Breast Cancer

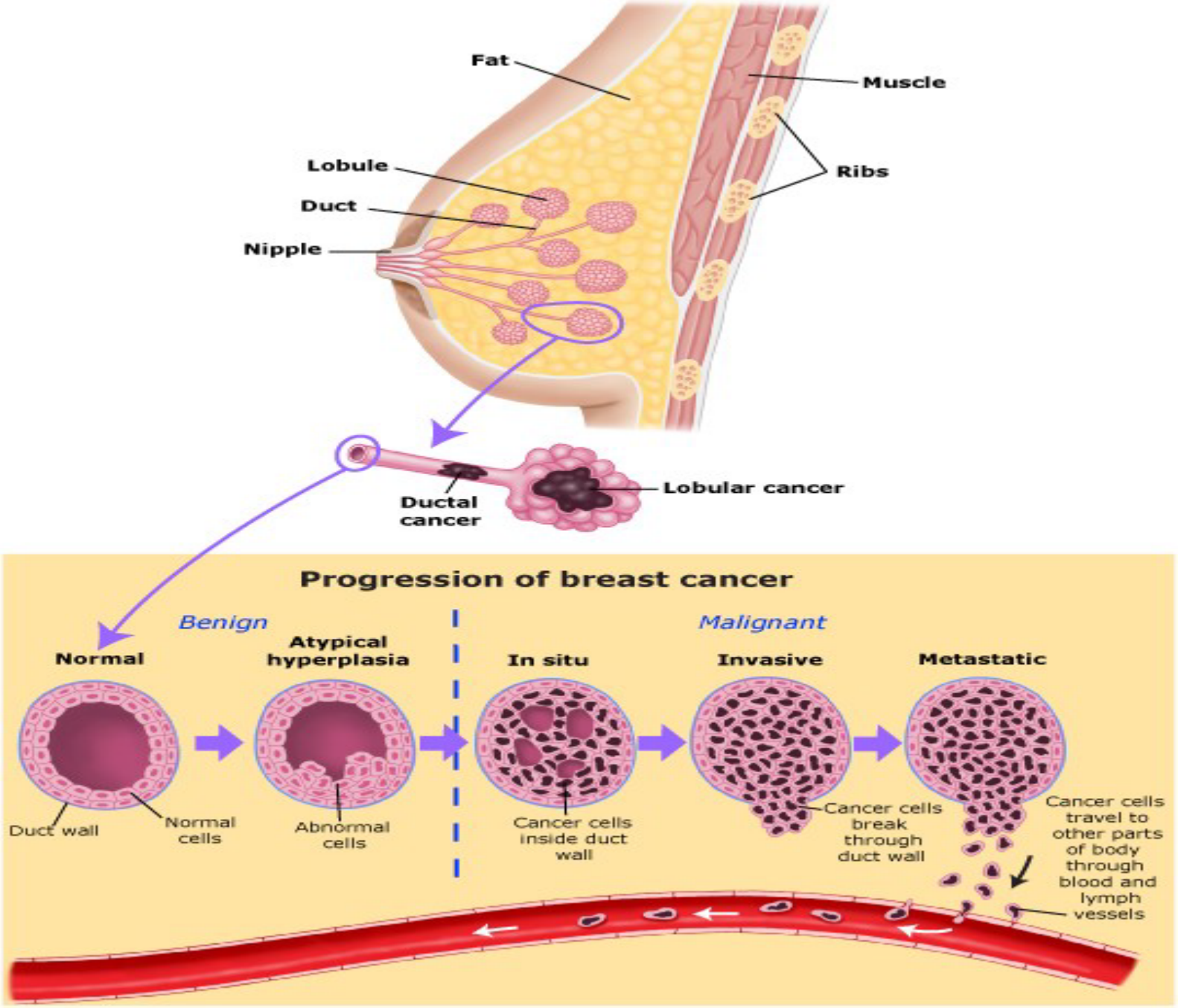
- Breast cancer is a malignancy originating from breast tissue.

- The strongest risk factors for breast cancer are female gender and increasing age.

- Additional risk factors include endocrine factors (e.g., early menarche, nulliparity, late age at first birth, hormone replacement therapy), genetic factors (e.g., personal and family history, mutations of tumor suppresser genes [*BRCA1 and BRCA2]), and environmental and lifestyle* factors (e.g., radiation exposure).

- 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.


Fat
Muscle
Lobule
Ribs
Duct
Nipple
Ductal cancer
Lobular cancer
Progression of breast cancer
Benign
Malignant
Normal
Atypical hyperplasia
In situ
Invasive
Metastatic
Duct wall
Normal cells
Abnormal cells
Cancer cells inside duct wall
Cancer cells break through duct wall
Cancer cells travel to other parts of body through blood and lymph vessels

CLINICAL PRESENTATION:

- The initial sign in more than 90% of women with breast cancer is a painless lump that is typically solitary, unilateral, solid, hard, irregular, and nonmobile.

- Less common initial signs are pain and nipple changes. More advanced cases present with prominent skin edema, redness, warmth, and induration.

- Symptoms may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, and mental status changes.

- Many women first detect some breast abnormalities themselves, but it is increasingly common for breast cancer to be detected during routine screening mammography in asymptomatic women.

DIAGNOSIS:

- INITIAL WORKUP FOR A WOMAN PRESENTING WITH A LOCALIZED LESION OR SUGGESTIVE SYMPTOMS SHOULD INCLUDE A CAREFUL HISTORY, PHYSICAL EXAMINATION OF THE BREAST, THREE-DIMENSIONAL MAMMOGRAPHY, AND, POSSIBLY, OTHER BREAST IMAGING TECHNIQUES SUCH AS ULTRASOUND.

- BREAST BIOPSY IS INDICATED FOR A MAMMOGRAPHIC ABNORMALITY THAT SUGGESTS MALIGNANCY OR A MASS THAT IS PALPABLE ON PHYSICAL EXAMINATION.

- Stage is based on the size of the primary tumor (T1–4), presence and extent of lymph node involvement (N1–3), and presence or absence of distant metastases (M0–1).

- Simplistically stated, these stages may be represented as follows:
- ✓ *Early Breast Cancer*
- Stage 0: Carcinoma in situ or disease that has not invaded the basement membrane.
- **Stage I:** Small primary tumor without lymph node involvement.
- **Stage II:** Involvement of regional lymph nodes.
- ✓ *Locally Advanced Breast Cancer*
- **Stage III**: Usually a large tumor with extensive nodal involvement in which node or tumor is fixed to the chest wall; also includes inflammatory breast cancer, which is rapidly progressive.
- ✓ *Advanced or Metastatic Breast Cancer*
- **Stage IV:** Metastases in organs distant from the primary tumor.

- The goal of therapy with early and locally advanced breast cancer is cure.

- The goals of therapy with MBC are to improve symptoms, improve quality of life, and prolong survival.

TREATMENT:

- The treatment of breast cancer is rapidly evolving. Specific information regarding the most promising interventions can be found only in the primary literature.

- Treatment can cause substantial toxicity, which differs depending on the individual agent, administration method, and combination regimen.

EARLY BREAST CANCER

Local-Regional Therapy

- Surgery alone can cure most patients with in situ cancers and approximately one-half of those with stage II cancers.

- Breast-conserving therapy (BCT) is appropriate primary therapy for most women with stage I and II disease; it is preferable to modified radical mastectomy because it produces equivalent survival rates with cosmetically superior results.

- BCT consists of lumpectomy (i.e., excision of the primary tumor and adjacent breast tissue) followed by radiation therapy (RT) to prevent local recurrence.

- RT is administered to the entire breast over 4 to 6 weeks to eradicate residual disease after BCT.

- Simple or total mastectomy involves removal of the entire breast without dissection of underlying muscle or axillary nodes.

- Axillary lymph nodes should be sampled for staging and prognostic information.

- Systemic adjuvant therapy is the administration of systemic therapy following definitive local therapy (surgery, radiation, or both) when there is no evidence of metastatic disease but a high likelihood of disease recurrence.

- Chemotherapy, hormonal therapy, or both result in improved disease-free survival and/or overall survival (OS) for all treated patients.

- 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.

- ✓ Anthracycline-containing regimens (e.g., doxorubicin and epirubicin) significantly reduce the rate of recurrence and improve OS 5 and 10 years after treatment as compared with regimens that contain cyclophosphamide, methotrexate, and fluorouracil.

- ✓ The addition of taxanes, docetaxel and paclitaxel, a class of agents, to adjuvant regimens comprised of the drugs listed above resulted in consistently and significantly improved disease-free survival and OS in node-positive breast cancer patients.

- ✓ Chemotherapy should be initiated within 3 weeks of surgical removal of the primary tumor. The optimal duration of treatment is about 12 to 24 weeks.

- Trastuzumab in combination with adjuvant chemotherapy is indicated in patients with early stage, HER2-positive breast cancer.

- The risk of recurrence was reduced up to 50% in clinical trials.

- Tamoxifen has been the gold standard for adjuvant endocrine therapy. It has both estrogenic and antiestrogenic properties, depending on the tissue and gene in question.

- Tamoxifen 20 mg daily, beginning soon after completing chemotherapy and continuing for 5 years, reduces the risk of recurrence and mortality.

LOCALLY ADVANCED BREAST CANCER (STAGE III):

- Neoadjuvant or primary chemotherapy is the initial treatment of choice.
- Benefits include rendering inoperable tumors resectable and increasing the rate of BCT.
- Primary chemotherapy with either an anthracycline- or taxane-containing regimen is recommended. The use of trastuzumab with chemotherapy is appropriate for patients with HER2-positive tumors.
- Surgery followed by chemotherapy and adjuvant RT should be administered to minimize local recurrence.
- Cure is the primary goal of therapy for most patients with Stage III disease.

METASTATIC BREAST CANCER (STAGE IV):

- Endocrine therapy is the treatment of choice for patients who have hormone receptor-positive metastases in soft tissue, bone, pleura, or, if asymptomatic, viscera.

- Compared with chemotherapy, endocrine therapy has an equal probability of response and a better safety profile.

- **Aromatase inhibitors** reduce circulating and target organ estrogens by blocking peripheral conversion from an androgenic precursor, the primary source of estrogens in postmenopausal women.

- Newer agents are more selective and better tolerated than the prototype, aminoglutethimide.

- Anastrozole, letrozole, and exemestane are approved as second-line therapy; anastrozole and exemestane have been shown to improve OS and time to progression compared with progestins.

- As first-line therapy, anastrozole and letrozole increase time to progression and are better tolerated compared with tamoxifen.

- Ovarian ablation (oophorectomy) is considered by some to be the endocrine therapy of choice in premenopausal women and produces similar overall response rates as tamoxifen.

- Medical castration with an LHRH analog, goserelin, leuprolide, or triptorelin, is a reversible alternative to surgery.

Endocrine Therapies Used for Metastatic Breast Cancer

Class	Drug	Dose	Side Effects
Aromatase inhibitors			
Nonsteroidal	Anastrozole	1 mg orally daily	Hot flashes, arthralgias, myalgias, headaches, diarrhea, mild nausea
	Letrozole	2.5 mg orally daily	
Steroidal	Exemestane	25 mg orally daily	
Antiestrogens			
SERMs	Tamoxifen	20 mg orally daily	Hot flashes, vaginal discharge, mild nausea, thromboembolism, endometrial cancer
	Toremifene	60 mg orally daily	
SERDs	Fulvestrant	250 mg IM every 28 days	Hot flashes, injection site reactions, possibly thromboembolism
LHRH analogs	Goserelin	3.6 mg SC every 28 days	Hot flashes, amenorrhea, menopausal symptoms, injection site reactions (extended formulations are not recommended for the treatment of breast cancer)
	Leuprolide	3.75 mg IM every 28 days	
	Triptorelin	3.75 mg IM every 28 days	
Progestins	Megestrol acetate	40 mg orally four times a day	Weight gain, hot flashes, vaginal bleeding, edema, thromboembolism
	Medroxyprogesterone	400–1,000 mg IM every week	
Androgens	Fluoxymesterone	10 mg orally twice a day	Deepening voice, alopecia, hirsutism, facial/truncal acne, fluid retention, menstrual irregularities, cholestatic jaundice
Estrogens	Diethylstilbestrol	5 mg orally three times a day	Nausea/vomiting, fluid retention, anorexia, thromboembolism, hepatic dysfunction
	Ethinyl estradiol	1 mg orally three times a day	
	Conjugated estrogens	2.5 mg orally three times a day	

- Chemotherapy is preferred to endocrine therapy for women with hormone receptor-negative tumors; rapidly progressive lung, liver, or bone marrow involvement; or failure of endocrine therapy.

- The choice of treatment depends on the individual. Agents used previously as adjuvant therapy can be repeated unless the cancer recurred within 1 year.

- Single agents are associated with lower response rates than combination therapy, but time to progression and OS are similar.

- Single agents are better tolerated, an important consideration in the palliative metastatic setting.

- ANTHRACYCLINES AND TAXANES PRODUCE RESPONSE RATES OF 50% TO 60% WHEN USED AS FIRST-LINE THERAPY FOR MBC.

- SINGLE AGENT CAPECITABINE, VINORELBINE, OR GEMCITABINE HAVE RESPONSE RATES OF 20% TO 25% WHEN USED AFTER AN ANTHRACYCLINE AND A TAXANE.

- TRASTUZUMAB, A MONOCLONAL ANTIBODY THAT BINDS TO HER2, PRODUCES RESPONSE RATES OF 15% TO 20% WHEN USED AS A SINGLE AGENT AND INCREASES RESPONSE RATES, TIME TO PROGRESSION, AND OS WHEN COMBINED WITH CHEMOTHERAPY.

- IT HAS BEEN STUDIED IN DOUBLET (TAXANE-TRASTUZUMAB; VINORELBINETRASTUZUMAB) AND TRIPLET (TRASTUZUMAB-TAXANE-PLATINUM) COMBINATIONS BUT THE OPTIMUM REGIMEN IS UNKNOWN.

- TRASTUZUMAB IS WELL TOLERATED, BUT THE RISK OF CARDIOTOXICITY IS 5% WITH SINGLE-AGENT TRASTUZUMAB AND UNACCEPTABLY HIGH IN COMBINATION WITH AN ANTHRACYCLINE.

- ✓ **Lapatinib**, a tyrosine kinase inhibitor that targets both HER2 and the epidermal growth factor receptor, improved response rates and time to progression in combination with capecitabine, as compared to capecitabine alone, in patients previously treated with an anthracycline, taxane, and trastuzumab.

- ✓ The most common adverse events were rash and diarrhea.

- ✓ The role of bevacizumab, a monoclonal antibody targeted against vascular endothelial growth factor, in MBC is currently not clearly defined.