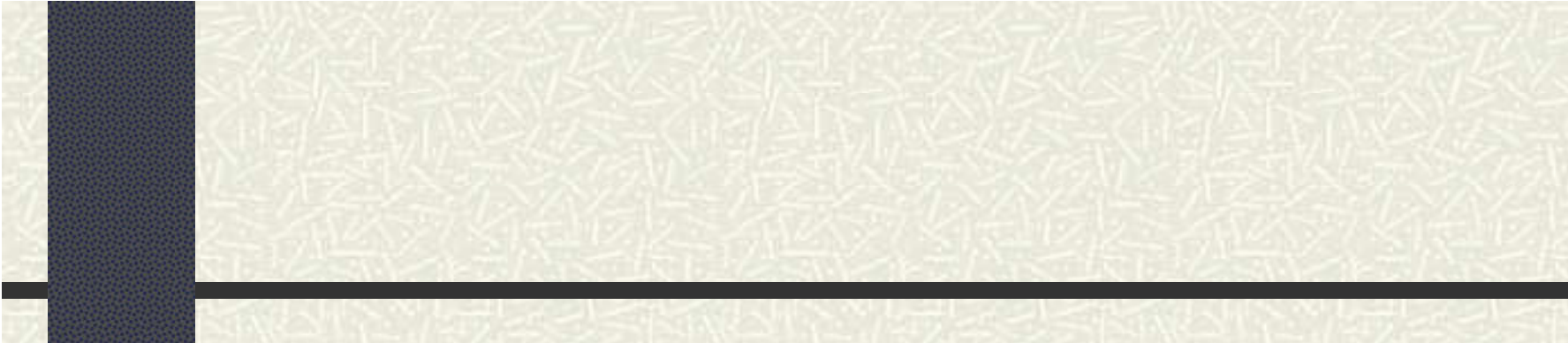




Breast cancer (II)

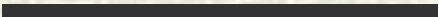
By

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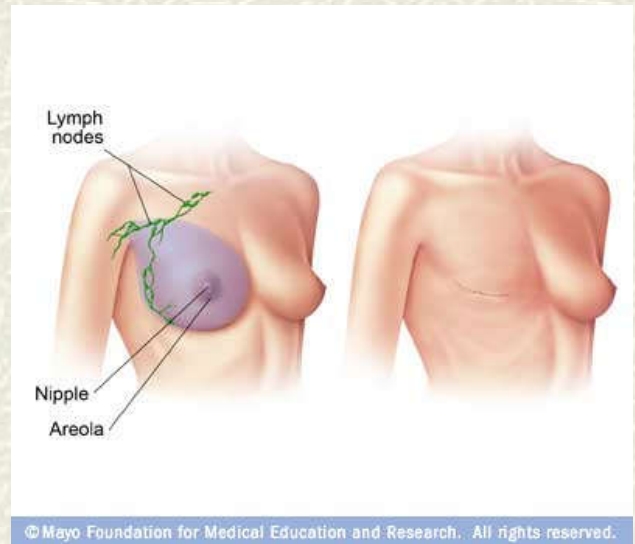


Outline

- # Investigation for cancer
- # Breast biopsy techniques
- # Staging for breast cancer
- # Biologic types of cancer
- # Treatment of breast cancer

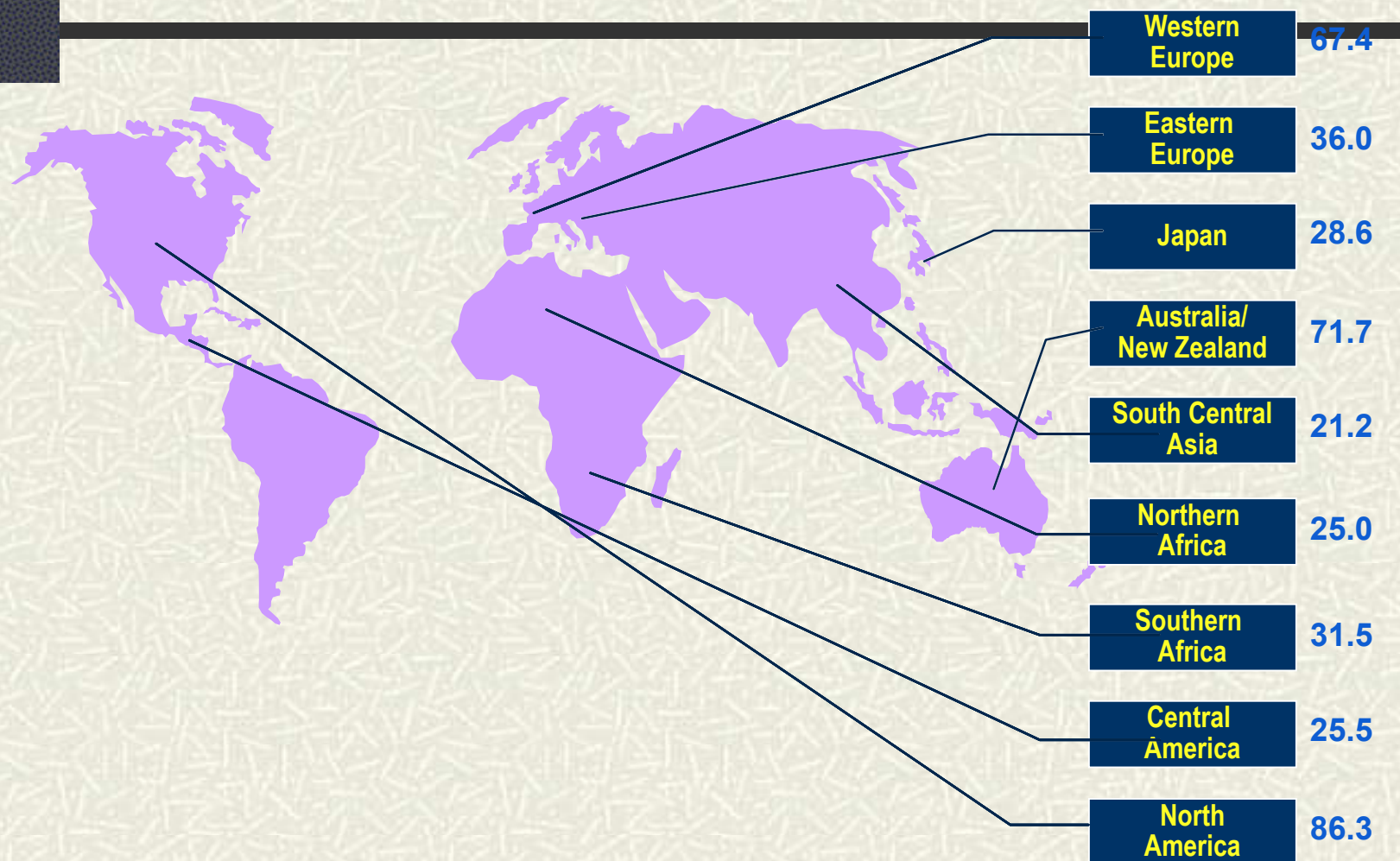
Breast Cancer

- # Breast cancer is second only to lung cancer as a cause of cancer deaths in American women
- # One out of every seven women will be diagnosed with breast cancer in 2012
- # Fortunately, radical mastectomy (surgical removal) is rarely needed today with better treatment options

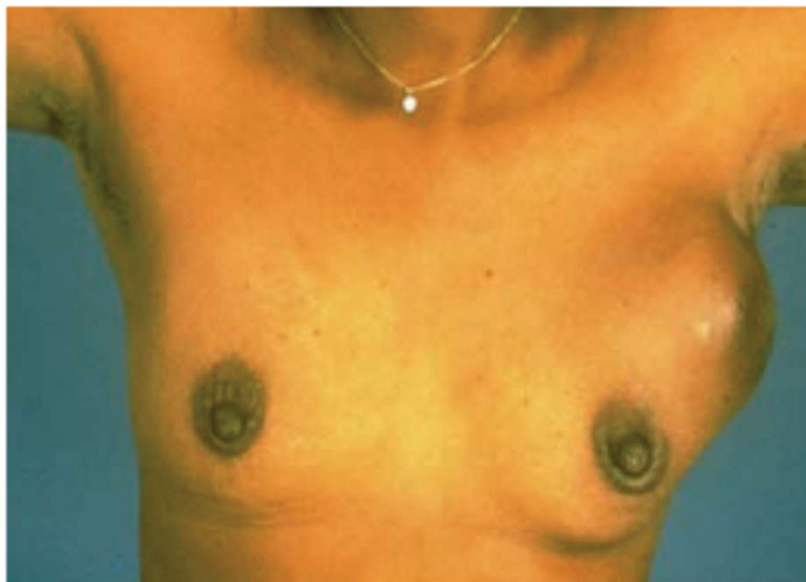
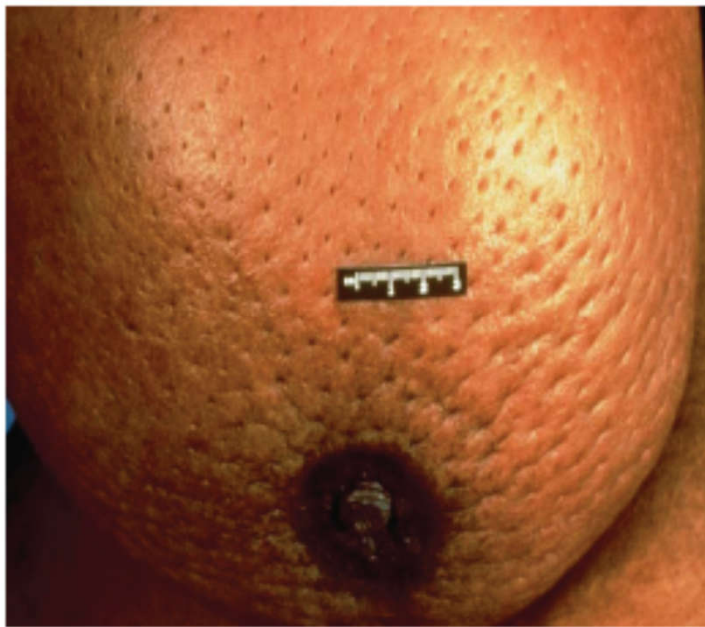


BREAST CANCER

Worldwide incidence in females*



*Incidence per 100,000 population.



Staging Classification of Breast Tumour



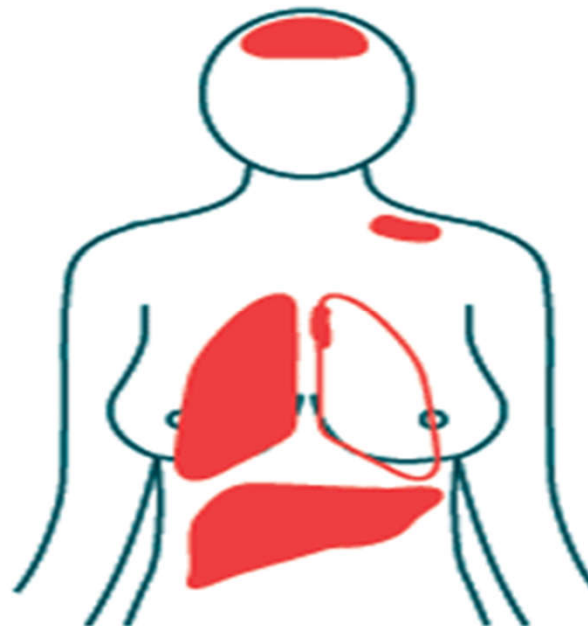
Stage 1
Early disease: tumour confined to the breast (node-negative)



Stage 2
Early disease: tumour spread to movable ipsilateral axillary node(s) (node-positive)



Stage 3
Locally advanced disease: tumour spread to the superficial structures of the chest wall; involvement of ipsilateral internal mammary lymph nodes



Stage 4
Advanced (or metastatic) disease: metastases present at distant sites, such as bone, liver, lungs and brain and including supraclavicular lymph node involvement

A. International TNM staging

T = Tumour

T_{is} Carcinoma in situ. Paget's disease with no palpable tumour.

T₀ No evidence of primary tumour.

T₁ 2cm diameter or less.

T₂ 2-5 cm diameter.

T₃ Tumour larger than 5cm.

T₄ Any size with direct extension to chest wall or to skin; or inflammatory carcinoma

N = Nodes

N₀ No palpable axillary nodes.

N₁ Mobile palpable homolateral axillary nodes.

N₂ Fixed homolateral axillary nodes.

N₃ Palpable homolateral supraclavicular nodes. Oedema of the arm.

M = Metastases

M₀ No evidence of distant metastases.

M₁ Distant metastases.

Table (27.7): UICC staging

Stage UICC		Description	Category	5 year survival (%)
I		T1, N0, M0	Early breast cancer	93
II	IIA	T2, N1, M0	Early breast cancer	72
	IIB	T3, N0, M0		
III	IIIA	T1-3, N0-2, M0	Locally advanced breast cancer	41
	IIIB	T4, any N, M0		
IV		Any T, any N, M1	Metastatic	18

Stage Classifications for Early Stage Disease

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0

Singletary SE, et al. *J Clin Oncol*. 2002;20:3576-3577.

Stage Classifications for Locally Advanced Breast Cancer

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

Singletary SE, et al. *J Clin Oncol*. 2002;20:3576-3577.

Stage Classifications for Locally Advanced Breast Cancer (cont.)

Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Ductal Carcinoma in situ (DCIS)

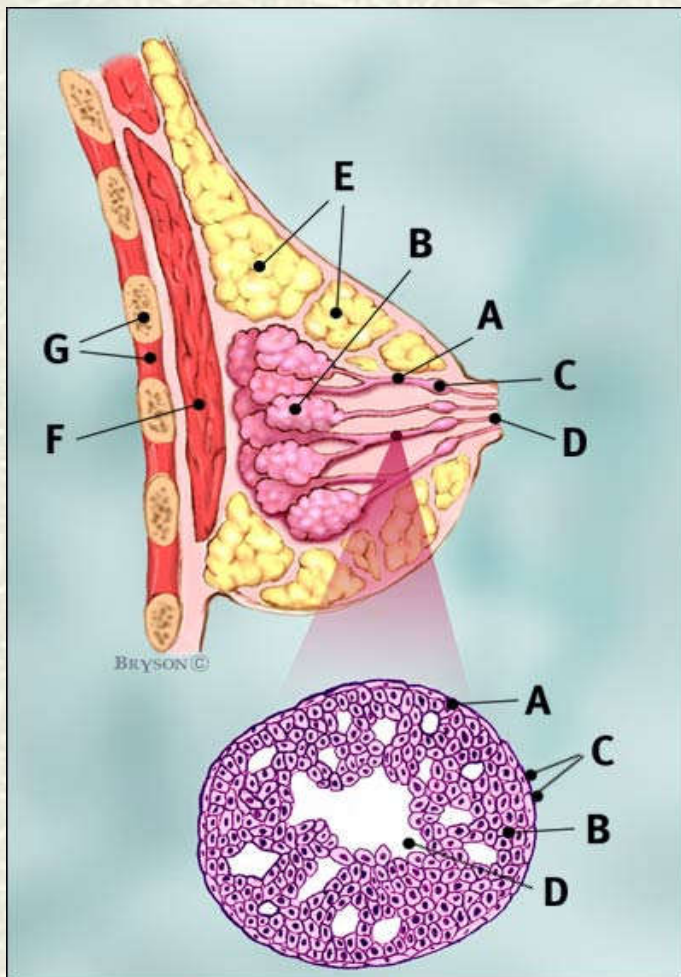
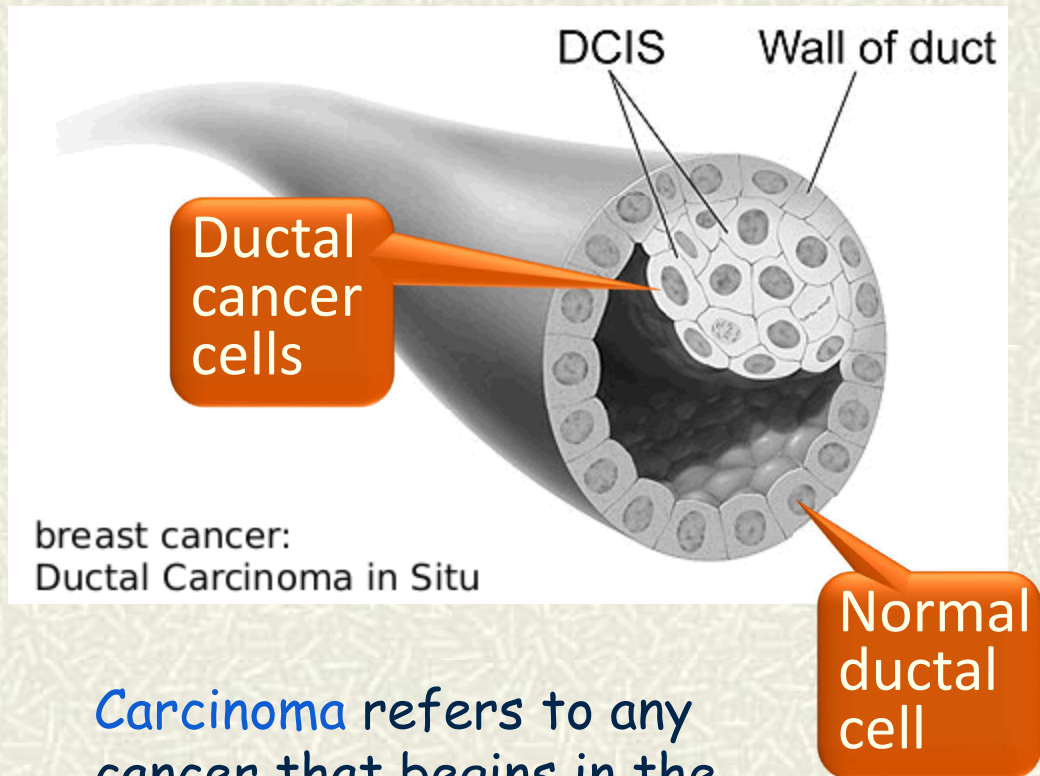


Illustration © Mary K. Bryson



breast cancer:
Ductal Carcinoma in Situ

Carcinoma refers to any cancer that begins in the skin or other tissues that cover internal organs

Invasive Ductal Carcinoma (IDC - 80% of breast cancer)

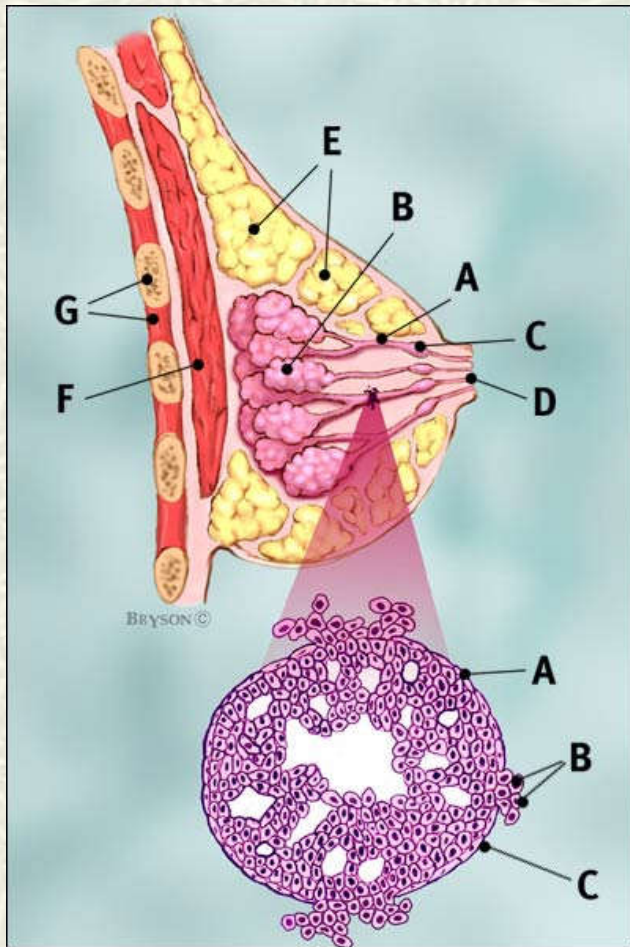
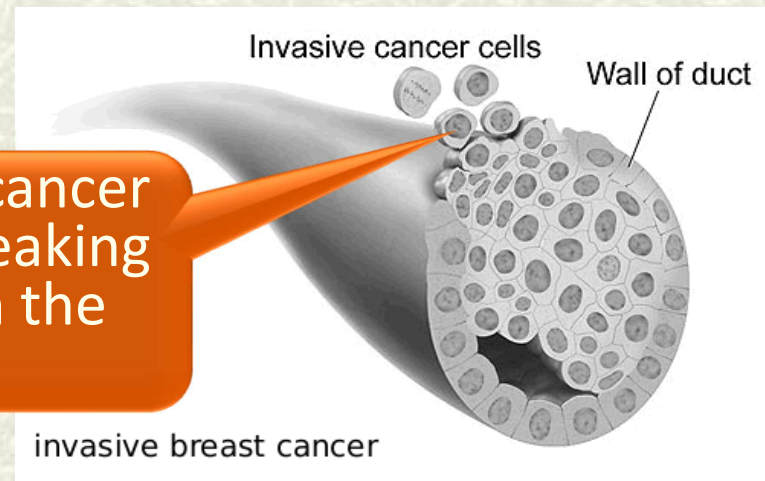


Illustration © Mary K. Bryson

Ductal cancer cells breaking through the wall



The cancer has spread to the surrounding tissues

Range of Ductal Carcinoma in situ

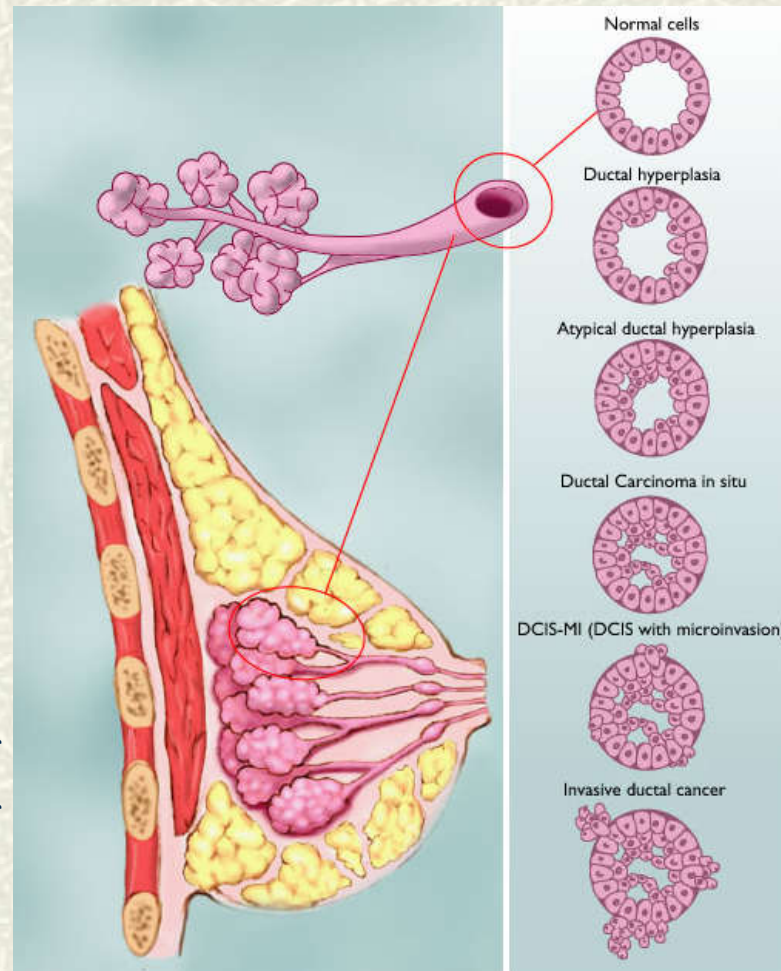


Illustration © Mary K. Bryson

Invasive Lobular Carcinoma (ILC)

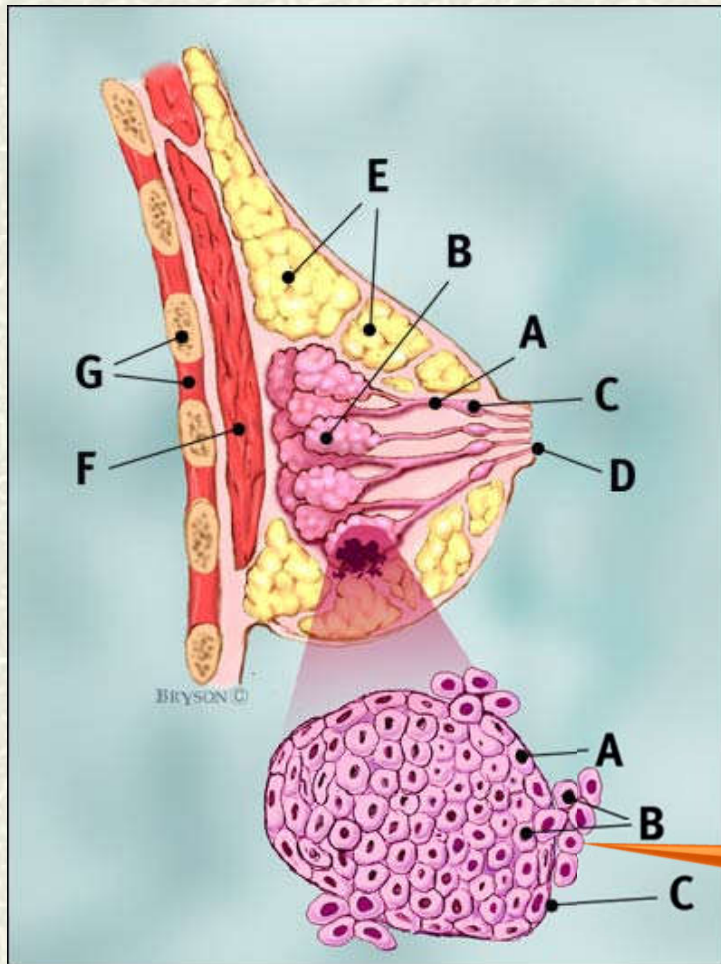
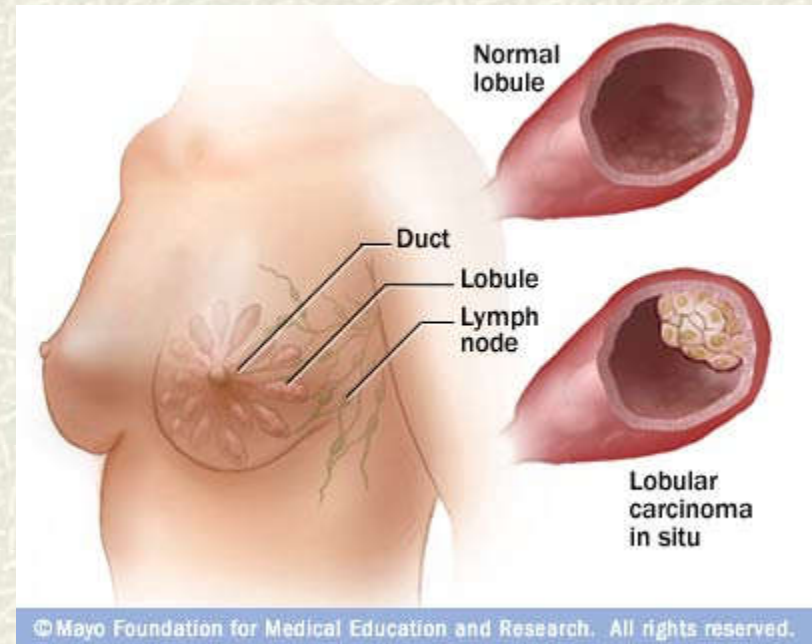
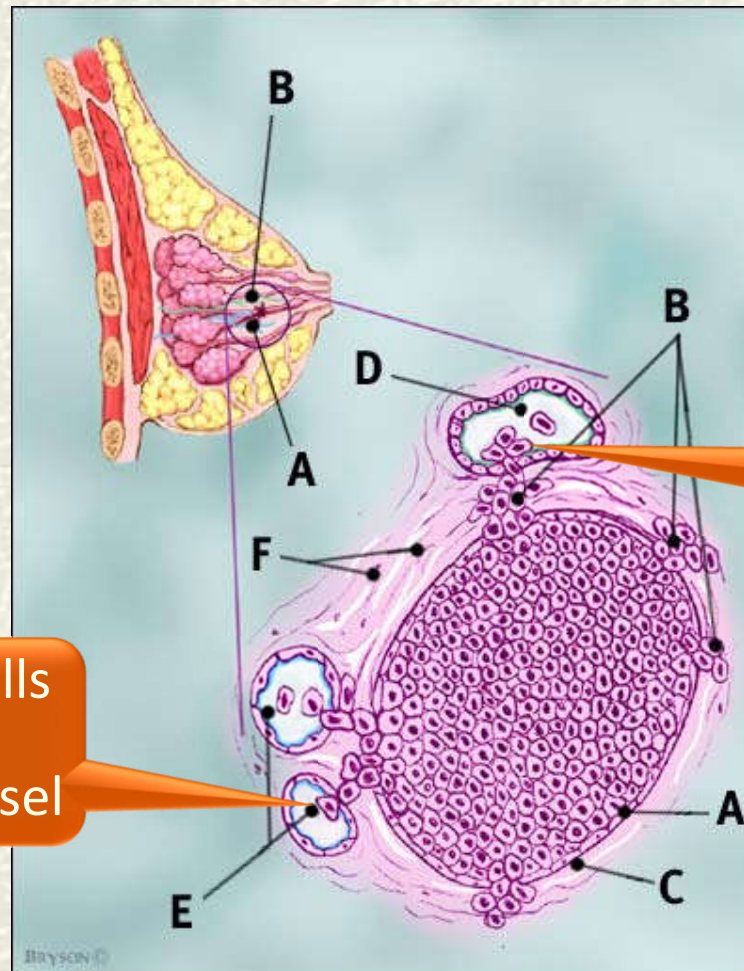


Illustration © Mary K. Bryson



Lobular cancer cells breaking through the wall

Cancer Can also Invade Lymph or Blood Vessels



Cancer cells
invade
blood vessel

Cancer cells
invade
lymph duct

Illustration © Mary K. Bryson

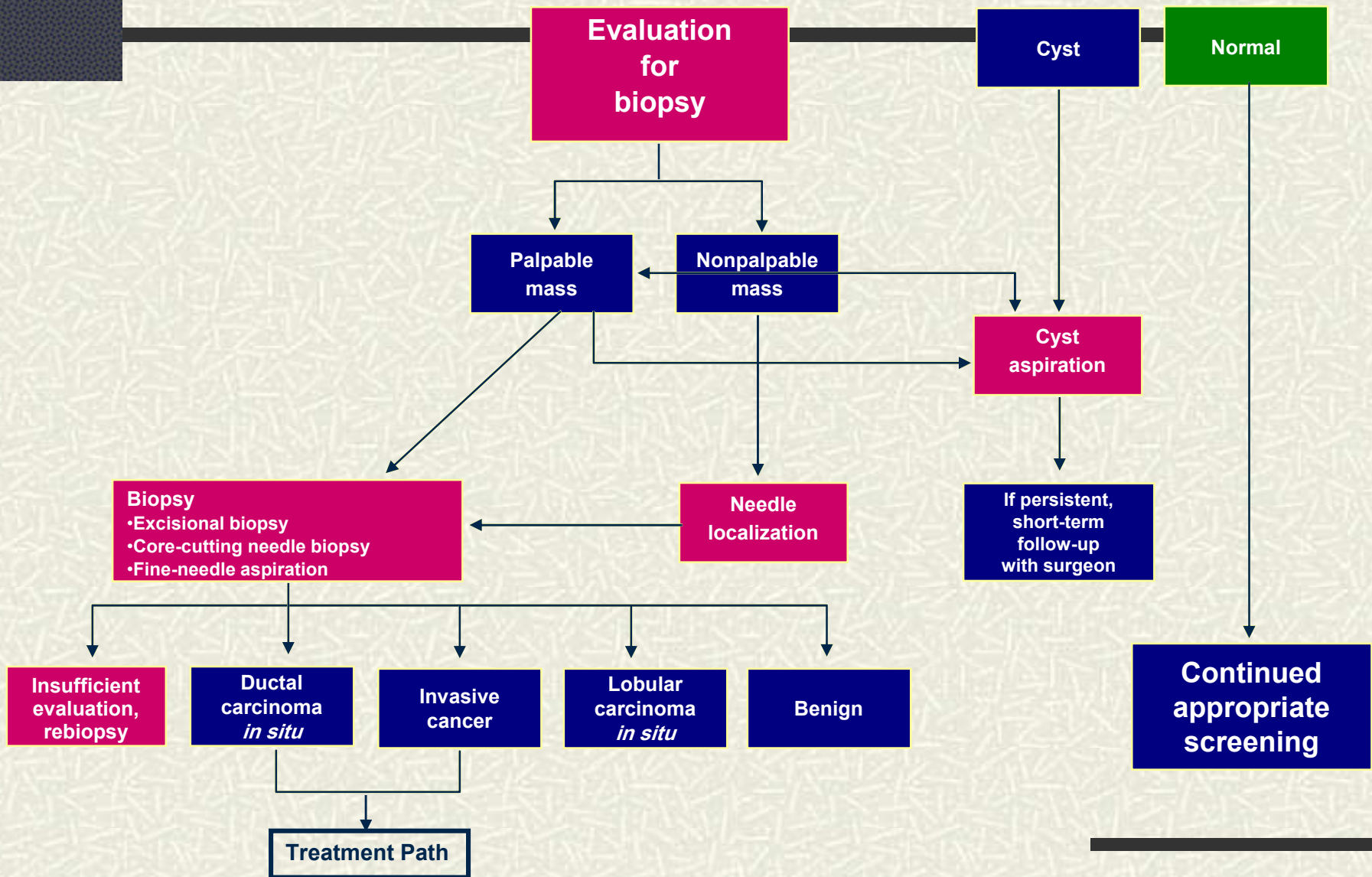
Inflammatory Breast Cancer (IBC)



- ◎ Swollen
- ◎ Erythema
- ◎ Peau d'Orange
- ◎ Frequently Mistaken for Mastitis

BREAST CANCER

Diagnosis path



Investigations

Aim of Investigations

1. Diagnosis of carcinoma by imaging (mammography, ultrasonography) and biopsy.
2. Staging the disease is routinely done by chest X-ray, ultrasound examination of the abdomen and pelvis, and by alkaline phosphatase (a high level indicates bone or liver deposits).
3. Further tests are needed in special situations. Bony pains require X-rays and isotope bone scan. Suspicion of cerebral secondaries is an indication for CT examination. Whole body PET CT scan can detect metastases throughout the body.

Mammography

This is soft tissue radiology of the breast. In expert hands it is 95% accurate in diagnosing breast cancer. If combined with Tru-cut biopsy, or fine needle aspiration, their accuracy of diagnosis is improved. It is also useful for detecting multifocal lesions in the same or other side, before embarking on radical surgery. A cancer appears as

- A dense opacity that has an indefinite outline from which irregular spicules penetrate into the surrounding breast (Fig. 27.18).
- Clustered microcalcifications (Fig. 27.19).

Mammography is of less diagnostic value in young women, in whom the density of the lesion differs little from that of the surrounding tissue. Digital mammography allows magnification and transfer of images for a second opinion.

Mammography

- ✦ Use a low-dose **x-ray** system to examine breasts
- ✦ **Digital mammography** replaces **x-ray film** by **solid-state detectors** that convert x-rays into electrical signals. These signals are used to produce images that can be displayed on a computer screen (similar to digital cameras)
- ✦ Mammography can show changes in the breast up to two years before a physician can feel them



Computer-Aided Diagnosis

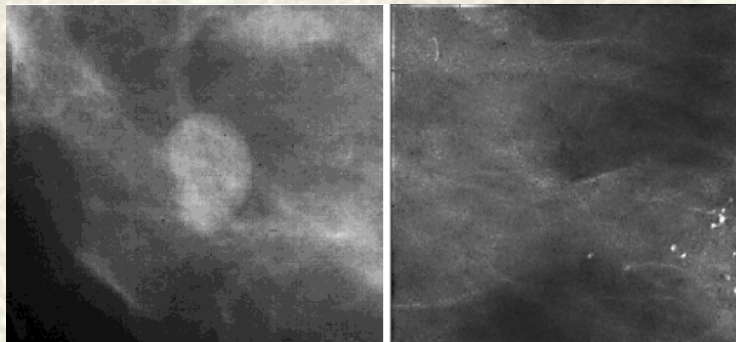
- # Mammography allows for efficient diagnosis of breast cancers at an earlier stage
- # Radiologists misdiagnose 10-30% of the malignant cases
- # Of the cases sent for surgical biopsy, only 10-20% are actually malignant

CAD systems
can assist
radiologists to
Reduce these
problems

What Mammograms Show

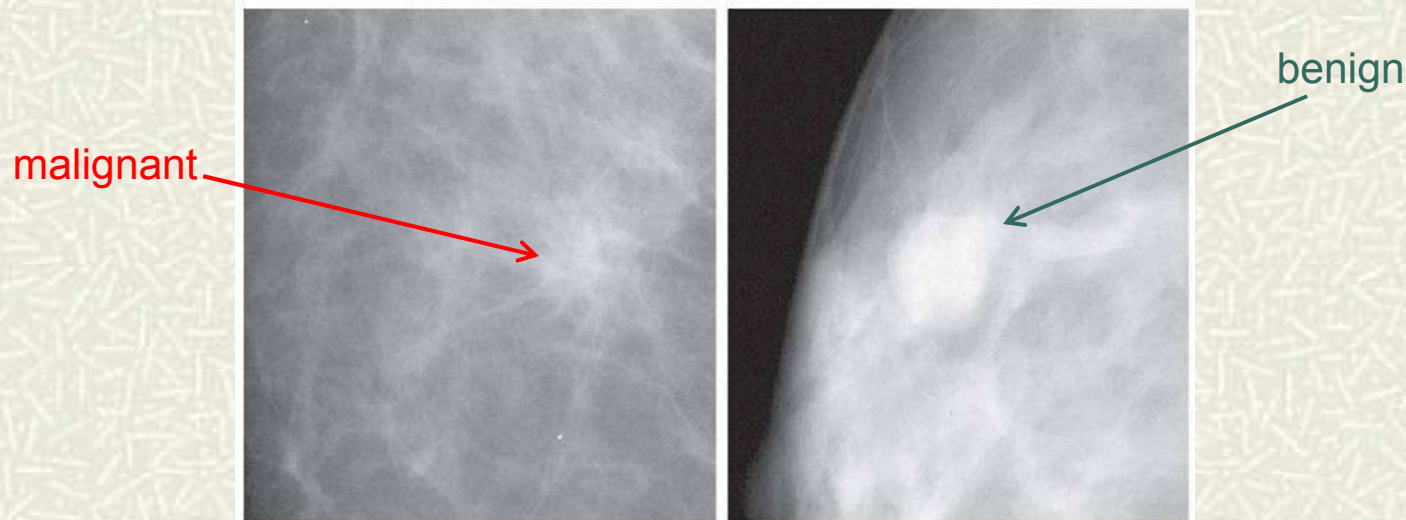
Two of the most important mammographic indicators of breast cancers

- **Masses**
- **Microcalcifications:** Tiny flecks of calcium - like grains of salt - in the soft tissue of the breast that can sometimes indicate an early cancer.

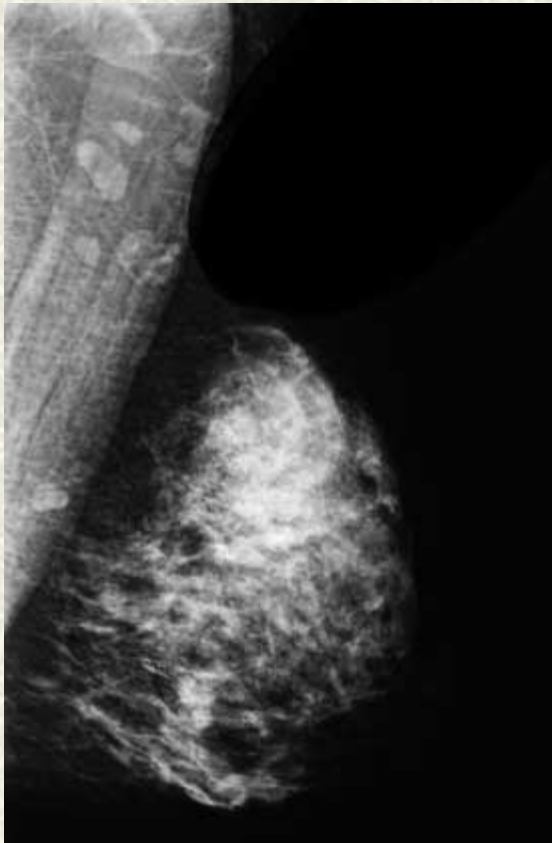


Detection of Malignant Masses

Malignant masses have a more **spiculated** appearance

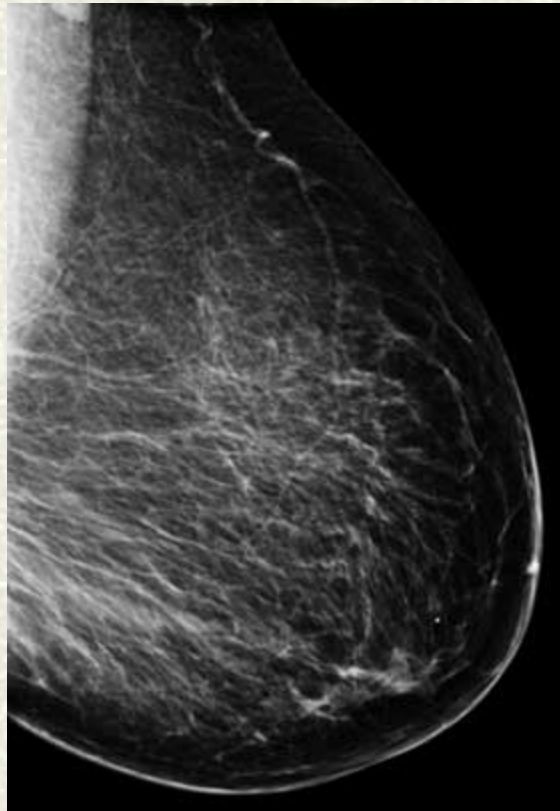


Mammogram - Difficult Case



- # Heterogeneously dense breast
- # Cancer can be difficult to detect with this type of breast tissue
- # The fibroglandular tissue (white areas) may hide the tumor
- # The breasts of younger women contain more glands and ligaments resulting in dense breast tissue

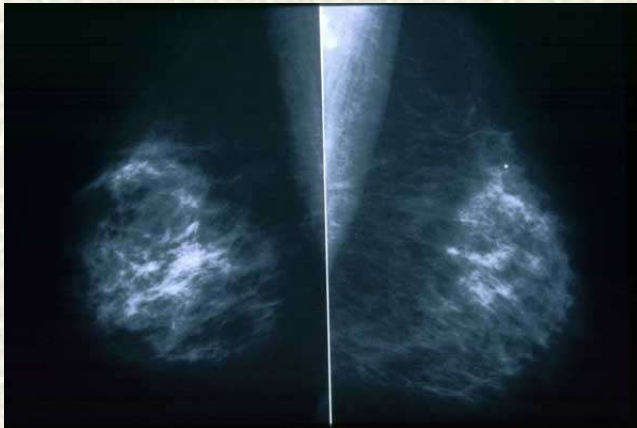
Mammogram - Easier Case



- # With age, breast tissue becomes fattier and has fewer glands
- # Cancer is relatively easy to detect in this type of breast tissue

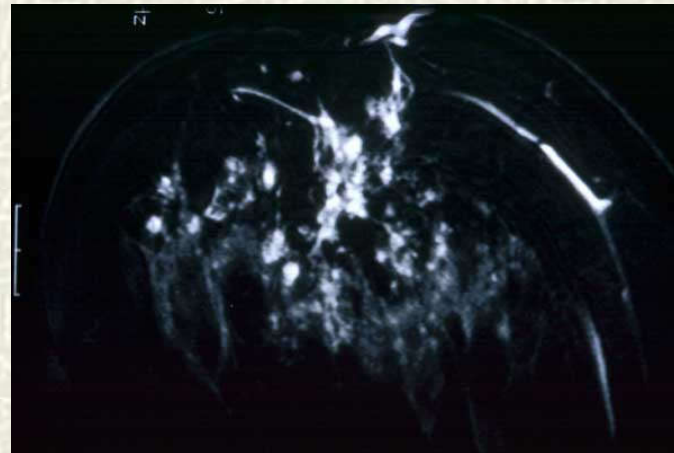
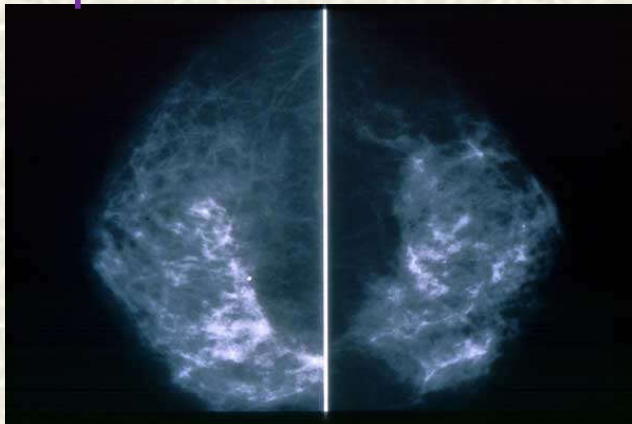
Different Views

Side-to-Side



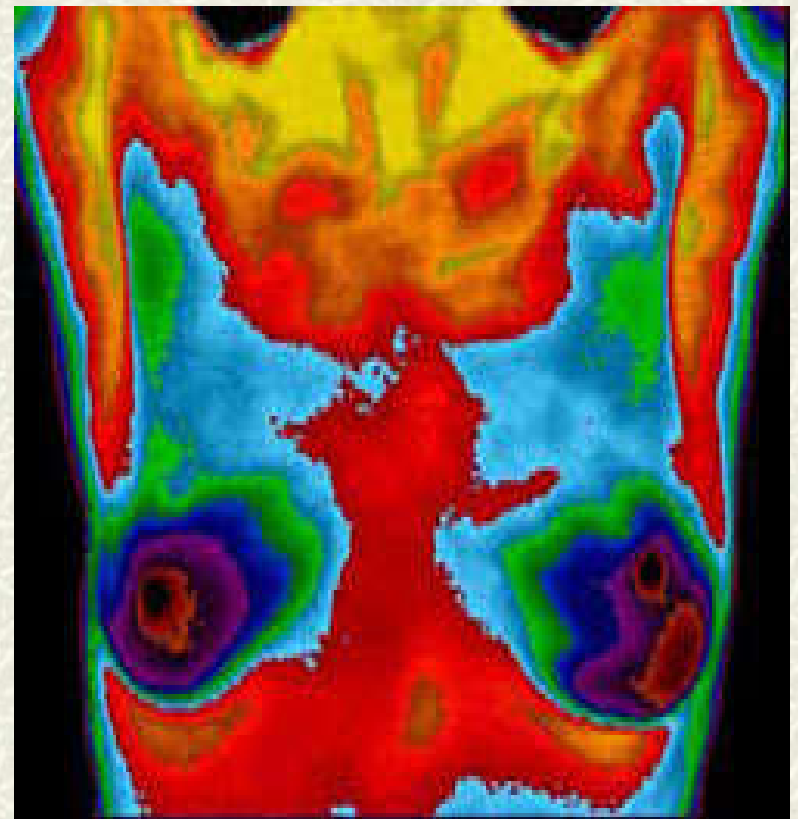
MRI - Cancer can have a unique appearance – many small irregular white areas that turned out to be cancer (used for diagnosis)

Top-to-Bottom



Thermograph

- ⌘ Thermograph is one of the newest ways to detect breast cancer.
- ⌘ Thermograph is a thermal image of the breast tissue.
- ⌘ It can also detect cancer before the traditional mammogram can.
- ⌘ www.breastthermography.com
- ⌘ Picture from breastthermography.com



Ultrasonography

It can differentiate cystic from solid lesions. A speculated hypoechoic mass more deep than wide suggests a malignant lesion. The addition of colour coded Duplex ultrasound identifies the vascularity of the lesion. Malignant lesions receive blood flow from all around with turbulent speed whereas benign lesions receive blood flow from one side at a low speed. It is particularly useful in young women in whom mammography may not be very helpful. U/S guided biopsy can be done.

Classification

BI-RADS 0: incomplete

- need additional imaging evaluation (additional mammographic views or ultrasound) and/or
- for mammography, obtaining previous images not available at the time of reading

BI-RADS 1: negative

- symmetrical and no masses, architectural distortion, or suspicious calcifications

BI-RADS 2: benign

- 0% probability of malignancy

BI-RADS 3: probably benign

- <2% probability of malignancy
- short interval follow-up suggested

BI-RADS 4: suspicious for malignancy

- 2-94% probability of malignancy
- for mammography and ultrasound, these can be further divided:
 - BI-RADS 4A: low suspicion for malignancy (2-9%)
 - BI-RADS 4B: moderate suspicion for malignancy (10-49%)
 - BI-RADS 4C: high suspicion for malignancy (50-94%)
- biopsy should be considered

BI-RADS 5: highly suggestive of malignancy

- >95% probability of malignancy
- appropriate action should be taken

BI-RADS 6: known biopsy-proven malignancy

- # When there are multiple findings, the BI-RADS category for the exam is assigned the highest category in the following hierarchy, from lowest to highest: 1, 2, 3, 6, 0, 4, 5.
- # The vast majority of screening mammograms fall into BI-RADS 1 or 2. Screening mammograms with suspicious findings should generally be assigned BI-RADS 0 to indicate a callback for diagnostic evaluation, meaning additional views to confirm and further evaluate the finding.

Magnetic resonance imaging (MRI)

It is indicated with contrast in certain situations e.g.

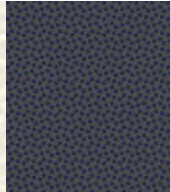
- Postoperative scarring to differentiate between fibrosis and local recurrence of malignancy.
- After neoadjuvant therapy to monitor response.
- In the presence of breast implants.

Biopsy

Fine needle aspiration cytology (FNAC). Depends on examination of cells to detect criteria of malignancy in them. The aspiration can be done in the outpatient clinic using a 10-20 ml syringe and a 21-gauge needle. The mass is fixed between the fingers of one hand, and the needle is passed in it several times while keeping constant suction, by the other hand. The suction is then released and the needle is withdrawn out of the breast. This procedure will draw some cells from the lesion into the needle, the contents of which are expressed on a slide and smears are prepared for staining and examination. A skilled cytologist is needed for accurate interpretation.

Sometimes aspiration reveals a cyst. A breast cyst is considered benign if the fluid is not blood stained, the cyst disappears completely with aspiration, and does not recur within two weeks. In case of doubt, the fluid is subjected to cytological examination. Large pleomorphic nuclei, ill-defined cytoplasm and abnormal nuclear chromatin ratio are criteria of malignancy.

FNAC is a very simple, inexpensive, and accurate procedure. It can give a definite diagnosis in 90% of cases. It allows for proper preoperative planning of the definitive treatment. False negative results may occur in up to 10% of cases.



Tru-cut biopsy is done under local anaesthesia with a special needle that cuts a core of tissue out of the tumour. The obtained specimen allows for histological examination.

Excision biopsy. The whole mass is excised through a circumareolar or a transverse incision. Paraffin sections are stained and examined to produce a result within two days. Excision biopsy is the most reliable and provides a big enough specimen to allow for hormone receptor estimation as well. It is, however, gradually losing popularity in favour of the simpler fine needle aspiration cytology and Tru-cut biopsy.

Frozen section biopsy. This is a form of preparation of the specimen for examination by the pathologist. The tumour is either excised or, if large, a small piece is obtained by incising it (incision biopsy). The biopsy specimen is frozen and slides are prepared from the frozen block. A diagnosis is obtained within 20 minutes. Meanwhile, the patient is kept under general anaesthesia, and the surgeon proceeds to obtain haemostasis and close the wound. If the result of examination is negative for malignancy, the patient is awakened. If it is positive, the surgeon proceeds with radical surgery. The possibilities should have been discussed with the patient before the operation, and a consent for mastectomy should have been obtained. Sometimes a firm diagnosis cannot be obtained by frozen section examination, and the result of a paraffin section study should be waited for.

Biopsy from impalpable breast masses. The radiologist can place a wire inside the lesion under mammographic guidance. At operation, the mass is removed with the wire for histological assessment.

Triple assessment

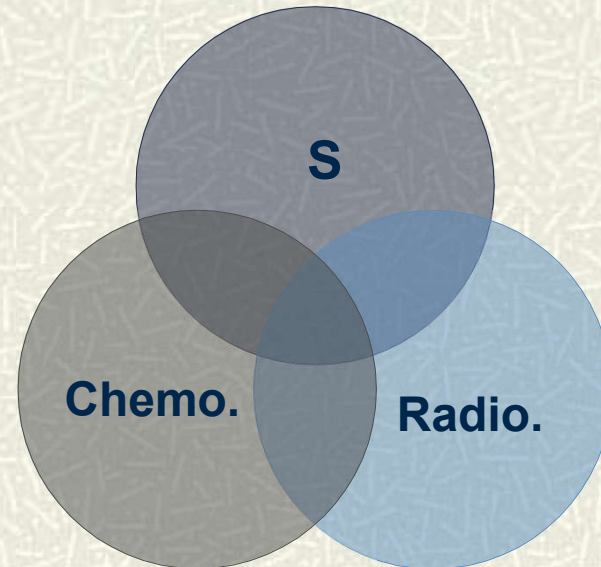
This means comparing the results of:

- Clinical examination.
- Soft tissue mammography or ultrasonography.
- Fine needle aspiration cytology.
 - o If the three parameters are concordant, the surgeon can rely on the diagnosis.
 - o If the three parameters are not concordant, a further investigation e.g. excision biopsy is needed.

Cancer Treatment



Cost of cancer treatment



Types of cancer treatment

Application of cancer treatment

Prognosis

Prognosis of patients with carcinoma of the breast depends on the following factors

1. **Type of the tumour.** The best prognosis is provided by the in situ carcinoma, and Paget's disease, while the worst is the inflammatory carcinoma. The common invasive duct carcinoma is of intermediate prognosis.
2. The **T stage** of the primary tumour. The higher the T stage, the worse is the prognosis.
3. **Number, size, mobility, and location** of the involved lymph nodes. Assessment of lymph node involvement depends on the histological examination as the clinical evaluation is very inaccurate in this regard.
 - Large fixed nodes are of bad prognosis.
 - The number of involved nodes largely affects the prognosis.
 - Patients with negative axillary nodes have a 10-year survival rate of 65%.
 - Patients with 1-3 positive axillary nodes have a 10-year survival rate of 38%.
 - Patients with more than 4 positive axillary nodes have a 10-year survival rate of 13%.
 - The prognosis worsens the higher the affected nodes in the axilla. Involvement of level III nodes carries a bad prognosis.
4. The presence of **distant metastases** markedly worsens the prognosis.
5. **Hormone receptor status.** Receptor positive tumours respond more often to hormonal therapy and have a better prognosis than those that are receptor negative.
6. The **site of the tumour.** Medial half tumours have a worse prognosis than those of the lateral half due to early involvement of the internal mammary lymph nodes.
7. Measurement of tumour proliferation by **thymidine labelling** index and measurement of oncogene products.

Early detection

This aims at the detection of breast cancer very early in the asymptomatic females in order to offer them a better chance of cure. There are two main methods for early detection of breast cancer.

Breast self examination (BSE)

All women over age 20 should be advised to examine their breasts monthly, one week after the menstrual period. The physician instructs the women as how to conduct a systematic inspection and palpation. If the woman suspects the presence of a lump, skin dimpling, or recent nipple retraction, she should report to the surgeon.

Screening programs

In some Western countries high risk women are subjected to regular clinical examination and mammography. The frequency of examination is every one, two, or three years, depending on the program. Polymorphic (variable in size and shape) dots of calcification detected on mammograms are suspicious and are, thus, subjected to biopsy. Screening programs proved to be most useful in reducing breast cancer mortality in women above 50 years.

Screening soft tissue mammography can detect breast cancer at an earlier stage. This will allow more conservative surgery and improved survival.

Treatment of early (potentially curable) breast cancer

- Early breast cancer is defined as those cases categorized as stages I and II in UIC staging.
- Local eradication of the disease is the mainstay of treatment. This is usually achieved by surgery in combination of some form of adjuvant therapy as outlined below.

There is now a definite shift towards more conservative surgical techniques as there has been no actual survival benefit from the more radical procedure as evidenced from clinical trials.

Either of the following two strategies may be adopted with full explanation to the patient:

1. **Conservative breast surgery** is gaining popularity in recent years. If done for properly indicated patients, the operation provides good results that are equal to radical mastectomy, while the breast is preserved minimizing psychological trauma.

The term therapy is used because it includes a combination of surgery and radiotherapy.

Wide local excision with a 2 cm safety margin. If the lesion is close to the skin, part of it may be excised to ensure the required safety margin.

Sentinel lymph node biopsy or level I sampling of axillary lymph nodes. If the nodes prove to be positive (harbouring metastases) then axillary lymph node dissection is done. If axillary lymph nodes are negative there is no need to axillary dissection.

Postoperative radiotherapy for 4 weeks directed to the whole breast with a boost at the site of the operation in order to kill any residual malignant cells.

The operation is suitable for:

- Small tumour ≤ 4 cm.
- Sometimes large lesions (up to 5 cm) in large breasts.
- Peripheral lesions.

Contraindications

- Pregnancy
- In situ breast cancer more than 20% due to the common incidence of multicentricity.
- Large or central tumours in small breasts (no cosmetic advantage).
- Multicentric disease as detected by soft tissue mammography.
- Collagen vascular disease (poor tolerance to radiotherapy).

Early Breast Cancer

Local and Systemic Therapy

- Local
 - Breast-conserving surgery plus radiation preferred
 - Surgical options include lumpectomy or total mastectomy
 - No role for radical mastectomy
- Systemic
 - Hormone therapy
 - Chemotherapy

Breast-Conserving Surgery: Criteria

- Small tumor-to-breast size
- Not more than one tumor in the same breast (unicentric)
- Negative tumor margins
- No contraindications for radiation



Radiation Therapy

- Mandatory following breast-conserving surgery
- Whole-breast radiation following breast-conserving surgery reduces chance of local recurrence by about two-thirds
- Accelerated partial breast radiation as an alternative to whole-breast radiation is currently being evaluated in randomized trials

Reconstructive procedures after mastectomy

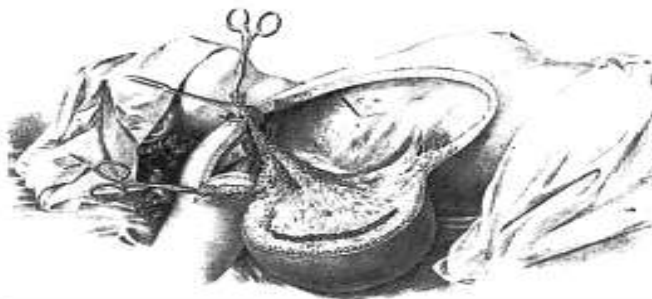
There is now great tendency to offer the patient who had mastectomy, some form of reconstructive surgery so that there will be minimal cosmetic deformity. Two procedures are available.

1. **A synthetic implant** may be inserted behind the pectoralis major muscle and it is inflated gradually until it attains the desired size.
2. **A myocutaneous flap** is used to reconstruct the breast. The transverse rectus abdominis myocutaneous flap (TRAM) is very efficient. The idea is take a transverse flap of the skin of the lower abdominal wall together with the rectus muscle with the blood supply based on the superior epigastric vessels. The flap is transposed upwards to form a breast substitute.

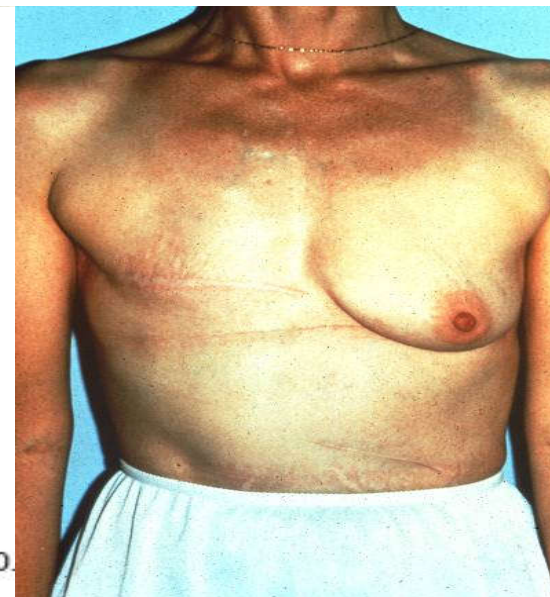
Types of Mastectomy

- Total mastectomy (removal of skin, nipple, areola, and glandular breast)
- Radical mastectomy (removal of pectoralis major and minor muscles)

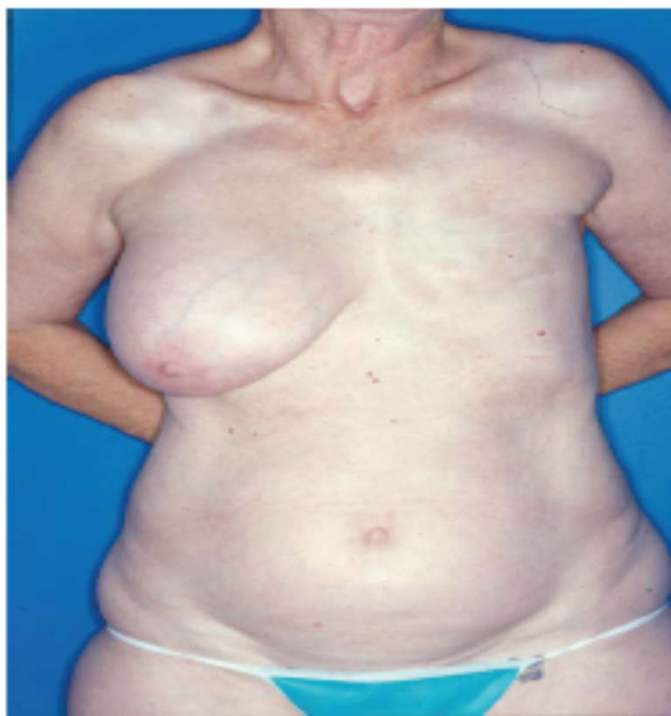
Halsted Radical Mastectomy



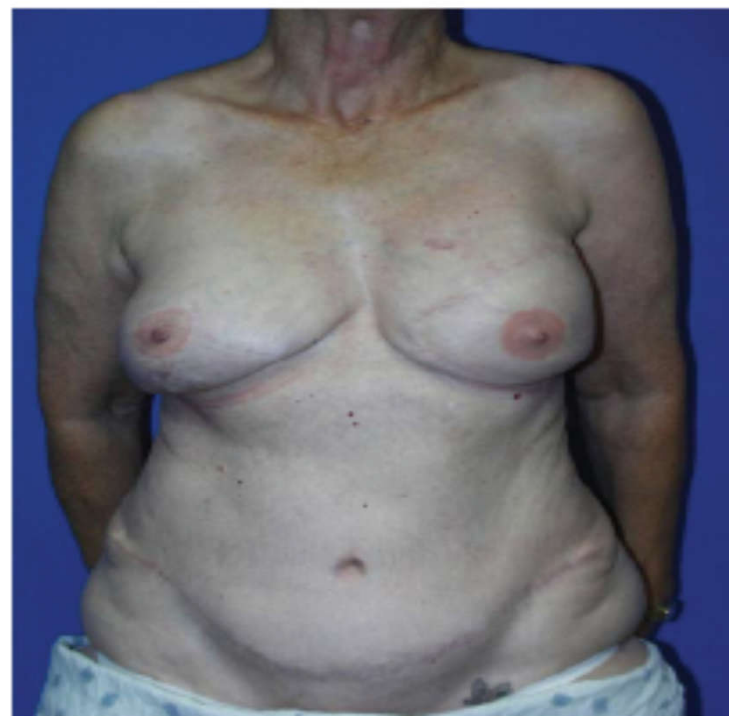
Haagensen CD, et al. *Ann Surg.* 1943;118:859-870.



Mastectomy and Breast Reconstruction



Without reconstruction



With reconstruction

Axillary Lymph Node Dissection

- Goals
 - Accurate staging
 - Regional control
 - Survival advantage?
- No benefit in removing healthy lymph nodes
- Is complete node dissection necessary for staging?

Lymphatic Mapping and Sentinel Lymph Node Biopsy

1



2



3



4



Sentinel lymph nodes biopsy

The sentinel lymph node is the first lymph node in the axilla to be affected by metastases. Injection of patent blue violet or a radioactive sulphur colloid near the tumour will allow, identification, excision and immediate pathological examination of the sentine lymph node.

If the node is positive for metastases → axillary clearance

If the node is negative for metastases → no further excision of lymph nodes.

Further management

Hormonal therapy (HT) for all hormone receptor positive cases. It reduces ipsilateral and contralateral breast recurrence by 40%. Tamoxifen blocks estrogen receptors and anastrozole is an aromatase inhibitor which inhibits peripheral conversion of androgen to estrogens.

Chemotherapy is indicated for

1. Positive axillary nodes.
2. All patients below 70 years.
3. Tumours more than 1 cm.
4. Hormone receptor negative and Her2/neu positive tumours (denote aggressive tumours).

Targeted therapy for Her2/neu positive cases. Monoclonal antibodies are given against Her2/neu receptors (herceptin)

Radiation top 10

- # Radiation kills the cancer cells left after surgery.
 - # Radiation therapy doesn't make you radio active.
 - # Radiation is painless when it's delivered, but it will become more painful over time.
 - # Treatments will be given up to 5-7 weeks, 5 days a week.
 - # Treatments only take ½ hour so you can keep your routine.
 - # Your hair won't fall out unless you are also taking chemotherapy.
 - # Your skin in the area may become red and easily irritated.
 - # You may feel tired even after its over.
 - # Radiation after surgery reduces the chances of the cancer reoccurring.
-

Systemic Therapy for Breast Cancer

- Goals
 - Attain cure, prevent recurrence, eradicate micrometastases
- Appropriate treatments
 - Tamoxifen or aromatase inhibitors for postmenopausal women
 - Ovarian ablation
 - Chemotherapy
 - Monoclonal antibody therapy
 - Supportive care

Advantages of Neoadjuvant Chemotherapy

- Increased rate of breast-conserving surgery
- Earlier treatment of micrometastases
- Treatment serves as in vivo chemosensitivity assay
- Improved rates of local control and disease-free survival

Treatment of advanced disease

This category comprises stages III and VI UICC, T4 patients, fungation, ulceration, inflammatory carcinoma or recurrent cases as well as distant metastases are included in this category. The aim is palliation and improving the quality of life.

Modalities of treatment

1. Radiotherapy

- a. It is used locoregionally for palliation of pain or ulceration.
- b. Systemically for brain metastases to decrease edema and intracranial tension, for spinal metastases to decrease local edema and spinal cord compression and for bone secondaries and pathological fractures.
- c. Superior vena cava obstruction.

2. Hormone therapy The following issues are relevant

- a. It is only given to hormone receptor positive patients, with a 60-70% response.
- b. It is more effective in postmenopausal women.
- c. It is not very effective in hormone negative patients (response, 10%), with visceral metastases or young patients below 35 years.
- d. Tamoxifen, the primary antioestrogen is given for not more than five years to avoid the risk of endometrial cancer or thrombogenicity. If no response to tamoxifen, aromatase inhibitors may be used.

3. Chemotherapy The following issues are relevant

- a. It is the basic treatment of metastatic disease; response 60-80%.
- b. It can be used as a targeted therapy for Her2/neu positive cases.
- c. It is given for visceral metastases as the liver, lungs or brain, for hormone negative patients and failure of hormone therapy.

4. Surgery is indicated for the following cases

- a. Simple mastectomy to remove an unpleasant, malodorous fungating tumour
- b. Internal fixation of pathological fractures.
- c. Urgent decompression and stabilization of the spine if a vertebral collapse causes spinal cord compression.

Thank You!



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