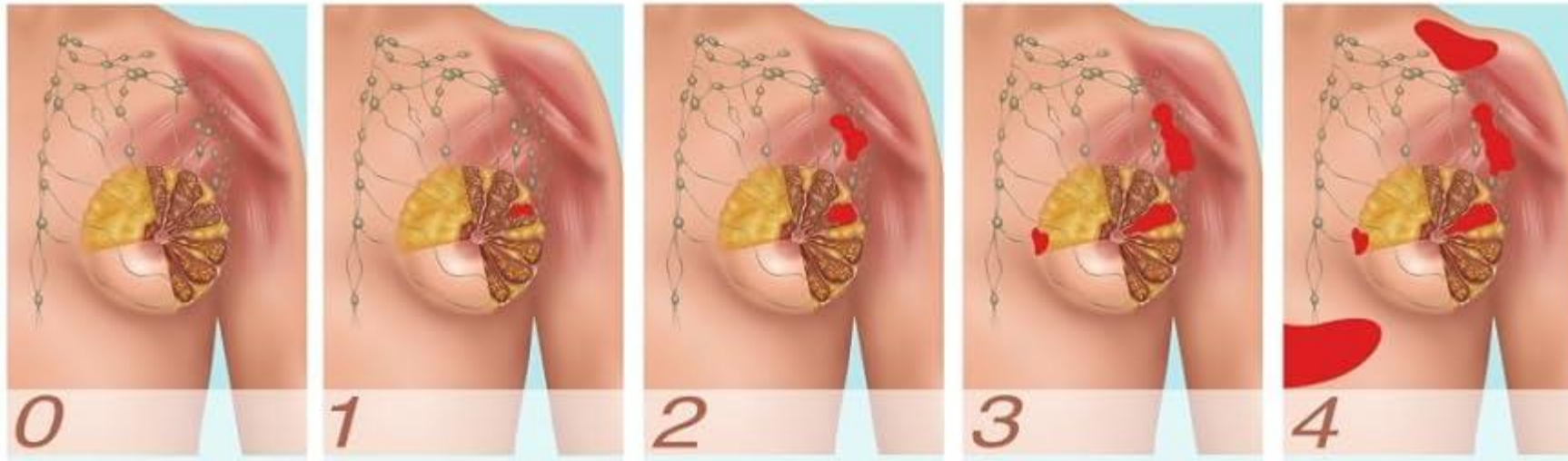


BREAST CANCER

Stages of Breast Cancer



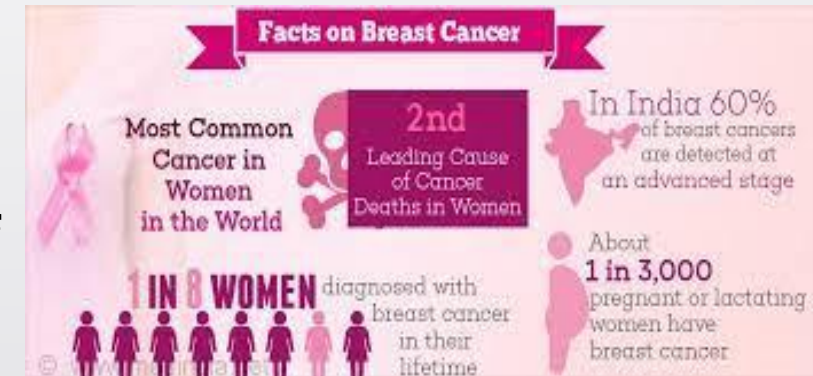
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Breast cancer is a malignant tumor originating from breast tissue, most commonly from the ductal or lobular epithelium.

- When the disease is confined to the breast or regional lymph nodes, it is referred to as early, localized, or curable breast cancer.
- When it spreads beyond the breast to distant organs, it is termed advanced or metastatic breast cancer (MBC), which is generally considered incurable.
- Breast cancer cells often spread undetected by contiguity, lymph channels, and through the blood early in the course of the disease, resulting in metastatic disease after local therapy. The most common metastatic sites are lymph nodes, skin, bone, liver, lungs, and brain.

Epidemiology

- Second leading cause of cancer-related death in women, after lung cancer.
- In 2019:
 - 271,270 new invasive breast cancer cases were diagnosed.
 - 42,260 deaths occurred due to breast cancer.
 - 62,930 cases of non-invasive (in situ) breast cancers were reported.
- Median age at diagnosis: 62 years.
- Most common cause of cancer death in women aged 20–59 years.
- Incidence rose since 1980, peaked in the 1990s, declined after 2000.
- A 7% drop in incidence (2002–2003) correlated with decreased use of hormone replacement therapy (HRT) in postmenopausal women.
- In situ cancer rates increased with widespread screening mammography.



Men and Breast Cancer

- ~2,670 cases of male breast cancer were estimated in 2019.
- Men are often diagnosed at a later stage and have worse survival rates.

Etiology and Risk Factors

1. Non- Modifiable Risk Factors

Gender

- Breast cancer predominantly affects women;
- men are also affected but less commonly.

Age

- Risk increases with age.
- 1 in 8 women (~12.5%) will develop breast cancer during her lifetime.

Genetic Factors

- BRCA1 and BRCA2 mutations increase risk to up to 70% by age 80.
- Other genes: TP53, CHEK2, PALB2, PTEN, ATM.
- Family history (first- or second-degree relatives), Ashkenazi Jewish women have a high BRCA mutation prevalence (2.1%).

Dense Breast Tissue

- Higher breast density reduces mammogram sensitivity and increases risk (4–5 times higher).
- Influenced by age, BMI, parity, menopausal

History of Benign Breast Disease

Type of Lesion	Relative Risk
Non-proliferative (e.g., simple cysts)	No increase
Proliferative without atypia	1.5–2x
Atypical hyperplasia (ductal/lobular)	~4x

Age Group	Impact
Premenopausal Women	No clear risk
Postmenopausal Women	↑ Risk

2. Endocrine and Reproductive Risk Factors

Factor	Impact on Risk
Early menarche (<12 years)	↑ Risk
Late menopause (≥55 years)	↑ Risk
Late first childbirth (≥30 years)	↑ Risk
Nulliparity (no childbirth)	↑ Risk
Bilateral oophorectomy before 45 yrs	↓ Risk
Hormone Replacement Therapy (HRT)	↑ Risk (especially estrogen + progestin)

3. Lifestyle and Environmental Risk Factors

a. Radiation Exposure

- High risk if exposed between ages 10–30 (e.g., childhood cancer survivors treated with radiation).
- Diagnostic mammography does not pose a significant risk.

b. Obesity and Body Weight

- Likely due to increased **circulating estrogens** in adipose tissue.

c. Physical Activity

- Protective effect through modulation of hormones, inflammation, and energy balance.

d. Alcohol

- Increases risk; possibly due to increased estrogen levels.
- Moderation is advised.

e. Smoking

- Recent evidence suggests a slight increase in risk, especially with early onset and heavy use.

f. Diet

- No conclusive link between high-fat diets and breast cancer.
- Low-fat, high-fiber, plant-based diets may offer health benefits but evidence is mixed.
- Phytoestrogens (from soy, seeds, nuts): Controversial role—may have estrogenic or antiestrogenic effects.

Category	Risk Factor	Effect
Non-modifiable	Female gender, increasing age	Strong ↑ Risk
	BRCA1/2 and other gene mutations	Strong ↑ Risk
	Family history	↑ Risk
	Dense breast tissue	4–5x ↑ Risk
Endocrine/ Reproduction	Early menarche, late menopause	↑ Risk
	Nulliparity, late age at first birth	↑ Risk
	HRT (estrogen + progestin)	↑ Risk
	Oophorectomy before 45	↓ Risk
Environmental	Radiation exposure (age <30)	↑ Risk
	Alcohol	↑ Risk
	Obesity (esp. postmenopausal)	↑ Risk
	Physical activity	↓ Risk
	Smoking (esp. before 1st pregnancy)	Slight ↑ Risk
	Diet (high-fat, low fiber, excess calories)	Possible ↑ Risk

GENETICS OF BREAST CANCER

Gene	Chromosome	Function	Breast Cancer Risk
BRCA1	17q21	DNA repair via homologous recombination	Up to 65–70%
BRCA2	13q12.3	DNA repair via homologous recombination	Up to 60–70%
TP53	17p13	Tumor suppressor ("guardian of the genome")	>80%
CHEK2	22q12.1	Cell cycle checkpoint kinase	~25–30%
PALB2	16p12.2	BRCA2 partner in DNA repair	~33–58%
PTEN	10q23.3	Tumor suppressor, PI3K/AKT regulator	25–50%
ATM	11q22.3	DNA repair; checkpoint activation	~20–30%
STK11	19p13.3	Tumor suppressor	Increased
CDH1	16q22.1	Cell adhesion molecule (E-cadherin)	↑ risk of lobular breast cancer

BRCA Mutation Mechanism

- Both BRCA1 and BRCA2 code for proteins essential for homologous recombination, a high-fidelity DNA repair mechanism.
- Mutations impair DNA damage repair, leading to genomic instability, accumulation of mutations, and eventually malignant transformation.

BRCA1 and BRCA2:

1. Inheritance

- Autosomal dominant with high penetrance
- Inherited mutations are present in every cell from birth

2. Cancer Risks Associated

3. Ethnic Variations

- Ashkenazi Jewish population: ~1 in 40 carry a BRCA1/2 mutation
- General U.S. population: ~1 in 300–500 carry BRCA1/2 mutations

Cancer Type	BRCA1 Risk (%)	BRCA2 Risk (%)
Breast	60–70%	50–70%
Male breast cancer	Rare (~1–2%)	Up to 7–8%

CLINICAL PRESENTATION

Early Breast Cancer

- Painless breast lump is the most common presenting symptom
- Typically:
 - Solitary
 - Unilateral
 - Hard, irregular
 - Non-mobile
 - Located in upper outer quadrant
- Less commonly:
 - Nipple changes: discharge, retraction, or inversion
 - Skin dimpling or "peaud'orange" (due to lymphatic obstruction)
- Inflammatory breast cancer: presents with erythema, warmth, edema, and rapid enlargement

Advanced/Metastatic Breast Cancer (MBC)

- Symptoms depend on metastatic site:
 - **Bone:** bone pain, fractures
 - **Lungs:** dyspnea, cough, pleural effusion
 - **Liver:** abdominal pain, hepatomegaly, jaundice
 - **Brain:** headache, seizures, altered mental status
- Often in patients with neglected breast mass or recurrence after initial therapy

The most common early signs and symptoms of breast cancer that usually a female may notice is a painless nodes or lumps in her breast, potentially indicating a tumor. Breast cancer signs or symptoms varies from person to person. Some person do not have any symptoms.



Nipple Discharge



Lumping or Thickening



Skin texture change



Armpit Pain



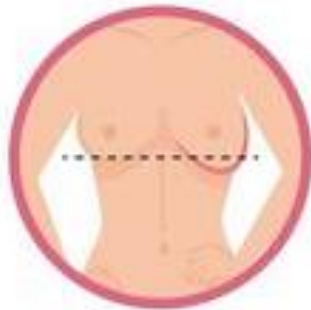
Change in how the nipple looks



Visible Lump



Dimpling



Pulled in Nipple



Skin Irritation



Skin Dimpling

DIAGNOSIS

Incidental Detection

Increasingly, breast cancer is diagnosed during routine mammography screening in asymptomatic women

Initial Evaluation

1. **Detailed history:** risk factors, family history, previous biopsies, HRT
2. **Physical Examination:**
 1. Inspection and palpation of both breasts
 2. Axillary and supraclavicular lymph node exam

BREAST SELF-EXAM



With the pads of the three middle fingers, check for lumps or knots

repeat using **light**, **medium**, then **firm** pressure



Circular motions on all parts of each breast



"Wedge" shaped movements from the outer breast to the nipple and back again



Up-and-down movements over the entire breast area

VISUAL CHANGES TO WATCH



shape or size



skin color and texture



nipple color, texture, and shape



vein patterns, especially an increase in the size or number of veins

3. Imaging Techniques

Imaging Modality	Indication	Features
3D Digital Mammography	First-line screening tool	Detects masses, calcifications
Ultrasound	Adjunct for dense breasts, young women, cystic vs solid mass	No radiation
MRI	High-risk patients, evaluation of extent in dense breasts or multifocal tumors	High sensitivity

4. Biopsy (Definitive Diagnosis)

Biopsy Type	Features	Preferred Use
Fine-Needle Aspiration (FNA)	Removes only cells	Limited — cannot distinguish in situ vs invasive
Core-Needle Biopsy	Removes tissue core	Preferred for most cases
Excisional Biopsy	Surgical removal of entire lesion	For ambiguous or non-diagnostic needle biopsy

3 Types of Breast Biopsies

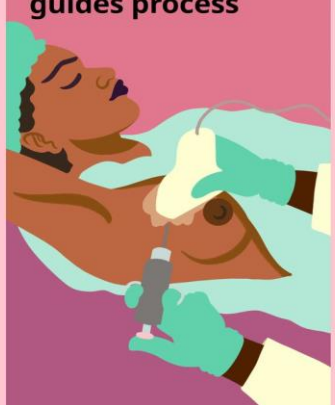
1. Fine needle aspiration

- Collects sample of cells



2. Core needle biopsy

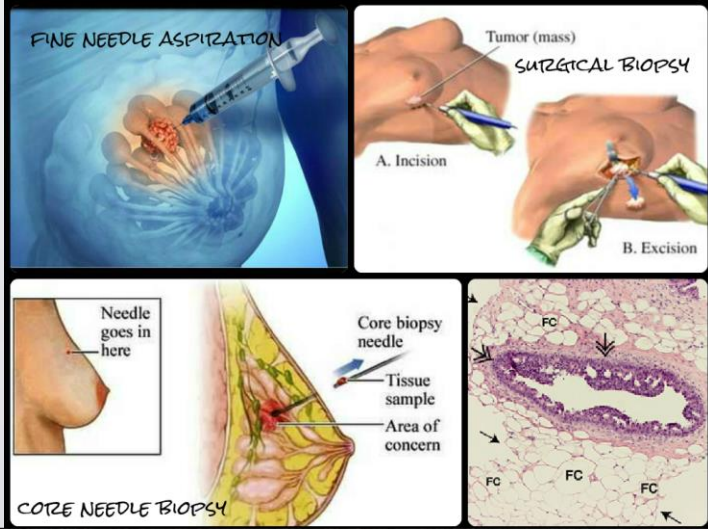
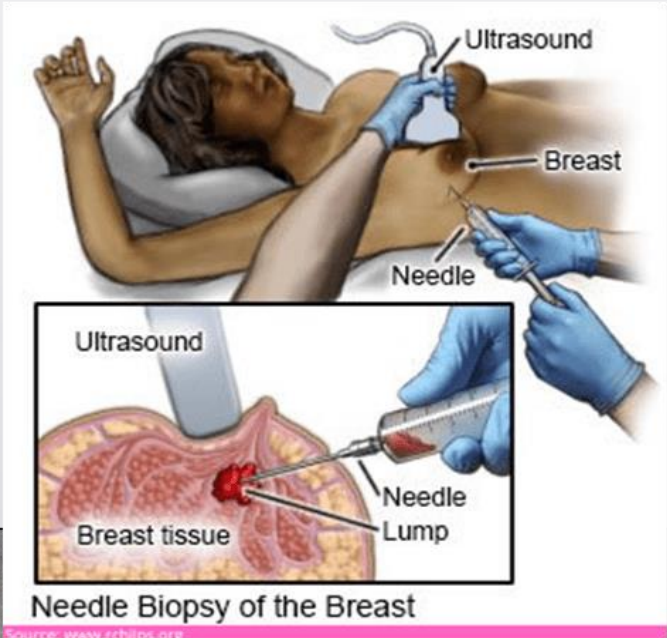
- Collects core of tissue
- Ultrasound or MRI guides process



3. Open (surgical) biopsy

- Removes all or part of abnormality



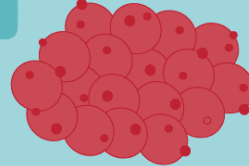
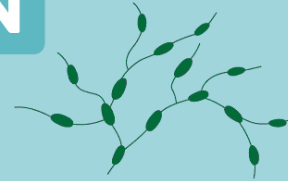
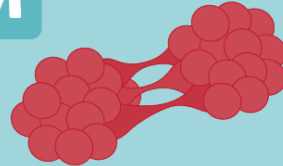


STAGING OF BREAST CANCER

- Breast cancer staging is based on the TNM system (Tumor, Node, Metastasis) by AJCC.
- It guides prognosis and treatment planning.

TNM System

Component	Definition
T (Tumor)	Size and local extent of primary tumor
N (Nodes)	Regional lymph node involvement
M (Metastasis)	Distant spread to other organs

T 	N 	M 
Tumor size	Lymph Node Status	Metastasis
T-1: 0-2 centimeters	N-0: Surgeon can't feel any nodes	M-0: Tested nodes are cancer-free
T-2: 2-5 centimeters	N-1: Surgeon can feel swollen nodes	M-1: Tested nodes show cancer cells or micrometastasis
T-3: >5 centimeters	N-2: Nodes feel swollen and lumpy	
T-4: Tumor has broken through skin or attached to chest wall	N-3: Swollen nodes located near collarbone	

T Category	Description
Tis	Carcinoma in situ (DCIS or LCIS)
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm but ≤ 5 cm
T3	Tumor > 5 cm
T4	Tumor of any size with extension to chest wall or skin; includes inflammatory breast cancer

N Category	Description
N0	No regional lymph node involvement
N1	1–3 axillary lymph nodes or internal mammary nodes (microscopic)
N2	4–9 axillary lymph nodes or internal mammary nodes (clinically detected)
N3	≥ 10 axillary nodes or involvement of infraclavicular, supraclavicular, or internal mammary nodes (more extensive)

M Category	Description
M0	No distant metastasis
M1	Distant metastasis present (bone, liver, lungs, brain)

Early Breast Cancer

Stage	Definition
Stage 0	Carcinoma in situ (DCIS or LCIS); non-invasive
Stage I	Small, invasive tumor (≤ 2 cm), no lymph node involvement
Stage II	Larger tumor (2–5 cm), or spread to 1–3 axillary lymph nodes

Locally Advanced Breast Cancer

Includes inflammatory breast cancer, which presents as rapid swelling, redness, and skin thickening.

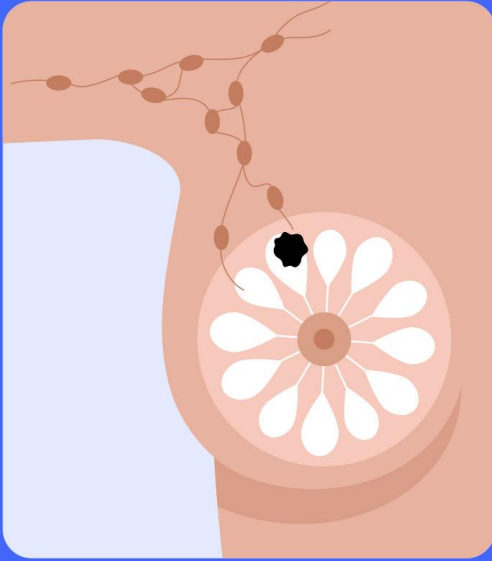
Stage III	Large tumor (>5 cm), or fixed to chest wall/skin or extensive nodal involvement (≥ 4 nodes, or nodes fixed/matted)
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Advanced/Metastatic Breast Cancer

Metastatic breast cancer is not curable but treatable and manageable.

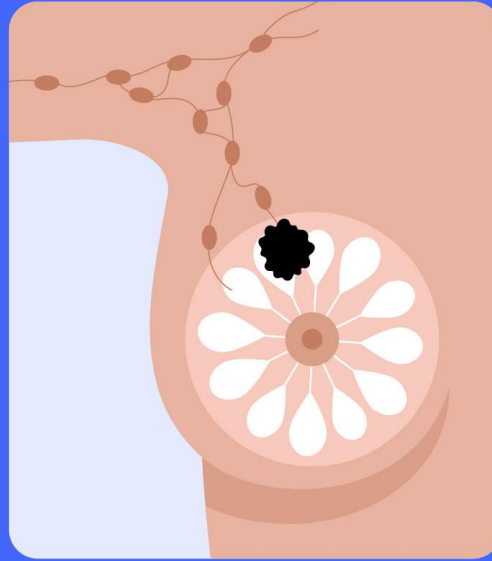
Stage IV	Evidence of distant metastases: bone, brain, liver, lungs
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Breast Cancer Stages



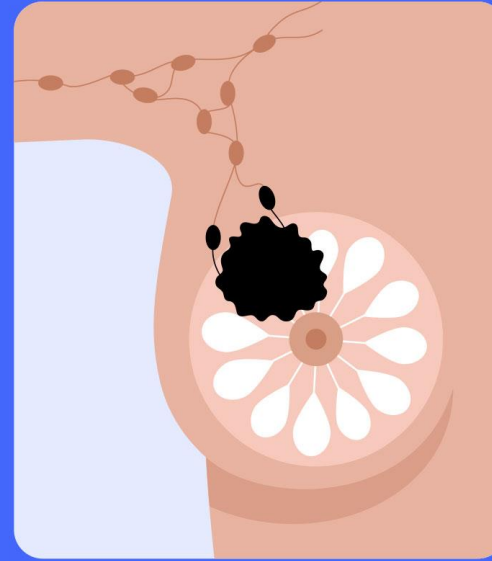
Stage 1

Invasive
tumor <2 cm



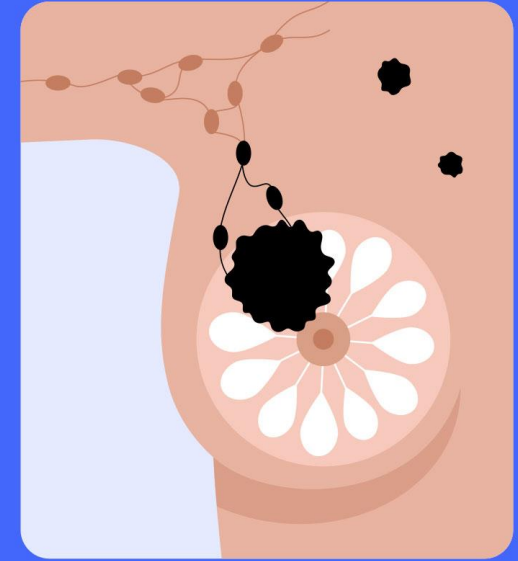
Stage 2

Tumor is
2-5 cm



Stage 3

Tumor is
>5 cm



Stage 4

Tumor spreads
to other organs

Clinical Stages

Stage	Description	Key Features
Stage 0	Carcinoma in situ (non-invasive)	• DCIS (Ductal carcinoma in situ) or LCIS (Lobular carcinoma in situ) • No invasion into surrounding breast tissue
Stage I	Early-stage invasive	• Tumor ≤ 2 cm • No lymph node involvement (or microscopic only) • No metastasis
Stage II	Localized with limited nodal spread	• Tumor 2–5 cm with or without spread to 1–3 axillary lymph nodes • No distant metastasis
Stage III	Locally advanced	• Tumor > 5 cm with ≥ 4 lymph nodes involved • Tumor fixed to chest wall or skin • Inflammatory breast cancer included
Stage IV	Metastatic disease	• Cancer has spread to distant organs: bone, liver, lungs, brain • Not curable but treatable

SCREENING AND EARLY DETECTION

- Early-stage detection significantly improves **cure rates** and **reduces mortality**
- Screening aims to detect **asymptomatic tumors** before they become advanced

Current Screening Guidelines (for Women at Average Risk)

Organization	Age to Start	Frequency	Modality
ACS (American Cancer Society)	45 (option at 40)	Annual 45–54; biennial ≥ 55	2D/3D mammography
USPSTF	40	Biennial (every 2 years)	Mammography
NCCN	40	Annual	Mammography

Pathophysiology of Breast Cancer

•Initiation Phase

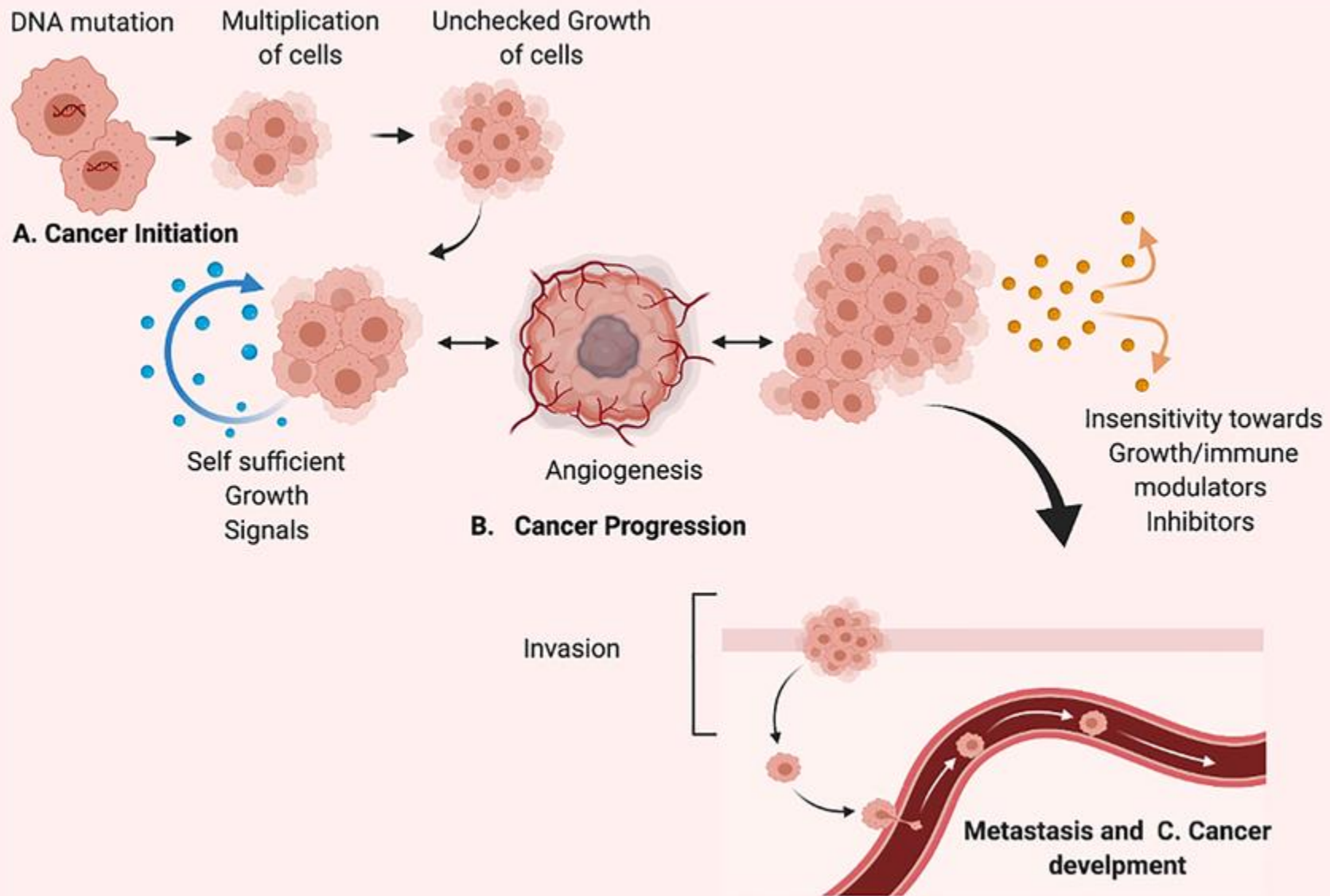
- Mutations occur in breast epithelial cells (often in terminal duct-lobular unit).
- Common driver mutations affect DNA repair, cell cycle regulation, or hormonal response pathways.

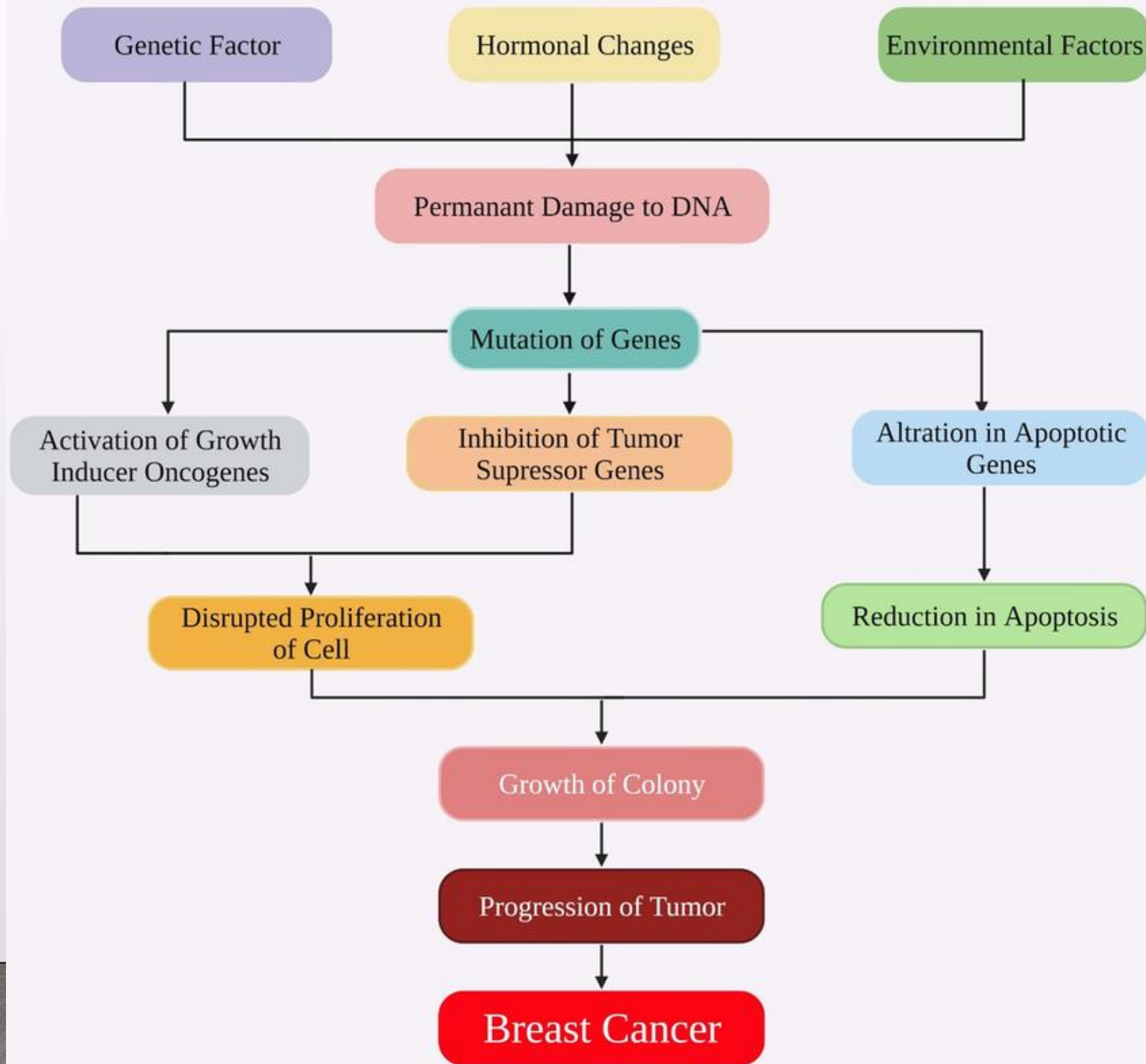
•Promotion Phase

- Estrogens act as mitogens, promoting clonal expansion of mutated cells.
- Additional mutations accumulate (multi-step carcinogenesis).
- Neoplastic cells invade the basement membrane (transition from in situ to invasive carcinoma).
- Cells spread via lymphatics (axillary nodes) or bloodstream to distant sites (lung, liver, brain, bone).

•Progression Phase

- Neoplastic cells invade the basement membrane (transition from in situ to invasive carcinoma).
- Cells spread via lymphatics (axillary nodes) or bloodstream to distant sites (lung, liver, brain, bone).





PATHOLOGY OF BREAST CANCER

Breast cancer pathology involves examining tissue to:

1. Confirm the **histologic diagnosis**,
2. Identify **tumor type and grade**,
3. Evaluate **prognostic and predictive markers** (e.g., ER, PR, HER2).

Category	Types
Non invasive (in situ)	1. Ductal carcinoma in situ (DCIS) 2. Lobular carcinoma in situ (LCIS)
Invasive (infiltrating)	1. Invasive ductal carcinoma (IDC) 2. Invasive lobular carcinoma (ILC) 3. Special types: • Medullary, • Mucinous, • Tubular 4. Others: Paget's disease, Inflammatory breast cancer (IBC), Phyllodes tumor

1. Invasive Carcinomas

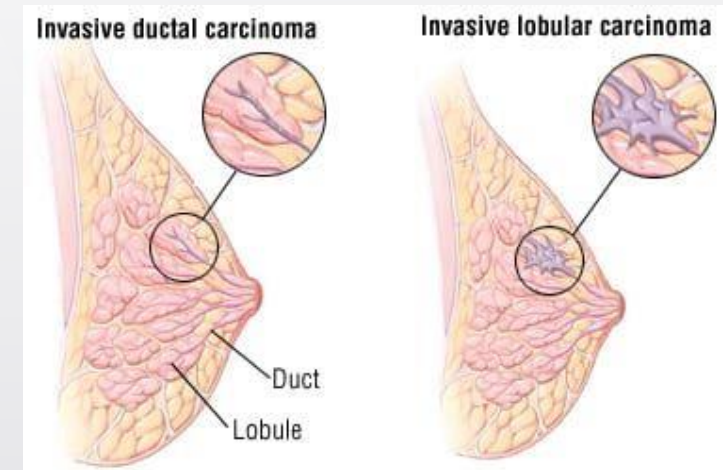
- Invasive (or infiltrating) carcinomas penetrate the basement membrane, allowing for local invasion and metastasis.

a. Invasive Ductal Carcinoma (IDC) – *Most common (75%)*

- Arises from ducts.
- Grossly: Hard, irregular, firm mass.
- Histology: Infiltrating atypical epithelial cells in a dense fibrous stroma.
- Tends to metastasize to axillary nodes, bone, liver, lungs, brain.

b. Invasive Lobular Carcinoma (ILC) – 5–10%

- Arises from lobular epithelium.
- Often bilateral or multifocal.
- Histology: "Single-file" linear pattern of invasion.
- Difficult to detect on mammogram.
- Unique spread: GI tract, peritoneum, meninges, ovaries.



2. Non invasive (In Situ) Carcinomas

In situ carcinomas are precancerous lesions confined within ducts or lobules—no invasion of basement membrane.

a. Ductal Carcinoma in Situ (DCIS)

- Most common in situ lesion.
- Detected via microcalcifications on mammogram.
- Histologic types: Comedo (high-grade, central necrosis), cribriform, micropapillary.
- ~14–50% risk of progression to invasive cancer if untreated.
- Treated with excision ± radiotherapy ± endocrine therapy.

b. Lobular Carcinoma in Situ (LCIS)

- Incidental finding on biopsy; no mass or calcification.
- Marker of increased bilateral breast cancer risk (0.5–1%/year).
- Histology: Small, round, uniform cells in lobules.
- Management: Observation or risk reduction strategies (SERMs, AIs, prophylactic surgery).

d. Inflammatory Breast Cancer (IBC)

- *Aggressive and rare (<2%)*
- Clinical signs: Rapid onset of redness, warmth, edema (“peaud’orange”).
- Histology: Tumor emboli in dermal lymphatics.
- Often misdiagnosed as mastitis.
- Poor prognosis due to early lymphatic spread.

e. Paget’s Disease of the Breast

- Eczematous changes of the nipple–areola complex.
- Associated with underlying DCIS or invasive carcinoma.
- Histology: Paget cells (large, pale-staining malignant cells in epidermis).

c. Special Histologic Types (Rare but important):

Type	Features
Medullary carcinoma	Large, high-grade tumor with lymphoid infiltrate; better prognosis.
Mucinous (colloid) carcinoma	Abundant extracellular mucin; occurs in older women; favorable prognosis.
Tubular carcinoma	Well-formed tubules; small tumors; excellent prognosis.

TREATMENT & MANAGEMENT OF BREAST CANCER

Goals of Treatment in Breast Cancer

Adjuvant Therapy

- Aims to eradicate micrometastatic disease, it is used as curative intent—to reduce the risk of recurrence and potentially cure the patient.
- Given for a predetermined number of cycles or fixed duration.
- Includes chemotherapy, hormonal therapy, or targeted/biologic therapy.

Neoadjuvant Therapy

- Aims to shrink the primary tumor to allow breast-conserving surgery (e.g., lumpectomy instead of mastectomy).
- Helps in eradicating micrometastatic disease early.
- Assists in determining prognosis by observing tumor response to therapy.
- Can guide modification of postoperative (adjuvant) treatment plans.

Metastatic (Advanced) Breast Cancer Therapy

- Aims to control disease, prolong survival, and relieve symptoms.
- Has a palliative intent—not curative.
- Focuses on maintaining quality of life.

Early Breast Cancer (Stage I and II)

I. Locoregional Therapy

Locoregional therapy is designed to treat the tumor within the breast and the regional lymph nodes (especially axillary nodes) to:

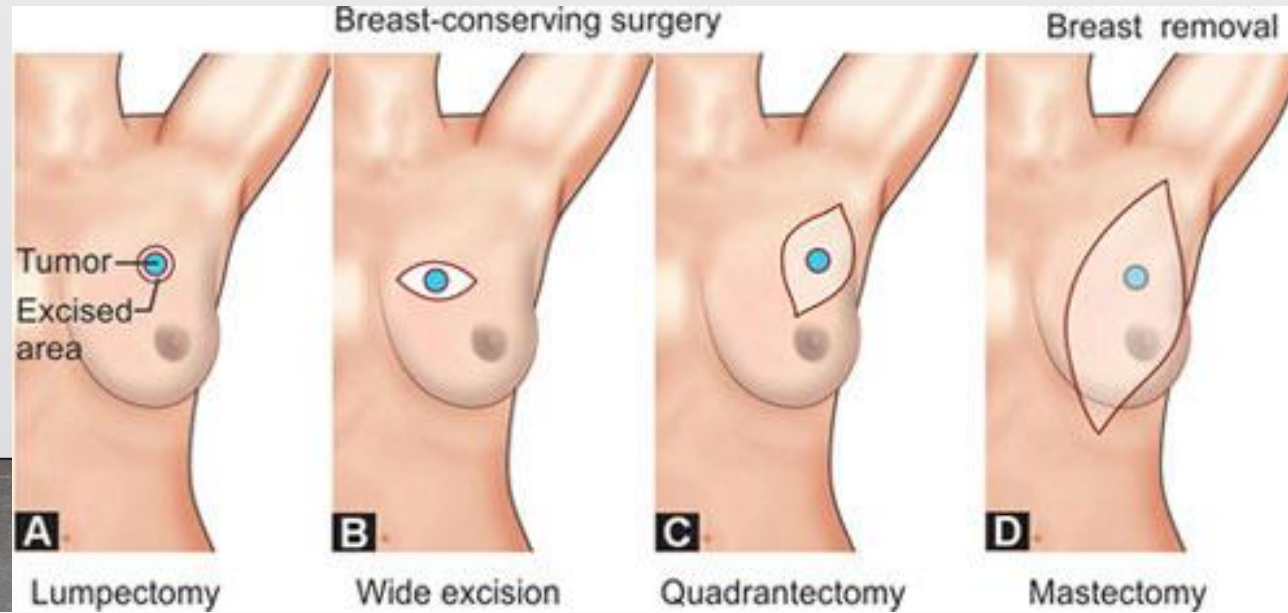
- Achieve complete local control of the disease.
- Prevent locoregional recurrence (recurrence in the breast or nearby lymph nodes).
- Improve long-term survival, particularly when combined with systemic therapy.

It includes surgery (lumpectomy or mastectomy), radiation therapy, and lymph node management (sentinel lymph node biopsy or axillary dissection).

Surgery :

a. Breast-Conserving Therapy (BCT)

- Surgical removal of the tumor (lumpectomy, wide local excision, or quadrantectomy) followed by radiation therapy to the remaining breast tissue.
- Indicated to Remove the cancer while preserving the breast.
- Types of BCT Procedures:
 - **Lumpectomy:** Removal of the tumor with a small rim of normal tissue.
 - **Wide local excision:** Larger margin around the tumor.
 - **Quadrantectomy:** Removal of one quadrant of the breast containing the tumor.
- These are also referred to as segmental mastectomy.

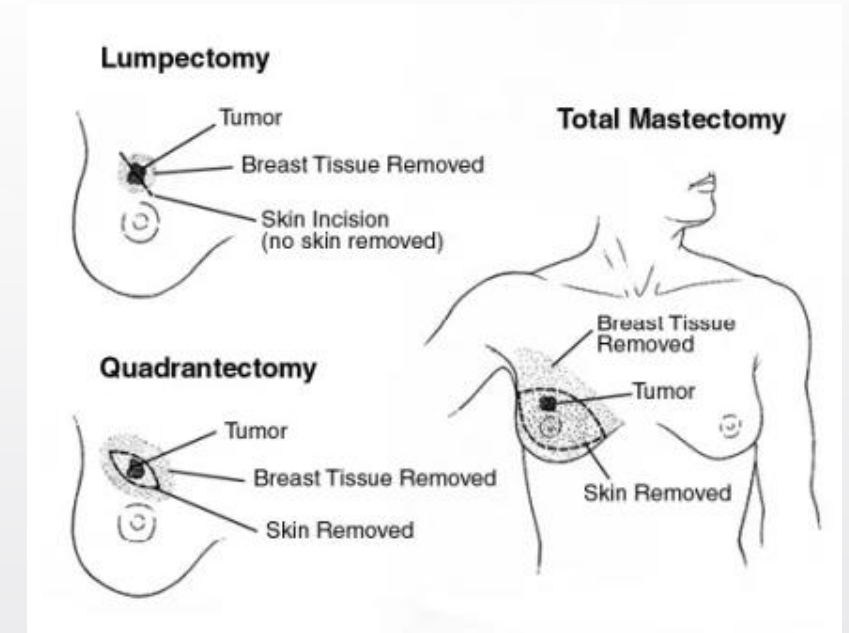


Patient Selection for BCT

- BCT is appropriate for most **Stage I and II** breast cancer patients.
- **Not suitable for:**
 - Multiple tumors in different parts of the breast.
 - Prior radiation to the chest.
 - Inability to get negative surgical margins.
- Contraindicated in Collagen vascular diseases (e.g., scleroderma, lupus) due to sensitivity to radiation.
- **Other considerations:**
 - Cosmetic outcomes (some women may prefer mastectomy).
 - Willingness and ability to complete radiation therapy.
 - Access to radiation facilities.

b. Mastectomy

- Complete removal of breast tissue.
- Indications:
 - Multifocal or multicentric disease (multiple tumors in different parts of the breast).
 - Genetic mutations (BRCA1 or BRCA2 carriers).
 - Inability to get clear margins despite multiple surgeries.
 - Contraindications to radiation (e.g., scleroderma, SLE).
- **Types:**
 - Total mastectomy.
 - Modified radical mastectomy (includes axillary dissection).
 - Bilateral mastectomy in high-risk patients (e.g., BRCA mutation).



Radiation Therapy

a. After BCT

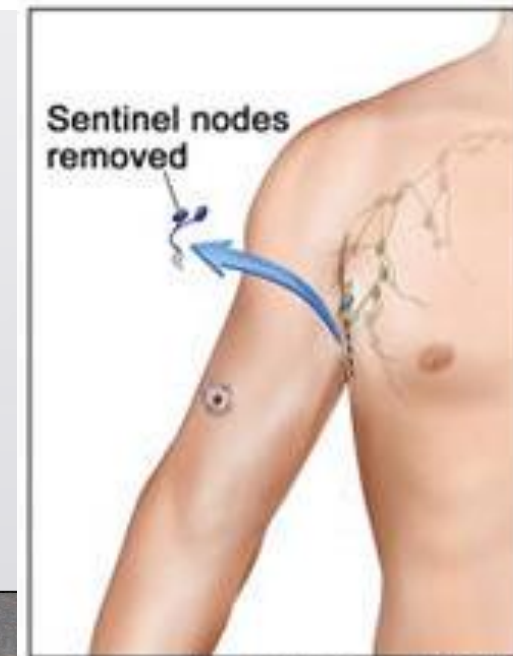
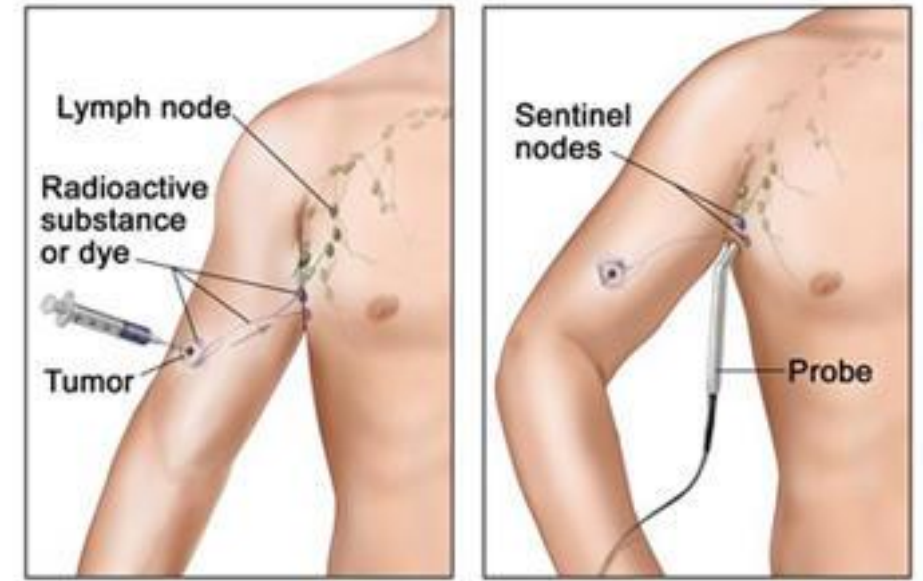
- Radiation is mandatory after breast-conserving surgery.
- It is used to Destroy any remaining cancer cells in the breast tissue and to reduce the risk of reoccurrence.
- Regimens:
 - Standard: 40–50.4 Gy total, over 15–28 fractions (daily sessions).
 - An optional boost dose (e.g., 10 Gy) may be given to the tumor bed.
- Side Effects:
 - Reddening/erythema of skin, breast shrinkage, edema, telangiectasias.
 - Long-term fibrosis (rare with modern techniques).

b. After Mastectomy (Postmastectomy Radiation Therapy - PMRT)

- Not needed for all patients.
- **Indicated in:**
 - Tumor >5 cm.
 - Positive margins after surgery.
 - ≥ 4 positive axillary lymph nodes.
 - 1–3 positive lymph nodes (consider case-by-case).
- **Target areas:** Chest wall and regional lymph nodes.
- It is used to Decrease risk of chest wall recurrence and improve survival.

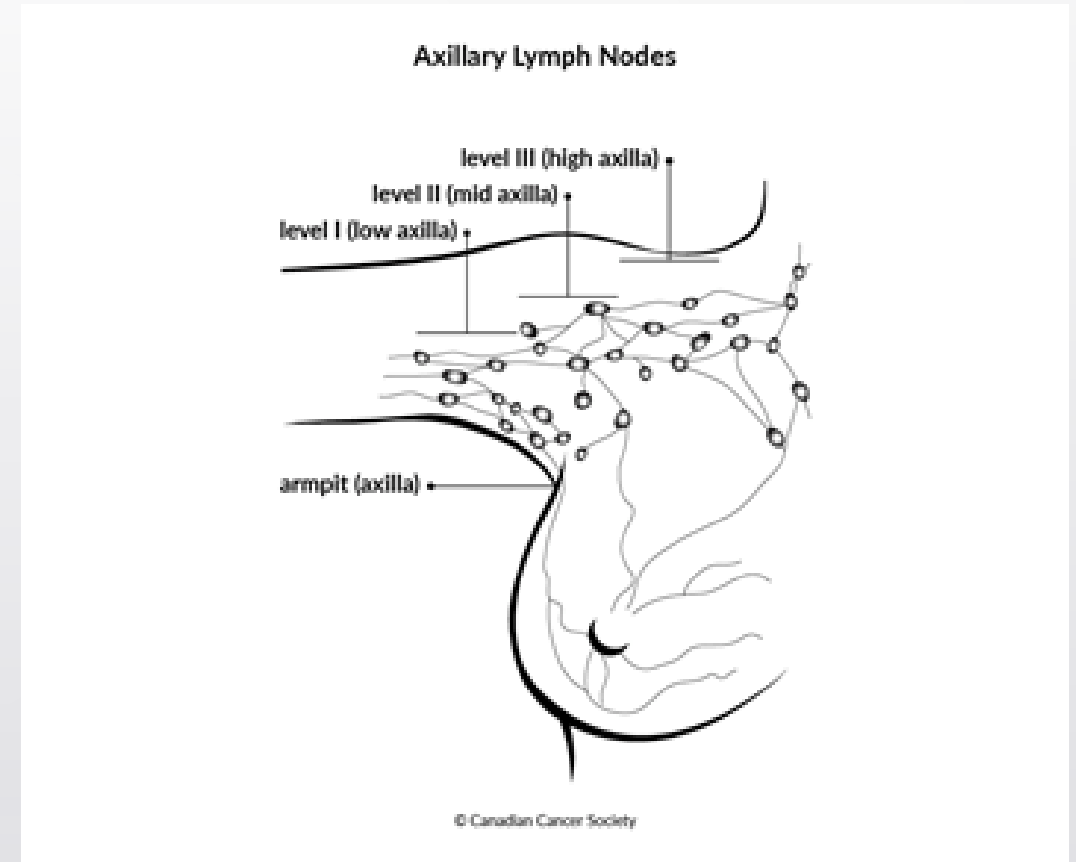
Sentinel Lymph Node Biopsy (SLNB)

- A minimally invasive method to evaluate if breast cancer has spread to the axillary (underarm) lymph nodes.
- A **radioactive tracer and/or blue dye** is injected near the tumor.
- The **sentinel node(s)** (first node draining the tumor) is identified and removed.
- **Indications:** Patients with **clinically node-negative** disease.
- **Contraindications to SLNB:**
 - Large tumors (>5 cm).
 - Inflammatory breast cancer.
 - DCIS if mastectomy planned.
 - Pregnancy/lactation.



Axillary Lymph Node Dissection (ALND)

- Removal of level I and II axillary lymph nodes.
- **Indications:**
 - Positive sentinel nodes in patients undergoing mastectomy.
 - More than 2 positive sentinel nodes.
- **Complications:**
 - Lymphedema (arm swelling).
 - Arm pain, numbness, and decreased mobility.
 - Long-term reduction in quality of life.



II. Systemic Adjuvant Therapy

- Systemic adjuvant therapy refers to treatment administered after primary local therapy (surgery and/or radiation) when the cancer is confined to the breast and regional lymph nodes and there is no clinical evidence of metastasis.
- To eliminate micrometastatic disease and prevent recurrence and improve survival outcomes.
- Systemic therapy includes:
 - 1. Chemotherapy**
 1. Kills rapidly dividing cancer cells.
 - 2. Endocrine (Hormonal) Therapy**
 1. Blocks estrogen or progesterone effects in HR-positive cancers.
 2. Options include tamoxifen or aromatase inhibitors.
 - 3. Targeted (Biologic) Therapy**
 1. Targets specific receptors like HER2 (e.g., trastuzumab, pertuzumab).

Systemic therapy is based on:

1. Tumor size: >1 cm generally considered for chemo.
2. Lymph node involvement: Any positive node raises recurrence risk.
3. Hormone receptor (HR) status: Determines use of endocrine therapy.
4. HER2 status: HER2-positive tumors get anti-HER2 therapy.
5. Menopausal status and age: Younger women often have more aggressive tumors.
6. Comorbidities and preferences: Elderly or frail patients may avoid chemo.

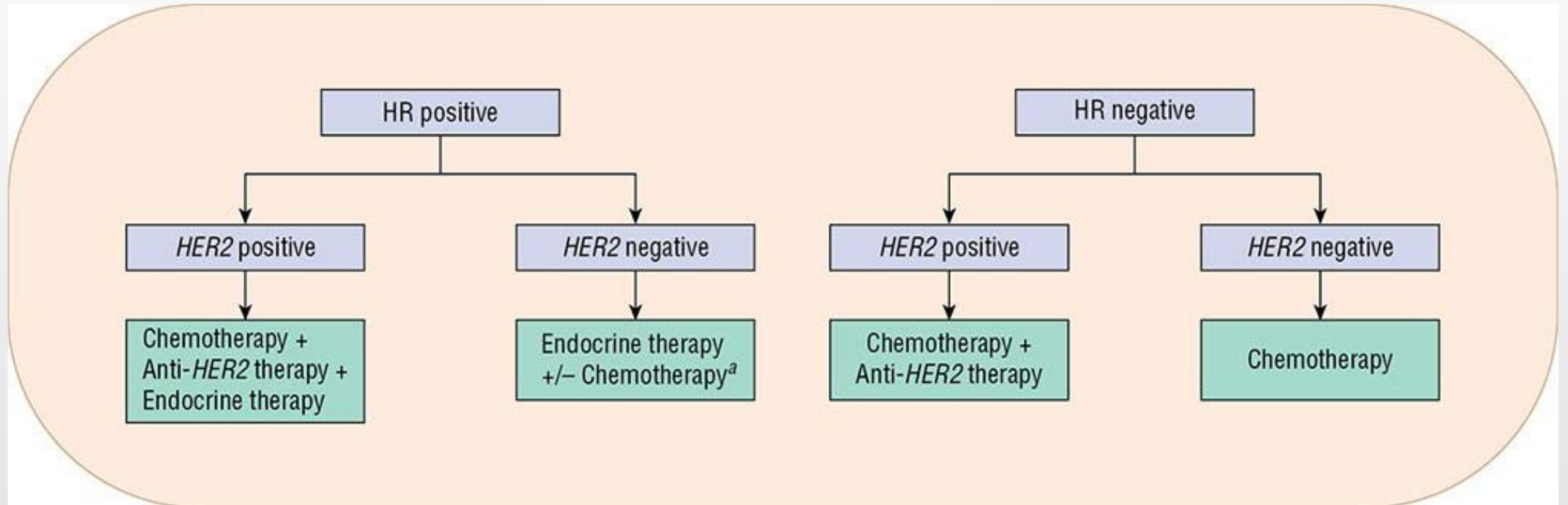
Neoadjuvant Therapy (Preoperative Systemic Therapy)

Used in:

1. Locally advanced breast cancer (LABC)
2. Patients with large tumors desiring breast-conserving surgery (BCS)

Advantages:

1. Tumor shrinkage, enabling surgery.
2. Provides early assessment of treatment response.



Treatment of patients with breast cancers larger than 1 cm or with positive lymph nodes.

Adjuvant Chemotherapy

Adjuvant chemotherapy after local treatment (surgery $\pm$ radiation) to eliminate microscopic cancer cells that may have spread beyond the breast but are not yet detectable (micrometastases).

Commonly Used Agents

Key cytotoxic agents include:

1. **Anthracyclines:** doxorubicin, epirubicin (DNA intercalators, topoisomerase II inhibitors).
2. **Alkylating agents:** cyclophosphamide.
3. **Antimetabolites:** methotrexate, fluorouracil.
4. **Taxanes:** paclitaxel, docetaxel (microtubule stabilizers).
5. **Platinum compounds:** carboplatin (used particularly in triple-negative breast cancer).

AC

Doxorubicin 60 mg/m² IV, day 1

Cyclophosphamide 600 mg/m² IV, day 1

Repeat cycles every 21 days for 4 cycles

FAC

Fluorouracil 500 mg/m² IV, days 1 and 4

Doxorubicin 50 mg/m² IV continuous infusion over 72 hours

Cyclophosphamide 500 mg/m² IV, day 1

Repeat cycles every 21–28 days for 6 cycles

AC → Paclitaxel

Doxorubicin 60 mg/m² IV, day 1

Cyclophosphamide 600 mg/m² IV, day 1

Repeat cycles every 21 days for 4 cycles

Followed by:

Paclitaxel 80 mg/m² IV weekly

Repeat cycles every 7 days for 12 cycles

FEC

Fluorouracil 500 mg/m² IV, day 1

Epirubicin 100 mg/m² IV bolus, day 1

Cyclophosphamide 500 mg/m² IV, day 1

Repeat cycle every 21 days for 6 cycles

TC

Docetaxel 75 mg/m² IV, day 1

Cyclophosphamide 600 mg/m² IV, day 1

Repeat cycles every 21 days for 4 cycles

TAC

Docetaxel 75 mg/m² IV, day 1

Doxorubicin 50 mg/m² IV bolus, day 1

Cyclophosphamide 500 mg/m² IV, day 1 (doxorubicin should be given first)

Repeat cycles every 21 days for 6 cycles (must be given with growth factor support)

Paclitaxel → FAC

Paclitaxel 80 mg/m² per week IV over 1 hour every week for 12 weeks

Followed by:

Fluorouracil 500 mg/m² IV, days 1 and 4

Doxorubicin 50 mg/m² IV continuous infusion over 72 hours

Cyclophosphamide 500 mg/m² IV, day 1

Repeat cycles every 21–28 days for 4 cycles⁹

CEF

Cyclophosphamide 75 mg/m² per day orally on days 1–14

Epirubicin 60 mg/m² IV, days 1 and 8

Fluorouracil 600 mg/m² IV, days 1 and 8

Repeat cycles every 21 days for 6 cycles (requires prophylactic antibiotics or growth factor support)

- Early administration of effective combination chemotherapy at a time of low tumor burden should increase the likelihood of cure and minimize emergence of drug resistant tumor cell clones.

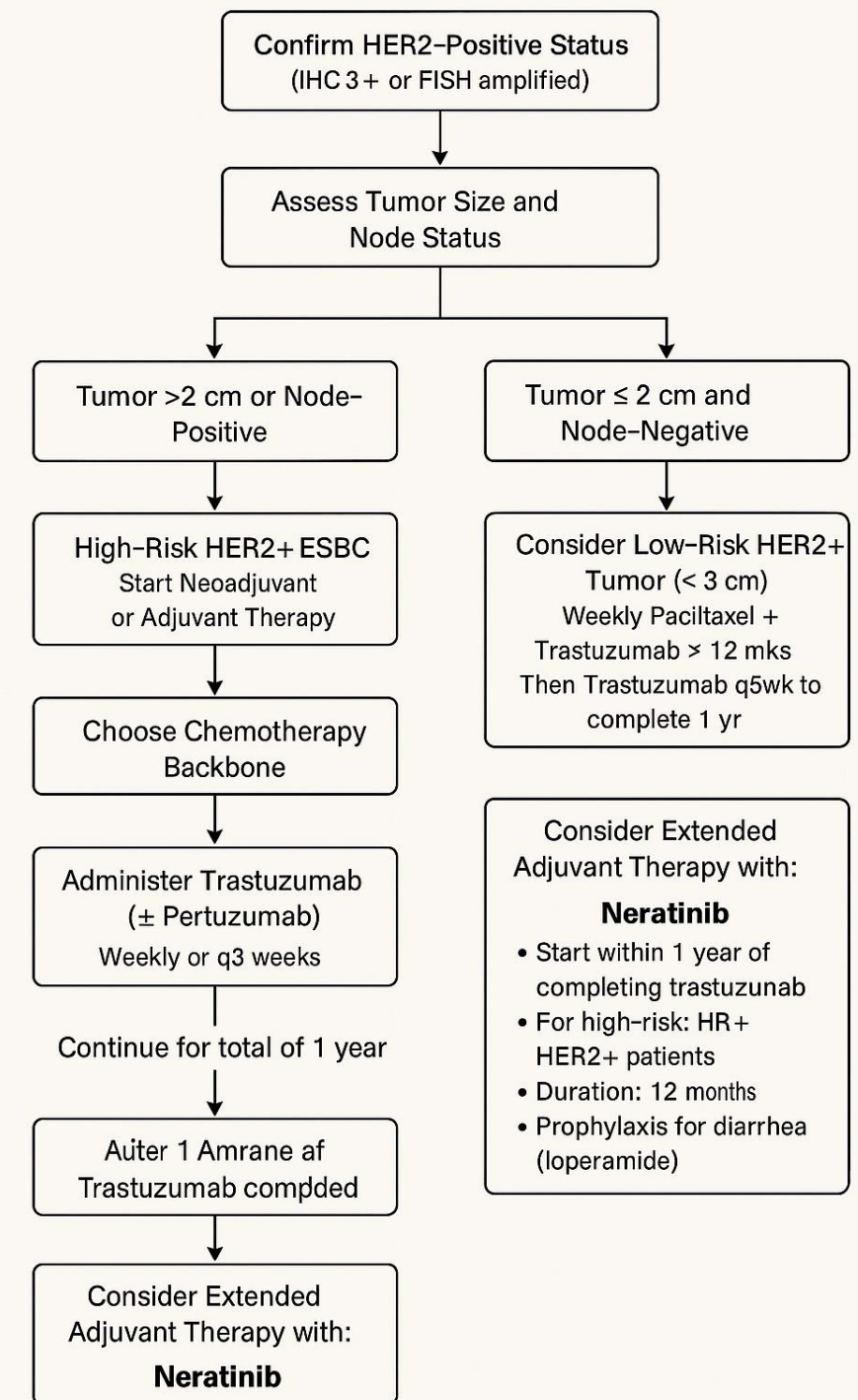
Combination regimens have historically been more effective than single-agent chemotherapy .

- Anthracycline-containing regimens (eg, **doxorubicin** and **epirubicin**) reduce the rate of recurrence and death as compared with regimens that contain **cyclophosphamide**, **methotrexate**, and **fluorouracil**.
- The addition of taxanes, **docetaxel** and **paclitaxel**, to adjuvant regimens comprised of the drugs listed above resulted in reduced risk of distant recurrence, any recurrence, and overall mortality compared with a non taxane regimen in node-positive breast cancer patients.
- The use of taxane-containing regimens in node-negative patients remains controversial.
- Initiate chemotherapy within 12 weeks of surgical removal of the primary tumor.
- Optimal duration of adjuvant treatment is unknown but appears to be 12 to 24 weeks, depending on the regimen used.
- Concomitant or sequential administration of a taxane with an anthracycline-based regimen is standard of care in node-positive breast cancer.

- Dose increases in standard regimens appears to not be beneficial and may be harmful.
- Avoid dose reductions in standard regimens unless necessitated by severe toxicity.
- Short-term toxicities of adjuvant chemotherapy are generally well tolerated, especially with the availability of serotonin-antagonist and substance P/neurokinin 1–antagonist antiemetics and myeloid growth factors.
- Survival benefit for adjuvant chemotherapy in stage I and II breast cancer is modest.
- The absolute reduction in mortality at 10 years is 5% in node-negative and 10% in node-positive disease.

Targeted and Biologic Therapy

- Targeted therapy: Drugs designed to specifically act on molecular targets involved in cancer progression (e.g., HER2 receptor, HER2 (Human Epidermal growth factor Receptor 2) is overexpressed in ~20–25% of breast cancers.).
- Biologic therapy: Often refers to monoclonal antibodies (MoABs), which are biologically derived proteins that bind to specific antigens.



Trastuzumab: Trastuzumab (Herceptin) is a monoclonal antibody that binds to the extracellular domain of HER2.

- It:
 - Blocks HER2-mediated signaling.
 - Promotes antibody-dependent cellular cytotoxicity (ADCC).
 - Prevents HER2 receptor dimerization.
- Timing of Trastuzumab Administration
 - There are two main strategies:
 1. Concomitant (given together with chemotherapy) Better outcomes in both DFS and OS.
Example: Paclitaxel + trastuzumab after AC (anthracycline + cyclophosphamide).
 2. Sequential (trastuzumab given after chemotherapy) Improves DFS, but no significant benefit in OS.
- Common Chemotherapy Regimens with Trastuzumab : Anthracycline + taxane, followed or combined with trastuzumab.
- Duration of Trastuzumab Therapy 52 weeks (1 year).
- Cardiotoxicity is the main adverse effect.
- Infusion reactions: Fever, chills, rigors (most common during first infusion).
- Rare but serious: Pulmonary toxicity. Anaphylaxis.

Endocrine Therapy

These agents work by blocking estrogen receptor activity or suppressing estrogen production, essential because estrogen drives growth of hormone-receptor–positive (HR+) breast cancer.

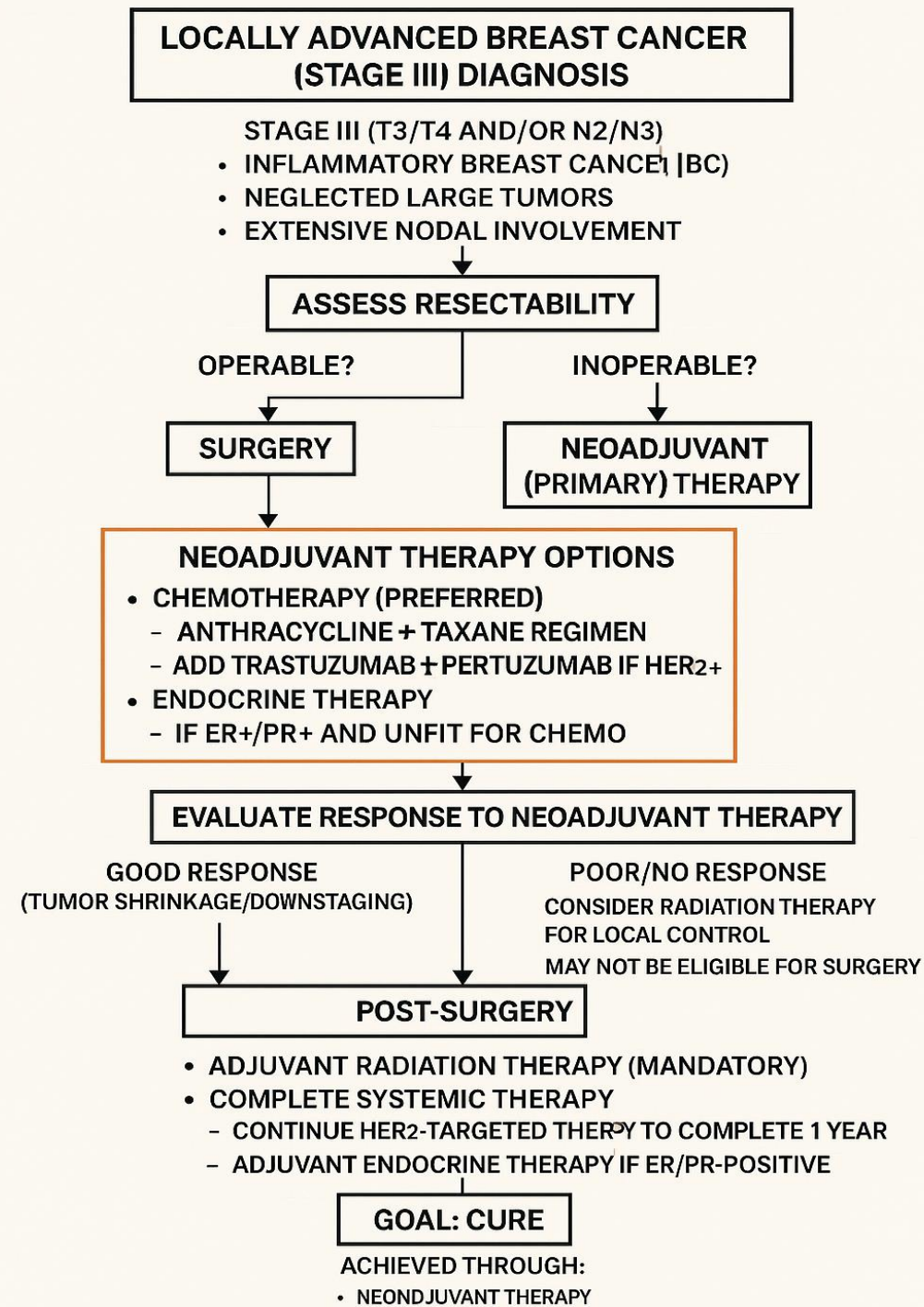
1. Selective Estrogen Receptor Modulator – Tamoxifen, Toremifene
2. Aromatase Inhibitors (AIs) – Anastrozole, Letrozole, Exemestane
3. LHRH Agonists (GnRH Agonists) – Goserelin, Leuprolide, Triptorelin
4. Oophorectomy – Surgical removal of ovaries
5. Ovarian Irradiation – Destruction of ovarian function via radiation

Tamoxifen

1. Tamoxifen as a Prodrug: Metabolized mainly by CYP2D6 → active metabolite endoxifen
2. Endoxifen has ~100× greater affinity for estrogen receptor than tamoxifen
3. Acts as an estrogen antagonist in breast tissue → inhibits tumor growth
4. Acts as a partial agonist (estrogen-like) in bone and uterus
5. Dose and Administration: 20 mg orally once daily
6. Traditionally used for 5 years, but newer data support 10 years in some patients
7. Risks of 10-year Therapy:
 - ↑ Endometrial cancer (due to estrogenic effect on endometrium)
 - ↑ Pulmonary embolism
 - ↑ Deep vein thrombosis
8. These toxicities are especially pronounced in women over 50 years
9. Common Side Effects: Hot flashes, Vaginal discharge, Irregular menses
10. Serious Adverse Effects (esp. ≥50 years): Endometrial cancer, Pulmonary embolism, Stroke, Deep vein thrombosis
11. Drug–Drug Interactions: Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine) ↓ endoxifen levels
May reduce tamoxifen effectiveness → avoid if possible

Locally Advanced Breast Cancer (LABC – Stage III)

- Locally advanced breast cancer (LABC) is defined as stage III disease, where the cancer is extensive within the breast and/or regional lymph nodes but has not metastasized to distant organs.
- It includes a broad spectrum of presentations such as:
 1. T4 tumors (involving skin or chest wall).
 2. N2/N3 nodal disease (fixed or matted axillary nodes, or internal mammary/supraclavicular node involvement).
- Inflammatory Breast Cancer (IBC) is a specific aggressive subtype of LABC:
 - ✓ Presents with rapid onset of breast swelling, redness, warmth, and “peau d’orange” appearance.



Goal of Therapy

- Despite the advanced nature of LABC, the goal remains curative.
- Cure is possible through multimodal therapy, including:
 - Systemic therapy (chemotherapy $\pm$ targeted/endocrine therapy).
 - Surgery (mastectomy or BCT).
 - Radiation therapy (essential for local control).
- Patients who respond well to all modalities have a reasonable chance of long-term survival and cure.

Initial Treatment Strategy

1. For inoperable LABC, including IBC, the first step is systemic chemotherapy for tumour shrinkage to allow surgical resection.
 - a. Anthracyclines (e.g., doxorubicin, epirubicin): Interfere with DNA replication.
 - b. Taxanes (e.g., paclitaxel, docetaxel): Inhibit microtubule function.
 - c. In HER2+ cases: Add trastuzumab ± pertuzumab.
 2. In selected patients, especially:
 1. Hormone receptor–positive (ER+/PR+) tumors.
 2. Elderly or frail patients with significant comorbidities who cannot tolerate chemotherapy.
- Use endocrine therapy such as:
- a. Aromatase inhibitors (letrozole, anastrozole, exemestane) for postmenopausal women.
 - b. Tamoxifen for premenopausal women, or with LHRH agonists.

Local Therapy Following Chemotherapy

After response to neoadjuvant therapy, the patient is evaluated for surgery:

1. Type of surgery depends on:
 - a. Degree of tumor shrinkage.
 - b. Patient's cosmetic preferences and breast size.
2. Mastectomy or Breast-Conserving Therapy (BCT) may be chosen.

Adjuvant Radiation Therapy

1. Regardless of surgery type, radiation therapy is mandatory in LABC to:
 1. Destroy residual microscopic disease.
 2. Minimize local recurrence.
2. Radiation is especially important in:
 1. Post-mastectomy cases with T3/T4 tumors or ≥ 4 positive lymph nodes.
 2. Patients undergoing BCT always need whole breast radiation.

Metastatic Breast Cancer (MBC – Stage IV)

Metastatic Breast Cancer (MBC) is not curable, but many treatments can help control disease, relieve symptoms, and prolong life.

The main goals of therapy are:

1. Disease control
2. Symptom relief
3. Prolongation of survival
4. Improved quality of life (QoL)

Treatment Modalities

A. Endocrine (Hormonal) Therapy Used in HR-positive (ER/PR+) tumours.

Slows down or blocks hormone-driven cancer growth.

B. Targeted Therapy Directed against specific molecular targets

- HER2-targeted therapy (e.g., trastuzumab) is used in HER2-positive tumours.
- CDK4/6 inhibitors, PI3K inhibitors, and mTOR inhibitors used to overcome endocrine resistance in HR+ tumours.

C. Cytotoxic Chemotherapy Kills rapidly dividing cancer cells.

- Used when Tumour is hormone receptor–negative

TABLE 60-2 Endocrine Therapies Used for Metastatic Breast Cancer		
Drug	Brand Name	Initial Dose
<i>Aromatase Inhibitors: Nonsteroidal</i>		
Anastrozole	Arimidex, generic	1 mg orally daily
Letrozole	Femara, generic	2.5 mg orally daily
<i>Aromatase Inhibitor: Steroidal</i>		
Exemestane	Aromasin	25 mg orally daily
<i>Antiestrogens: SERMs</i>		
Tamoxifen	Nolvadex, generic	20 mg orally daily
Toremifene	Fareston	60 mg orally daily
<i>Antiestrogen: SERD</i>		
Fulvestrant	Faslodex	500 mg IM every 28 days (after loading days 1, 15, 29)
<i>LHRH Agonists</i>		
Goserelin	Zoladex	3.6 mg SC every 28 days
Leuprolide	Lupron (IM), generic	3.75 mg IM (SC) every 28 days
Triptorelin	Trelstar	3.75 mg IM every 28 days

TABLE 60-2 Endocrine Therapies Used for Metastatic Breast Cancer (<i>Continue</i>)		
Drug	Brand Name	Initial Dose
<i>Progestins</i>		
Megestrol acetate	Megace, generic	40 mg orally 4 times a day
Medroxyprogesterone	DepoProvera, generic	400 mg IM every week
<i>Androgens</i>		
Fluoxymesterone	Androxy, generic	10 mg orally twice a day
<i>Estrogens</i>		
Ethinyl estradiol	Multiple generics	1 mg orally 3 times a day
Conjugated estrogens	Premarin	2.5 mg orally 3 times a day

TABLE 60-3

Selected Chemotherapy Regimens for Metastatic Breast Cancer

Single-	
Paclitaxel Paclitaxel 175 mg/m ² IV over 3 hours Repeat cycles every 21 days <i>or</i> Paclitaxel 80 mg/m ² /week IV over 1 hour Repeat dose every 7 days	
Docetaxel Docetaxel 60–100 mg/m ² IV over 1 hour Repeat cycles every 21 days <i>or</i> Docetaxel 30–35 mg/m ² /week IV over 30 minutes Repeat dose every 7 days	
Protein-Bound Paclitaxel Protein-bound Paclitaxel 260 mg/m ² IV over 30 minutes Repeat cycles every 21 days <i>or</i> Protein-bound paclitaxel 100–150 mg/m ² IV over 30 minutes on days 1, 8, and 15 Repeat cycle every 28 days	
Capecitabine Capecitabine 2,000–2,500 mg/m ² per day orally, divided twice daily for 14 days Repeat cycles every 21 days	
Combination	
Docetaxel + Capecitabine Docetaxel 75 mg/m ² IV over 1 hour, day 1 Capecitabine 2,000–2,500 mg/m ² per day orally divided twice daily for 14 days Repeat cycles every 21 days	
Ixabepilone + Capecitabine Ixabepilone 40 mg/m ² IV over 3 hours, day 1 Capecitabine 1,750–2,000 mg/m ² /day orally divided twice daily for 14 days Repeat cycles every 21 days	

Treatment Based on Tumour Subtype

A. HR-positive / HER2-negative

- First-line: Endocrine therapy (e.g., aromatase inhibitors, tamoxifen, fulvestrant)
- Targeted therapy:
 - *CDK4/6 inhibitors* (e.g., palbociclib, ribociclib, abemaciclib)
 - Delay progression significantly
 - *PI3K inhibitors* (e.g., alpelisib for PIK3CA-mutant tumors)
 - *mTOR inhibitors* (e.g., everolimus)
- Continue sequential endocrine therapies until resistance occurs.

B. HER2-positive Tumors (HR+ or HR–)

- First-line regimen:
 - Trastuzumab + pertuzumab + docetaxel (based on CLEOPATRA trial)
- Other options:
 - Trastuzumab-emtansine (T-DM1)
 - Tucatinib, lapatinib, neratinib (HER2 TKIs)
- For HR+ HER2+ tumors:
 - Combine endocrine therapy + HER2-targeted agent if chemotherapy isn't urgent.