# Breast Cancer

## Premalignant and Malignant Lesions

Dr. Mahmoud Al-Balas. MBBs, MSc

Consultant Breast Oncoplastic and Reconstructive Surgery
Assistant Professor of Surgery – The Hashemite University

# Impact?

- With 1 million new cases in the world each year, breast cancer is the most common malignancy in women and comprises 18% of all women's cancers.
- Breast cancer incidence in women in the United States is 1 in 8 (about 13%). Women have a 3% chance of breast cancer causing their death.
- For women in the U.S., breast cancer death rates are higher than those for any other cancer besides lung cancer.
- The American Cancer Society estimates that each year, about 2000 new cases of invasive breast cancer are diagnosed in men.
- It is estimated that about $8.1 billion is spent each year on breast cancer treatment in the U.S.

# Breast cancer in Jordan – Facts

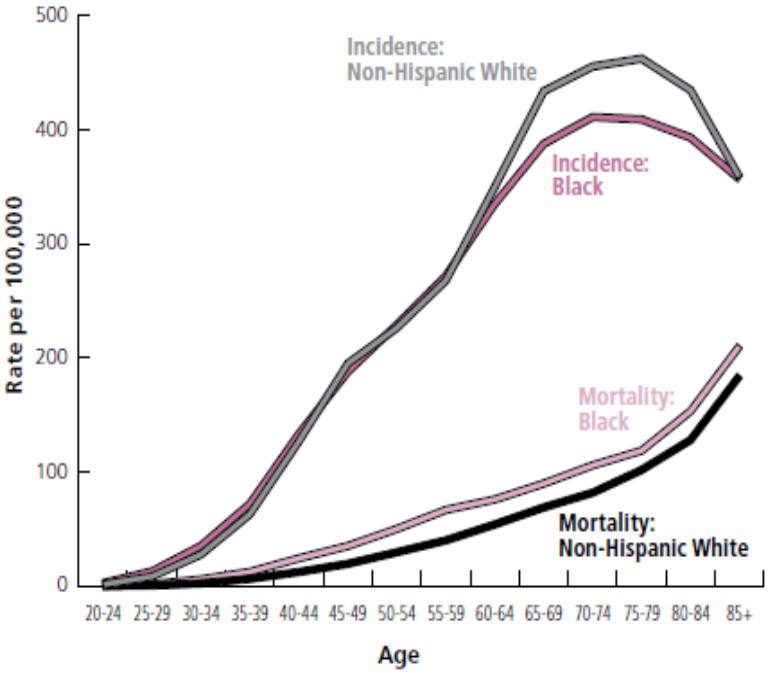
- BC accounts for the highest incidence of all cancers in Jordan (36.7%)
- The leading cause of cancer deaths among Jordanian women
- Ranks number one among the five most common cancers affecting all Jordanians (King Hussein Cancer Center (KHCC), 2004
- The median age of BC among Jordanian women is 51 years (vs. 61 in USA)
- (33.9%) of the newly diagnosed Jordanian women with BC, in 2001,were between 30-39 years old (KHCC, 2004)
- BC incidence rates in Jordan are increasing at a rate of 4% per year
- A national Jordanian program titled, the Jordan Health Cancer Program, has been in effect since 2005

# Epidemiology:

- Over 75% of women who are diagnosed with breast cancer are age 50 or older.
- Over 232,000 cases were reported in 2013, > 99% in women.
- The five-year relative survival rate is now 98 percent for women with breast cancer caught before it spreads beyond the breast (compared to 72 percent in 1982).
- Breast cancer incidence is greater in women of higher socio-economic background.
  - Life style differences like number of pregnancies and age at first childbirth.
- Death rates have been decreasing since 1990.
  - Advances in treatment, earlier detection through screening, and increased awareness.

- The decrease in incidence rates that occurs in women 80 years of age and older may reflect lower rates of screening, the detection of cancers by mammography before 80 years of age, and/or incomplete detection

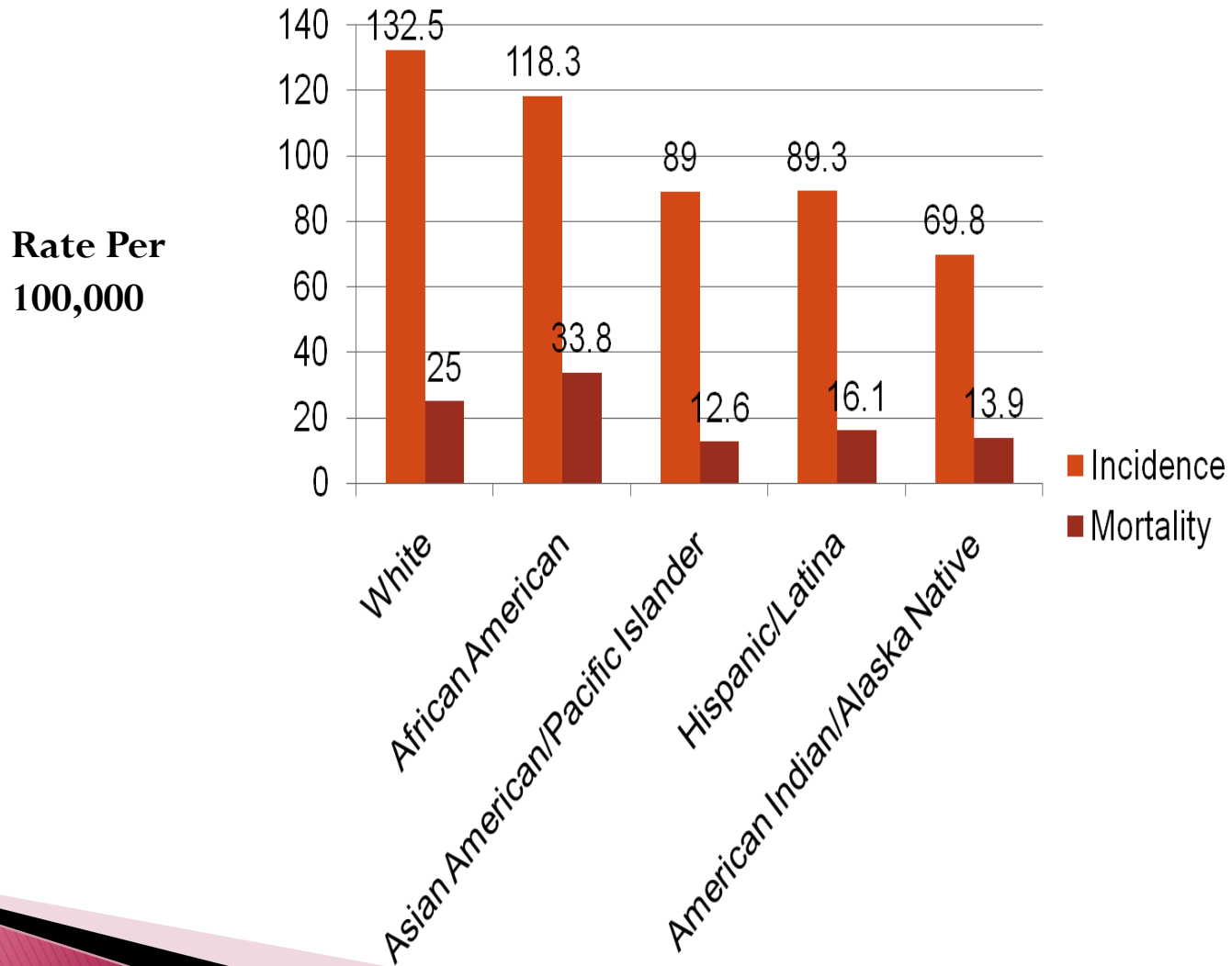
**Figure 1. Age-specific Female Breast Cancer Incidence and Mortality Rates, US, 2008-2012**




**Sources:** Incidence: North American Association of Central Cancer Registries (NAACCR), 2015. Mortality: US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention.

American Cancer Society, Inc., Surveillance Research, 2015

# Incidence and Mortality of Female Breast Cancer Based on Race and Ethnicity in the U.S.



- About 90% of breast cancers are due to genetic abnormalities that happen as a result of the aging process and life in general, not to inherited mutations.
- Lifetime risk for developing BC is 12.28% (1 in 8 women)

**Table 5. Age-specific Probabilities of Developing Invasive Female Breast Cancer***

| If current age is ... | The probability of developing breast cancer in the next 10 years is:† | or 1 in: |
|---|---|---|
| 20 | 0.1% | 1,674 |
| 30 | 0.4% | 225 |
| 40 | 1.4% | 69 |
| 50 | 2.3% | 44 |
| 60 | 3.5% | 29 |
| 70 | 3.9% | 26 |
| Lifetime risk | 12.3% | 8 |

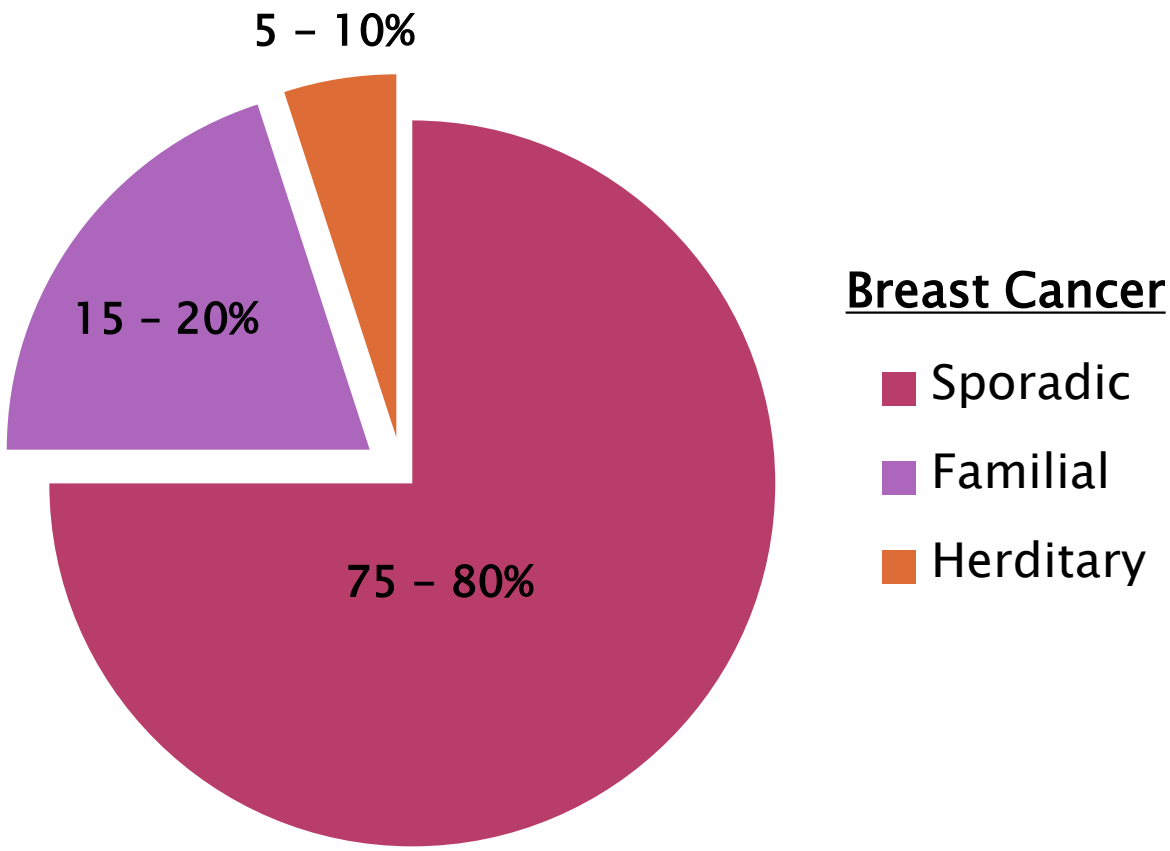
*Among those free of cancer at beginning of age interval. Based on cases diagnosed 2010-2012. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.

**Source:** 18 SEER Registries, National Cancer Institute. Probabilities derived using NCI DevCan Software, Version 6.7.3.

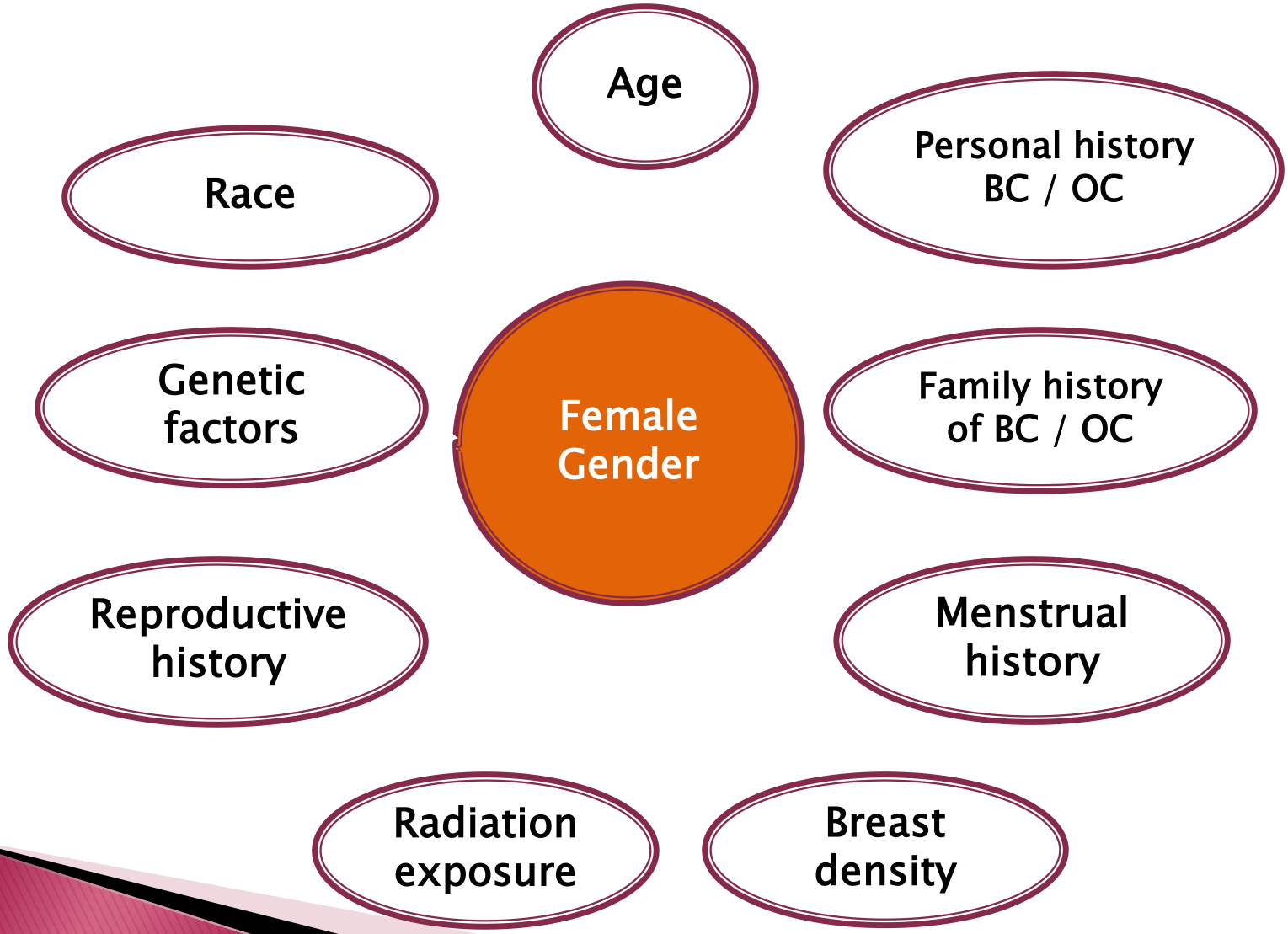
American Cancer Society, Inc., Surveillance Research, 2015

# Breast Cancer:

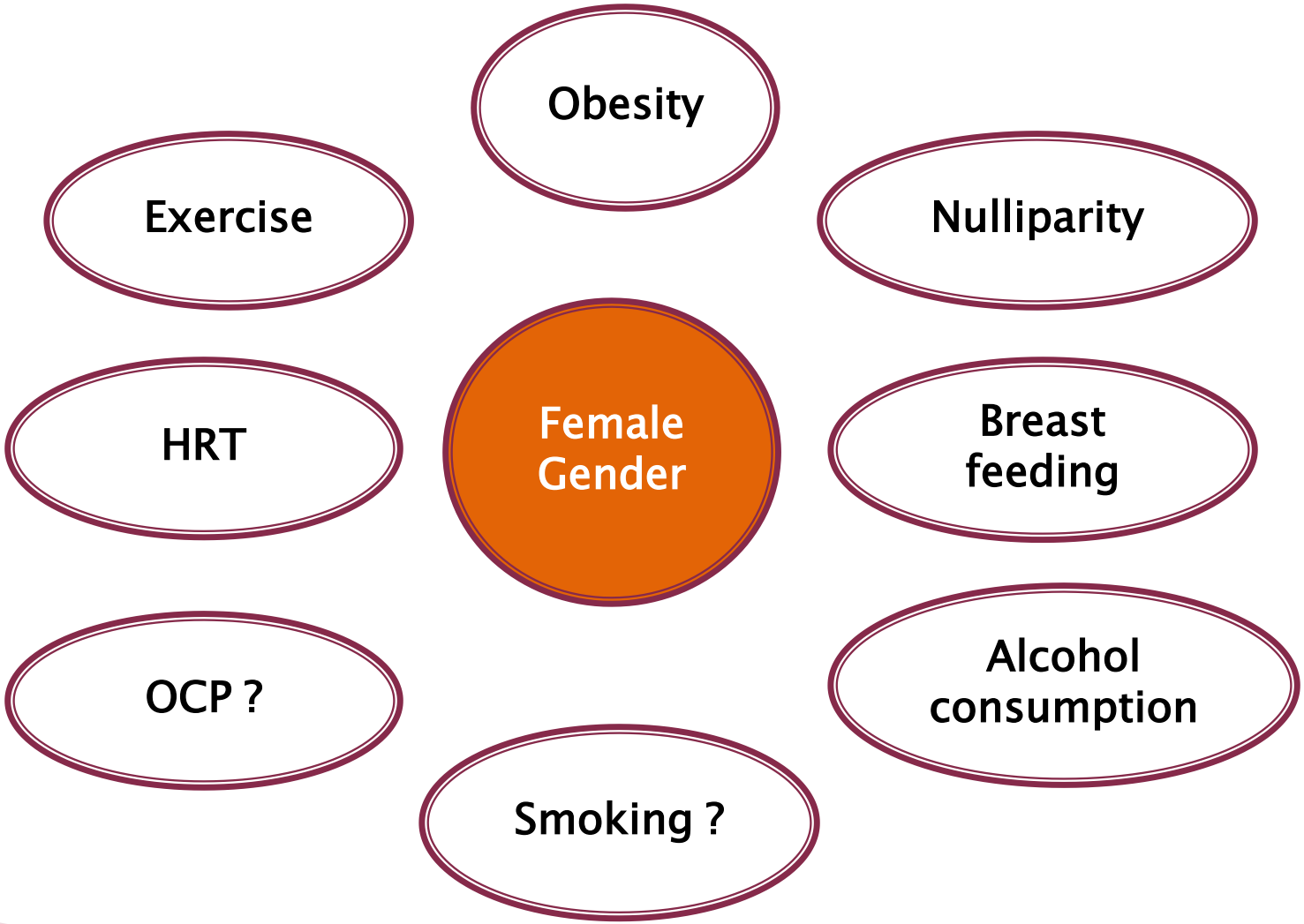
## Risk Factors


5 – 10%
15 – 20%
75 – 80%
Breast Cancer
Sporadic
Familial
Herditary

# Non modifiable risk factors



# Modifiable risk factors



# Factors that Increase the Relative Risk (RR) for Breast Cancer in Women

| | |
|---|---|
| RR>4.0 | ❑ Female<br>❑ Age (65+)<br>❑ Inherited genetic mutations associated with breast cancer such as BRCA1/BRCA2<br>❑ Two or more first-degree relatives with breast cancer diagnosed at an early age<br>❑ Personal history of breast cancer<br>❑ Biopsy-confirmed atypical hyperplasia<br>❑ DCIS, LCIS |
| 2.1<RR<4.0 | ❑ One first-degree relative with breast cancer<br>❑ High-dose radiation to chest<br>❑ High bone density (post-menopausal)<br>❑ Breast density > 50% |
| 1.1<RR<2.0 | **Factors affecting circulating hormones:**<br>❑ Late age at first full-term pregnancy (>30 yrs)<br>❑ Early menarche(<12 yrs)<br>❑ Late menopause<br>❑ No full-term pregnancies<br>❑ No breastfeeding<br>❑ Recent oral contraceptive use<br>❑ Recent and long-term hormone replacement therapy<br>❑ Obesity<br>❑ Breast density 26-50%<br><br>**Other factors:**<br>❑ Personal history of endometrium, ovary or colon cancer<br>❑ Alcohol consumption<br>❑ Height (tall)<br>❑ High socioeconomic status<br>❑ Jewish heritage |

# Classification of Breast Cancer

- Breast cancer is unanimously considered a highly heterogeneous disease under several distinct viewpoints.
- Different types of this neoplasm exhibit variable histopathological and biological features, different clinical outcome and different response to systemic intervention.
- Breast cancer cannot be viewed as a single clinico-pathological entity, but it must be necessarily dissected into a number of more homogeneous entities
- Suitable classification of any disease has to be scientifically sound, clinically useful, easily applicable and widely reproducible

# ❑ Histopathologic Classification

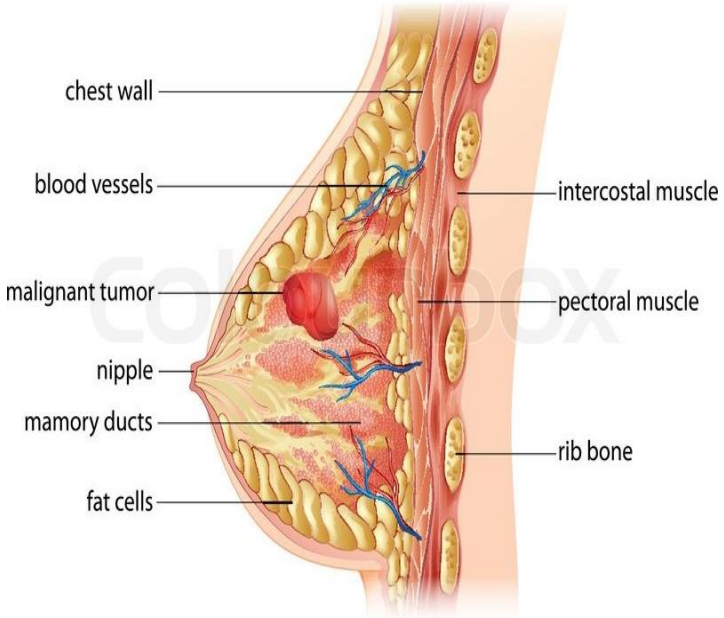
- ❑ BIOLOGIC CLASSIFICATION
- ❑ MOLECULAR CLASSIFICATION

Histological classification of breast cancers

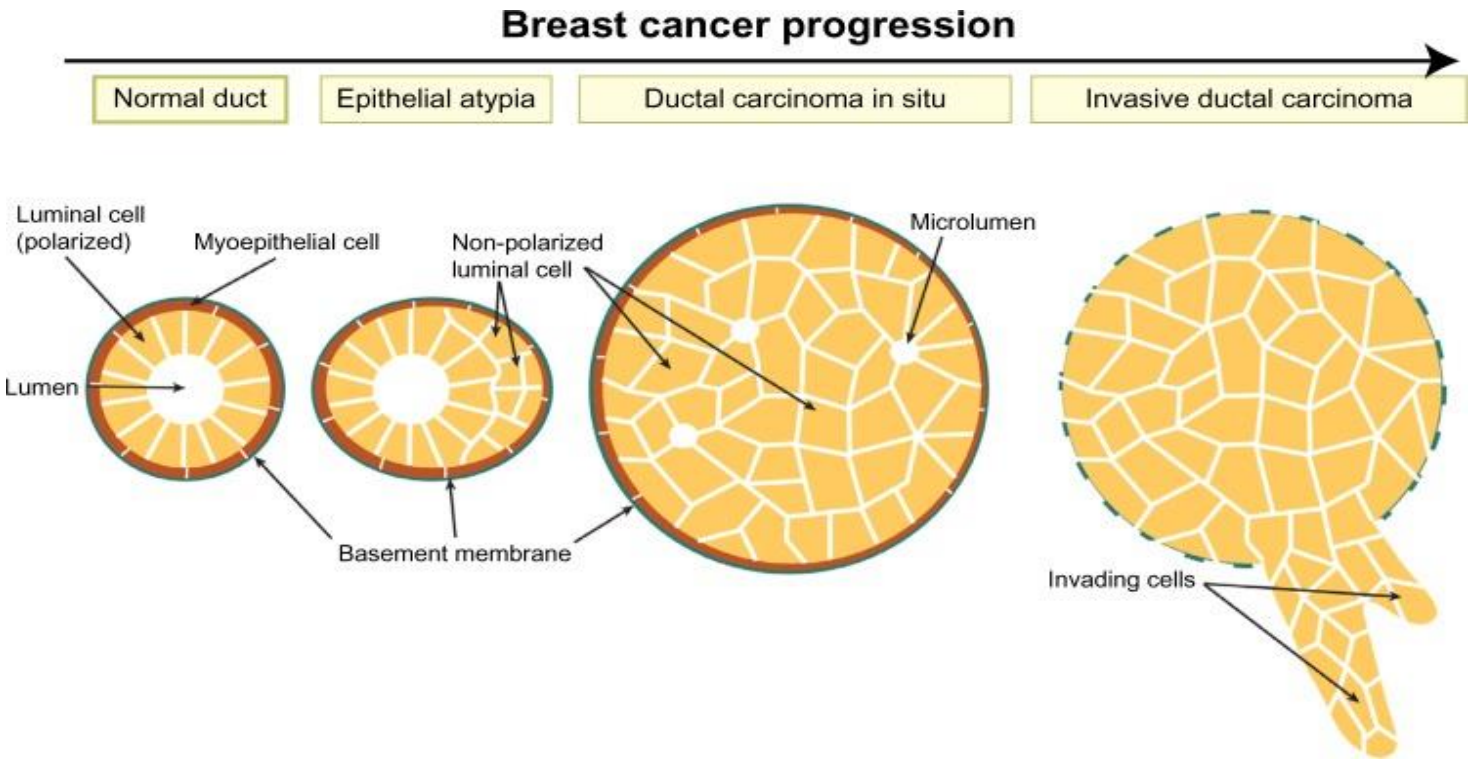
- Breast Cancer
  - In Situ Carcinoma
    - Ductal
      - Comedo
      - Cribiform
      - Papillary
      - Micropapilary
      - Solid
    - Lobular
      - Low histological variation
  - Invasive (infiltrating) Carcinoma
    - Tubular
    - Ductal Lobular
    - Invasive Lobular
    - Infiltrating Ductal
    - Mucinous (colloid)
    - Medullary
    - Infiltrating Ductal
      - Well Differentiated
      - Moderately Differentiated
      - Poorly Differentiated

**IS THIS ENOUGH IN 21ST CENTURY??**

This classification is based on
1. Nuclear Pleomorphism
2. Glandular/Tubule Formation
3. Mitotic Rate (per 10 HPF)




***But Biologic and Molecular Classification provides better understanding for the behavior and treatment of breast cancer***


Breast cancer progression
Normal duct
Epithelial atypia
Ductal carcinoma in situ
Invasive ductal carcinoma
Luminal cell (polarized)
Myoepithelial cell
Non-polarized luminal cell
Microlumen
Lumen
Basement membrane
Invading cells

# Carcinoma in Situ

# Ductal Proliferation

- They are arise and confined to the breast ducts (duct-lobular) unit.
- Benign or malignant lesions.
- Divided into 2 large groups:

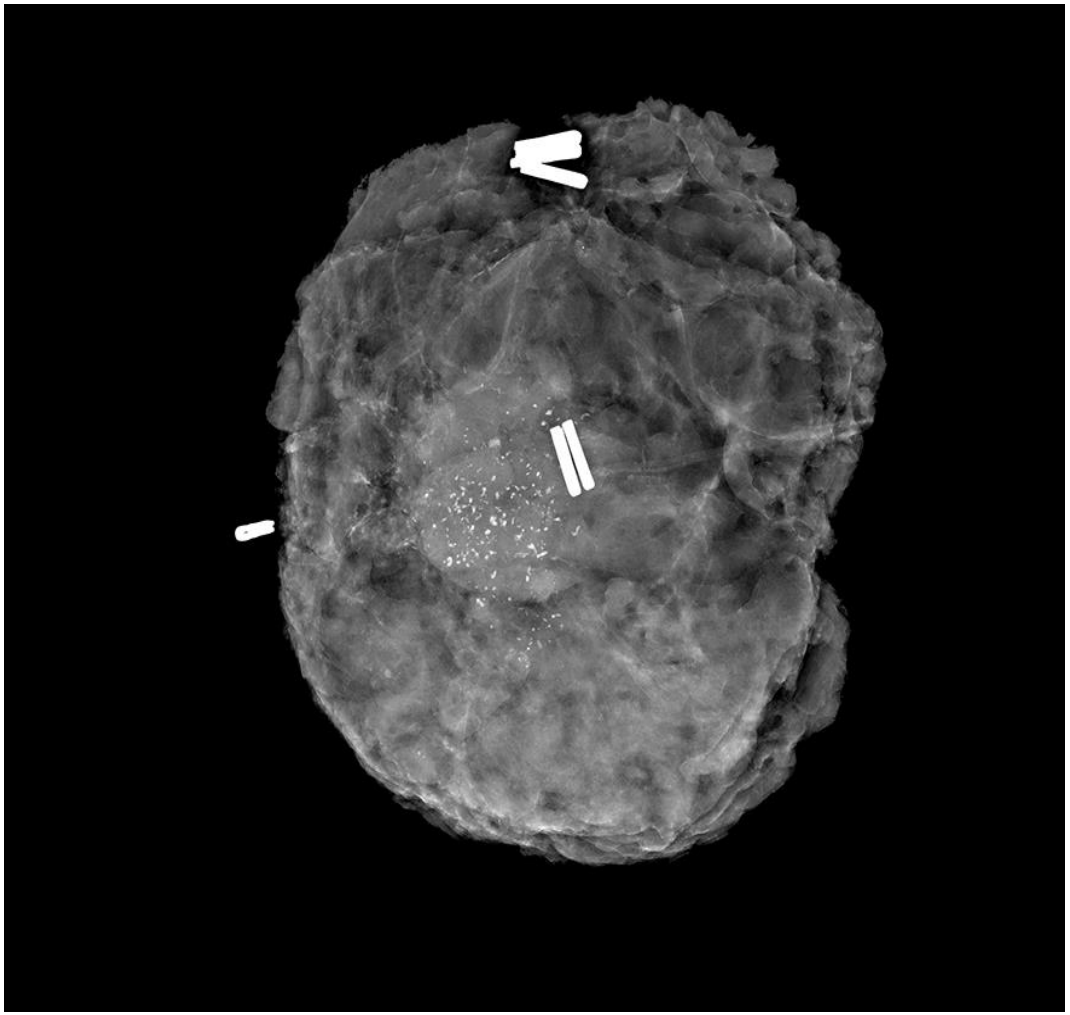
1. Intraductal benign proliferation (usual ductal hyperplasia) (ductal hyperplasia without atypia)
2. Ductal intraepithelial neoplasia (DIN) → ADH + DCIS

| Proliferative Ductal Lesions | |
|---|---|
| Old terminology | New terminology |
| Flat epithelial atypia | DIN1a |
| Atypical ductal hyperplasia | DIN1b |
| Low grade (G1) DCIS | DIN1c |
| Intermediate grade (G2) DCIS | DIN2 |
| High grade (G3) DCIS | DIN3 |

| A correlation between ductal proliferative lesions and risk of breast cancer | |
|---|---|
| UDH | 1.5-2 fold |
| ADH | 4-5 folds |
| DCIS | 9-10 folds |

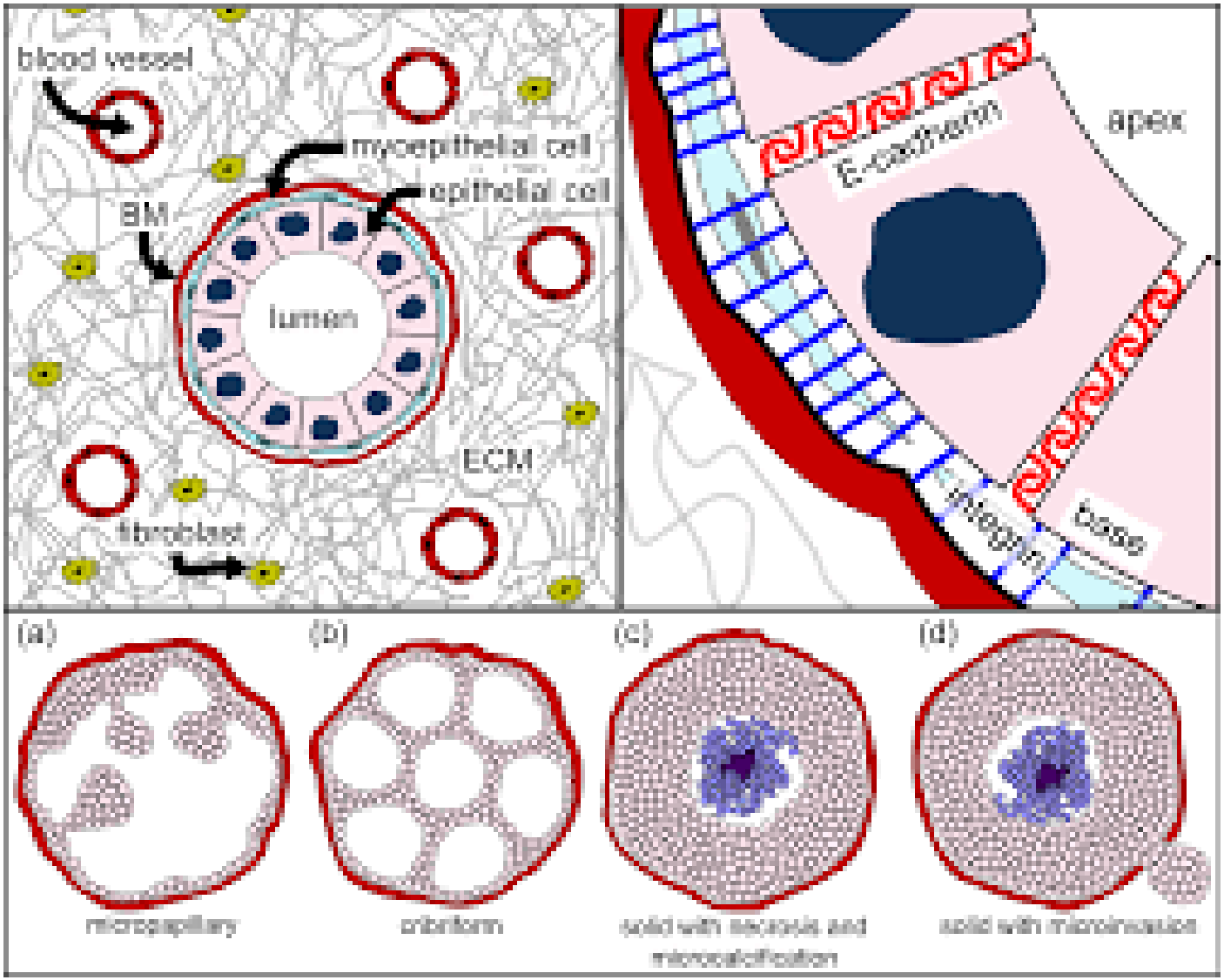
# DCIS

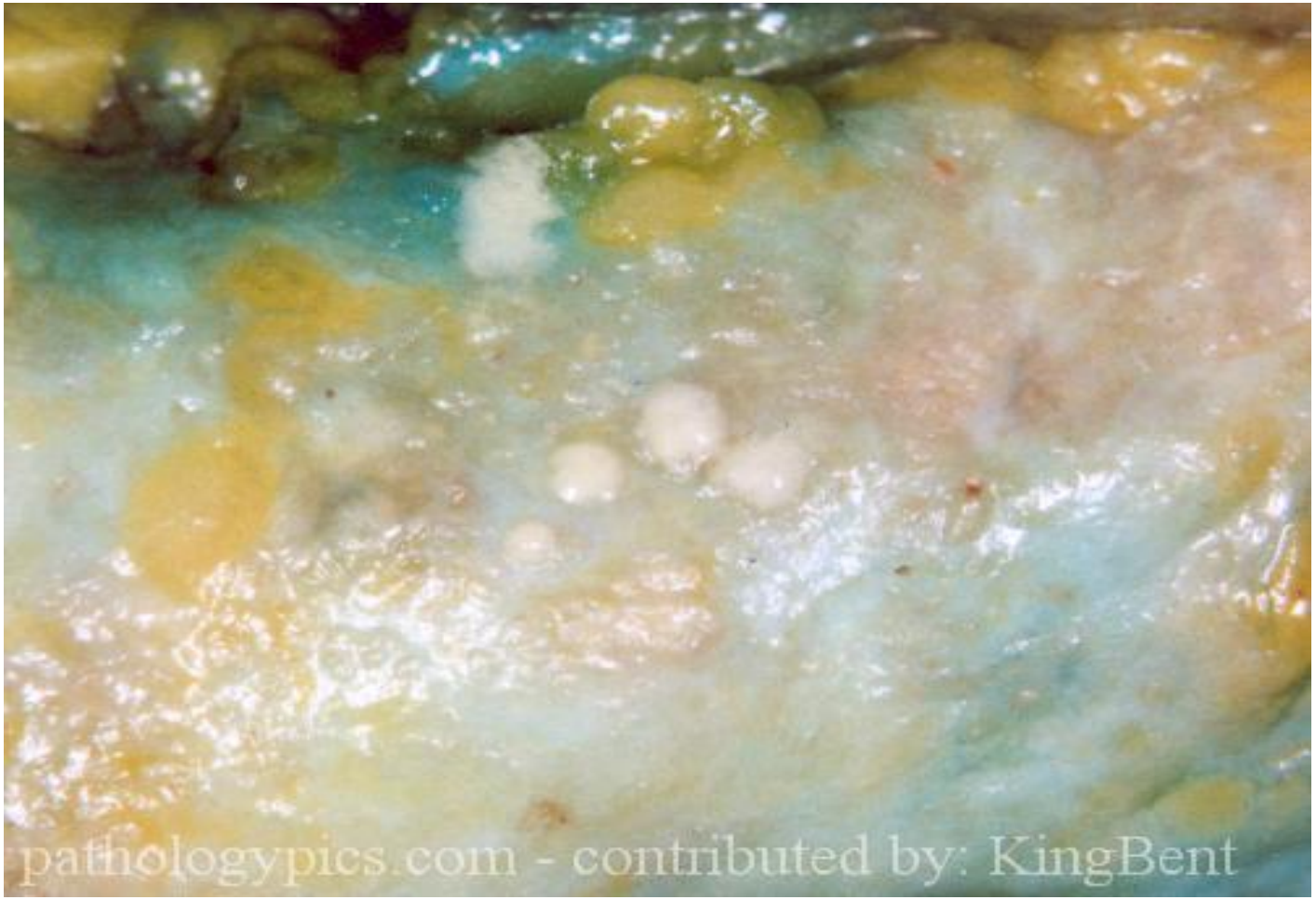
- Malignant proliferation of epithelial cells confined to ductal-lobular system.
- No invasion into surrounding stroma.
- 20-25% of newly diagnosed breast cancer in western countries.
- Considered as a non-obligate precursor for invasive carcinoma
- Incidence →
  - 1975; 1.9/100,000
  - 2005 ; 33/100,000



# Biology and classification

- It is considered a heterogeneous group of lesions with variable malignant potential.
- The average estimate of untreated DCIS to develop invasive carcinoma about 43%.
- Architectural classification:
  - Comedo → layers of neoplastic cells surround central area of necrosis.
  - Non-Comedo:
    - Cribriform → radially oriented neoplastic cells forming glandular lamina
    - Papillary → large papillae with fibrovascular stalk
    - Solid → ducts filled with neoplastic cells
    - Micropapillary → fingerlike projections into dilated ductal spaces


blood vessel
myoepithelial cell
epithelial cell
BM
lumen
ECM
fibroblast
E-cadherin
apex
basal
(a)
(b)
(c)
(d)
microcapillary
cribriform
solid with necrosis and microcalcification
solid with microinvasion




Comedo DCIS and isosulfan blue staining from sentinel lymph node mapping.

The cut section of the biopsy is oozing necrotic material from multiple ducts.

| DCIS Grade | LOW | Intermediate | High |
|---|---|---|---|
| Cells | Small – monomorphic | Mild to moderate Variable in shape, size, orientation | Highly Atypical cells |
| Nucleus | Small – uniform | Variable | Large – irregular Pleomorphic |
| Chromatin | Dispersed | Coarse | Clumped |
| Nucleoli | Not evident | Variably prominent | Very prominent |
| Mitosis | Rare | May be present | Common |
| Necrosis (Comedo) | Usually absent | May be present | Punctate or Comedo present |
| Intraluminal microcalcification | May be present | Frequently present | Very common Intraluminal debris of necrosis |

# Features of DCIS

- Grossly → no special characteristics
- Specimen radiography can be utilized to localize microcalcifications
- Usually confined to the ducts
- High grade can extend into lobules (lobular cancerization) and can harbor foci of invasive carcinoma.
- Architecture patterns → comedo – cribriform – solid – micropapillary – papillary – mixed
- Comedo Type → Comedo necrosis at cut surface of the ducts

- Comedo DCIS → more aggressive, higher nuclear grade, aneuploidy, higher Ki67, high HER2 amplification, high protein overexpression.

- Micropapillary DCIS is more associated with extensive distribution involving more than one quadrant.

| DCIS | ER / PR | HER2 neu |
|---|---|---|
| Low grade | +++ | Negative |
| High grade | – (43%) | Positive |

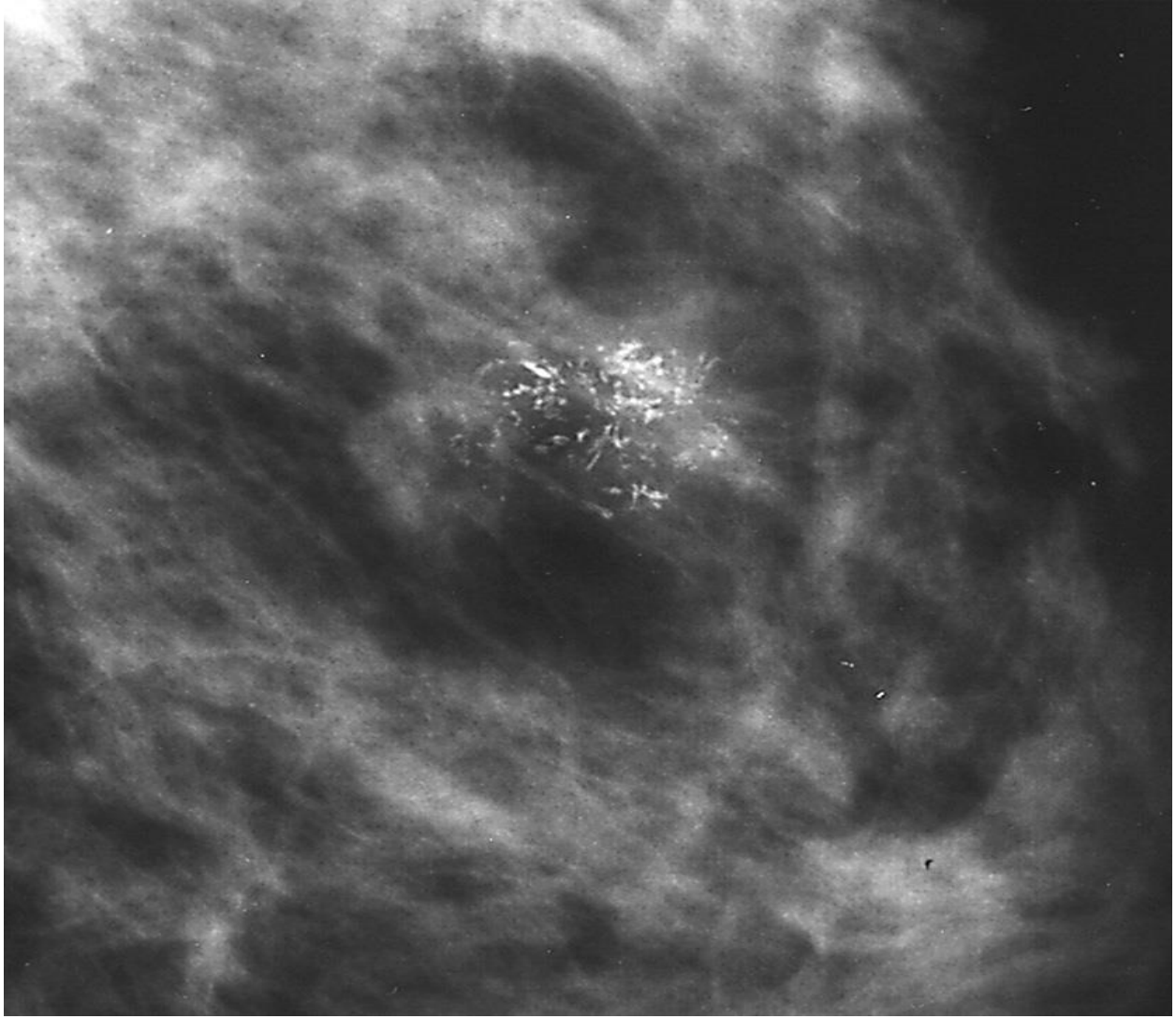
- Recurrence / invasive cancer progression in:
  - Young age
  - large size – High grade
  - Comedo
  - Positive margins

# Diagnosis

- Clinical Presentation
- Radiologic Assessment
- Diagnostic Biopsy

# Clinical Presentation

- DCIS is mostly a screening mammography detected form.
- Palpable breast mass:
  - As early as 1990, 30% of cases were manifested a palpable masses
  - Nowadays, less than 10% present with a mass.
- Pathological nipple discharge.
- Incidental finding on breast biopsy.



Typically, DCIS microcalcifications are pleomorphic, variable in size, density, grouped in segmental or linear arrangements reflecting their arrangements in ducts.

# Mammography & Ultrasound

- Mammogram:
  - Microcalcifications → most common mammographic finding
  - Soft tissue density or asymmetry
  - Magnification views more accurately predict the extent of disease.
  - Can underestimate the pathological extent of the disease especially with micropapillary DCIS

| Microcalcifications characteristics of DCIS | |
|---|---|
| High nuclear Grade<br>Comedo DCIS | Linear branching microcalcifications |
| Low nuclear grade<br>Micropapillary / Cribriform | Fine granular microcalcifications |

# MRI

- The gold standard for radiologic assessment of DCIS.
- Not routinely employed in preoperative assessment of DCIS.
  - Cost.
  - Accessibility.
- Higher sensitivity than mammography for DCIS.
  - Can over estimate DCIS.
  - Higher false positive.
  - Higher unnecessary biopsies.
- Can detect contralateral breast cancer in DCIS patients.
  - Sensitivity → 71%
  - Specificity → 90%
- May lead to overtreatment and increase the performance of mastectomies.

# Pathology

- Malignant proliferation of epithelial cells confined to ductal-lobular system.
- Within ductal lumen, No invasion into surrounding stroma.
- Lesions can be heterogeneous, variable histologic architecture, molecular and cellular characteristics, clinical behavior.
- Stromal changes → angiogenesis, fibroblast proliferation, lymphocytes infiltration.
- Progression sequence as below is supposed:
  - ADH → → → DCIS → → → IDC
  - Cause ?! Genetic defect … P53 mutation
  - Other genes of cell adhesion, signaling, motility, angiogenesis, ECM formation.

# Classification

- No single classification system is universally accepted.

- Subtypes:
  - Comedo
  - Non-Comedo
    - Cribriform
    - Solid
    - Papillary
    - Micropapillary

- Nuclear Grading → low – intermediate – high

# Multifocality Vs. Multicentricity

- Multifocality →
  - DCIS in 2 or more foci in same breast quadrant separated by 5 mm.
  - These foci found to originate from the same focus

- Multicentricity →
  - Separate discontinuous foci of DCIS outside of the index breast quadrant.

*Note → Recurrence most occur in the same quadrant as the index lesion*

# DCIS with microinvasion

- Microinvasion: invasion of breast cancer cells through the BM at one or more foci, non of which exceeding a dimension of 1 mm.
- DCIS microinvasion → AJCC staging "T1mic"
- DCIS features suggestive of having DCISM:
  - Size > 25 mm (29% vs. 2% if < 25 mm)
  - High Grade
  - Comedo DCIS
  - DCIS with palpable mass
  - DCIS with nipple discharge
- DCISM:
  - 5-10% of DCIS
  - ALN metastasis. 0 - 28%
  - Shorter distant metastasis free survival rate (91% vs. 98%)
  - Shorter overall survival (88.4% vs. 96.5%)

# Prognosis

- DCIS specific mortality is very low (1% – 2.6%)
- Aim of treatment is to maximize local control with the least aggressive treatment.
- Local recurrence range from 11-31%
  - At 8 years follow up after BCS + RTH:
    - High Grade + Comedo → 20% LR
    - Low Grade + non Comedo → 5%
- Mortality is related to
  - presence if an invasive cancer not recognized at time of diagnosis
  - Recurrence as IDC in 50% of cases

# DCIS Treatment

- Surgery
- Radiotherapy
- Hormonal therapy

# Ductal Carcinoma in Situ (DCIS)

- Surgery:
  - Mastectomy

  Vs.

  - Wide Local Excision (BCS)
    - Circumferential margin should be at least 2 mm

# Conservative treatment of dcis

| Treatment | BCT | BCT + Radiotherapy |
|---|---|---|
| 10 year cumulative risk for ipsilateral Recurrence DCIS or IDC | 28.1% | 12.9% |

- 50 % of recurrences after BCT are IDC and up to 20% are metastatic at presentation.

- Radiotherapy for low risk ?

  (negative margins, low grade and size)

# Axillary LN Assessment

- Usually, there is no need to perform SLNB
- Indications of SLNB in patients with DCIS:
  - Large diffuse DCIS that require mastectomy
  - High grade DCIS
  - High risk mammographic pattern
  - Extension above 5 cm

# Extent of the Disease

- Precise preoperative assessment of DCIS extension remains difficult.
- Traditional evaluation proved to be unreliable, new diagnostic tools have limitations.
- MRI showed high sensitivity in detecting invasive disease, it has high negative predictive value (NPP)
- MRI sensitivity for DCIS range from 40-80%, it can also over or underestimate the involvement.

# Extent of the Disease

- MRI can't show all microcalcifications visible on mammogram also mammogram can't show all lesions demonstrated on MRI.
- So → MRI and mammogram as complementary for DCIS assessment.
- Overall MRI sensitivity for high grade DCIS is more than mammogram.

# Intraoperative localization

- Methods of localization:
  - Methylene blue dye injection into the lesion
    - Diffuse easily in breast tissue (within hours)
    - Short interval between localization and surgery
  - vegetal carbon injection
    - Stain tissue black, not diffuse into surrounding tissue
    - Localization can be days or weeks before surgery
    - Low cost, easy
    - Difficult to follow in cases of multifocal lesions

- Hooked wire localization
  - Useful for multifocal localizations
  - Disadvantages :
    - Wire migration during patient's position changes and during surgery
    - High positive microscopic margins following excision
    - Difficult to localize small lesions due to wire thickness
    - Remote skin incision for insertion
- Radioguided localization (ROLL)
  - Depends on Tc injection and detecting it preoperatively, intraoperative gamma probe and postoperative imaging

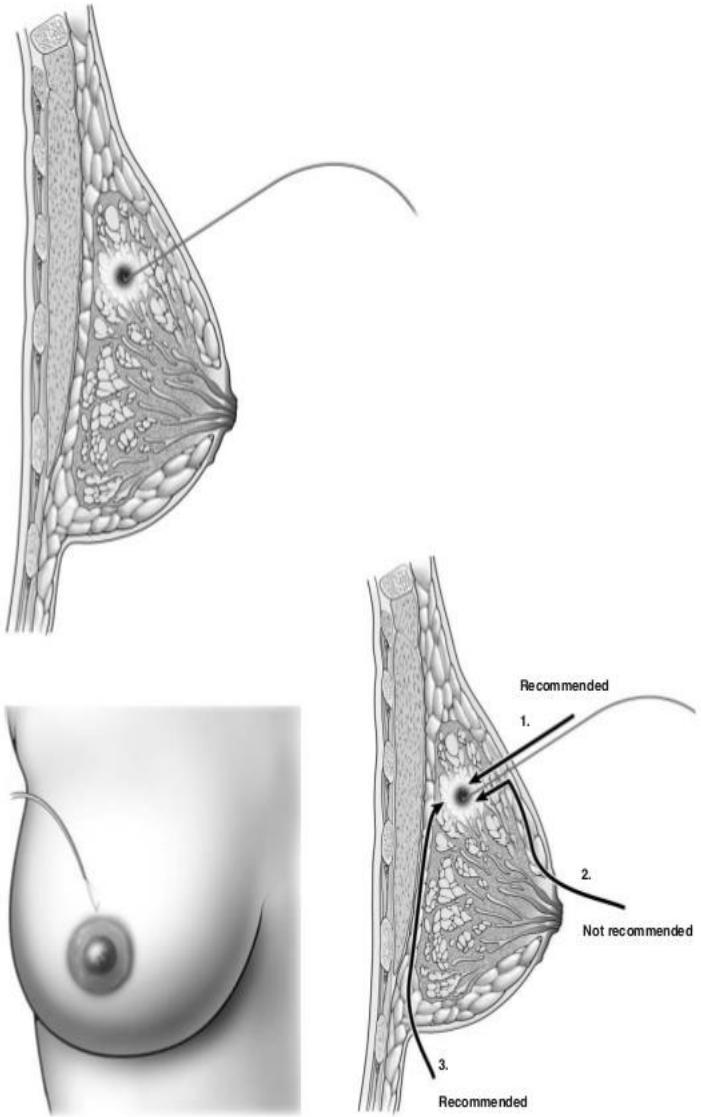
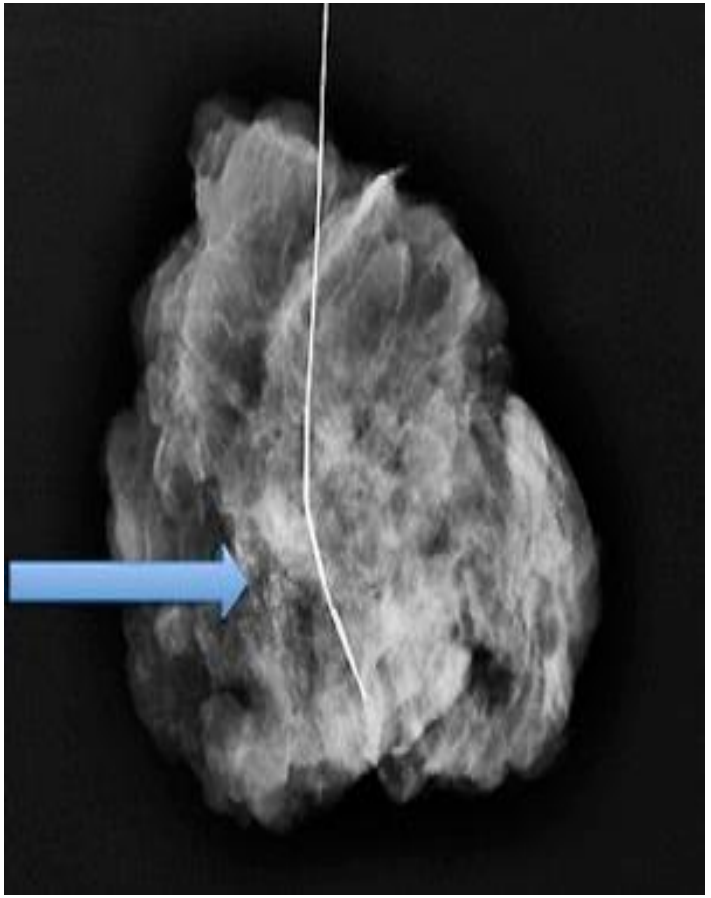
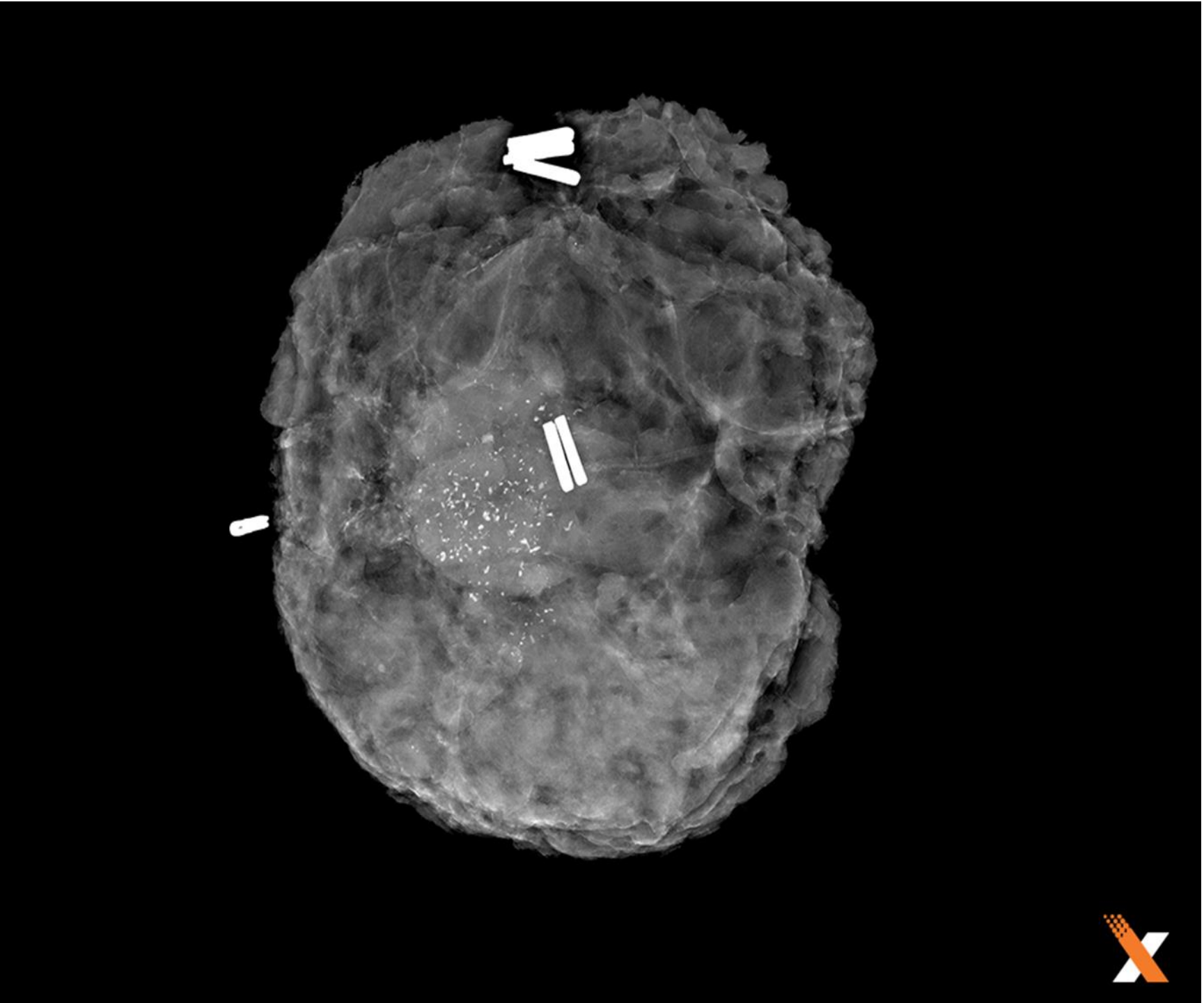



Fig. 3.23. Guidance for correct approach during needle-localized biopsy. The posterior glandular approach (*1* on *right*) is recommended, whereas periareolar (*2* on *right*) is not recommended. Inframammary approach (*3 on right*) is only recommended if the tumor is deeply located





# Radiotherapy

- Radiotherapy decreased the loco-regional recurrence after BCS by 50%.
- Whole breast radiation
  - 5-6 weeks duration
- Partial-Breast irradiation
  - High dose radiation over 4-5 days

# Endocrine Therapy

- National Comprehensive Cancer Network guidelines:
  - 5 years Tamoxifen 20mg/d for ER+ DCIS
  - 59% reduction on relative risk of BC vs. no tamoxifen.
- International Breast Cancer Intervention Study IBIS-II
  - Anastrozole decreased cumulative incidence of BC by 50% in postmenopausal women

| | BCS + Radiotherapy + Tamoxifen | BCS + Radiotherapy + Placebo |
|---|---|---|
| Ipsilateral IBC | 8.5% | 10% |
| Contralateral non IBC & IBC | 7.3% | 10.8% |

# Surveillance

- Annual physical exam and Annual Mammogram.

- Predictors of local relapse:
  - Age < 50 years.
  - Strong FH
  - Size > 3 cm
  - High nuclear grade
  - Comedo necrosis
  - Positive margins

# Lobular Neoplasia

# Lobular neoplasia

- Atypical Lobular Hyperplasia (ALH)
- Classic Lobular Carcinoma in Situ (cLCIS)
- Pleomorphic Lobular Carcinoma in Situ (pLCIS)

# Lobular carcinoma in situ

- First described in 1940s by foote and stewart.
- A high risk indicator lesion for breast cancer development.
- It doesn't itself progress to malignancy ?
  - There is increasing evidence that LCIS may also act as a non-obligate  precursor in the progression to invasive carcinoma

- Incidence ?
  - Difficult to assess →
    - it lacks specific clinical abnormalities.
    - Always as incidental finding (0.5-3.9% of breast biopsy specimens)

- 15% absolute risk at 15 years
  - Significant number develop BC more than 15 years

- LIN has been linked to increased risk for subsequent carcinoma in both breast
  - higher in ipsilateral breast (no significant difference than contralateral side)

| | ALH | LCIS |
|---|---|---|
| Breast Cancer RR | 4-5 folds | 8-9 folds |

# LCIS

- Mean age of Dx is between 40 & 50 years (10-15 years younger than invasive breast cancer).
- In women > 50 years → incidence of LCIS increased concurrently with incidence of ILC
  - Increase use of mammography, MRI
  - Use of hormone replacement
  - Improved molecular diagnosis
- In women < 50 years → incidence of ILC is not observed to increase with LCIS

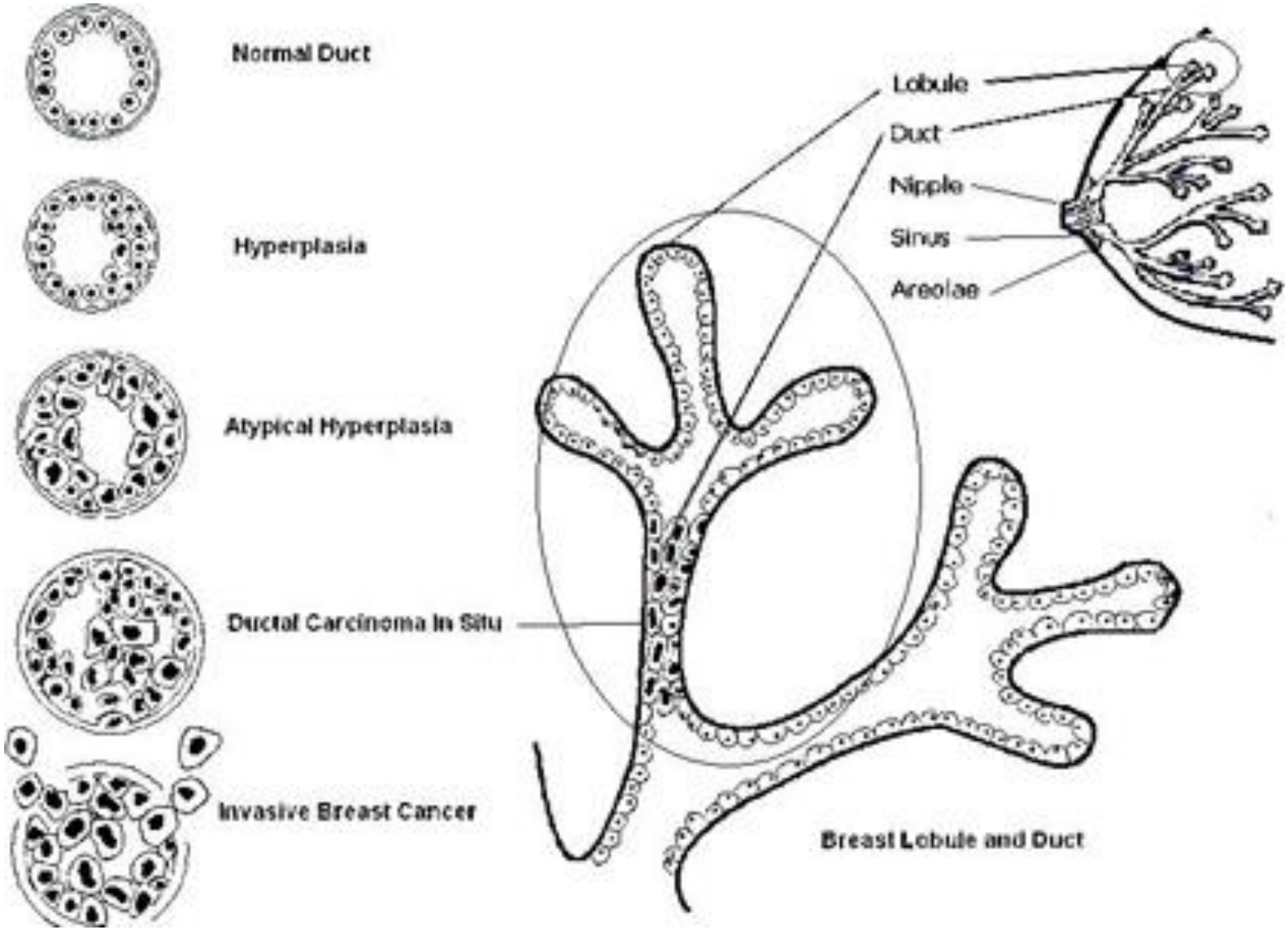
# Risk Assessment

- LCIS → 8-9 folds higher risk than general population.
- Multifocal in 50%
- Contralateral involvement in 30% of patients.
- Subsequent breast cancer development mostly IDC NST.
  - ILC represent 45% of tumors in patients with LIN
- In 90% of ILC, LCIS is identified.
- Time interval between LCIS and cancer development is 10-15 years

# Histopathology

- LN ( ALH , LCIS) [*page and colleagues criteria*]
  - *Small, round, monomorphic cells*
  - *Cells are dyshesive with an increased nuclear to cytoplasmic ratio*.
  - *Presence of intracytoplasmic vacuoles in LCIS*
- Both ALH and LCIS can co-exist in the same specimen

| | ALH | LCIS |
|---|---|---|
| Acini involvement in the affected TDLU are involved | < 50% | > 50% |
| Cells in Lumen | Partially occluding lumen | Lumen completely occluded |
| Acini Distention | Not distended | Distended |

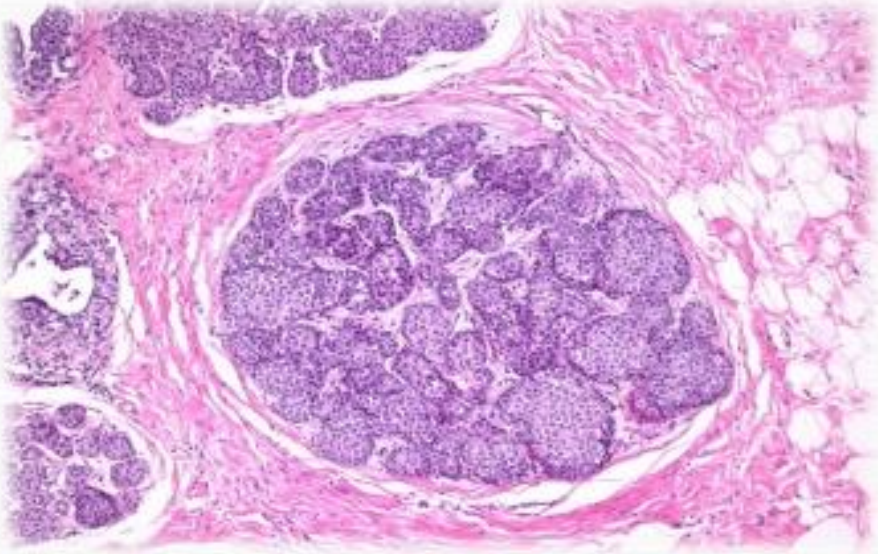

Normal Duct
Hyperplasia
Atypical Hyperplasia
Ductal Carcinoma In Situ
Invasive Breast Cancer
Lobule
Duct
Nipple
Sinus
Areolae
Breast Lobule and Duct

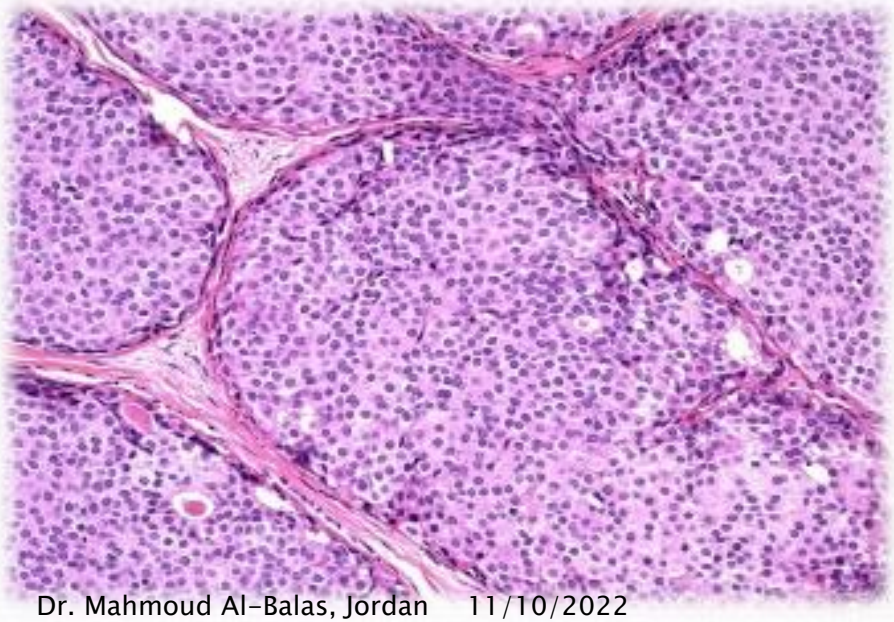
# ALH and cLCIS

- More common in premenopausal women
- Found in 0.5-4% of otherwise benign breast biopsies.
- Multicentricity in 85% of patients
- Bilateral in 30-67% of cases
- Arise in terminal duct lobular unit (TDLU)
- Both are negative for E-Cadherin (cell surface adhesion molecule) in 85% of cases

# LOBULAR CARCINOMA IN SITU - MORPHOLOGY

- Dyscohesive round cells with oval or round nuclei and small nucleoli. Absence of atypia, pleomorphism, mitoti activity, necrosis.
- Involved acini – recognizable as lobules.
- Mucin-positive signet-ring cells.
- ER and PR +ve.





# Classification of involved malignant cells

- Type A →
  - Bland nuclei
  - Scant cytoplasm
- Type B →
  - Mild to moderate nuclear atypia
  - More cytoplasm than type A cells
  - Larger than Type A cells

**Lesions that are composed of either cells types are referred to as 'classic' lobular neoplasia.**

# LCIS Variants

- Pleomorphic LCIS
- Pleomorphic apocrine LCIS
- LCIS with comedo necrosis
- Carcinoma in situ with mixed ductal and lobular features

# Pleomorphic LCIS

- First described as distinct entity in 1992 by Eusebi et al.
- Most widely recognized variant of LCIS
- Incidence less than ALH, cLCIS
- Common in older women than ALH, cLCIS
- Cellular Features:
  - Dyshesive cells (as cLCIS)
  - Higher degree of nuclear pleomorphisms
  - Abundant cytoplasm

# Pleomorphic lobular carcinoma in situ

- Histologic features similar to high grade DCIS
  - Large nucleated nuclei
  - Marked pleomorphism
  - Numerous mitosis
  - Comedo necrosis centrally
  - Microcalcification
- Central, comedo necrosis and microcalcifications are quiet common (can be confused with DCIS)
- Occasionally, cytoplasm is eosinophilic with fine granules → pleomorphic apocrine LCIS
- Intracytoplasmic vacuoles can present (signet ring cell appearance)
- Negative for E-Cadherin as ALH, cLCIS

# LCIS with comedo necrosis

- Have feature of classic LCIS (small, uniform cells with deshesive growth pattern) ***plus*** central area of comedo necrosis.
- Microcalcifications are often associated with areas of necrosis.
- It has strong association with invasive carcinoma (i.e. either purer lobular carcinoma or with focal lobular features)

# Carcinoma in situ with mixed ductal and lobular features

- Resemble both LCIS and DCIS
- Cells are small monotonous but are more cohesive than LCIS cells.
- E-cadherin immunohistochemistry may show heterogeneous staining (may be only positive, only negative or both positive and negative cells in the same lobular unit)

# Immunophenotype

| | cLCIS | cLCIS with comedo necrosis | pLCIS |
|---|---|---|---|
| ER / PR | Positive | Positive | Positive |
| E – cadherin | Negative | Negative | Negative |
| HER2 overexpression | Negative | Negative | Might be Positive |
| P53 mutation | Negative | Negative | Might be Positive |
| Ki67 | Low | Low | Moderate / High |

Antibody p120-catenin diffusely localize to cytoplasm in LN while remain localized to membrane in ductal lesions (Dabbs et al.)

pLCIS is often positive with gross cystic disease fluid protein-15, specially if It is with apocrine features.

| | cLCIS | pLCIS |
|---|---|---|
| ER | + | - (34%) |
| PR | + | - (38%) |
| HER2 | - | High Positive in 15% |
| Ki67 | Lower | Higher |
| P53 | Less frequent | More frequent |
| E-Cadherin | Negative | Negative |
| Comedo necrosis | Absent | Common (might be confused with DCIS) |

# Molecular pathology

**E-cadherin**

- Cell surface adhesion molecule.
- A product of CDH1 gene.
- Expressed on normal epithelial cells and span the cell membrane.
- Form dimers with E-cadherin on other cells
- Intracytoplasmic part binds to p120-catenin
- When E-cadherin lost →
  - Loss of adhesion between cells
  - p120-catenin accumulate in the cytoplasm and activate Rho-GTPases and increase cellular motility.

| PLCIS | DCIS |
| --- | --- |
| • Loss of E-cadherin | • Positive of E-cadherin |
| • Intracytoplasmic p120-catenin | • Epithelial p120-catenin |
| • Loss of High M. weight keratins<br>• CK 5/6, 14, 17 | • Positive for CK 5/6, 14, 17 |

# Clinical Presentation

- Usually no clinical features or mammographic changes.
- Mostly as an incidental finding during core needle biopsy or lumpectomy.
- Predominantly in premenopausal women
- Microcalcifications can be detected in mammography.
  - Punctate calcifications → cLCIS
  - Large, clustered calcifications → pLCIS

*Note → if LCIS cannot be differentiated from DCIS … patient should be treated as DCIS.*

# Surgical Treatment

- Incidental LCIS by percutaneous biopsy mandates performing surgical excisional biopsy.
- The aim of the excisional biopsy is to role out synchronous invasive carcinoma and DCIS.
- Preoperative placement of titanium clip in the index site to facilitate post operative identification of excised specimen.
- Preoperative localization techniques:
  - Wire guided localization.
  - Radioactive seed localization.
- Post excisional specimen mammography for detecting a clip within excised specimen.

# Lobular neoplasia in core biopsies, what is the next step?

- Variable upgrade rate of LN into DCIS and/or IBC.
  - Some recent studies showed DCIS or invasive cancer in 10-27% of LN cases in core biopsies (small, retrospective studies).
  - Other studies (Hwang et. al, Renshaw et.al, Nagi et. al)
    - Upgrade rate in subsequent excisional biopsy (1-3%)
    - 30% developed DCIS or IBC in ipsilateral or contralateral breast and many of them in sites not related to previous core biopsy.

# Microscopic Margins assessment

- Microscopically negative margins:

| 180 patients with margins negative after LCIS excision<br>12 years follow up | | | |
|---|---|---|---|
| Ipsilateral BC | Contralateral BC | Ipsilateral IBC | Contralateral IBC |
| 14.4% | 7.8% | 5.6% | 5.6% (later than ipsilateral IBC) |

- Microscopically positive margins:

| 2894 patients with BCS for IBC or DCIS 10% had synchronous LCIS (5 years follow up) | | | |
|---|---|---|---|
| Crude LR with LCIS | | | Crude LR without LCIS |
| 4.5% | | | 3.8% |
| LR +ve margins | LR LCIS +ve not at margin | LR LCIS -ve | |
| 6% | 1% | 2% | |

- **for Classis LCIS → no need for re-excision to achieve negative margins.**
- **For Pleomorphic LCIS → re-excision to achieve negative margins is indicated.**

# Bilateral Risk Reducing Mastectomy

- This approach is reserved for patients with additional risks for development of BC

Or

- For patients with significant anxiety regarding observation and/or chemoprevention

- NSM with immediate reconstruction is ideal for carefully selected women.

*Note → It reduces but doesn't eliminate the risk of BC development.*

# Risk reducing endocrine therapy

- In NSABP p1 trial → tamoxifen reduced the incidence of invasive BC by 56%.
  - 6.2% of patients had LCIS
  - The annual hazard for LCIS patients to develop BC was 5.69/1000 for those on Tamoxifen vs. 12.99/1000 for those without Tamoxifen

- In NSABP p2 trial → no difference in chemoprevention between tamoxifen and Raloxifene in postmenopausal women.

# Excisional Biopsy for LN, when to do?

- Presence of another lesion necessitates proceeding to excisional biopsy (e.g. ADH)
- Discordance between radiological and pathological findings
- Associated mass or architectural distortion
- Indeterminate features between ductal and lobular features
- Pleomorphic or other variants of LCIS

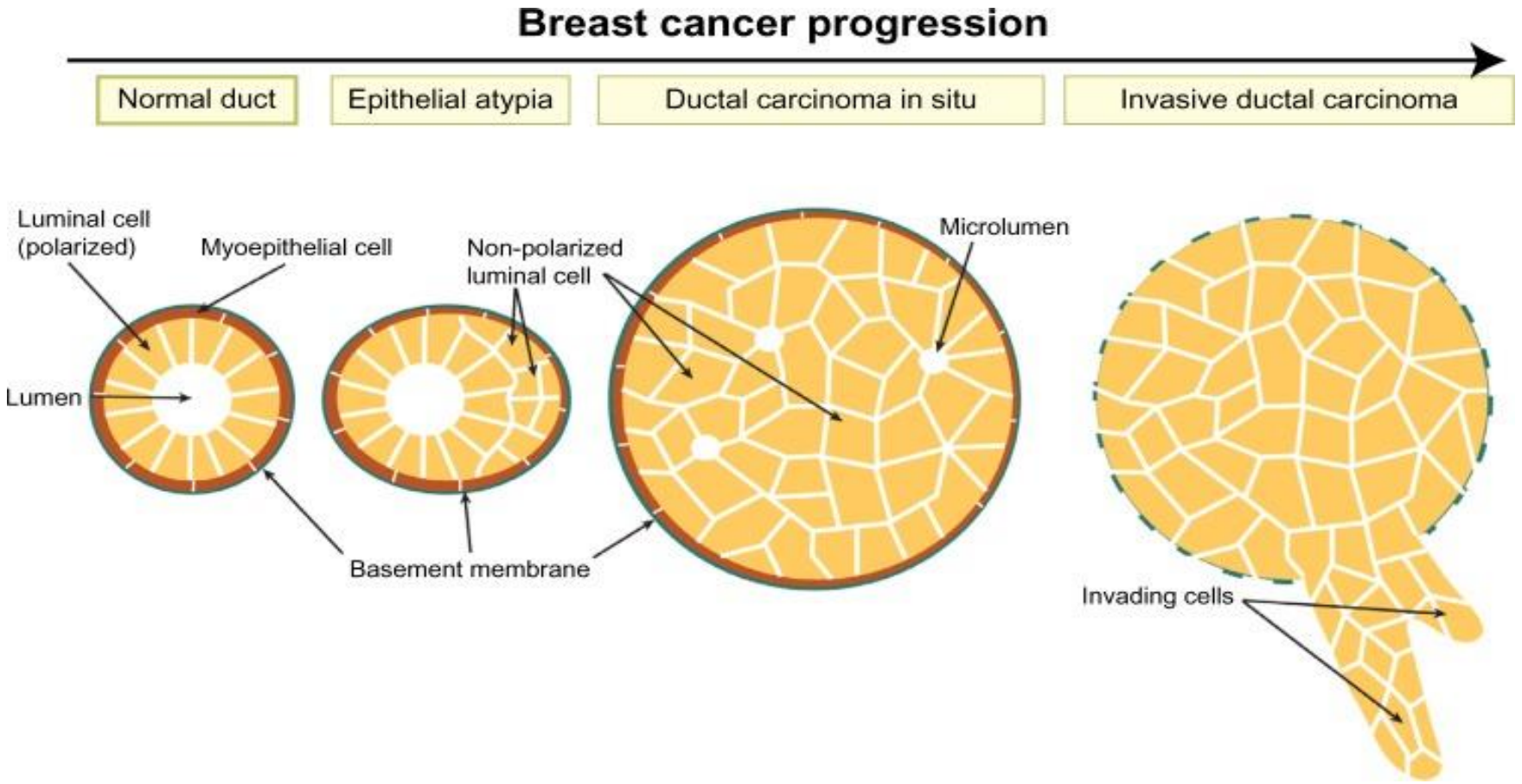
# Radiation Therapy

- No need for adjuvant radiotherapy.
- Only indicated if associated with DCIS or Invasive BC.

# Surveillance

- Annual bilateral breast physical exam.
- Annual bilateral mammography.
- Screening US for LCIS patients has high false positive result.
- Annual Mammography and MRI has similar detection rate (13%).
- The routine use for MRI in LCIS is not recommended.

# Invasive Breast Cancer


Breast cancer progression
Normal duct
Epithelial atypia
Ductal carcinoma in situ
Invasive ductal carcinoma
Luminal cell (polarized)
Myoepithelial cell
Lumen
Basement membrane
Non-polarized luminal cell
Microlumen
Invading cells

| Molecular subtype | Biomarker profile |
| --- | --- |
| Luminal A | ER+ and/or PR+, HER2−, and low Ki67 (<14%) |
| Luminal B | ER+ and/or PR+ and HER2+ (luminal-HER2 group)<br>ER+ and/or PR+, HER2−, and high Ki67 (>14%) |
| HER2 enriched | ER−, PR−, and HER2+ |
| Basal-like | ER−, PR−, HER2−, and CK5/6 and/or EGFR+ |

# Molecular subtypes

| | Luminal | HER2 | Basal |
|---|---|---|---|
| **Gene expression pattern** | ❑ High expression of hormone receptors and associated genes (luminal A>luminal B) | ❑ High expression of HER2 and other genes in amplicon<br>❑ Low expression of ER and associated genes | ❑ High expression of basal epithelial genes, basal cytokeratins<br>❑ Low expression of ER and associated genes<br>❑ Low expression of HER2 |
| **Clinical features** | ❑ ~70% of invasive breast cancers ER/PR positive<br>❑ Luminal B tend to be higher histological grade than luminal A<br>❑ Some overexpress HER2 (luminal B) | ❑ ~15% of invasive breast cancers ER/PR negative<br>❑ More likely to be high grade and node positive | ❑ ~15% of invasive breast cancers<br>❑ Most ER/PR/HER2 negative ('triple negative')<br>❑ BRCA1 dysfunction (germline, sporadic)<br>❑ Particularly common in African-American women |
| **Treatment response and outcome** | ❑ Respond to endocrine therapy (but response to tamoxifen and aromatase inhibitors may be different for luminal A and luminal B)<br>❑ Response to chemotherapy variable (greater in luminal B than in luminal A)<br>❑ Prognosis better for luminal A than luminal B | ❑ Respond to trastuzumab (Herceptin)<br>❑ Respond to anthracycline-based chemotherapy<br>❑ Generally poor prognosis | ❑ No response to endocrine therapy or trastuzumab (Herceptin)<br>❑ Appear to be sensitive to platinum-based chemotherapy and PARP inhibitors<br>❑ Generally poor prognosis (but not uniformly poor) |

# BREAST CANCER IN WOMEN: KNOW THE SUBTYPE

It's important for guiding treatment and predicting survival.

**HR+/HER2-** ····→ aka "Luminal A"

**73% of all breast cancer cases**

- Best prognosis
- Most common subtype for every race, age, and poverty level

**HR-/HER2-** ····→ aka "Triple Negative"

**13% of all breast cancer cases**

- Worst prognosis
- Non-Hispanic blacks have highest rate of this subtype at every age and poverty level

**HR+/HER2+** ····→ aka "Luminal B"

**10% of all breast cancer cases**

- Little geographic variation by state

**HR-/HER2+** ····→ aka "HER2-enriched"

**5% of all breast cancer cases**

- Lowest rates for all races and ethnicities

Breast cancer intrinsic subtying

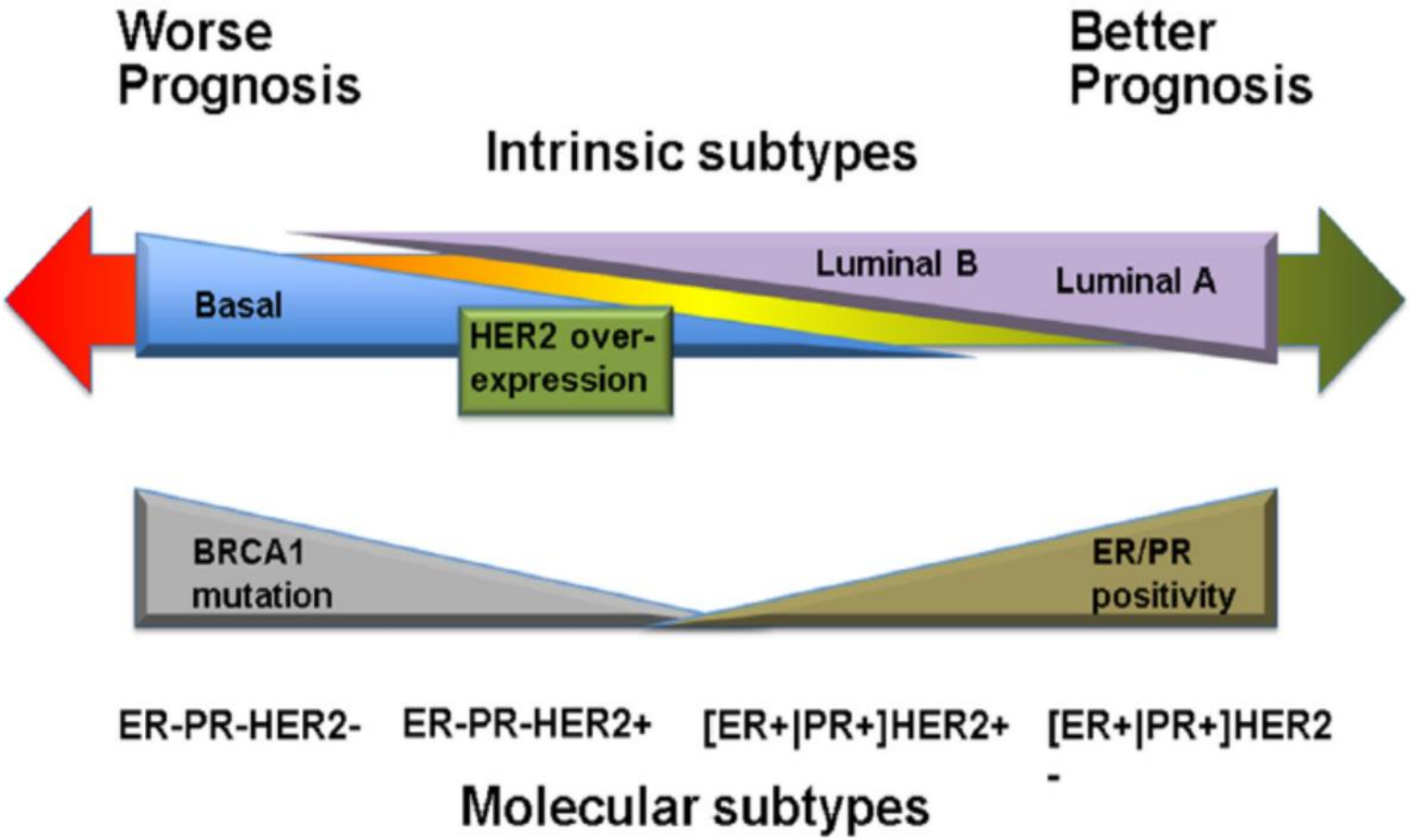
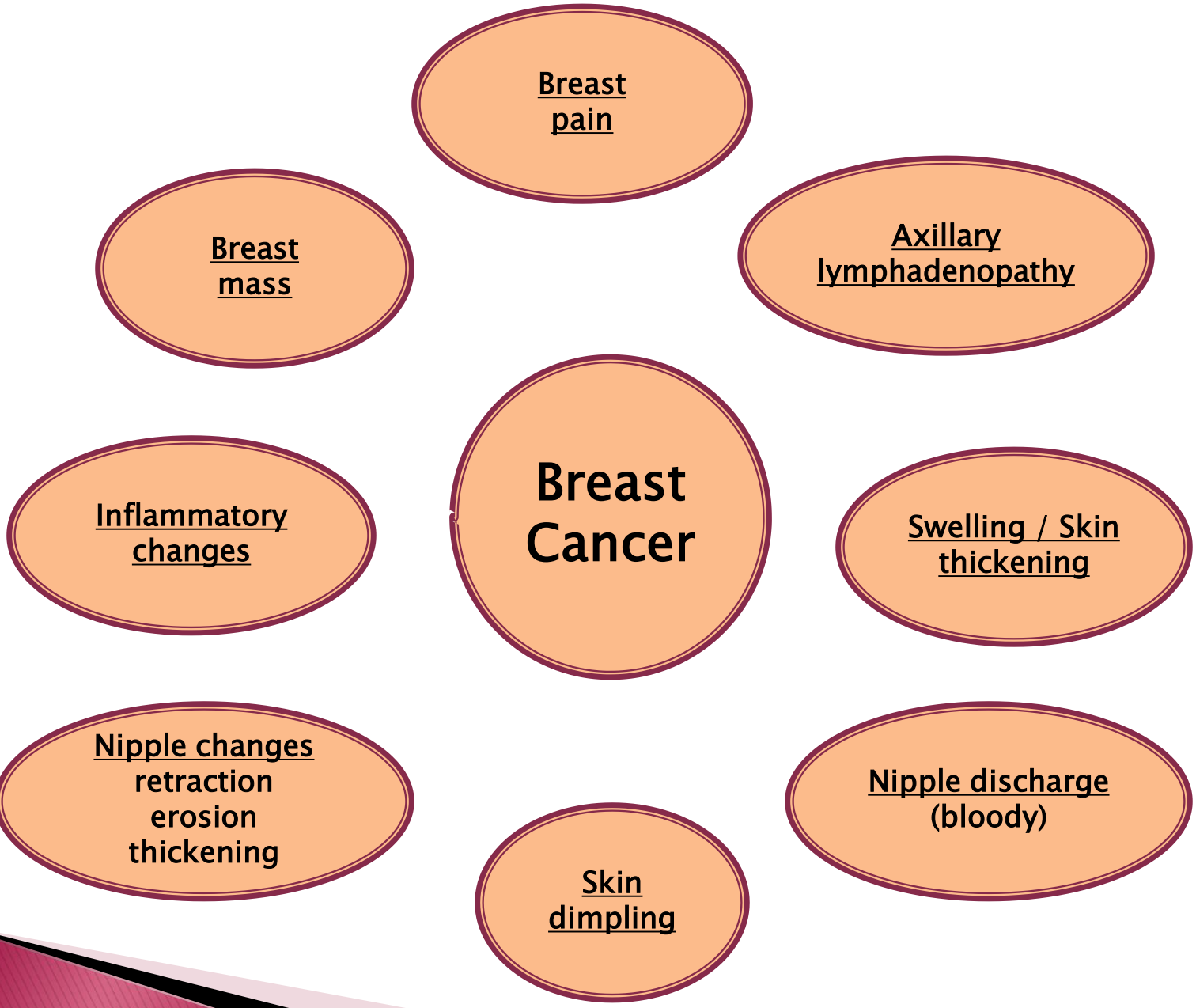


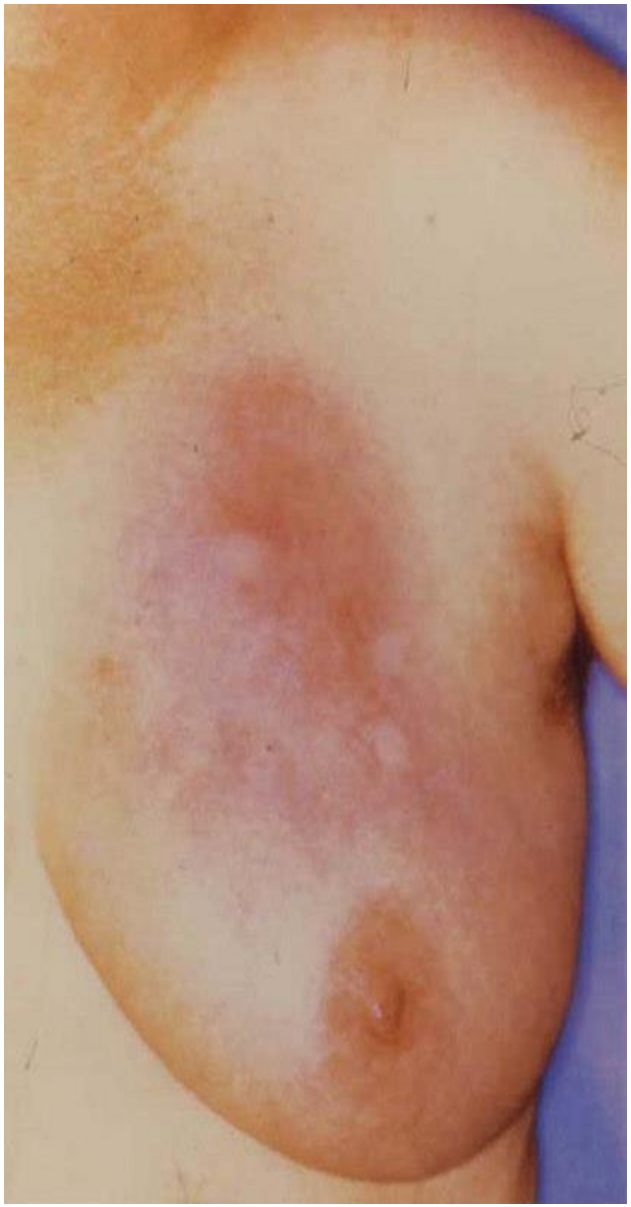

Figure 2. Patient outcome based on breast tumor intrinsic subtypes.

# CLINICAL PRESENTATION OF BREAST CANCER

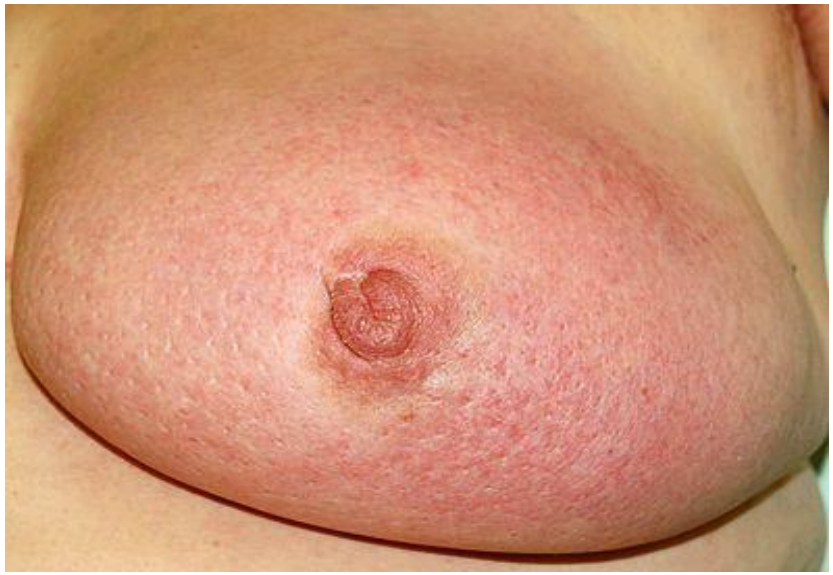
- Typically; small tumors are asymptomatic and usually discovered during screening.

- Symptomatic or palpable tumors are generally present in advanced stage.
  - Generally, more aggressive treatment will be required

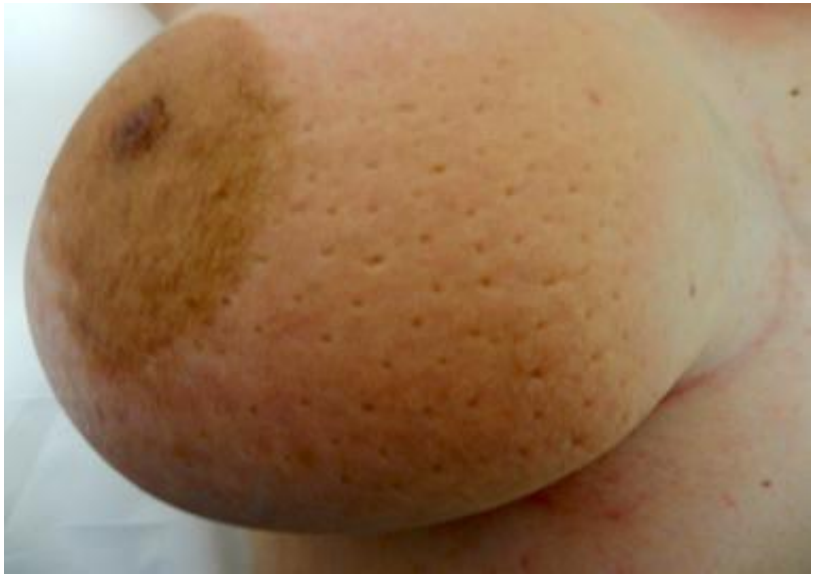

Breast pain
Breast mass
Axillary lymphadenopathy
Breast Cancer
Inflammatory changes
Swelling / Skin thickening
Nipple changes
retraction
erosion
thickening
Nipple discharge
(bloody)
Skin dimpling



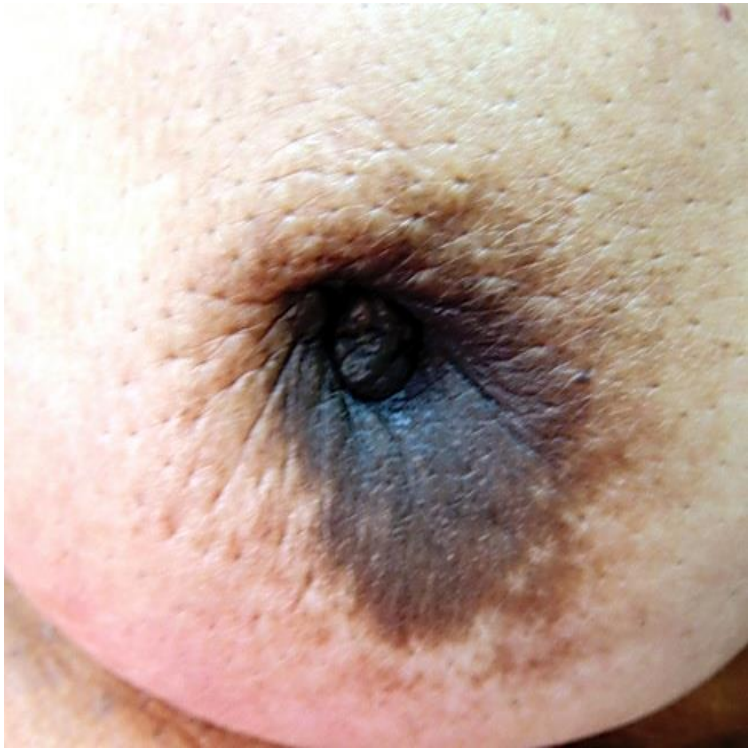
https://bugswong.smugmug.com/Medical-slides/Breast-disease/



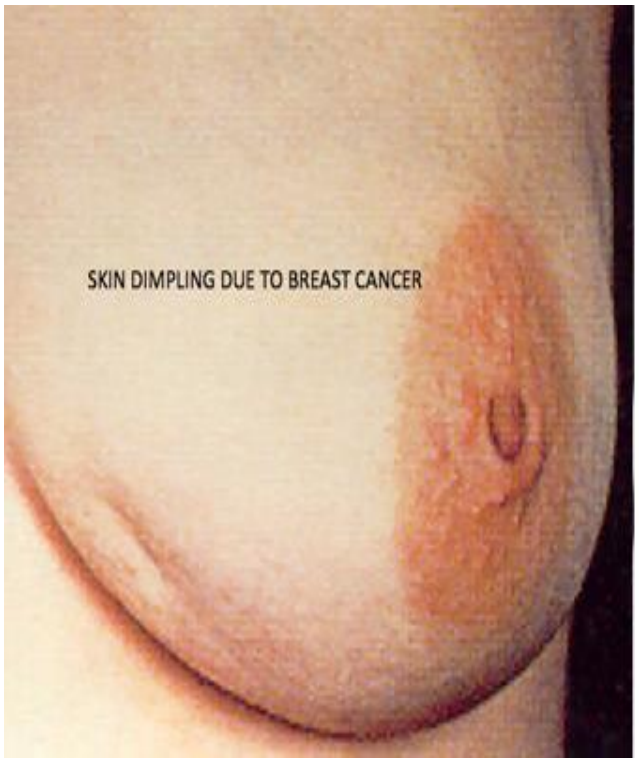
http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?15/24/15747

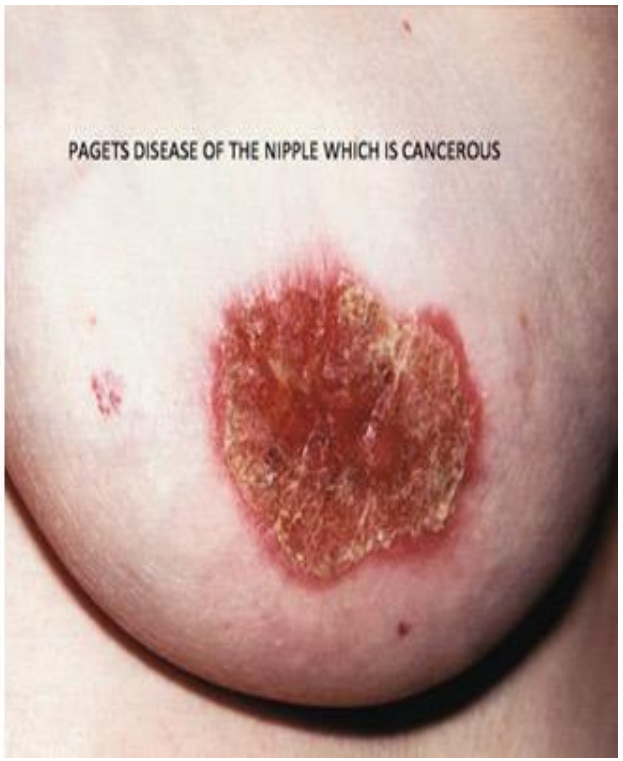


Inflammatory breast cancer illustrating the classical peau d'orange of involved skin. Courtesy of Dr Giorgio M Paratelli, Radiopaedia.org, rID 43353.



http://www.webpathology.com/image.asp?case=290&n=10




http://milliebello.co.uk/breast-cancer-diagnosis.htm

# Staging of B.C

## AJCC 7th Edition Staging for Breast Cancer

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1* | N0 | M0 |
| Stage IB | T0-T1* | N1mi | M0 |
| Stage IIA | T0 | N1** | M0 |
| | T1* | N1** | M0 |
| | T2 | N0 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T0 | N2 | M0 |
| | T1* | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| Stage IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| | T4 | N2 | M0 |
| Stage IIIC | Any T | N3 | M0 |
| Stage IV | Any T | Any N | M1 |

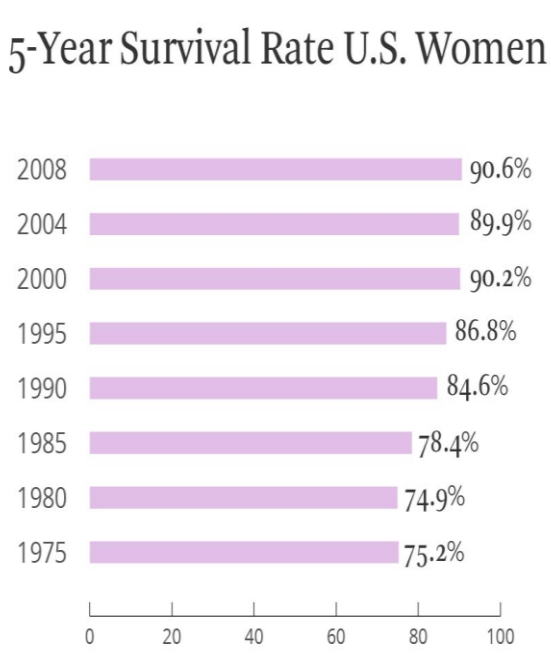
*T1 includes T1mi.

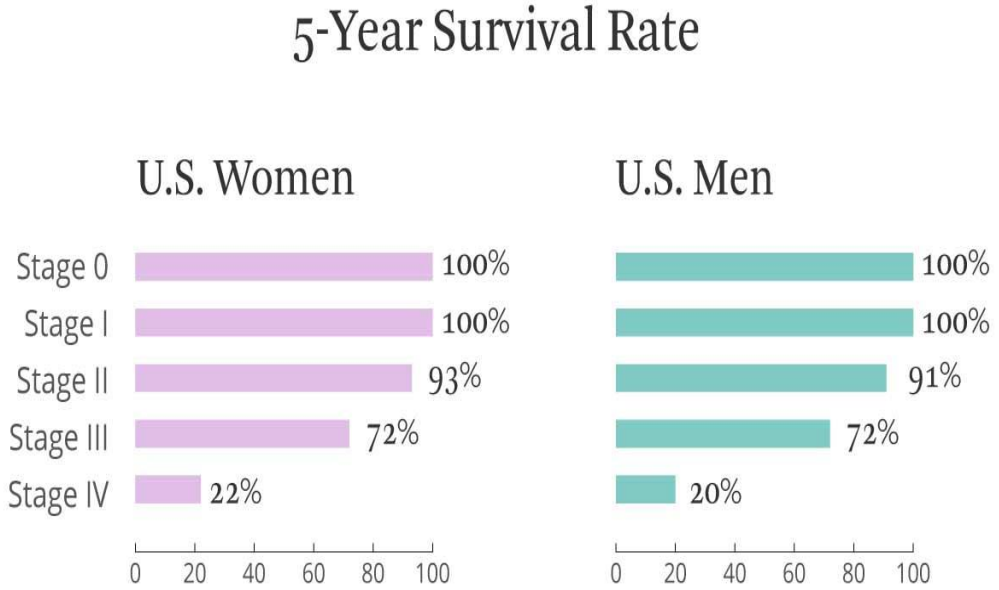
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA & are classified Stage IB.

| TNM Class | Criteria |
|---|---|
| T0 | No evidence of primary tumor |
| T1a | Carcinoma in situ |
| T1 | < or = 2 cm |
| T1m1c | microinvasion .1 cm or less |
| T1a | >.1 to .5 cm |
| T1b | >.5 to 1 cm |
| T1c | >1 to 2 cm |
| T2 | >2 to 5 cm |
| T3 | >5cm |
| T4 | Any size tumor with direct extension to : a) Chest wall or b) skin |
| T4a | Chest wall, not including pectoralis muscle |
| T4b | Skin edema, ulceration, satellite skin nodule |
| T4c | 4a and 4b |
| T4d | Inflammatory carcinoma |

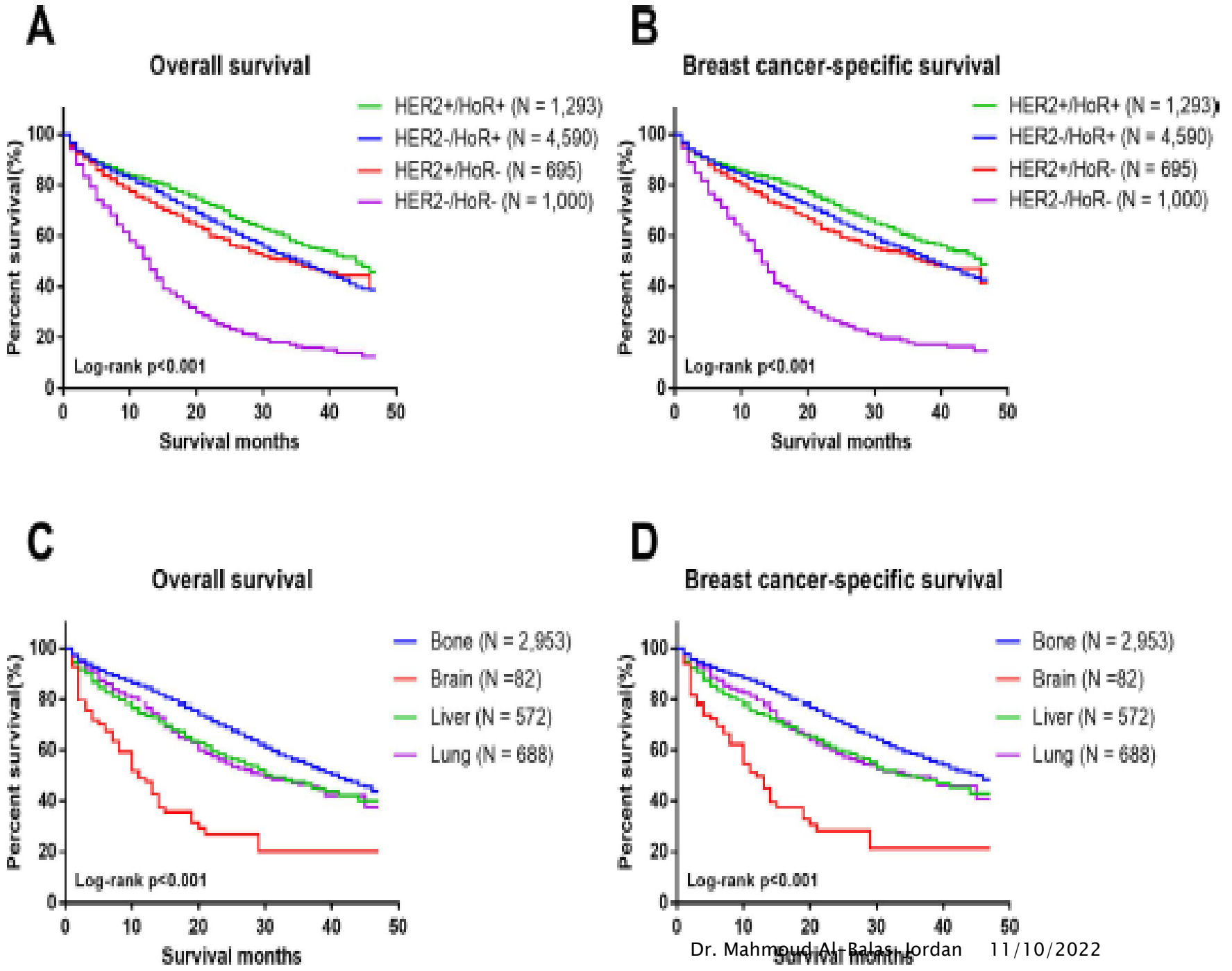
| TNM Class | Criteria |
| --- | --- |
| Nx | Regional lymph nodes cannot be removed |
| N0 | No regional lymph node metastasis |
| N1 | ❑ Metastasis to movable ipsilateral axillary lymph nodes<br>❑ 1-3 ALN |
| N2 | ❑ Metastases in ipsilateral axillary lymph nodes fixed of matted (N2a) or met. only in clinically apparent ipsilateral mammary nodes without clinically evident axillary lymph nodes. ( N2b)<br>❑ 4-9 ALN |
| N3 | ❑ Metastases in ipsilateral axillary or infraclavicular lymph nodes (N3a) or clinically apparent ipsilateral internal mammary lymph nodes (N3b) or ipsilateral supraclavicular lymph nodes (N3c)<br>❑ 10 or more ALN |
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

# Prognosis



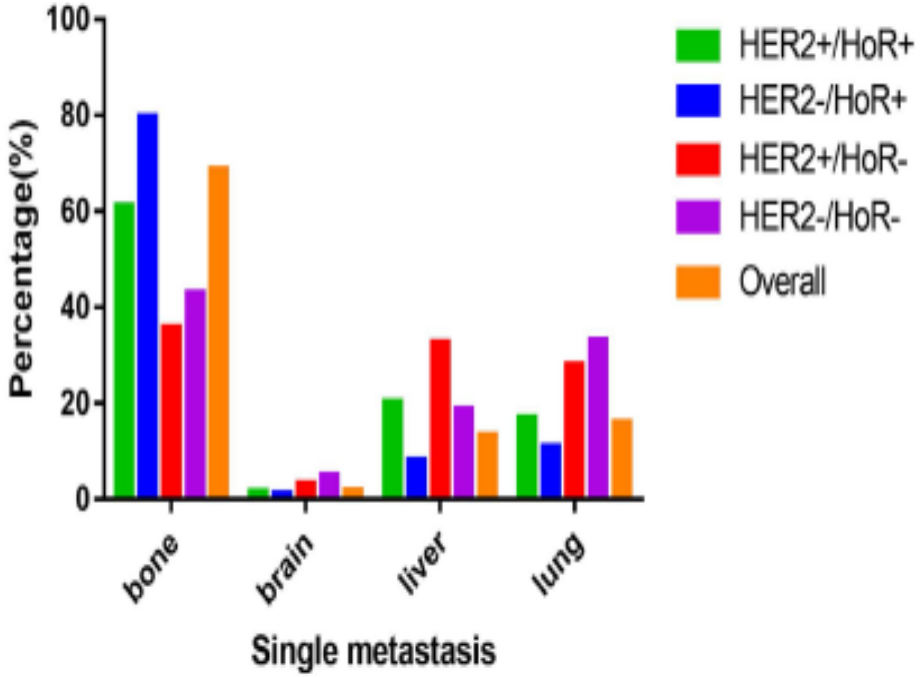

https://www.healthline.com/health/breast-cancer/survival-facts-statistics#1


A
Overall survival
HER2+/HoR+ (N = 1,293)
HER2-/HoR+ (N = 4,590)
HER2+/HoR- (N = 695)
HER2-/HoR- (N = 1,000)
Percent survival(%)
Log-rank p<0.001
Survival months
B
Breast cancer-specific survival
HER2+/HoR+ (N = 1,293)
HER2-/HoR+ (N = 4,590)
HER2+/HoR- (N = 695)
HER2-/HoR- (N = 1,000)
Percent survival(%)
Log-rank p<0.001
Survival months
C
Overall survival
Bone (N = 2,953)
Brain (N =82)
Liver (N = 572)
Lung (N = 688)
Percent survival(%)
Log-rank p<0.001
Survival months
D
Breast cancer-specific survival
Bone (N = 2,953)
Brain (N =82)
Liver (N = 572)
Lung (N = 688)
Percent survival(%)
Log-rank p<0.001
Survival months

# Breast cancer metastasis

**Impact of molecular subtypes on metastatic breast cancer patients: a SEER population-based study**

Yue Gong[1,2], Yi-Rong Liu[1,2], Peng Ji[1,2], Xin Hu[1] & Zhi-Ming Shao[1,2,3]



# Treatment of breast cancer

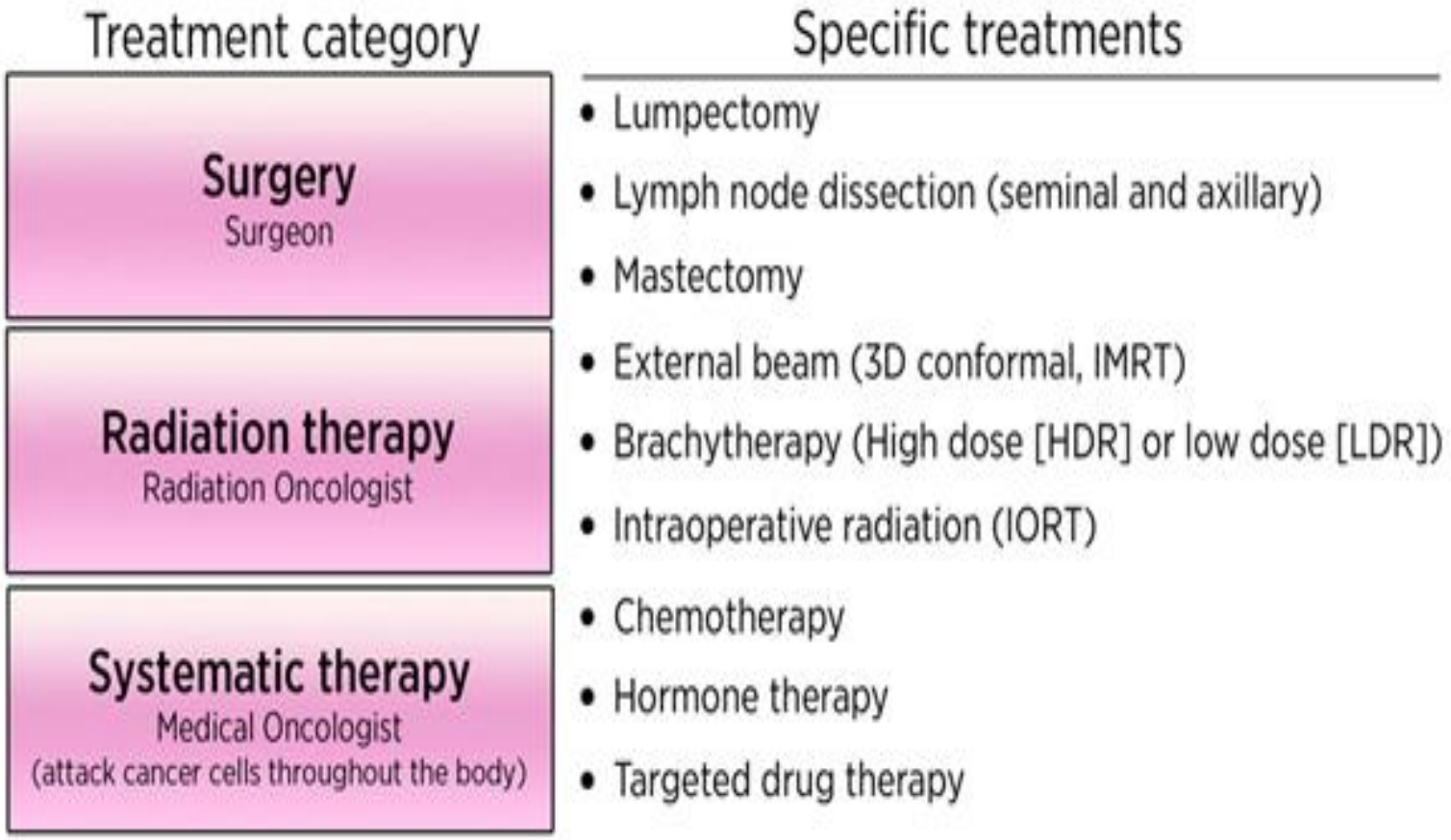

# TREATMENT SELECTION?

**Patient Factors:**

- Age
- Medical condition
- Expectations
- Family history
- Inherited BC
- Contraindication to BCS

**Tumor Factors:**

- Stage
- Histologic subtypes
- Biologic tumor features
- Unilateral or Bilateral
- Primary or recurrent tumor


Treatment category
Specific treatments
Surgery
Surgeon
Lumpectomy
Lymph node dissection (seminal and axillary)
Mastectomy
Radiation therapy
Radiation Oncologist
External beam (3D conformal, IMRT)
Brachytherapy (High dose [HDR] or low dose [LDR])
Intraoperative radiation (IORT)
Systematic therapy
Medical Oncologist
(attack cancer cells throughout the body)
Chemotherapy
Hormone therapy
Targeted drug therapy

# Surgical management

- Wide local excision / BCS
- Simple mastectomy
- Modified radical mastectomy
- Skin sparing mastectomy (SSM)
- Nipple – areola skin sparing

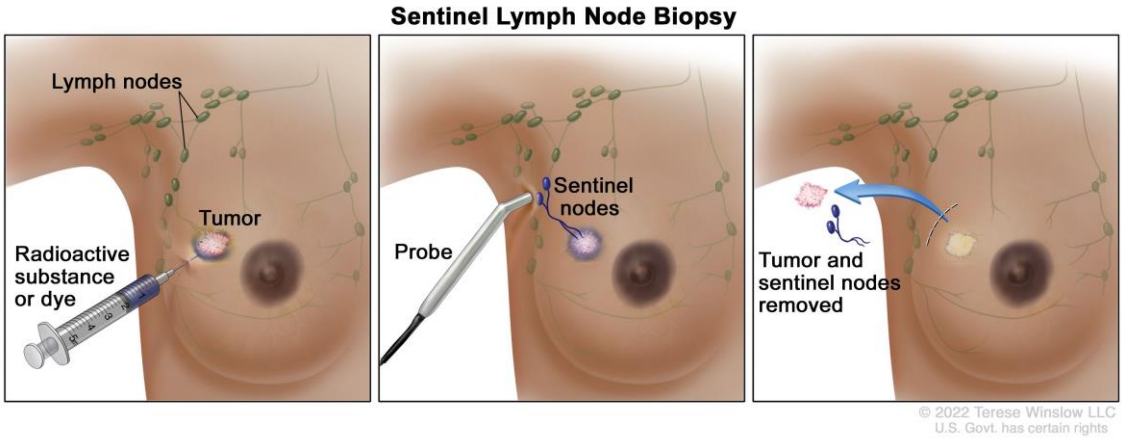
# Evaluation of Axilla in Breast Cancer

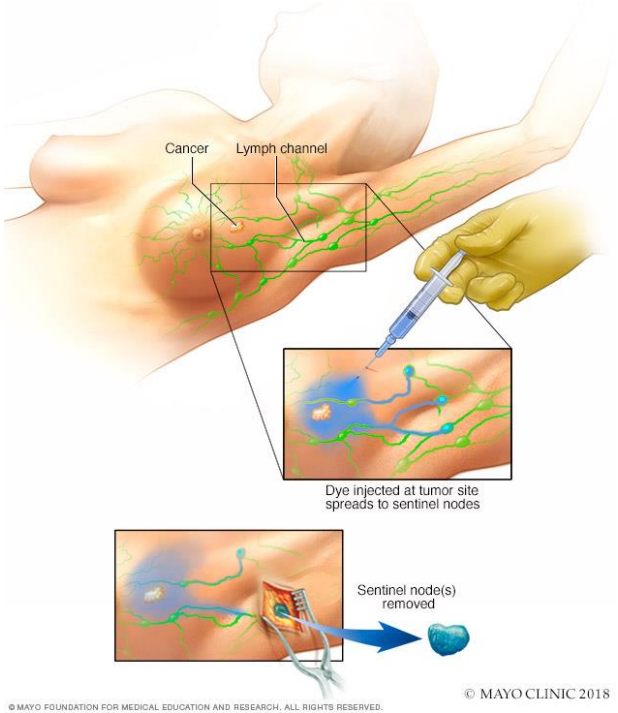
# Introduction

- T and N according to the TNM staging system were considered the most important major prognostic factors in predicting survival and selecting adjuvant treatment.
- Recently, Tumor biology is considered more important than other factors for prognosis and treatment selection.
- ALND was the standard for axillary management in patients with clinically negative axilla early breast cancer.
- Nowadays, there is no survival benefit form ALND in BC.

# Lymphatic drainage of the breast

- A network of interconnected superficial and deep lymphatic vessels.
- Sappey's plexus (i.e. retroareolar subdermal plexus) drain both areola and nipple.
- Interlobular connective tissue and peri lactiferous channel lymphatics also drain to Sappey's plexus.
- Efferent lymphatic channels leave this plexus and pass along the lateral border of pectorlais major muscle and enter the axilla through the clavicopectoral fascia.
- ALN drain 75% of breast lymphatics
- Internal mammary nodes drain 25%


Sentinel Lymph Node Biopsy
Lymph nodes
Tumor
Radioactive substance or dye
Probe
Sentinel nodes
Tumor and sentinel nodes removed
© 2022 Terese Winslow LLC
U.S. Govt. has certain rights


Cancer
Lymph channel
Dye injected at tumor site spreads to sentinel nodes
Sentinel node(s) removed
© MAYO CLINIC 2018
© MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH. ALL RIGHTS RESERVED.

# Sentinel Lymph node biopsy – SLNB

- SLN is the first lymph nodes drained by lymphatics from the breast.
- First used in Breast cancer by Armando Giuliano in 1994 (Blue dye)
- At least one SLN is required to assess the status of axillary nodes.
- If SLN is free, other lymph nodes are accepted to be clear.
- The detection rate for SLN range between 95-100%
  - False negative rate for one SLNB around 10%
  - FNR decrease to around 1% if 3 or more SLN are harvested
- No clinical significance for harvesting more than 3 SLN.

# SLNB – Indications

- It is accepted as a standard approach in all breast cancer patients with clinically negative axilla regardless the size and location of the tumor.

# SLNB – Contraindications

- Clinically metastatic lymph nodes (palpable or radiologic finding)
- Preoperative metastatic LN by a biopsy.
  - 40% of N+ patients can be detected with preoperative US and needle biopsy.
  - SLN has high FNR in clinically N1 cases due to blockage of lymphatic channels by tumor cells.
- LABC with inflammatory component or dermal edema (i.e. blocked lymphatics)
- Patients with allergic reaction to the dye 1-3%
- Pregnancy …
  - Blue due is contraindicated (fatal effects)
  - Radioactive substances can be used in low doses ! Caution …

# SLNB in DCIS

- ALN metastasis in 1-2% of DCIS (i.e. invasive component within DCIS)
- SLN metastasis detection rate in DCIS
  - 7.4% when DCIS diagnosed with needle biopsy
  - 3.7% when DCIS diagnosed by excisional biopsy

**Indications for SLNB in DCIS**

- DCIS diagnosed by needle biopsy
- High grade DCIS
- DCIS with microinvasion
- Multifocal DCIS
- Comedo-DCIS
- DCIS with a palpable mass
- Large DCIS ( > 2-3 cm)
- Candidates for mastectomy

# SLNB in Multifocal or multicentric BC

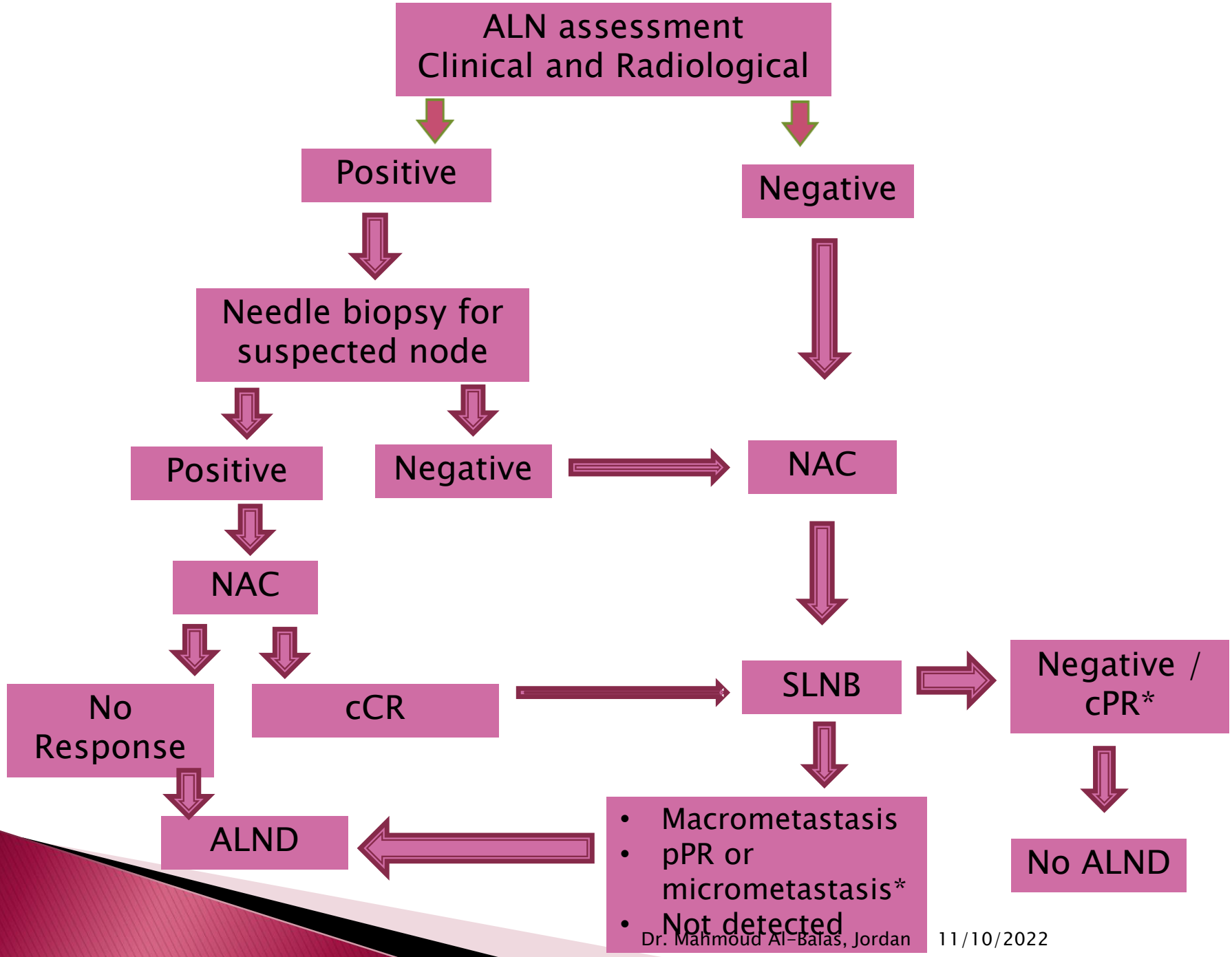
- Multicentric tumors → caner foci within the same quadrant and in close proximity to each other (< 3-4 cm apart)
- Multifocal tumors → tumors in 2 different quadrants (> 4cm apart)
- SLNB can be safely utilized in these cases
- Some studies reported higher false negative rates

# SLNB in previous axilla / breast surgery

- Patients with previous BCS, chest wall radiotherapy or ALND have altered lymphatics and SLN detection rate is considered low.
  - Compensatory flow of lymphatics to IMLN or contralateral axilla is noticed (i.e. secondary SLN sites)
- Postoperative SLN exploration (prior to adjuvant treatment) has low success rate.
- Second SLN exploration for recurrent breast cancer with completed adjuvant treatment have SLN detection rate (95-99%); this is related to reestablished lymphatic channels.
- SLNB can be performed after aesthetic breast surgery and even after mastectomy.

# SLNB after neoadjuvant chemotherapy

- Recently, NAC is considered in more clinical cases even in absence of ALN metastasis.
  - The axilla is negative in about 50% of patients with NAC plan.
- NAC results in 30-40% downstaging within clinically positive axilla.
- Chemotherapeutic impact on lymphatic drainage is abandoned.
- SLN detection rate after NAC 85% and reaches 98% if 2 or 3 lymph nodes are removed
  - Combined radiocolloid and blue dye improve detection rate.
- FNR 10.6-14%


ALN assessment
Clinical and Radiological
Positive
Negative
Needle biopsy for suspected node
Positive
Negative
NAC
NAC
No Response
cCR
SLNB
Negative / cPR*
ALND
• Macrometastasis
• pPR or micrometastasis*
• Not detected
No ALND

# SLNB in male Breast Cancer

- Male breast cancer is rare 1%
- Most common in elderly.
- Tumors are often larger with greater ALN metastasis
- Detection rate 97-100%
- High SLN and non-SLN positivity
- SLNB prevent unnecessary ALND in 50% of patients

# Do we need to perform ALND in all SLNB positive patients?

SLNB examination:

- No tumor cells
- Isolated tumor cells → metastasis < 0.2 mm
- Micrometastasis → metastasis 0.2-2 mm → Non-SLN metastasis 10-40%
- Macrometastasis → metastasis > 2 mm

# Z0011 Study

- T1/T2 clinically negative ALN
- 446 SLNB
- 445 SLNB + ALND
- Average follow up for 6.2 years

**3 or more positive LNs:**
5% in SLNB
17.6% SLNB + ALND
($P<0.001$)

| 5 year rates | Breast Recurrence | Axillary Recurrence | DFS | OS |
|---|---|---|---|---|
| SLNB | 2.1% | 1.3% | 82.8 % | 92.5 % |
| SLNB + ALND | 3.7% | 0.6% | 82.2 % | 91.9 % |

**No Significant Statistical Differences between these 2 Groups**

# The End