation of the regional nodes following neoadjuvant treatment.

❖ Note: As patients with locally advanced disease have an extremely high risk of local recurrence and distant metastases. As a result, we prefer to treat them with neoadjuvant systemic therapy first. However, for patients who proceed with primary surgery, based on pathologic results, postoperative radiation therapy and adjuvant

3) Adjuvant therapy:

-The use of postoperative (adjuvant) systemic therapy is guided by the patient's clinical status and tumor characteristics:

- Patients who did not receive neoadjuvant systemic therapy should receive adjuvant treatment.
- For patients who received the full course of planned neoadjuvant chemotherapy;
- For patients who initiated pembrolizumab (Immue therapy) in the neoadjuvant setting, this is typically continued in the adjuvant setting.
- Patients treated with neoadjuvant endocrine therapy who undergo surgery should continue endocrine therapy in the adjuvant setting

RADIATION THERAPY (RT)

- The purpose of adjuvant radiation therapy (RT) is to eradicate any tumor deposits remaining following surgery. Doing so reduces risk of locoregional recurrence and improves breast cancer-specific and overall survivals.
- **FOR WOMEN TREATED WITH BREAST-CONSERVING THERAPY:**

❑ For **most** women treated with breast-conserving surgery (BCS), we recommend adjuvant RT as part of local treatment, rather than surgery alone.

❑ For most women receiving Whole Breast Radiation Therapy (WBRT) after breast-conserving surgery, we suggest RT boost to the tumor bed to further reduce the risk of in-breast tumor recurrence (**Grade 2B**). Possible exceptions include patients ≥60 years old with small, low-grade, hormone receptor-positive tumors resected with negative margins.

❑ For women who have >3 involved lymph nodes, we recommend regional nodal Radiotherapy. For those with 1 to 3 involved lymph nodes or high-risk primary tumors, we also suggest regional nodal RT (**Grade 2B**). Our approach to regional nodal RT includes treatment of the supraclavicular and infraclavicular nodes as well as the internal mammary nodes.

❑ For patients who received neoadjuvant chemotherapy, we treat with WBRT, regardless of response. For patients with residual nodal disease and for those who presented with stage III disease (regardless of response), we additionally treat the regional nodes

- **Timing of Radiotherapy:**

✓ For patients in whom adjuvant chemotherapy is indicated, RT is generally administered after its completion.

✓ For patients in whom adjuvant endocrine therapy is indicated, RT can be given concurrently or prior to its initiation.

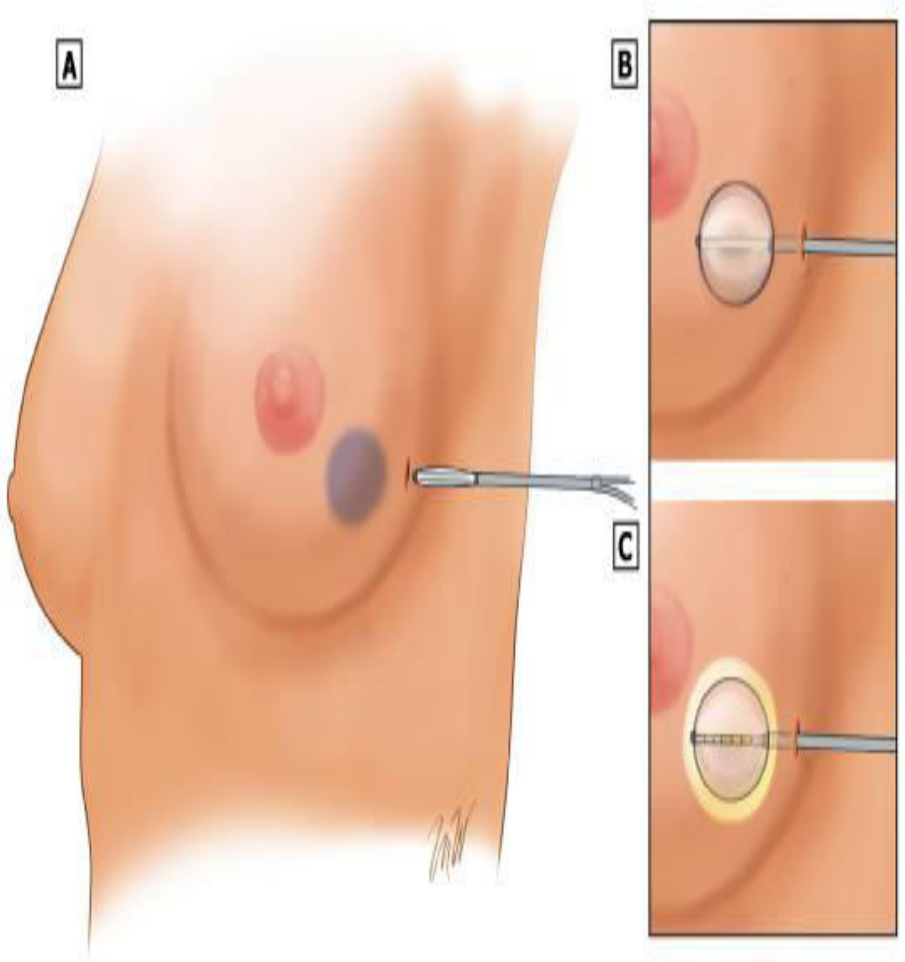
✓ For patients in whom **trastuzumab** with or without **pertuzumab** is indicated, RT is given concurrently.

- **COMPLICATIONS OF RT:**
  - Radiation to the chest wall can cause skin changes pain , hair loss , fatigue .
  - Infrequent complications include interstitial pneumonitis, spontaneous rib fracture, breast fibrosis, pericarditis, pleural effusion, and chest wall myositis. Radiation to the axilla can increase the incidence of lymphedema and axillary fibrosis.
  - **Angiosarcoma** can occur as a late complication.

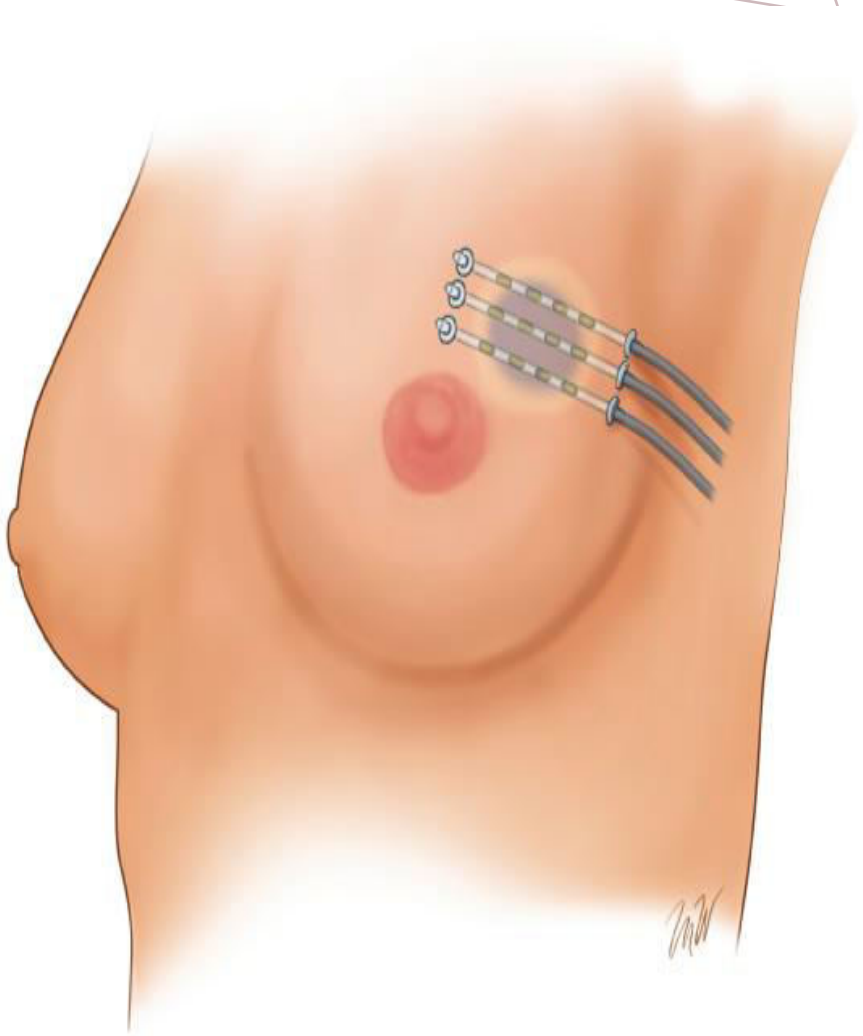
BRACHYTHERAPY

- also known as internal radiation, is another way to deliver radiation therapy. Instead of aiming radiation beams from outside the body, a device containing radioactive seeds placed into the breast tissue for a short time in the area where the cancer had been removed.

- For women who had (BCS), brachytherapy can be used along with external beam radiation.
- Tumor size, location, and other factors may limit who can get brachytherapy.
- For **interstitial brachytherapy**, several small hollow catheters are placed into the breast surrounding the partial mastectomy site. Potential disadvantages of this approach include the risk of infection and poor cosmesis with scarring due to the multiple catheters.
- For **intracavitary brachytherapy**, a radiation delivery device is placed into the partial mastectomy site. Single lumen and multi-lumen balloon catheter and non-balloon devices have all been used successfully. The presumed



INTERSTITIAL BRACHYTHERAPY



INTRACAVITARY BRACHYTHERAPY

CHEMOTHERAPY

- **Anti-cancer drugs that may be given IV or by mouth.**
- **Adjuvant chemotherapy: Adjuvant chemo is used to try to kill any cancer cells that might have been left behind or have spread but can't be seen**
- **Neoadjuvant chemotherapy; can be used to try to shrink the tumor** so it can be removed with less extensive surgery
- For advanced breast cancer be used as the main treatment for women whose cancer has spread outside the breast and underarm area
- **cyclophosphamide**, **methotrexate** and **5-fluorouracil (CMF)** will achieve a 25 per cent reduction in the risk of relapse over a 10- to 15-year period.
- Newer ‘biological’ agents will be used more frequently as molecular targets are identified – the first of these, **trastuzamab** (**Herceptin**), is active against tumours containing the growth factor receptor c-erbB2.

trastuzamab (Herceptin) : using in HER2 subtype molecular

Side effect of trastuzamab : cardiotoxicity; we must do ECHO

ADVERSE EFFECTS OF CHEMOTHERAPY

- Short – term side effects · Hair loss · Loss of appetite or increased appetite · Nausea and vomiting · A higher risk of infection · Stopping of menstrual periods · Easy bruising or bleeding.
- Long - term side effects

Menstrual changes: infertility

Nerve damage: pain, burning or tingling and sensitivity to cold or hot.

Heart damage

- Some types of breast cancer are affected by hormones in the blood. **ER-positive and PR-positive** breast cancer1 cells have receptors (proteins) that attach to estrogen
- adjuvant therapy VS neoadjuvant therapy
- These drugs work by stopping estrogen from stimulating breast cancer cells to grow.
- **Tamoxifen** has been the most widely used ‘hormonal’ treatment in breast cancer it has now been shown to reduce the annual rate of recurrence by 25 per cent
- It is usually taken for at least 5 years

Tamoxifen: selective estrogen receptor.

HORMONAL THERAPY

- The oral **aromatase inhibitors (AIs)** for postmenopausal women. The latter group of compounds are now licensed for treatment of recurrent disease, in which they have been shown to be superior to tamoxifen. anastrazole to tamoxifen in the adjuvant setting has shown a beneficial effect for the aromatase inhibitor in terms of relapse-free survival, although no benefit for overall survival. There is an additional reduction in contralateral disease, which makes this drug suitable for a study of prevention, and the side-effect profile is different from that of tamoxifen. The AIs have been more expensive than tamoxifen but are all coming off patent protection and generic copies may allow more widespread use.
- There is an increase in bone density loss with patients on an AI and a bone density scan is advised prior to commencement with treatment of underlying osteopenia or osteporosis.

- Mechanism of action: Prevent conversion of androgen to estrogen.

- Used in postmenopausal women.

- Anti-estrogen on breast , but agonist on endometrium (increases the risk for endometrial cancer)

THANK YOU