Breast Cancer
2024

Dr.Ghada Nazar Al-Jussani
MBCHB.,FRCpath(UK)
Assistant Professor
Faculty of medicine ,Hashemite University

Breast Cancer

- There are many types of breast cancers, and correctly identifying each one is important to determine the proper treatment.
- Breast cancers can be divided into two main overarching groups: the carcinomas and the sarcomas.
- Carcinomas are cancers that arise from the epithelial component of the breast. The epithelial component consists of the cells that line the lobules and terminal ducts; under normal conditions, these epithelial cells are responsible for making milk.
- Carcinomas comprise the vast majority of all breast cancers, and will be further discussed below.

Breast Cancer

- Sarcomas are rare cancers that arise from the stromal (connective tissue) components of the breast. These stromal component cells include myofibroblasts and blood vessel cells, and cancers arising from these "supportive" cells include phyllodes tumors and angiosarcoma.
- Sarcomas account for less than 1% of primary breast cancers.
- In the US, invasive Ca B is **2nd** to **lung cancer** as a cause of cancer death in women, & despite advances in diagnosis & treatment, **1/4 of women** who develop Ca B will die of it.
- **The lifetime risk of Ca B is one in eight (1/8) for women in the US**, with 75% of cases older than age 50.

Breast Cancer

about 5-6% are younger than the age of 40.

About 9% of all new cases of breast cancer in the United States are found in women younger than 45 years of age.

For unknown reasons (possibly related in some part to earlier detection via mammography) there has been worldwide increase in the incidence of Ca B.

Is The most common non-skin malignancy of women.

2nd most common cause of cancer deaths in women, following carcinoma of the lung.

The worldwide incidence and mortality are increasing at an alarming rate. This trend is due to social changes especially in the developing countries.

Those social changes Include delayed childbearing, fewer pregnancies, and reduced breastfeeding and with lack of access to optimal health care.

Breast Cancer

Since 1980s the mortality rate has dropped from 30% to <20% due to improvement in detecting cancers before they metastasize through screening (mammographic screening) and more effective systemic treatment.

Almost all breast malignancies are adenocarcinomas (>95%).

Classification system

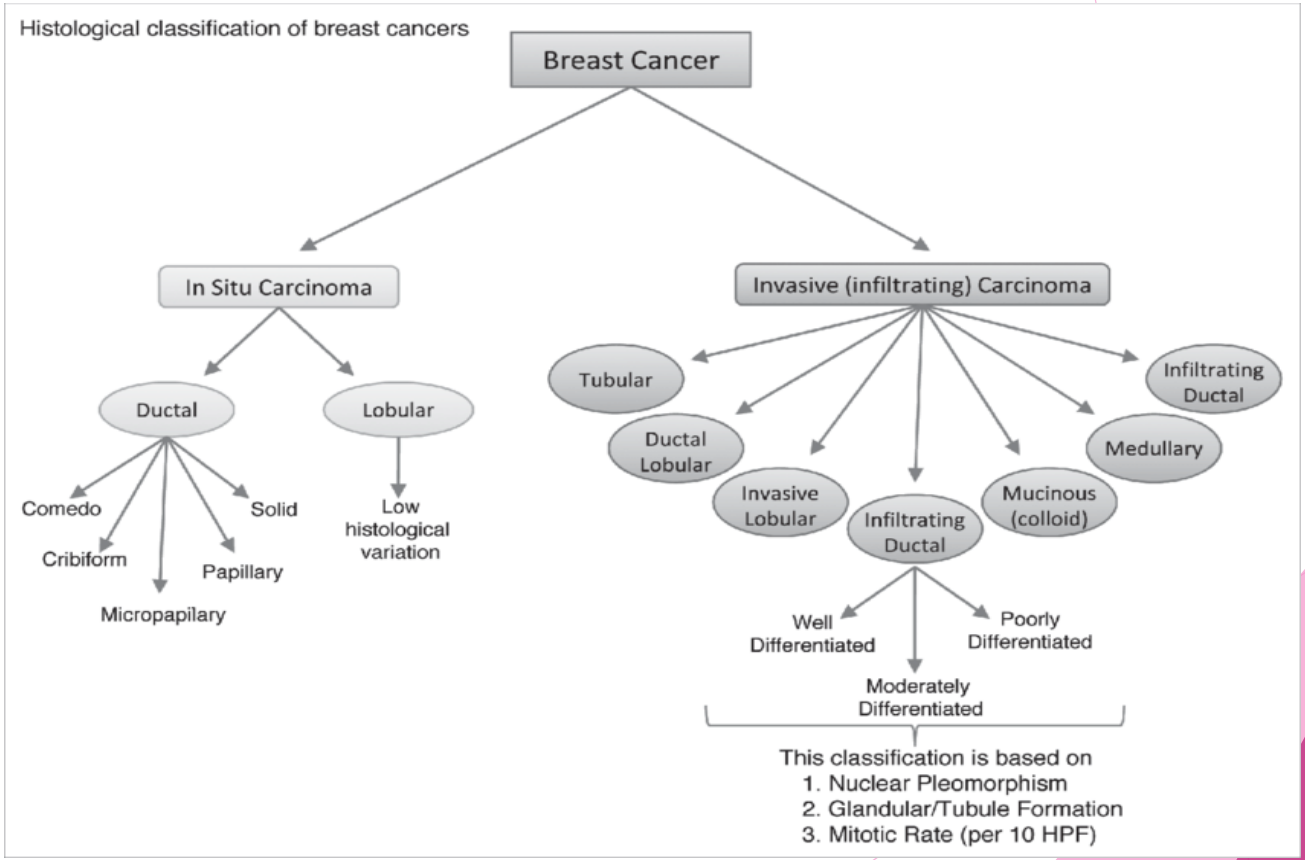
The most clinically used classification system for breast cancer depends on the expression of hormone receptors

hormone receptors are:

Estrogen receptor (ER), progesterone receptor (PR) & human epidermal growth factor receptor 2 (HER2, or ERBB2)

Can be classified according to expression of hormone receptors into three major groups:

- ER positive (HER2 negative; 50%–65% of cancers)
- HER2 positive (ER positive or negative; 10%–20% of cancers)
- Triple negative (ER, PR, and HER2 negative; 10%–20% of cancers)


Histological classification of breast cancers
Breast Cancer
In Situ Carcinoma
Invasive (infiltrating) Carcinoma
Ductal
Lobular
Comedo
Cribiform
Micropapilary
Papillary
Solid
Low histological variation
Tubular
Ductal Lobular
Invasive Lobular
Infiltrating Ductal
Mucinous (colloid)
Medullary
Infiltrating Ductal
Well Differentiated
Moderately Differentiated
Poorly Differentiated
This classification is based on
1. Nuclear Pleomorphism
2. Glandular/Tubule Formation
3. Mitotic Rate (per 10 HPF)

The three groups show striking differences in patient characteristics, pathologic features, treatment response, metastatic patterns, time to relapse, and outcome

Within each group are additional histologic subtypes, some of which also have clinical importance.

An alternative classification system relies on gene expression profiling.

used mainly in clinical research

divides breast cancers into four major types:

Luminal A. majority of cases are lower grade, ER-positive & HER2 negative cancers, has low levels of the protein Ki-67, which helps control how fast cancer cells grow. Luminal A cancers tend grow more slowly than other cancers, be lower grade, and have a good Px

2.Luminal B.Majority of cases are higher grade ER positive +ve
and HER2 negative cancers .Has High Ki67 protein which indicate faster growth of cancer cells Or progesterone Negative
3. **HER2-enriched**. overexpress HER2 and ER-negative.ER and PR Negative , Her2 Positive.HER2-enriched cancers tend to grow faster than luminal cancers and can have a worse prognosis, but are usually successfully treated with targeted therapy medicines aimed at the HER2

4.Triple Negative or Basal-like.
Triple-negative or basal-like breast cancer is estrogen receptor-negative, progesterone receptor-negative, and HER2-negative. Gene expression profiling resemble basally located myoepithelial cells
Triple-negative breast cancer is more common in:
people with
1-a BRCA1 mutation
2-younger women
3-Black women
4-Triple-negative breast cancer is considered more aggressive than either luminal A or luminal B

Risk Factors

Age:

It is considered rare in women younger than 25 and incidence increase after the age of 30. more than two thirds of women with breast cancer are older than the age of 50 and only 5% are younger than the age of 40.

Gender:

The incidence in men is only 1% of that in women.

Family History of Breast Cancer:

The greatest risk is for individuals with multiple affected first-degree relatives with early onset breast cancer mostly related to various combinations of low penetrance or weak cancer genes.

However, in about 5 to 10% of cases a highly penetrance germline mutations in the tumor suppressor genes is associated with lifetime risk greater than 90%

Geographic Factors:

higher in the Americas and Europe than in Asia and Africa

The mortality rates of breast cancer in America is 5 times greater than japan .

Immigration studies showed that immigration from low incidence to high incidence areas tends to acquire the rates of their new home countries.

In this context, diet, reproductive patterns, and breast feeding practices are thought to be involved .

Breast cancer rates appear to be raising in parts of the world that are adapting the western habits.

Race/Ethnicity:

- highest rate in women of European descent because of higher incidence of ER-positive cancers.
- Hispanic and African American develop cancer at a younger age and develop aggressive tumors.

This is thought to result from combination of differences in genetic social factors and access to health care.

Reproductive History.

Including Early age of menarche, nulliparity, absence of breastfeeding, with older age at first pregnancy are all associated with increased risk due to increased the exposure of the epithelial cells of the breast to estrogenic stimulation

Ionizing Radiation.

Chest Radiation especially if the breast is developing.

Other Risk Factors.

Postmenopausal obesity
postmenopausal hormone replacement therapy
mammographic density
alcohol consumption

Pathogenesis

Factors that contribute directly to the development of breast cancer can be grouped into:

- Genetic
- Hormonal
- Environmental

Genetic Factors

BRCA1 and BRCA2:Are classic tumor suppressor genes and the cancer only occur if both alleles are defected

- encode proteins that are required for repair of DNA damage.
- most carriers develop breast cancer by the age of 70 years

- For unclear reasons, BRCA2 mutations are primarily associated with ER-positive tumors, whereas BRCA1 mutations are associated with triple-negative cancers

Other mutated genes: *TP53* and *PTEN*

P53 (**A gene that makes a protein that is found inside the nucleus of cells and plays a key role in controlling cell division and cell death.** Mutations (changes) in the p53 gene may cause cancer cells to grow and spread in the body.It is guardian of the genome

The pathways in which familial breast cancer genes function also are often disturbed in sporadic cancers

HER2 gene amplification :

Cancers that overexpress HER2 are highly proliferative.

In the past they had a poor prognosis; Nowadays, the availability of therapeutic agents targeting HER2 has improved the prognosis.

It is a receptor tyrosine kinase that promotes the cell proliferation and suppress apoptosis

Hormonal factors

- Estrogens are considered an important hormonal factors since they stimulate the production of growth factors promoting the tumor development.

- Estrogen receptors regulate other genes in an estrogen dependent fashion. Some of those genes are important for the tumor development or growth.

- Estrogens also drives the proliferation from precursor regions to a fully malignant and metastatic carcinoma.
- **Estrogen antagonists**: reduce the development of ER-positive cancers in women at high risk and are mainstays in the treatment of established ER-positive tumors.

Morphology

Location:

Upper outer quadrant (50%)

- Central portion(20%).
- Lower outer quadrant 10%
- Upper inner quadrant 10%
- Lower inner quadrant 10%

4% have **bilateral** primary tumors or **sequential** lesions in the same breast.

Breast carcinoma

Noninvasive:(confined by a basement membrane and do not invade into stroma or lympho-vascular channels), include:

1. Ductal carcinoma in situ
2. Lobular carcinoma in situ

Invasive (infiltrating):

1. Invasive ductal carcinoma (includes all carcinomas that are of no special type)□70% to 80%
2. Invasive lobular carcinoma □10% to 15%
3. Carcinoma with medullary features□5%
4. Mucinous carcinoma (colloid carcinoma) □5%
5. Tubular carcinoma□5%
6. Other types

Invasive ductal carcinoma (NST)(NO SPECIAL TYPE)

70-80%

Arise from Milk Duct , This type of cancer forms in the lining of a milk duct within your breast. The ducts carry breast milk from the lobules, where it's made, to the nipple.

Ductal carcinoma can remain within the ducts as a noninvasive cancer (ductal carcinoma in situ), or it can break out of the ducts (invasive ductal carcinoma).

Previously called **Carcinomas "not otherwise specified"((NOS))**

Precancerous lesion: usually DCIS

Clinical presentation:

a mammographic density; a hard, palpable irregular mass, nipple retraction, or fixation to the chest wall can be seen in advanced cancers

Receptor profile:

ER (+ve in 50-60%)

HER2 (+ve in 20%)

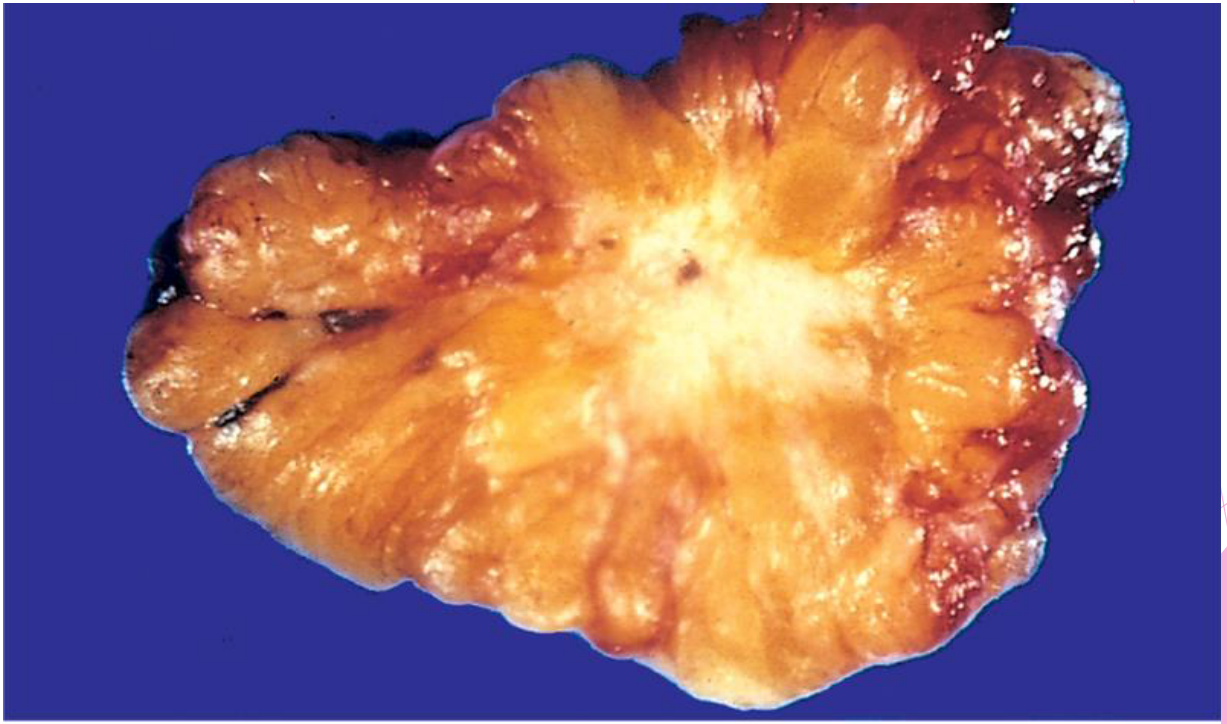
15% are negative for both

usually associated with DCIS.

Cases with invasive ductal carcinoma produces desmoplastic response which replaces the normal fat and result in mammographic densities

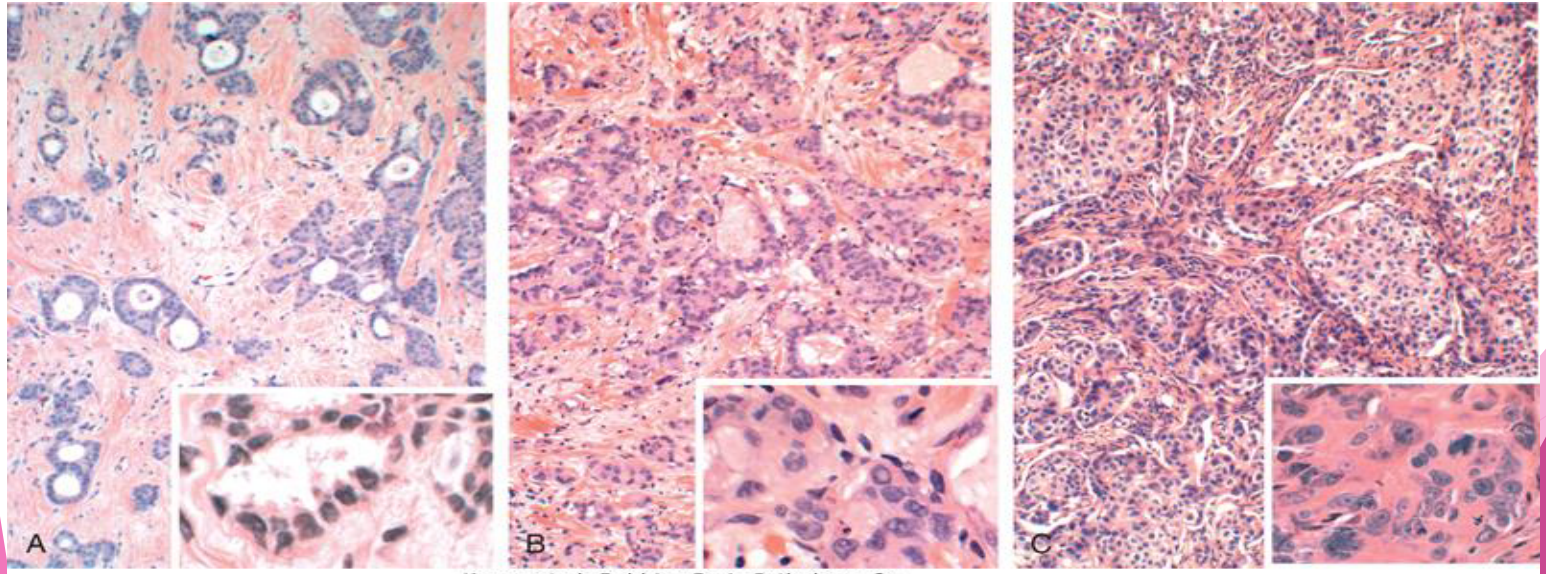
The most common immunohistochemical breast cancer prognostic and therapeutic markers used include: estrogen receptor, human epidermal growth factor receptor-2, Ki-67, progesterone receptor, and p53.

Breast carcinoma, not well circumscribed ,Irregular ,C/S showing gritty sensation , hard ,white because of desmoplasia



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

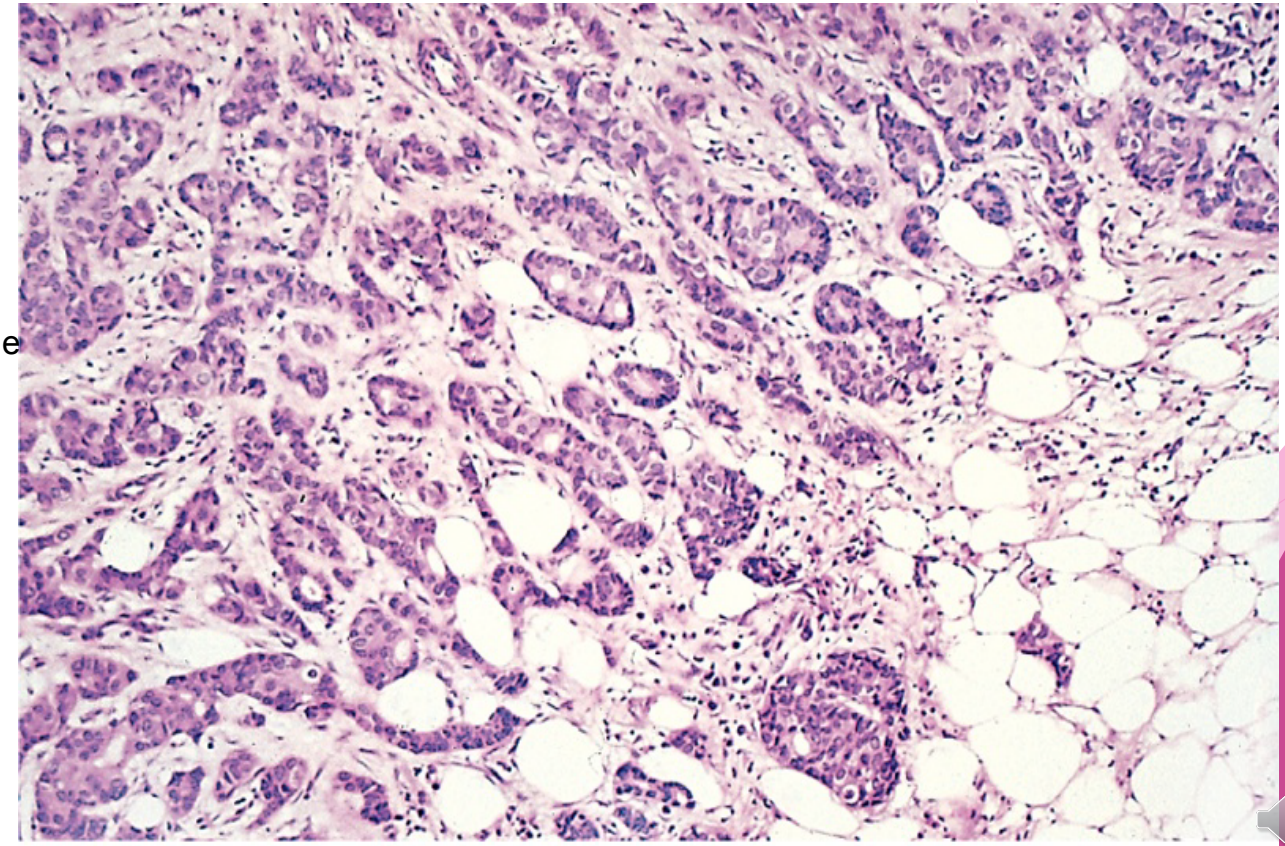
Invasive ductal carcinoma



Kumar et al: Robbins Basic Pathology, 9e.
Copyright © 2013 by Saunders, an imprint of Elsevier Inc.

A-Well differentiated carcinoma consisting of tubules with small monomorphic nuclei
B-Moderate differentiation carcinoma with less tubular formation more solidness of cells and monomorphic nuclei
C-Poorly differentiated carcinoma with sheets of pleomorphic cells containing numerous mitotic figures and central areas of tumor necrosis

Breast carcinoma margin, showing invasion & infiltration of the adjacent fatty tissue (on the right).



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

Invasive lobular carcinoma

- 10-15%
- **Arise from Milk producing lobule, Milk-producing lobules. Lobular carcinoma starts in the lobules of the breast, where breast milk is produced. When it breaks out of the lobules, it's considered invasive lobular carcinoma. The lobules are connected to the ducts, which carry breast milk to the nipple.**
- **Precancerous lesion**. associated with LCIS.
- 10% to 20% are multicentric and bilateral
- **Clinical presentation**. Most present as palpable masses or mammographic densities

- Invasive lobular carcinoma is generally composed of single (CD) small cells arrayed in a linear pattern with a targetoid pattern invading into stroma, TDLU, and adipose tissue of the breast. Neoplastic cells display round nuclei often eccentrically placed with occasional intracytoplasmic vacuoles.
- cells invade stroma i**ndividually** and often are aligned in **“single-file”**
- Almost all of these carcinomas express hormone receptors, but HER2 overexpression is very rare or absent.
- Markers. Loss of E-cadherin is a specific biomarker for invasive lobular carcinoma as opposed to invasive breast carcinoma of no special type which show E.cadherin Positive
- Metastasis of lobular carcinoma is unique since it frequently reaches the CSF, serosal surfaces, bone marrow , ovary, and uterus

Carcinoma with Medullary features

5%

Triple negative

Microscopically: large anaplastic cells with pushing, well-circumscribed borders with a pronounced lymphocytic infiltrate.

Precancerous lesions. usually absent

increased frequency in women with **BRCA1 mutations**,.

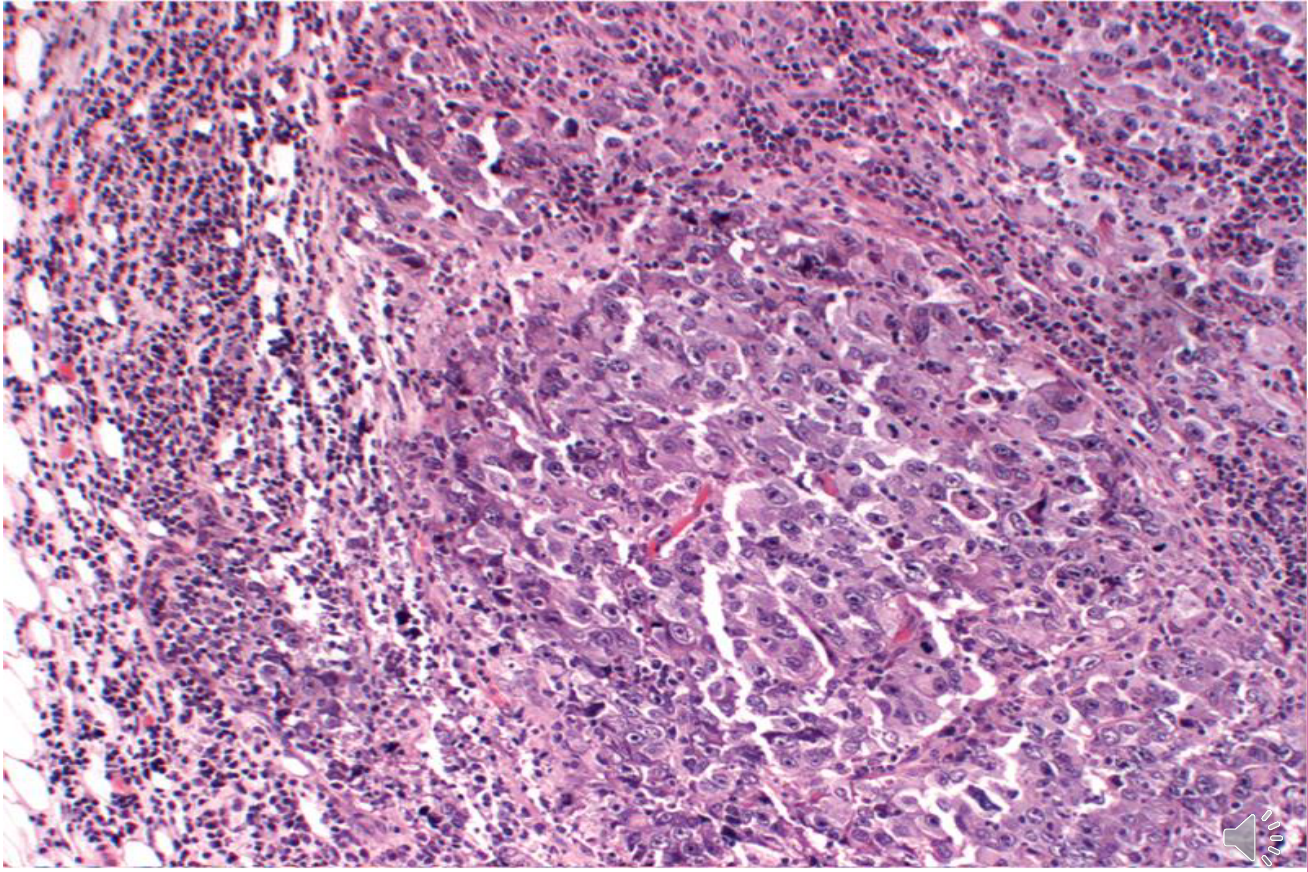
Receptor profile. lack hormone receptors and do not overexpress HER2/NEU.

Those carcinoma typically grow as rounded masses that can be difficult to distinguish from benign tumors on imaging

Histology with Carcinoma with medullary features

the tumor in the middle consist of tightly adhesive clusters of cells

At he periphery there is a dense lymphocytic infiltrate around the island of tumor cells



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

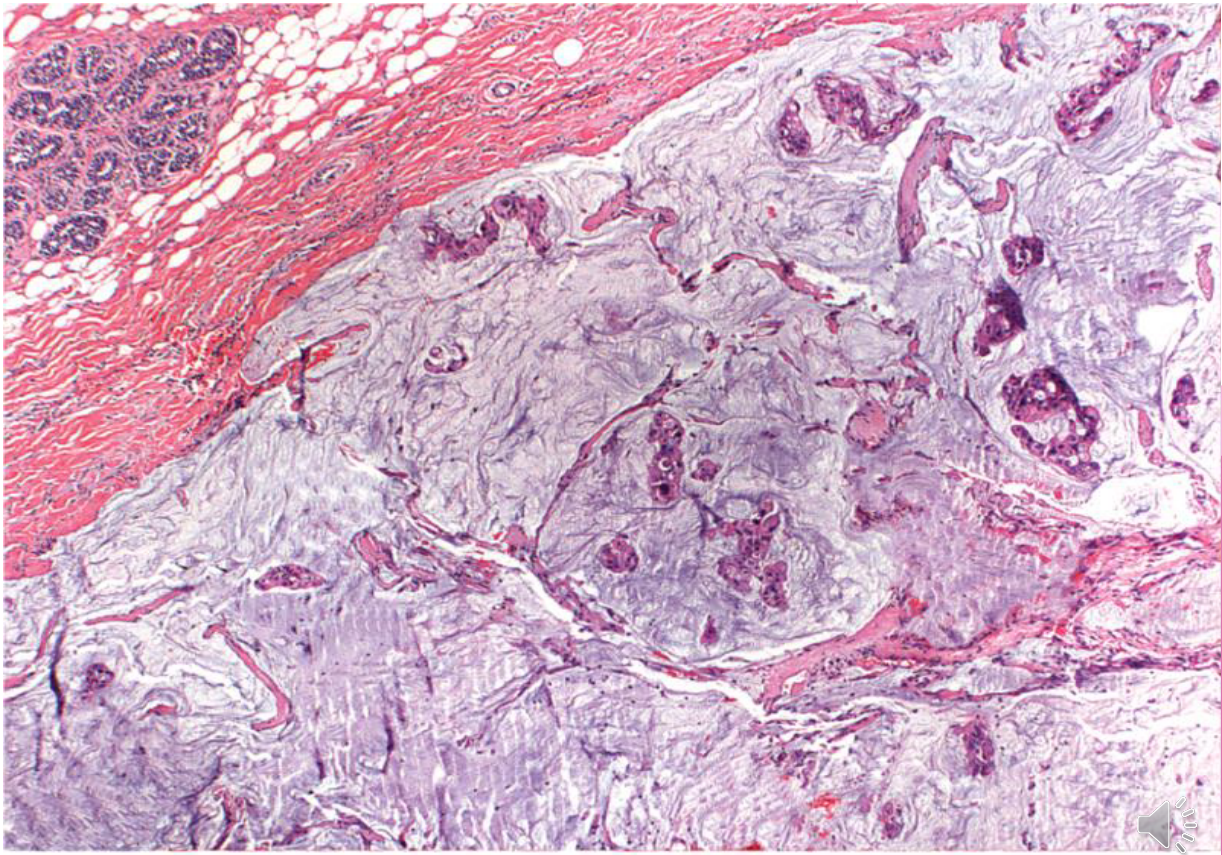
Colloid mucinous Carcinoma

- a rare subtype
- **Microscopic picture**. The tumor cells produce abundant quantities of extracellular **mucin** that dissects into the surrounding stroma. Grossly the tumors are usually soft and gelatinous.

- ER-positive/HER2-negative cancer

Shows abundant blue mucin and the carcinoma cells appears to be floating in those lakes of mucin

This mucin matrix gives the tumor the grossly soft blue to gray appearance



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

Tubular carcinoma

10% of invasive carcinomas

Clinical presentation. irregular mammographic densities.

Microscopically, well-formed tubules with low-grade nuclei.

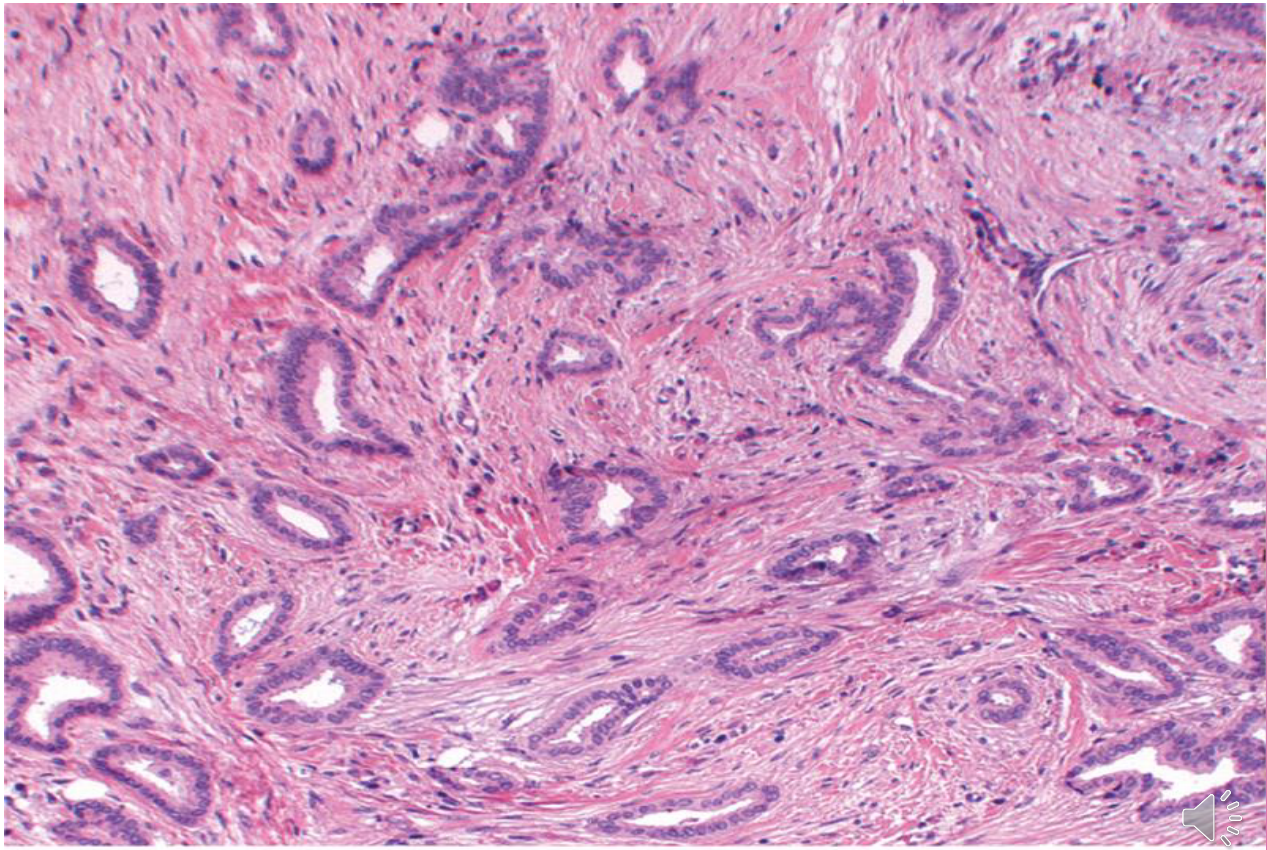
Lymph node metastases are rare, and prognosis is excellent.

ER-positive/HER2-negative cancer

Sometimes mistaken for benign sclerosing lesions.

Calcification may present in the tumor lumen

well-differentiated neoplastic cells form a single cuboidal layer in small,round to tear drop shaped ductules widely spaced in a fibrous stroma.



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

Inflammatory Carcinoma

clinically present as an enlarged, swollen, erythematous breast (resulting from the blockage of dermal lymphatic spaces by ca cells)usually without or, with ill-define palpable mass or presents with breast erythema and skin thickening

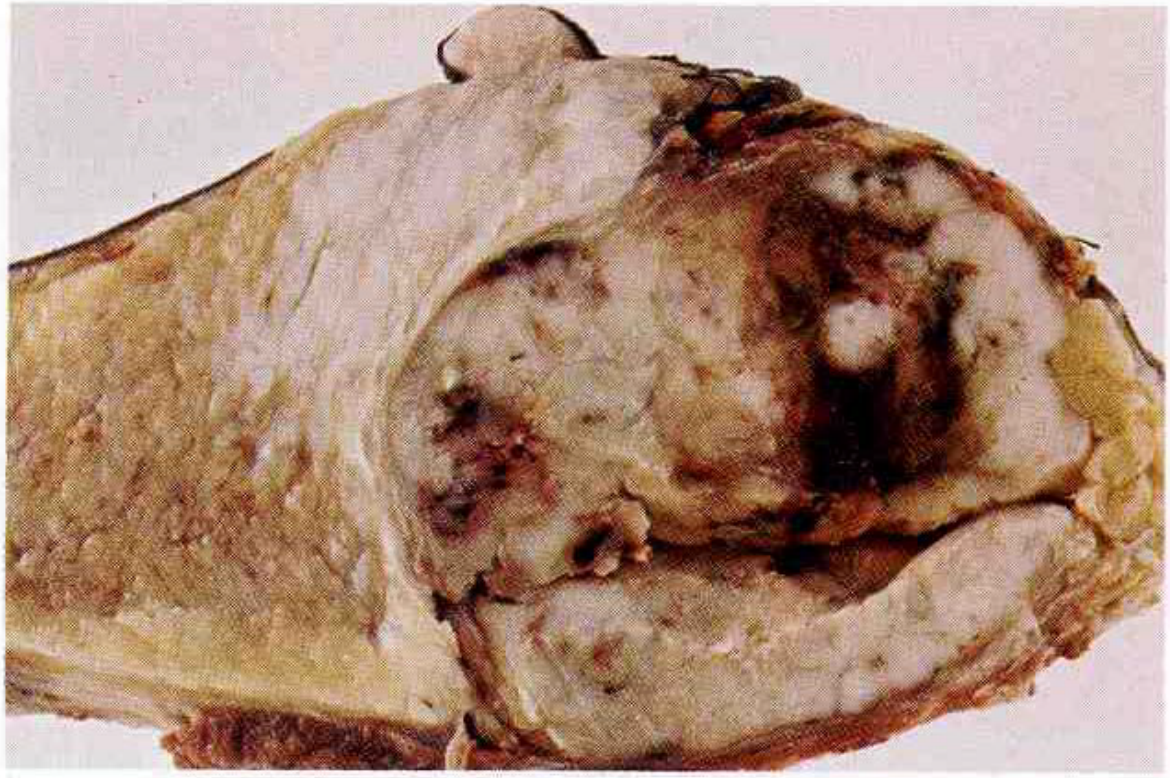
The ca is generally poorly differentiated & diffusely invading the breast tissue.

True inflammation is minimal or absent.

Most of these T have distant metastases & the prognosis is extremely poor.

mimics the surface of an orange peel, an appearance referred to as peaud'orange.

Lactating (Inflammatory) carcinoma: breast. A large greyish-white cancer with extensive central necrosis & hemorrhage. Clinically, the tumor resembles an acute inflammatory lesion & has a rapid malignant course with extremely poor prognosis.



12.18 'Lactational' carcinoma: breast

Spread of breast cancer

through **lymphatic** and **hematogenous** channels.

Favored metastasis are the **bone**, **lungs**, **skeleton**, **liver**, and **adrenals** and (less commonly) the brain, spleen, and pituitary.

Metastases may appear many years after apparent therapeutic control of the primary lesion that's why we use screening program

SCREENING:

mammographic screening

Magnetic resonance imaging, MRI

Spread of Breast Cancer

Spread eventually occurs through lymphatic & hematogenous channels. LN metastases are present in about 50% of ca presenting as palpable masses, but… in fewer than 15% of cases found by mammography.

Outer quadrants & centrally located catypically spread first to the axillary LN.

Ca B in the **inner quadrants**often involve the LN along the internal mammary arteries.

The supraclavicular LNare usually become involved only after the axillary & internal mammary LN are affected, but… sometimes are the primary site of spread (Skipped).

More **distant dissemination** eventually follows, with metastatic involvement of **almost any organ or tissue in the body. Favored** locations are the lungs, skeleton, liver, & adrenals & (less commonly) the brain, spleen, & pituitary. However, **no site is exempt!**

Metastases may appear many years (sometimes 15 years) after apparent therapeutic control of the primary ca!

Clinically,Ca B is often discovered by the woman or her physician as a solitary, painless, & movable mass. At this time, the ca is typically **2 to 3 cm**in ∅, with involvement of the **regional LNs**(most often axillary) in about **50% of patients.**

Breast cancer Prognosis

The outcome for women with breast cancer depends on the **biologic features of the carcinoma (molecular or histologic type)**and the extent to which the cancer has spread (**stage**) at the time of diagnosis.

Prognostic Factors

Tumor stage:

- **Invasive carcinoma versus carcinoma in situ**
- **Distant metastases.**
- **Lymph node metastases.**
- **Tumor size.**In cm
- **Locally advanced disease**
- **Inflammatory carcinoma**
- **Lymphovascularinvasion**
- **Molecular subtype.**
- **Special histologic types.**
- **Histologic grade**
- **Estrogen and progesterone receptors and HER2 expression**

Tumor Stage

Invasive carcinoma versus carcinoma in situ.

Distant metastases. Once distant metastases are present, cure is unlikely,

Lymph node metastases.

Axillary lymph node status is the most important prognostic factor for invasive carcinoma in the absence of distant metastases.

biopsy is necessary for accurate assessment.

With no lymph involvement the ten years survival is 70-80%

1 -3 lymph involvement □35-40%

If morthan 10 lymph nodes □10-15%

Tumor Stage

Tumor size. The risk of axillary lymph node metastases increases with the size of the primary tumor, but both are independent prognostic factors.

Locally advanced disease. Carcinomas invading into skin or skeletal muscle are usually large and may be difficult to treat surgically.

Lymphovascular Invasion

strongly associated with the presence of lymph node metastases.

poor prognostic factor

Special Histologic Types

The survival rate of women with **tubular, mucinous, lobular, papillary, and adenoid cystic** is greater than that of women with cancers of no special type.

Women with **metaplastic carcinoma or micro papillary carcinoma** have a poorer prognosis

Histologic grade

All invasive carcinomas are graded using Histologic Score composed of Nuclear grade, tubule formation, and mitotic rate

Proliferative rate:

measured by mitotic counts.

Highly proliferative tumors have poorer prognosis but may respond better to chemotherapy

ER,PR,HER2

ER & PR:

Eighty percent of carcinomas that are both ER-and PR-positive respond to hormonal manipulation

40% of CA positive for only ER or PR respond.

Strongly ER-positive cancers are less likely to respond to chemotherapy.

cancers that fail to express either ER or PR have a less than 10% likelihood of responding to hormonal therapy but are more likely to respond to chemotherapy.

HER2:

- HER2 overexpression is associated with poorer survival
- predictor of response to agents that target this receptor.

Stages of breast ca

Stage 0: DCIS or LCIS, with 5-year survival rate (5YSR):**92%**

Stage I: Invasive ca up to **2 cm**⌀(including ca in situ with micro invasion) without LN involvement **(**5YSR:**87%).**

Stage II: Invasive ca up to **5 cm**⌀ **with up to 3 involved axillary LNs** or invasive ca more than 5 cm without LN involvement **(**5YSR:**75%).**

Stage III. Invasive ca up to **5 cm**⌀ **with 4 or > involved axillary LNs**; invasive ca more than 5 cm⌀ with LN involvement; invasive ca with 10 or more involved axillary LNs; invasive ca with involvement of the ipsilateral internal mammary LNs; or invasive ca with skin involvement (edema, ulceration, or satellite skin nodules), chest wall fixation, or clinical inflammatory ca (5YSR:**46%).**

Stage IV. Any Ca B with **distant metastases**(5YSR: **13%**).

Why some cancers **recur** following postoperative therapy whereas others do not? Remains unknown & a **mystery**.