Breast cancer

Epidemiology

The most frequent cancer in women

- Second leading cause of cancer deaths among all US women (after lung cancer)
- Leading cause of cancer deaths among women ages 20 to 59

Risk Factors for Breast Cancer

- Genetic
- Hormonal
- Environmental
- Dietary

Genetic Risk Factors for Breast Cancer

Ashkenazi Jewish 1:40, compared with 1:500 in the general population

- BRCA1 or BRCA 2 mutation increases risk of breast cancer by 6.0-14.0 fold
- BRCA 1 and BRCA 2 are tumor suppressor genes that play a role in cellular DNA repair
- Approximately 10% of breast cancer is familial and related to BRCA1 or BRCA2

BRCA1 and BRCA2

- Associated cancers tend to be more aggressive, of a higher grade, and hormone receptor negative
- Confer 50 to 87% lifetime risk of breast cancer
- Also increase risk of ovarian cancer
- Genetic testing is available for women with appropriate family history

+ prostate and pancreatic

Genetic Risk Factors

- Li-Fraumeni Syndrome, abnormal TP53 gene on chromosome 17p, associated with premenopausal breast cancer, childhood sarcomas, brain tumors, leukemia, and adrenocortical adenomas

Genetic Risk Factors

- Cowden's Syndrome, abnormal PTEN tumor suppressor gene on chromosome 10 associated with premenopausal breast cancers, gastrointestinal malignancies, and benign and malignant thyroid disease

Cowden's syndrome

- Hamartomas on the skin and mucous membranes.
- Enlarged head, a rare noncancerous brain tumor called **Lhermitte–Duclos disease**

Genetic Risk Factors

- Peutz-Jegher's Syndrome, abnormal STK11 tumor suppressor gene on chromosome 19, associated with cancers of the stomach, colon, pancreas, small intestine, thyroid, breast, lung, and uterus

Hormonal Factors

- Menarche < age 12 increases risk
- Menopause > age 55 increases risk
- 1st child after age 30 or nulliparous
- Greater than 5 years on oral contraceptives
- Prolonged combined estrogen-progesterone replacement therapy

Benign Breast Disease

- Atypical Hyperplasia
- Hyperplasia
- Breast Biopsy

Environmental Factors

- Exposure to ionizing radiation

Irradiation for the treatment of Hodgkin lymphoma before age 30 years.

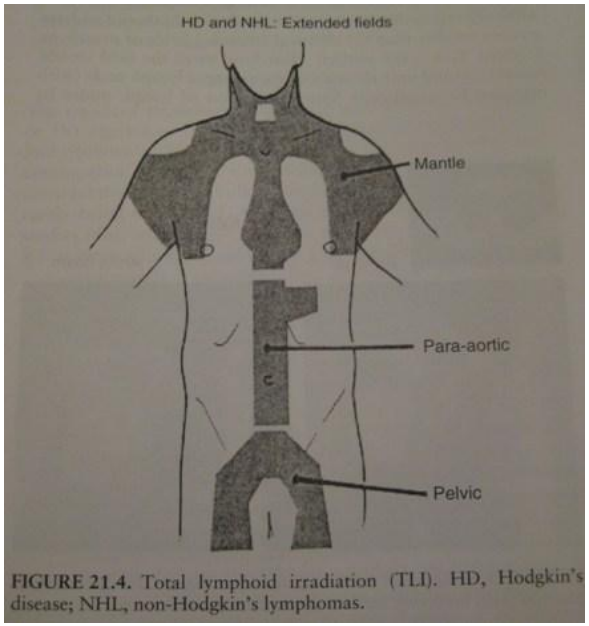


FIGURE 21.4. Total lymphoid irradiation (TLI). HD, Hodgkin's disease; NHL, non-Hodgkin's lymphomas.

Dietary Factors

- Alcohol consumption, greater than 1 drink/day
- Obesity, especial postmenopausal

Magnitude of Risk of Known Breast Cancer Risk Factors

Relative Risk <2	Relative Risk 2–4	Relative Risk >4
Early menarche	One first-degree relative with breast cancer	Mutation *BRCA1* or *BRCA2*
Late menopause		LCIS
Nulliparity	*CHEK2* mutation	Atypical hyperplasia
Estrogen plus progesterone	Age >35 y for first birth	Radiation exposure before 30
HRT	Proliferative breast disease	
Alcohol use	Mammographic breast density	
Postmenopausal obesity		

Prevention

- Tamoxifen for high risk women
- For consideration:

Early childbearing

Prolonged lactation

Weight reduction

Regular exercise, especially during adolescence

Prophylactic mastectomy + **PBSO**

Prevention for BRCA patients

- Tam ↓contralater - 40-50%,
- ↓ Risk BC in unaffected only in BRCA 2 (started from age 35)
- PBSO -↓OC up to 90-%.
  ↓ BC -50% (before age 50)
- BME ↓ BC 90%

Chemoprevention with Tamoxifen

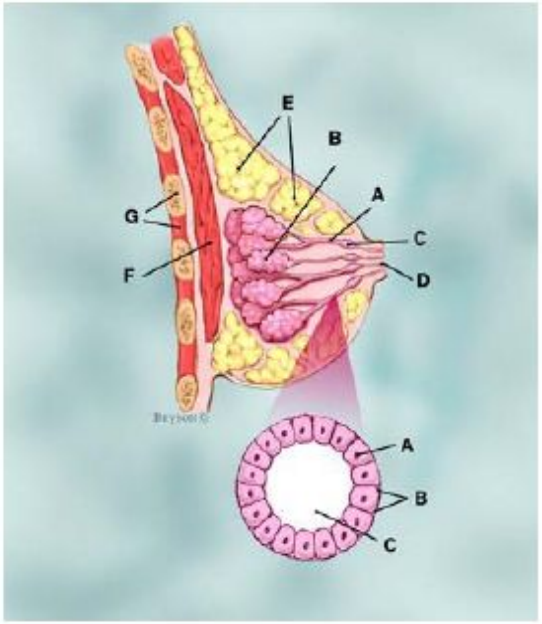
+	-
• RR 50% (0.51) (47 treated - 1 BC prevented) • ADH - RR 84% • LCIS – RR 40%	• PE (>50y) • Flashes • Endometrial Ca (mostly >50y)

- ↓ 30% bone fractures

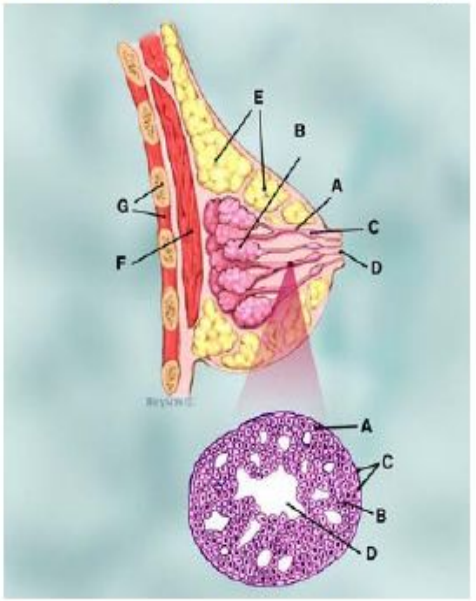
Diagnosis and Treatment

- Patient feels a breast mass or has an abnormal radiologic screening exam
- Surgical biopsy or aspiration
- Observation (LCIS), lumpectomy or mastectomy
- Staging
- Delivery of adjuvant therapies—radiation and/or chemotherapy, hormonal therapies

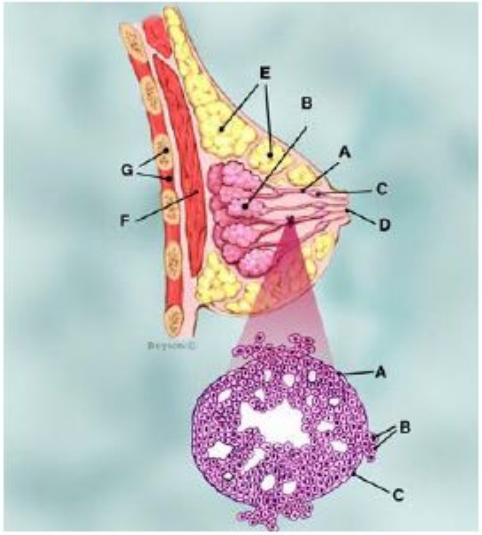
Normal Breast



DCIS (Ductal Carcinoma in Situ)



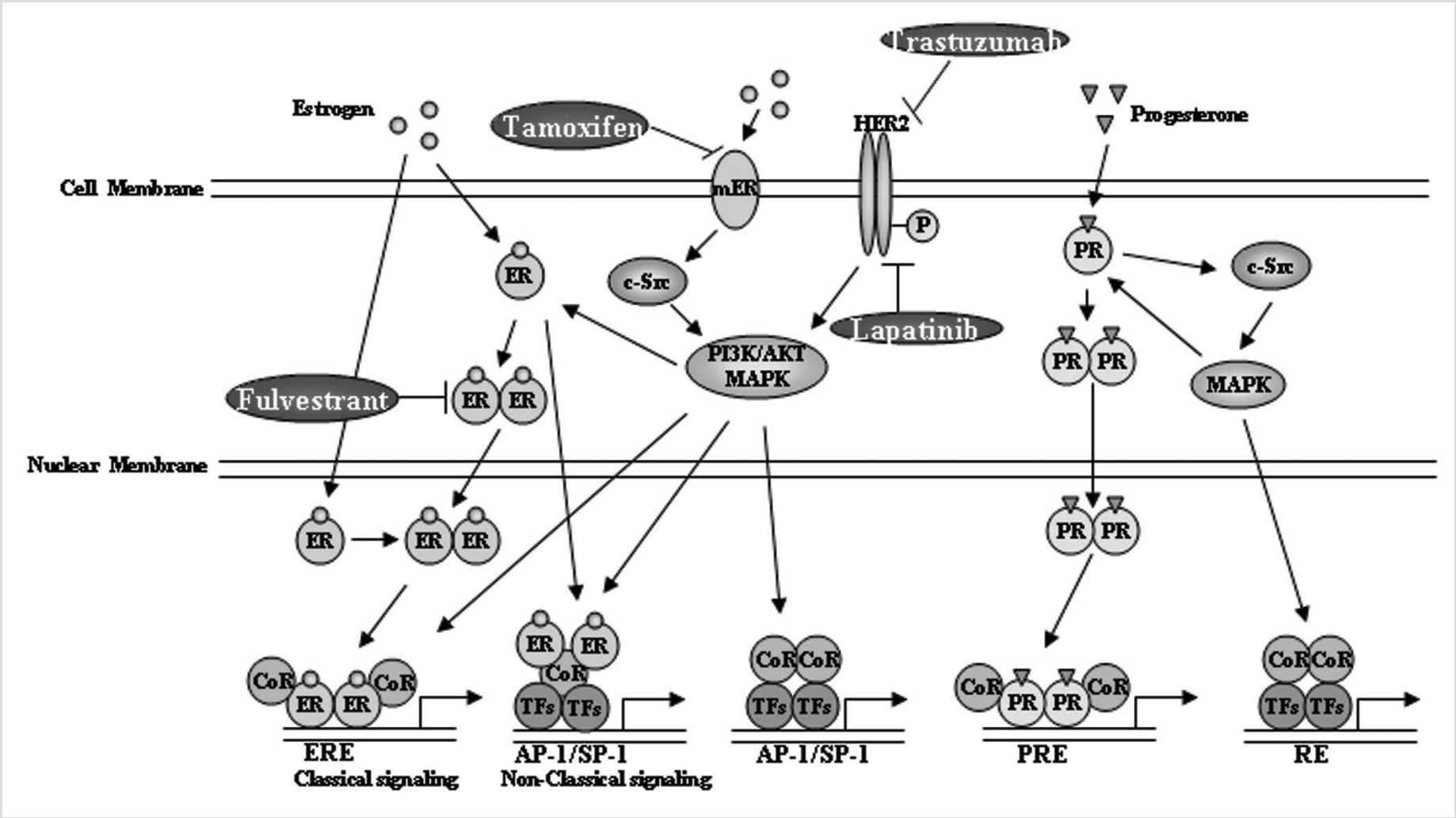
Invasive Cancer



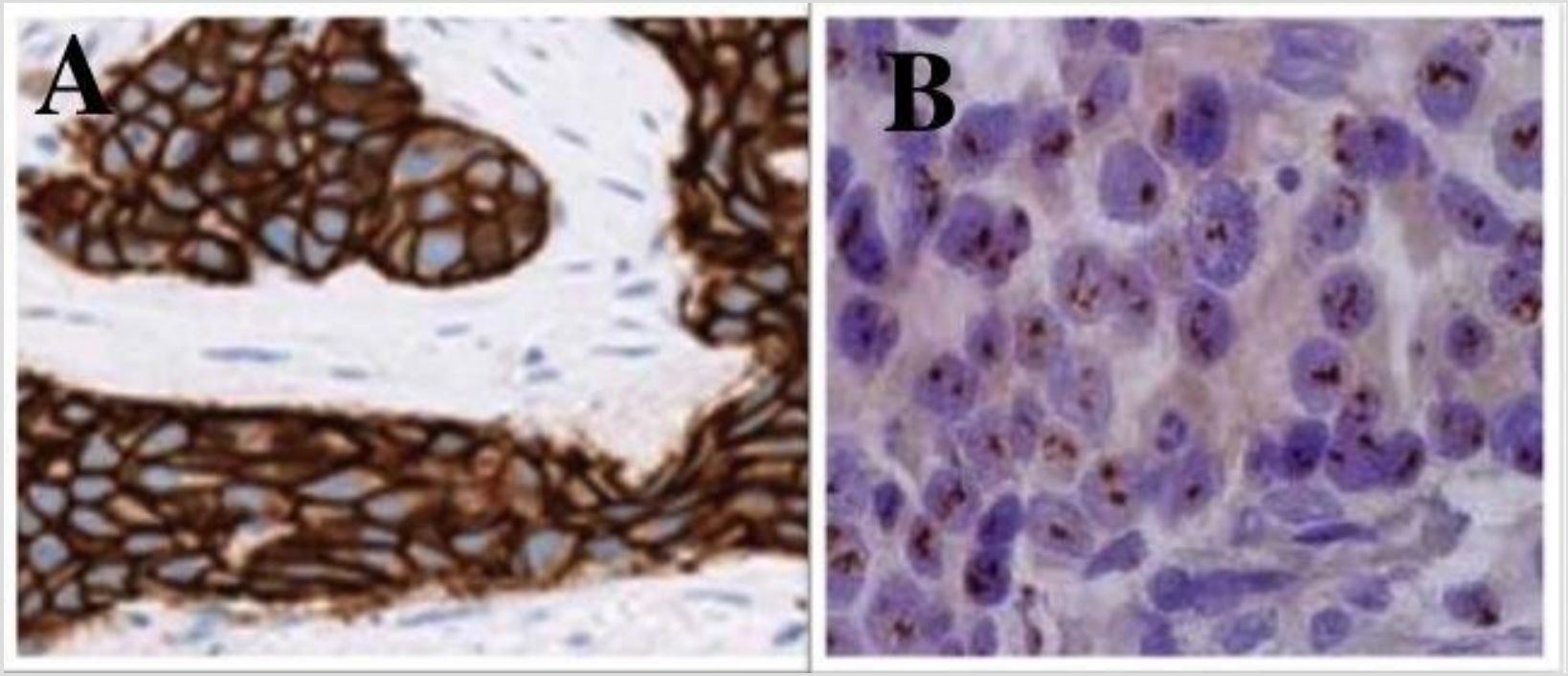
Pathology Report

- Invasive vs. Non-invasive
- Histologic Type- Ductal (85%) vs. Lobular
- Grade (estimate of the agressiveness under microscope)
- Size
- Margins
- Lymph Nodes
- Estrogen/ Progesterone Receptor (2/3 positive)
- Her-2/ neu

BC Receptors



BC Receptors

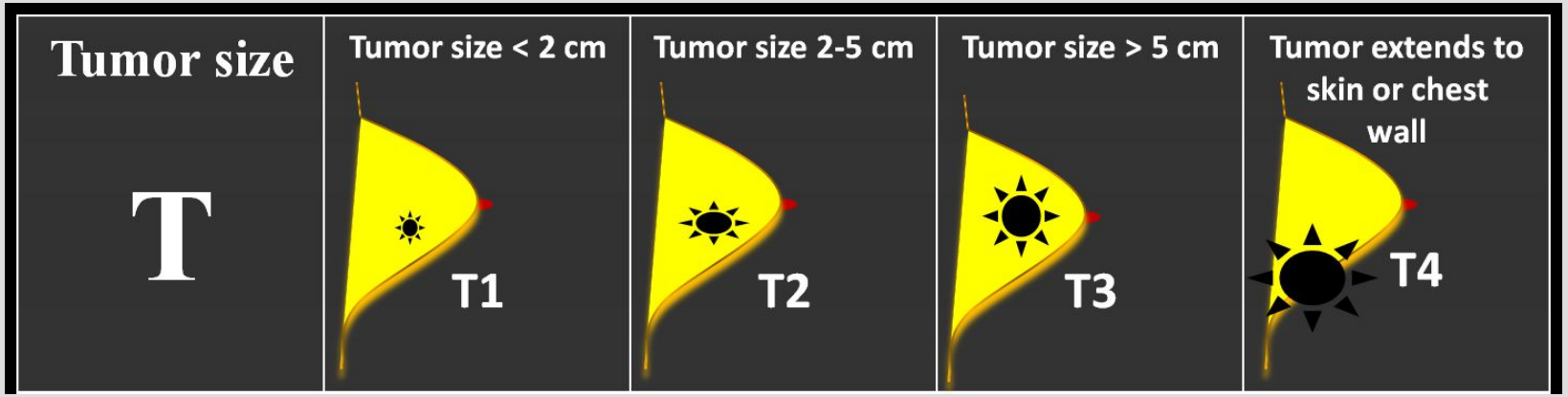


Biological subtypes

Subtype1	Characteristics1	Prognosis2,3,4
Luminal A	ER+ and/or PR+ HER2- Low Ki67	Better prognosis High survival Lower recurrence
Luminal B	ER+ and/or PR+ HER2+ **or** HER2- with high Ki67	Poorer prognosis than Luminal A High survival
HER2	ER- and PR- HER2+	Poor prognosis Early and frequent recurrence
Basal-like*	Triple negative ER- and PR- HER2-	Poor prognosis Aggressive

Staging

Stage	Primary Tumor	Nodes	Metastases
Stage 1A	≤ 20 mm	None	None
Stage 1B	≤ 20 mm	Nodal Micrometastases (>0.2 mm <2.0 mm)	None
Stage IIA	≤ 20 mm > 20 mm ≤ 50 mm	N1 None	None None
Stage IIB	> 20 mm ≤ 50 mm > 50 mm	N1 None	None
Stage IIIA	≤ 50 mm > 50 mm	N2 N1 or N2	None
Stage IIIB	Extension to chest wall and/or skin	N0 - N2	None
Stage IIIC	Any size	N3	None
Stage IV	Any size	Any involvement	Detectable



DS

- Mammography
- US

- MRI

- CT (chest/abdomen)
- Bone scan or PET CT
- CT/MRI head
- Tumor markers

Treatment of breast cancer

- Systemic therapy:
  - Hormonal therapy
  - Chemotherapy
  - Targeted therapies

- Local therapy:
  - Surgery
  - Radiation therapy

Surgery

- In the patient with clinical stage I, II, and T3N1 disease, the initial management is usually surgical.
- **BCT : Lumpectomy + RT ＝ Mastectomy**

Contraindications for BCT:

- Previous RT
- Pregnancy
- Widespread disease
- Pos margins
- Tumors >5 cm, small breast

Axilla

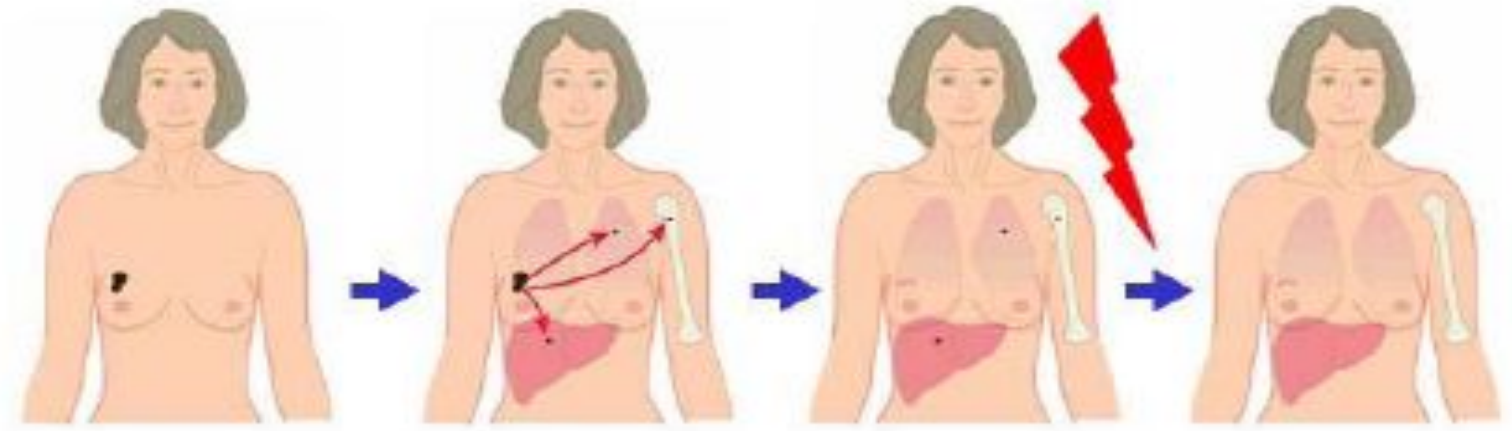
- ALND
- SLNB (less lymphedema)

- Majority of stage I-II BC pts
- Contraindications to the procedure: pregnancy, lactation, and locally advanced breast cancer.

What now?

- Stage 0-III
  - Risk of recurrence is individual
  - What can we do to reduce the risk of recurrence in the breast, and systemically ?
  - Meet with Radiation Oncologist and Medical Oncologist

Principle of Adjuvant Treatment

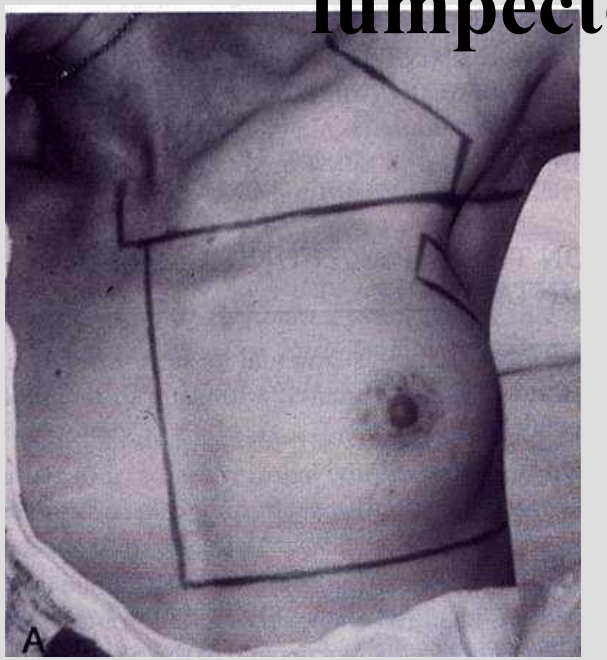


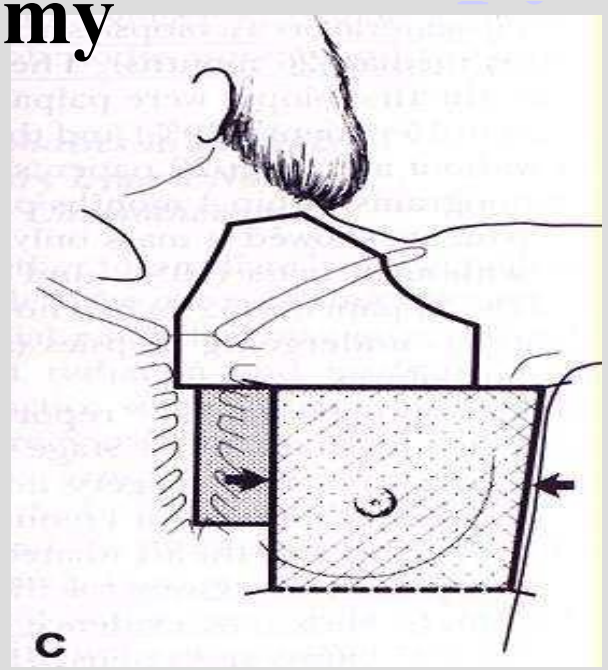
Adjuvant Therapy

- Radiation Therapy (local)
- Chemotherapy (systemic)
- Hormonal agents (systemic)

- Each therapy adds to reduction of recurrent disease.
- Therapy is individualized, discussion with health care provider.

Adjuvant radiation therapy – for everyone after lumpectomy





- *5* - 6.5 weeks
- Local control rates > 90%
- Minimal toxicity

Postmastectomy RT

All women with > 3 positive nodes.

All women with any positive node and a tumor larger than 5 cm.

Women with recurrent positive margins

? Women with T3N0

? Women with 1-3 positive nodes and T1/T2.

Chemotherapy Drugs

- Adriamycin, Epirubicin
- Cytoxan
- Methotrexate, 5-fluorouracil
- Taxol, Taxotere

- Intravenous
- Nausea, hair loss, low blood counts, cardiac toxicity, bladder toxicity, nerve damage

Hormonal agents

- Tamoxifen
- Can be given to pre or post menopausal women
- Works by blocking estrogen receptors in breast cells, inhibiting their growth
- Side effects include hot flashes, depression, increased risk of uterine cancer and blood clots
- Taken daily by mouth for 5 years

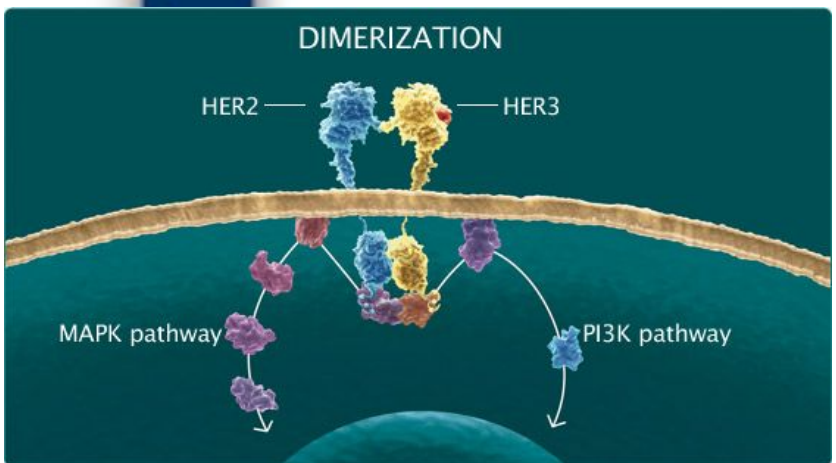
Aromatase Inhibitors

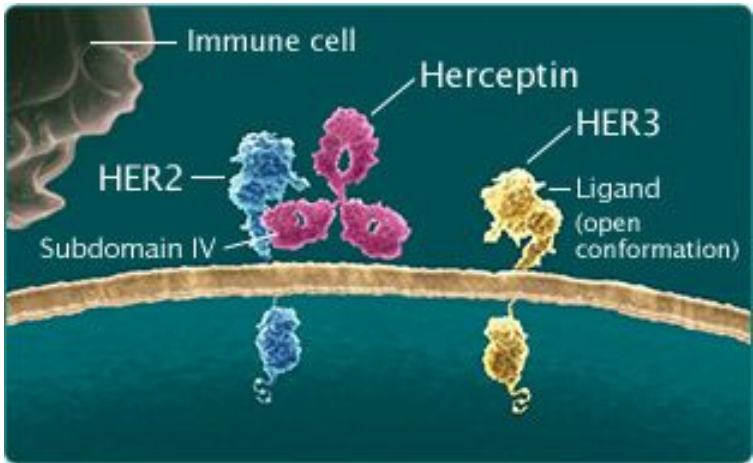
- Aromatase is the enzyme that converts androgens to estrogen
- AI s are only given to postmenopausal women
- "May" be more effective than Tamoxifen
- Examples: Anastrozole/Arimidex, Letrozole/Femara, Exemestane/Aromasin
- Side effects include hot flashes, depression, osteoporosis, joint pains
- Taken daily by mouth for variable periods of time

Monoclonal antibodies

For 1 year every 3 weeks

- Trastuzumab/Herceptin
- Given to patients whose cancer cells overexpress Her-2-neu as measured by IHC or FISH (25 to 30% of patients)





Neoadjuvant chemotherapy

Indications

- T4
- cN pos
- Inflamatory BC

Rationale

- Tumor shrinkage
- Opportunity for BCS
- Early treating of micrometastasis
- Aggressive biological subtypes ---- high rate of PCR (associated with better prognosis)

What now?

- Stage IV (spread outside the breast and regional lymph nodes)
  - Common locations of metastatic disease (bone, liver, lung)
  - Meet with Medical Oncologist and perhaps a Radiation Oncologist
  - Considered treatable, but not curable
  - Treatment options- Hormonal, Herceptin, Chemotherapy, Radiation Therapy

Therapeutic Endpoints

- **Overall Survival**
- **Quality of Life**
- Response Rate
- Time to Progression
- Time to Treatment Failure
- Safety Profile

First-line Therapy Options

- No single "Gold Standard" for chemotherapy in metastatic breast cancer
- Therapy should be individualized based on goals
  - Palliation vs Cure
- Options
  - Sequential single-agents
  - Combination therapy

First-line Therapy Options

Pre-1990

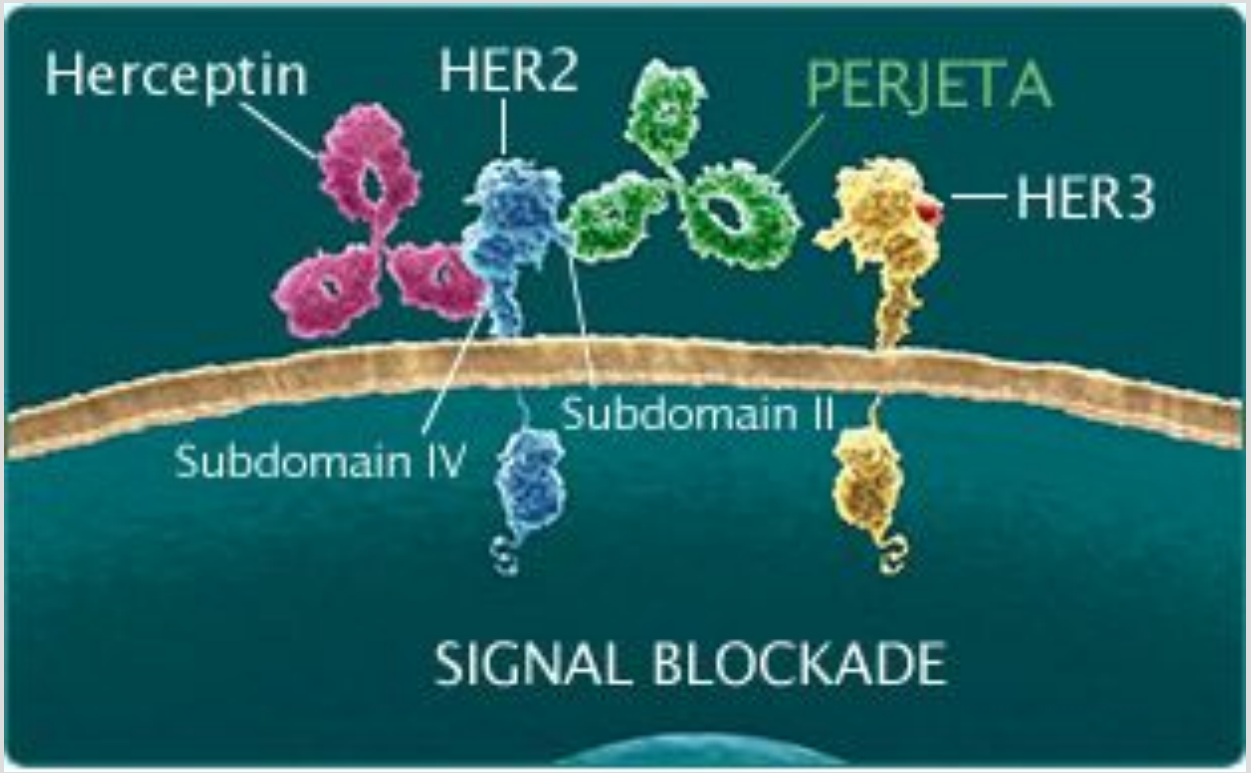
- FAC (CAF, FEC)
- AC (EC)
- CMF
- NFL

Current

- Single-agent taxane, vinorelbine, capecitabine
- FAC (CAF, FEC)
- Anthracycline/Taxane
- A/T/cyclophosphamide
- A/T/gemcitabine
- Anthracycline/ vinorelbine
- Taxane/fluorouracil
- Taxane/platin

Herceptin +/- Pergeta (Trastuzumab+/- Pertuzumab) & CMT

- Her 2 pos BC



Lapatinib

- Her 2 pos BC
- A tyrosine kinase inhibitor
- A potent and selective oral dual inhibitor of ErbB1 (EGFR) and ErbB2 (HER2)
- Approved by FDA March 13, 2007

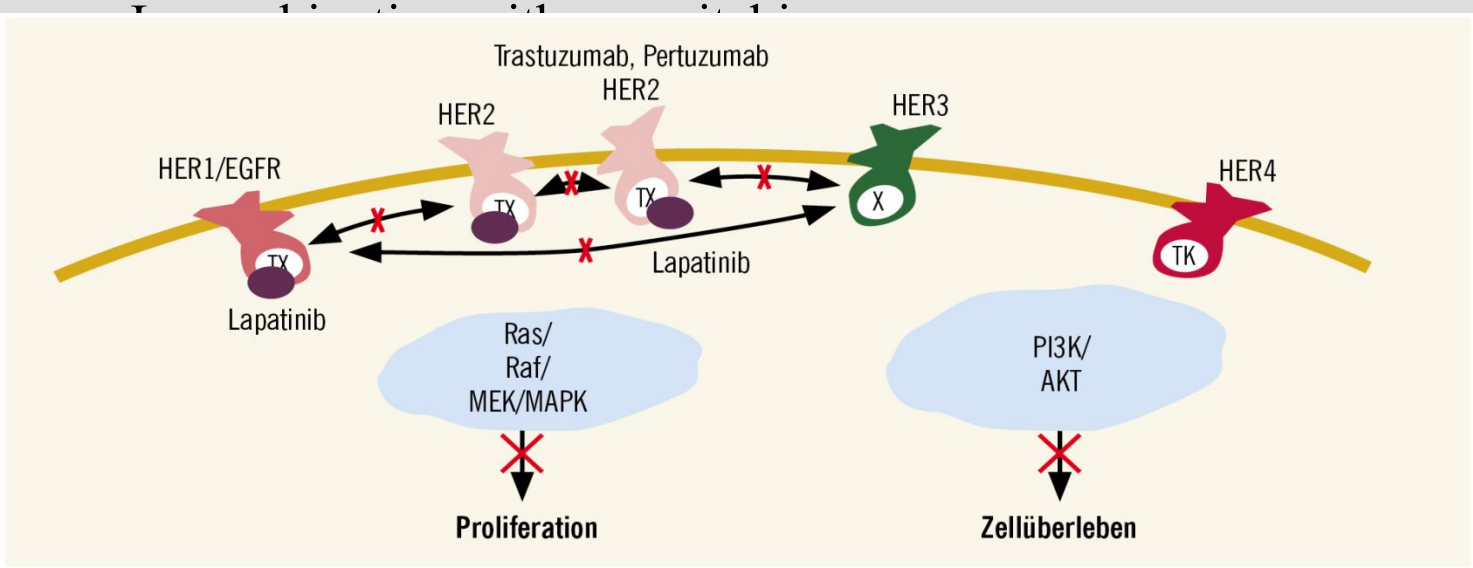
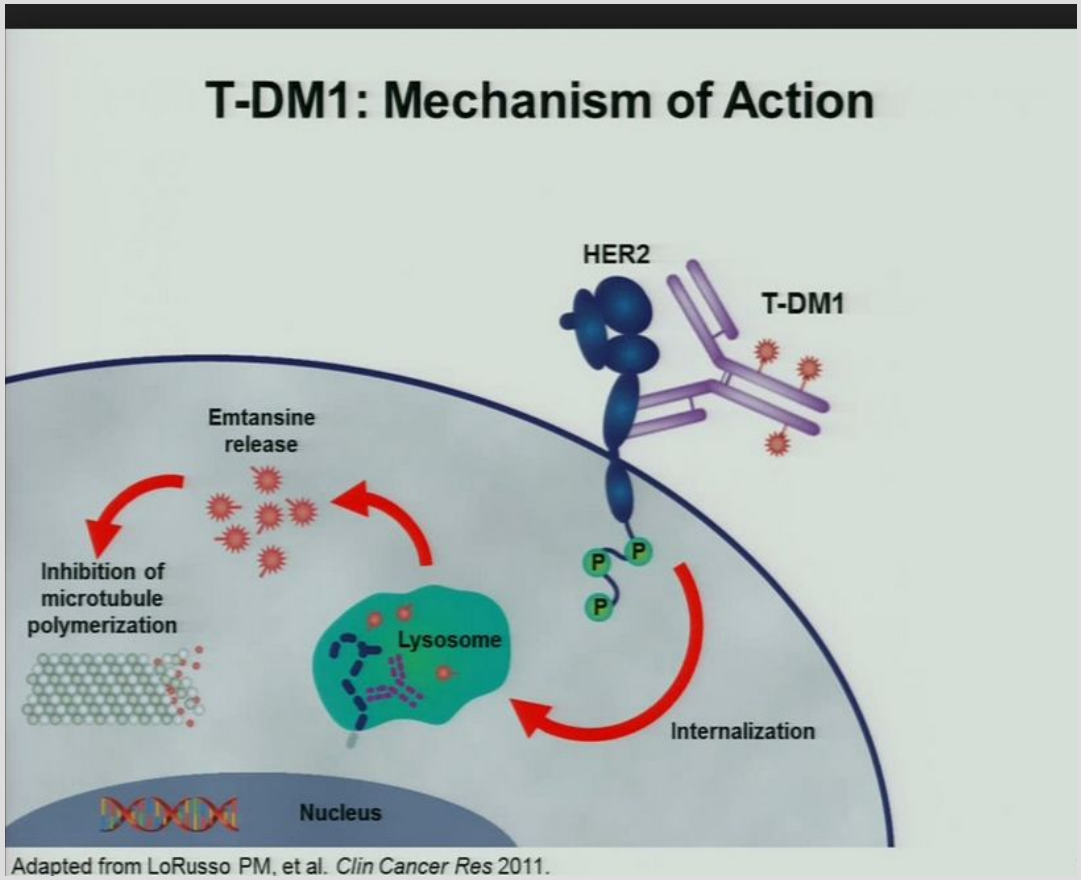


Abb. 3: Mit Lapatinib die Resistenz gegen Anti-HER2-Therapien überwinden

Trastuzumab emtansine (TDM1= KADCYLA)

- Her 2 pos BC



Inflammatory BC

- T4
- 1% to 5% of all cases
- Aggressive
- Neoadjuvant CMT +/- RT
- Surgery is contraindicated in IBC unless there is complete resolution of the inflammatory skin changes.

Paget disease

- 1 to 4.3% of all breast cancers
- Ca in situ in the nipple epidermis
- Paget cells (large cells with clear cytoplasm and atypical nuclei) within the epidermis of the nipple.

(1) associated with invasive cancer (staged by the invasive cancer)

(2) with underlying DCIS (Tis)

(3) alone (Tis).

Thank you.