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.

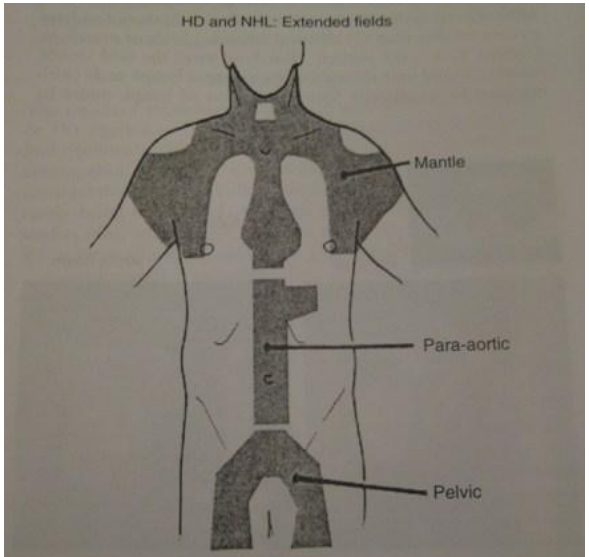


FIGURE 21.4. Total lymphoid irradiation (TLI). HD, Hodgkin's disease; NHL, non-Hodgkin's lymphomas.

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

- Tamoxifen ↓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)
- Bilateral mastectomy ↓ BC 90%

Chemoprevention with Tamoxifen

+

- RR 50% (0.51) (47 treated - 1 BC prevented)
- ADH - RR 84%
- LCIS – RR 40%

- ↓ 30% bone fructures

-

- PE (>50y)
- Flashes
- Endometrial Ca (mostly >50y)

Screening Mammography

- Recommendations
  - Biannually or annually in 40-49 y/o
  - Annually in >50 y/o
- 15% relative risk reduction
- Birads
  - 0 - Incomplete assessment; need additional imaging evaluation
  - 1 - Negative; routine mammogram in 1 year recommended
  - 2 - Benign finding; routine mammogram in 1 year recommended
  - 3 - Probably benign finding; short-term follow-up suggested (3%)
  - 4 - Suspicious abnormality; biopsy should be considered (30%)
  - 5 - Highly suggestive of malignancy; appropriate action should be taken (94%)

Biopsy techniques

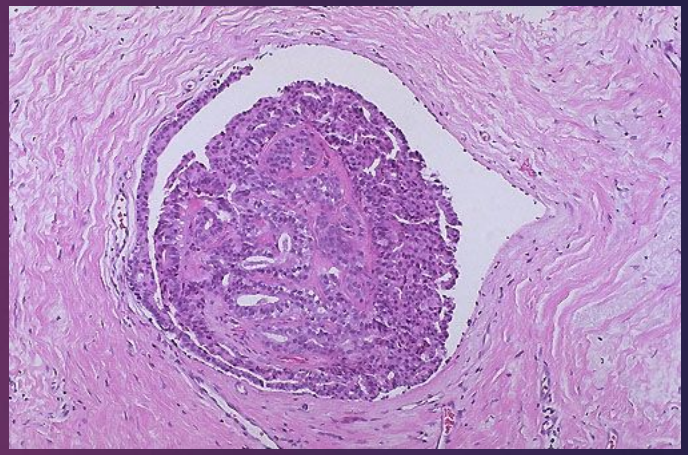
- FNA
  - Diagnostic and therapeutic in cystic lesions
- Core needle
  - U/S guided or sterotatic
  - 90% effective in establishing diagnosis
  - Atypia – need excision
- Sterotatic
- Needle localization
- Excision biopsy

Risk of Future Invasive Breast Carcinoma Based on Histologic Diagnosis from Breast Biopsies

- *No Increase*
  - Adenosis
    Apocrine metaplasia
    Cysts, small or large
    Mild hyperplasia (>2 but <5 cells deep)
    Duct ectasia
    Fibroadenoma
    Fibrosis
    Mastitis, inflammatory
    Periductal mastitis
    Squamous metaplasia
- *Slightly Increased (relative risk, 1.5–2)*
  - Moderate or florid hyperplasia, solid or papillary
    Duct papilloma with fibrovascular core
    Sclerosing adenosis, well-developed
- *Moderately Increased (relative risk, 4–5)*
  - Atypical hyperplasia, ductal or lobular

Benign Breast Masses

- Cysts
- Fibroadenoma
- Hamartoma/Adenoma
- Abscess
- Papillomas
- Sclerosing adenosis
- Radial scar
- Fat necrosis

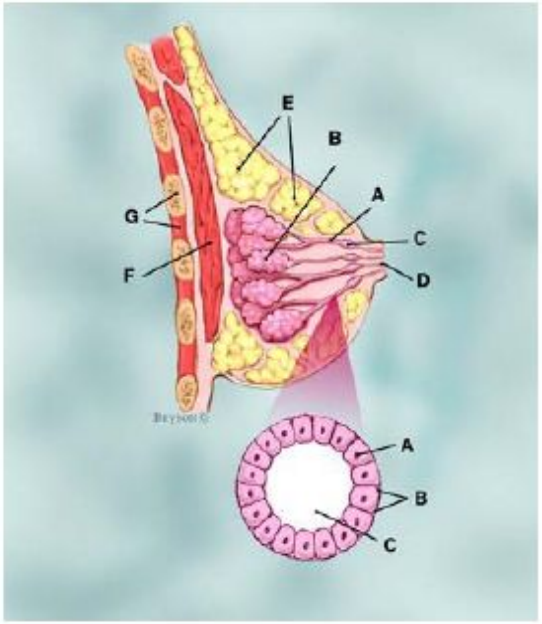


Papilloma

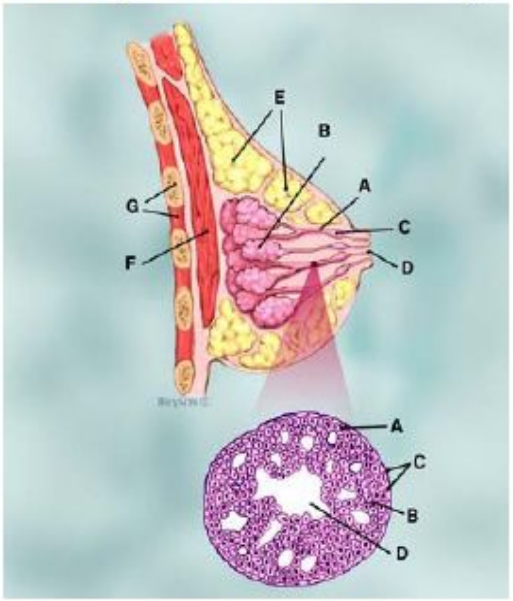
Maligant Breast Masses

- Ductal carcinoma
  - DCIS
  - Invasive
- Lobular carcinoma
  - LCIS
  - Invasive
- Inflammatory carcinoma
- Paget's disease
- Phyllodes tumor
- Angiosarcoma

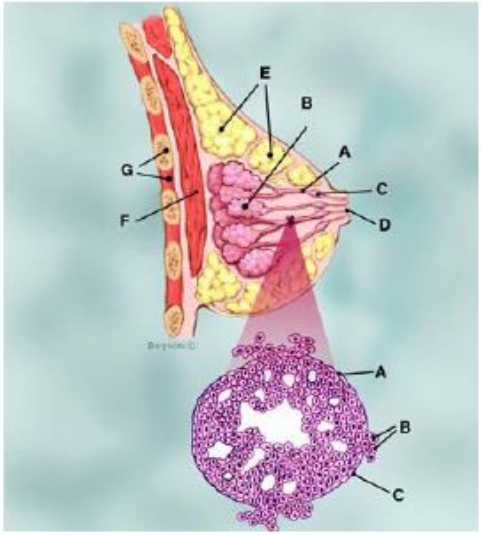
Normal Breast



DCIS (Ductal Carcinoma in Situ)



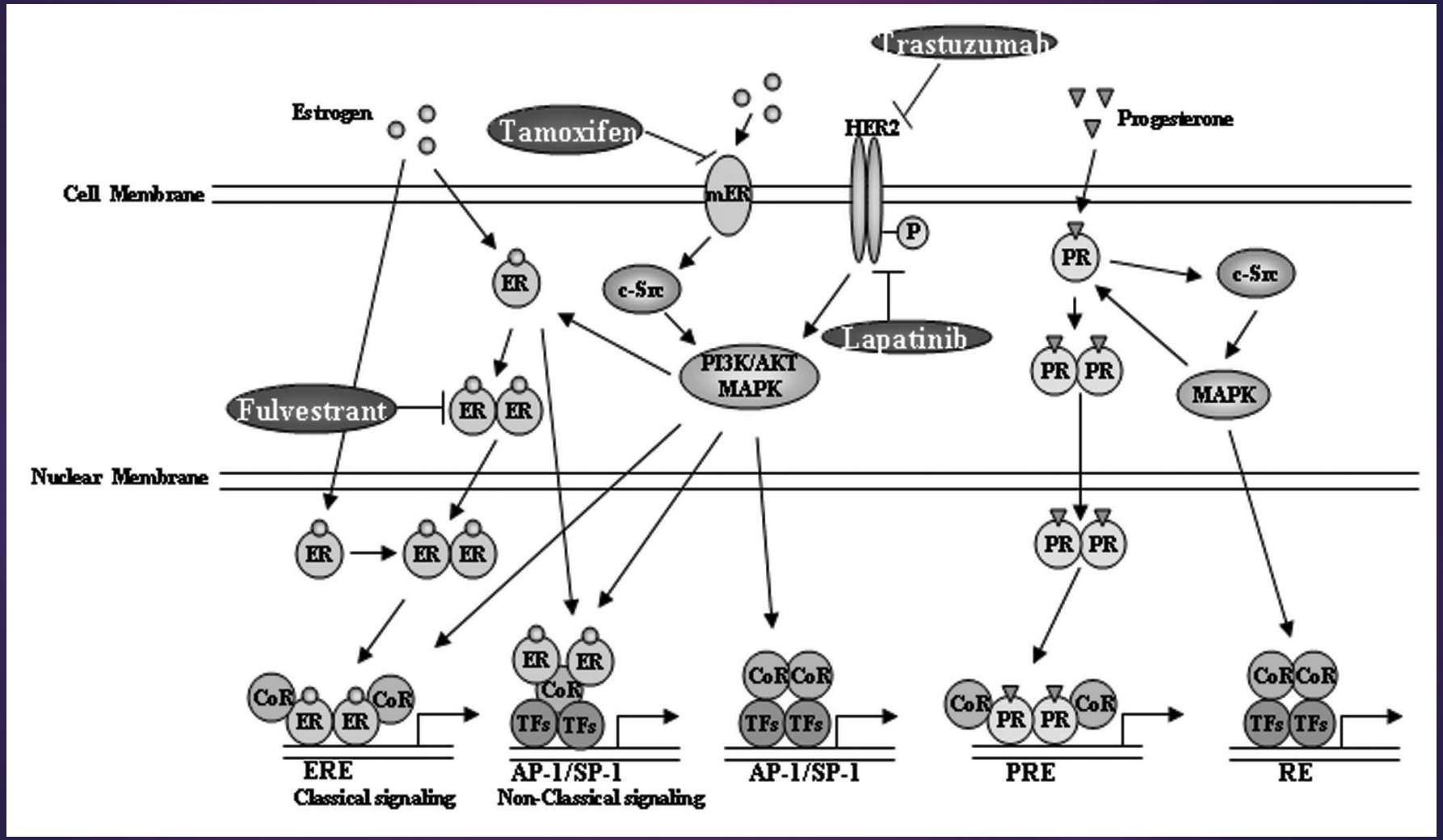
Invasive Cancer



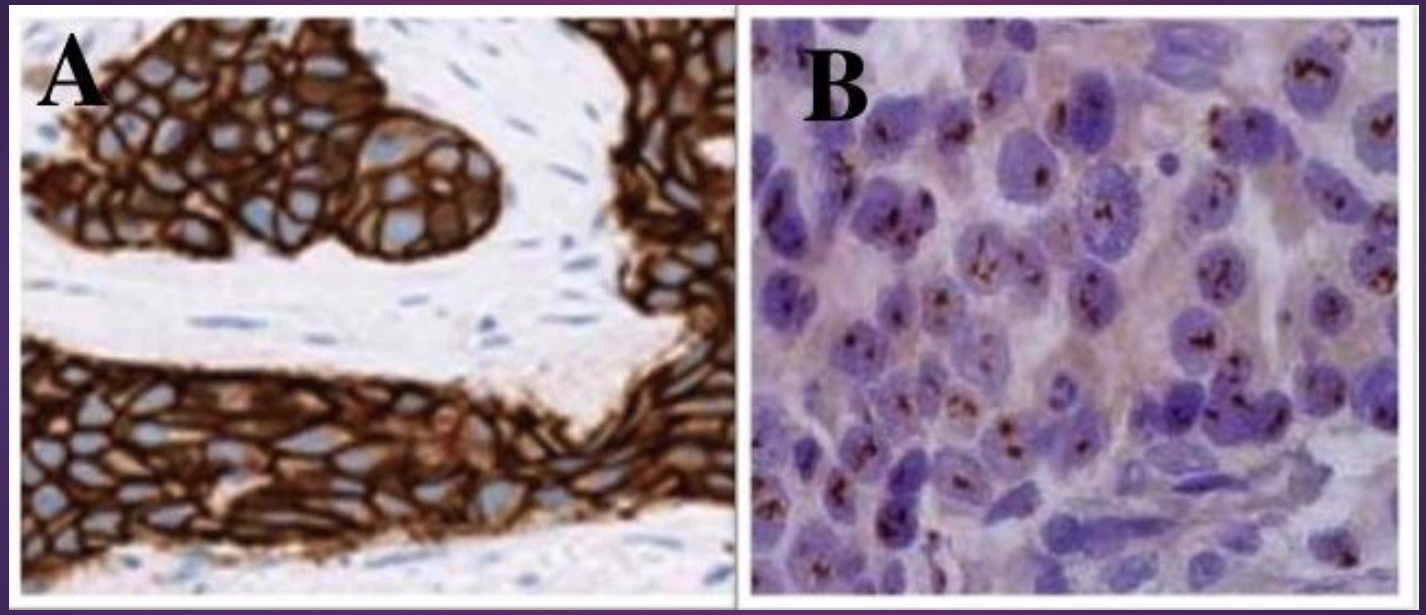
Pathology Report

- 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



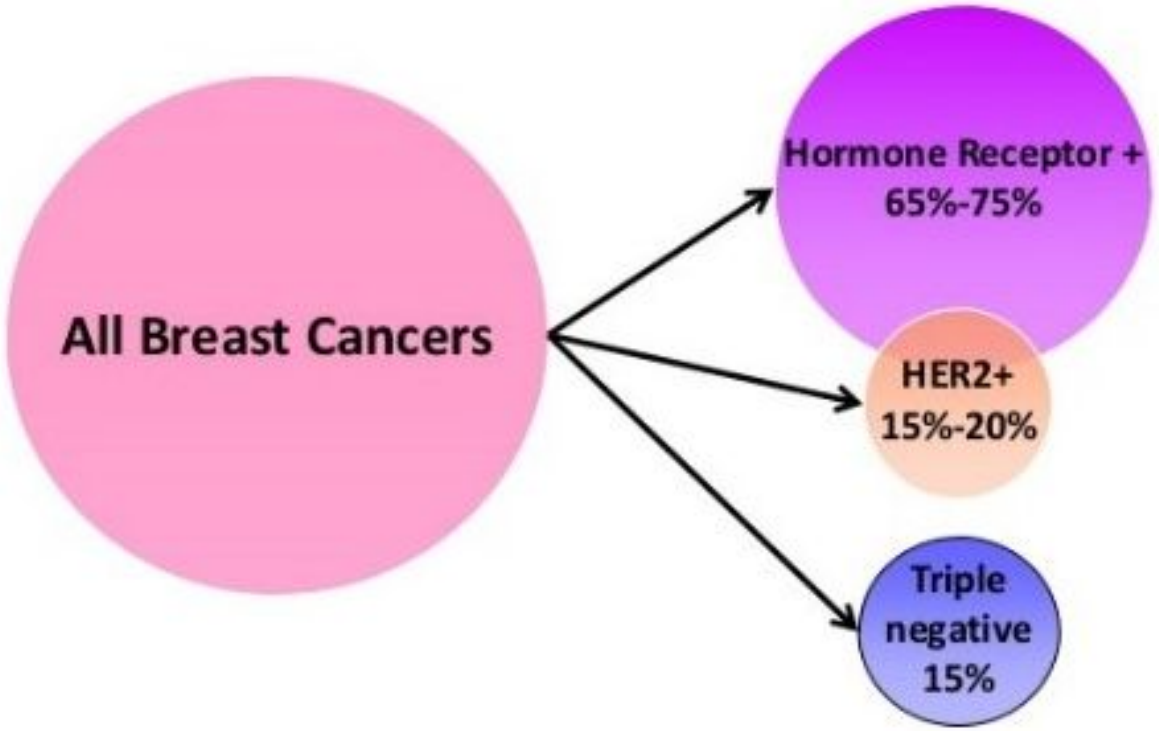
BC Receptors



Biological subtypes

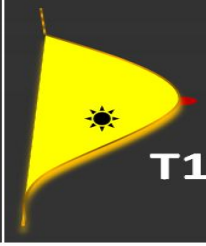
Subtype1	Characteristics1	Prognosis2,3,4
Luminal A	ER+ and/or PR+ HER2- Low Ki67	Better prognosis High survival Lower recurrence
Luminal B	ER+ and/or PR+ HER2+ **or** HER2- with high Ki67	Poorer prognosis than Luminal A High survival
HER2	ER- and PR- HER2+	Poor prognosis Early and frequent recurrence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

Clinical Breast Cancer Subsets



Burstein, Goldhirsch. St Gallen 2007.

STAGING

Tumor size **T**	Tumor size < 2 cm  	Tumor size 2-5 cm  	Tumor size > 5 cm  	Tumor extends to skin or chest wall 
Lymph Nodes **N**	**N0** No lymph node metastasis	**N1** Metastasis to ipsilateral, movable, axillary LNs	**N2** Metastasis to ipsilateral fixed axillary, or IM LNs	**N3** Metastasis to infraclavicular/ supraclavicular LN, or to axillary and IM LNs
Metastasis **M**	**M0** No distant metastasis	**M1** Distant metastasis	أحسن اونكولوجيست www.TheBestOncologist.com © The Best Oncologist ™ LNs= Lymph Nodes; IM= Internal Mammary	

STAGING cont.

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

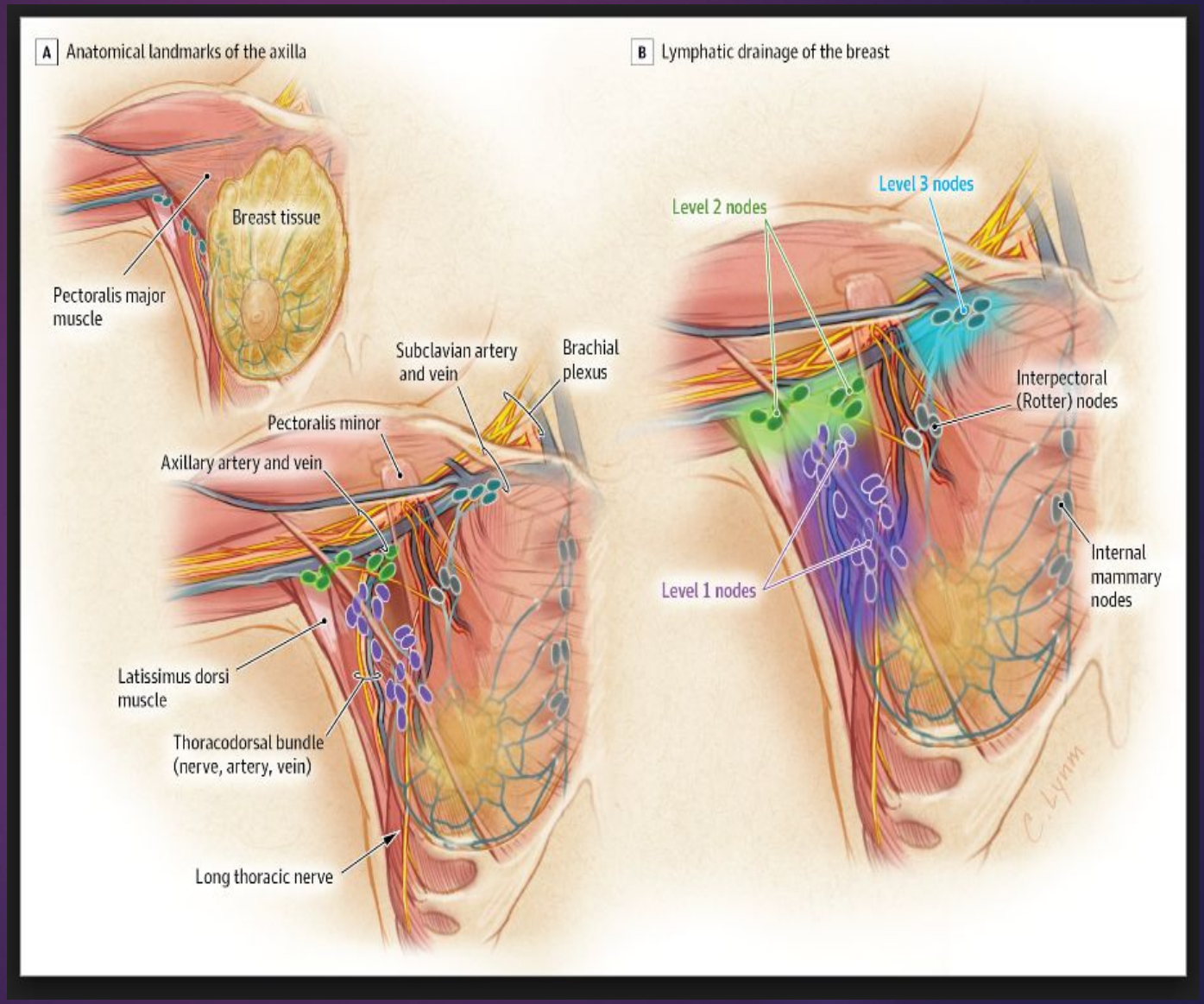
- In the patient with clinical stage I, II, and T3N1 disease, the initial management is usually surgical.
- **BCT : Lumpectomy + RT = Mastectomy**

Contraindications for BCT:

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

Axilla

- ALND

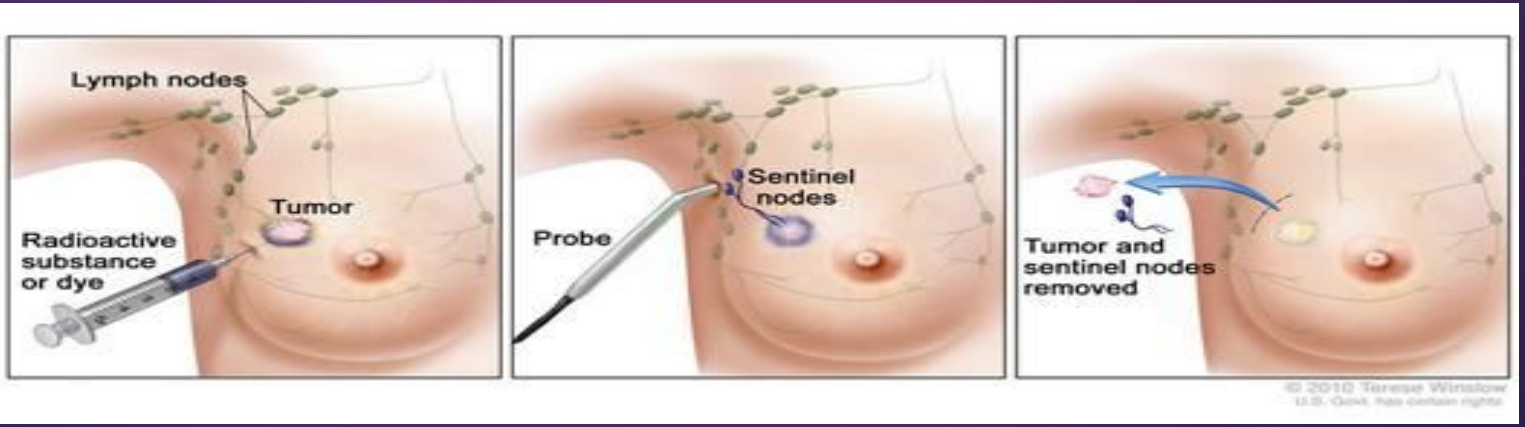

A Anatomical landmarks of the axilla
Breast tissue
Pectoralis major muscle
Subclavian artery and vein
Brachial plexus
Pectoralis minor
Axillary artery and vein
Latissimus dorsi muscle
Thoracodorsal bundle (nerve, artery, vein)
Long thoracic nerve
B Lymphatic drainage of the breast
Level 2 nodes
Level 3 nodes
Interpectoral (Rotter) nodes
Level 1 nodes
Internal mammary nodes

Axilla

- SLNB (less lymphedema)

- Majority of stage I-II BC pts

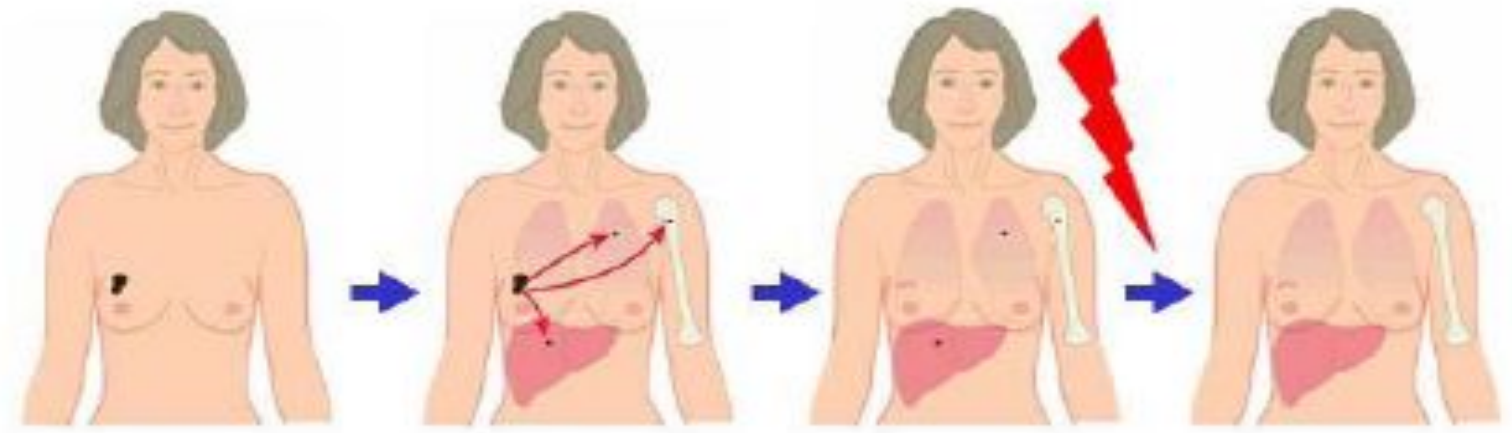
- Contraindications to the procedure: pregnancy, lactation, and locally advanced breast cancer.



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

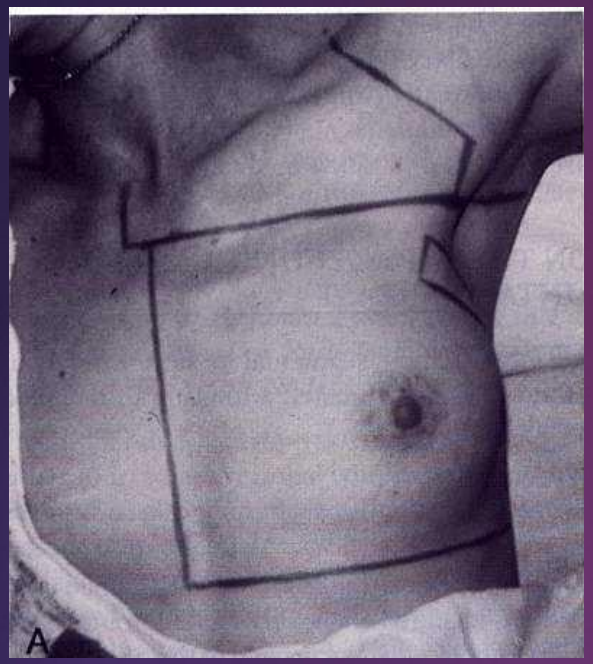


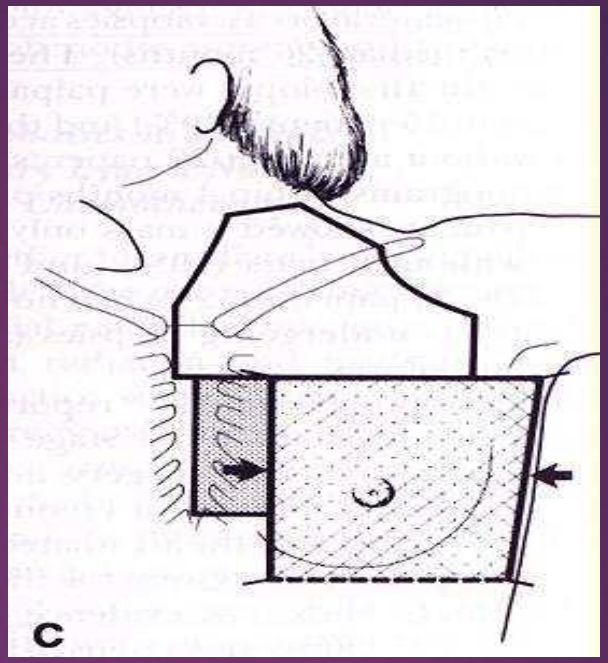
Adjuvant Therapy

- 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:

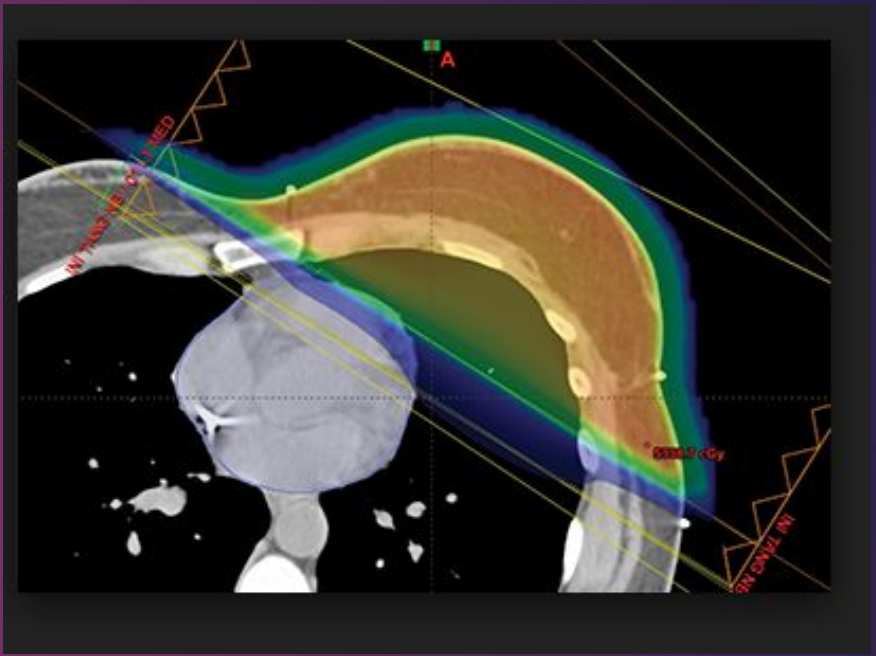




- 5 - 6.5 weeks
- Local control rates > 90%
- Minimal toxicity

Adjuvant radiation therapy – for everyone after lumpectomy

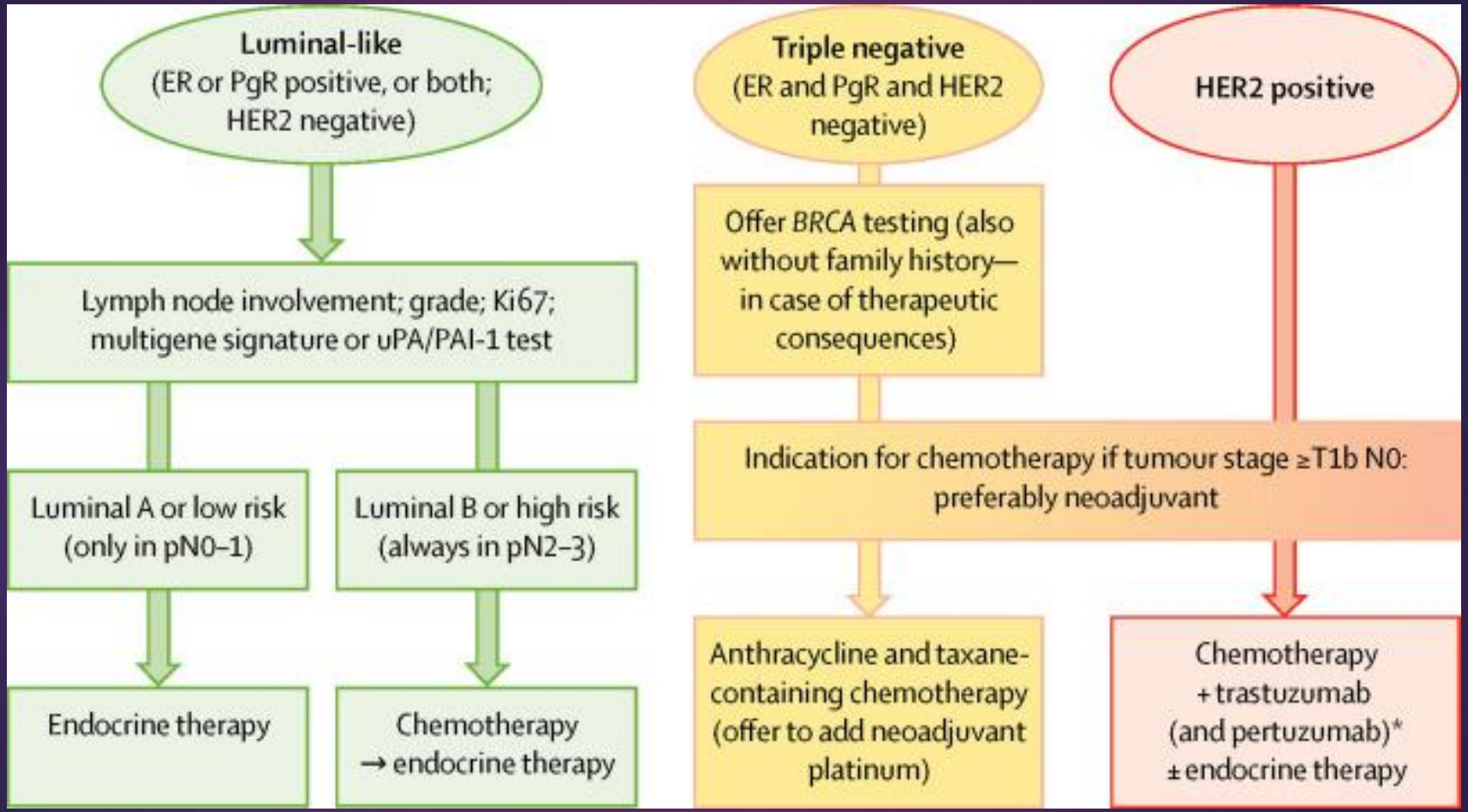
Breast cancer treatment Radiotherapy



Postmastectomy RT

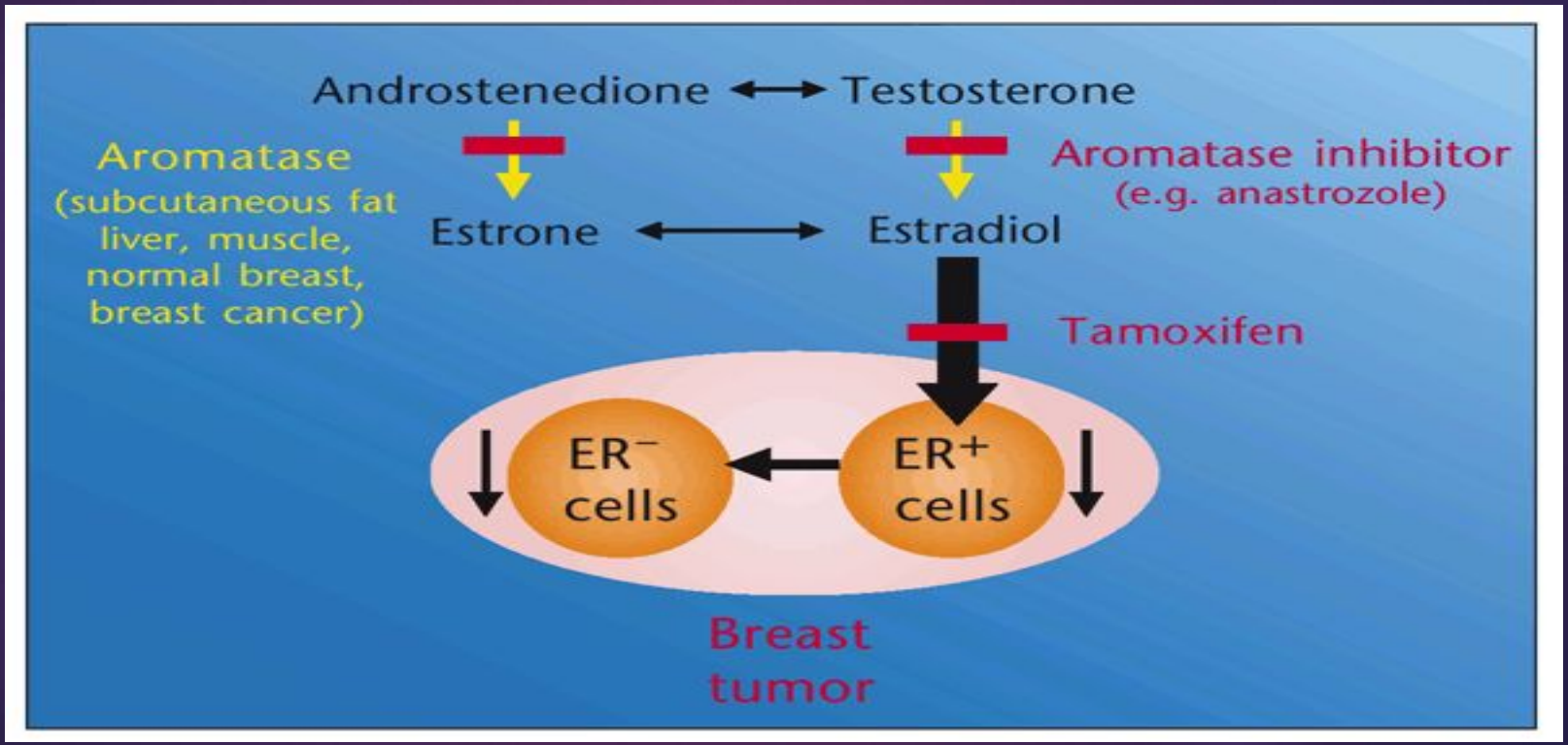
- All women with > 3 positive nodes.
- a tumor larger than 5 cm.
- spreading to the skin
- Women with recurrent positive margins
- ? Women with 1-3 positive nodes and T1/T2

APPROACH TO BC MEDICAL TREATMENT



HORMONAL THERAPY

- IN LOW-RISK HORMONE POSITIVE BREAST CA- FOR 5 YEARS
- IN HIGH-RISK HORMONE POSITIVE BC-FOR 7.5-10Y
- IN PREMENOPAUSAL –ADD OVARIAN SUPRESSION TO AROMATASE INHIBITORS /TAMOXIFEN



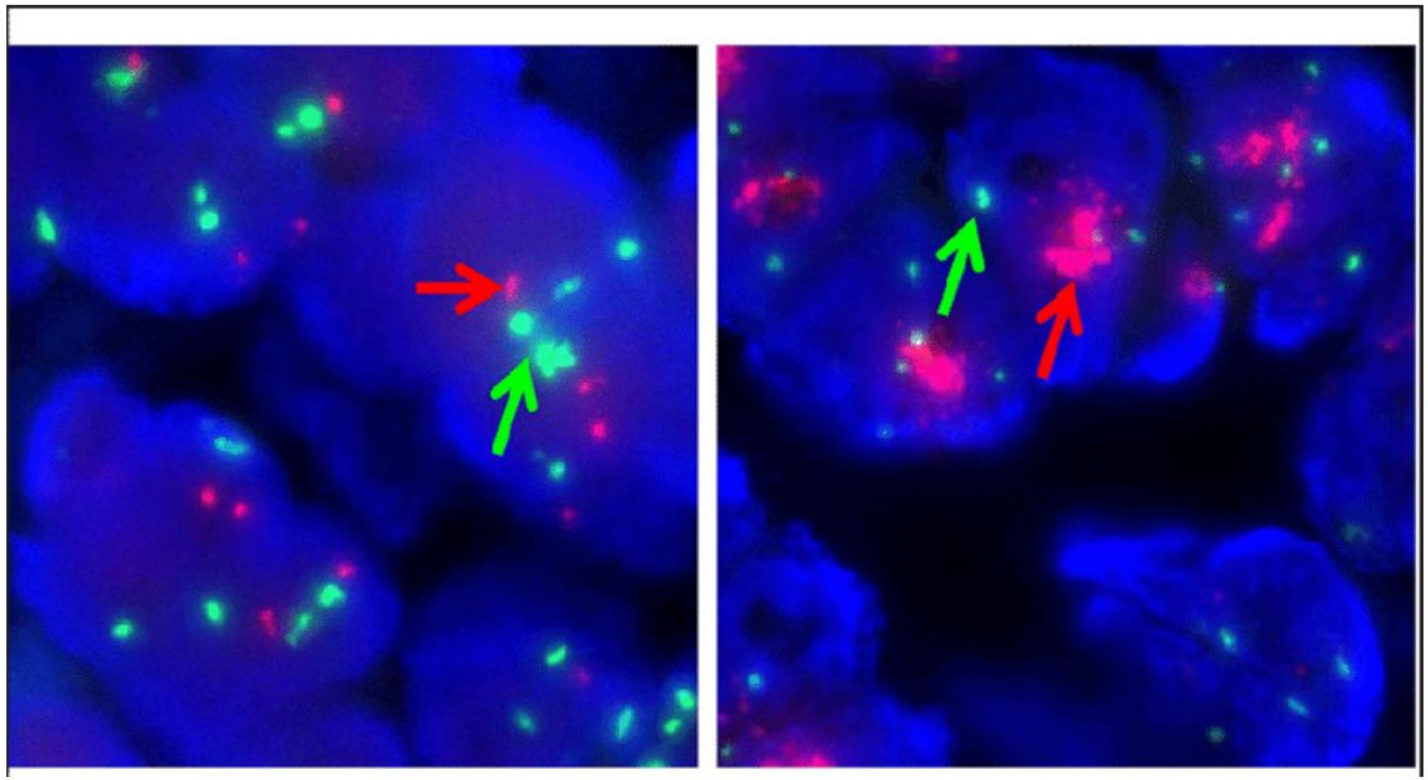
AI VS TAMOXIFEN –SIDE EFFECTS

Side Effects → AIs vs. Tamoxifen	Aromatase Inhibitors	Tamoxifen
Common side effects	• Hot flashes and night sweats • Joint and muscle pain • Loss of BMD (may lead to osteoporosis or bone fractures) • Loss of sex drive • Vaginal dryness or itching	• Hot flashes and night sweats • Loss of sex drive • Vaginal discharge • Vaginal dryness or itching
Less common/ rare side effects (Some side effects, including uterine or endometrial cancer and stroke, are very rare)	• Carpal tunnel syndrome • Hair thinning • Heart problems • Increased blood pressure • Increased cholesterol • Mood swings and depression	• Blood clots in the large veins (deep vein thrombosis) • Blood clots in the lungs (pulmonary embolism) • Bone loss (postmenopausal women only) • Uterine or endometrial cancer

SSRI?

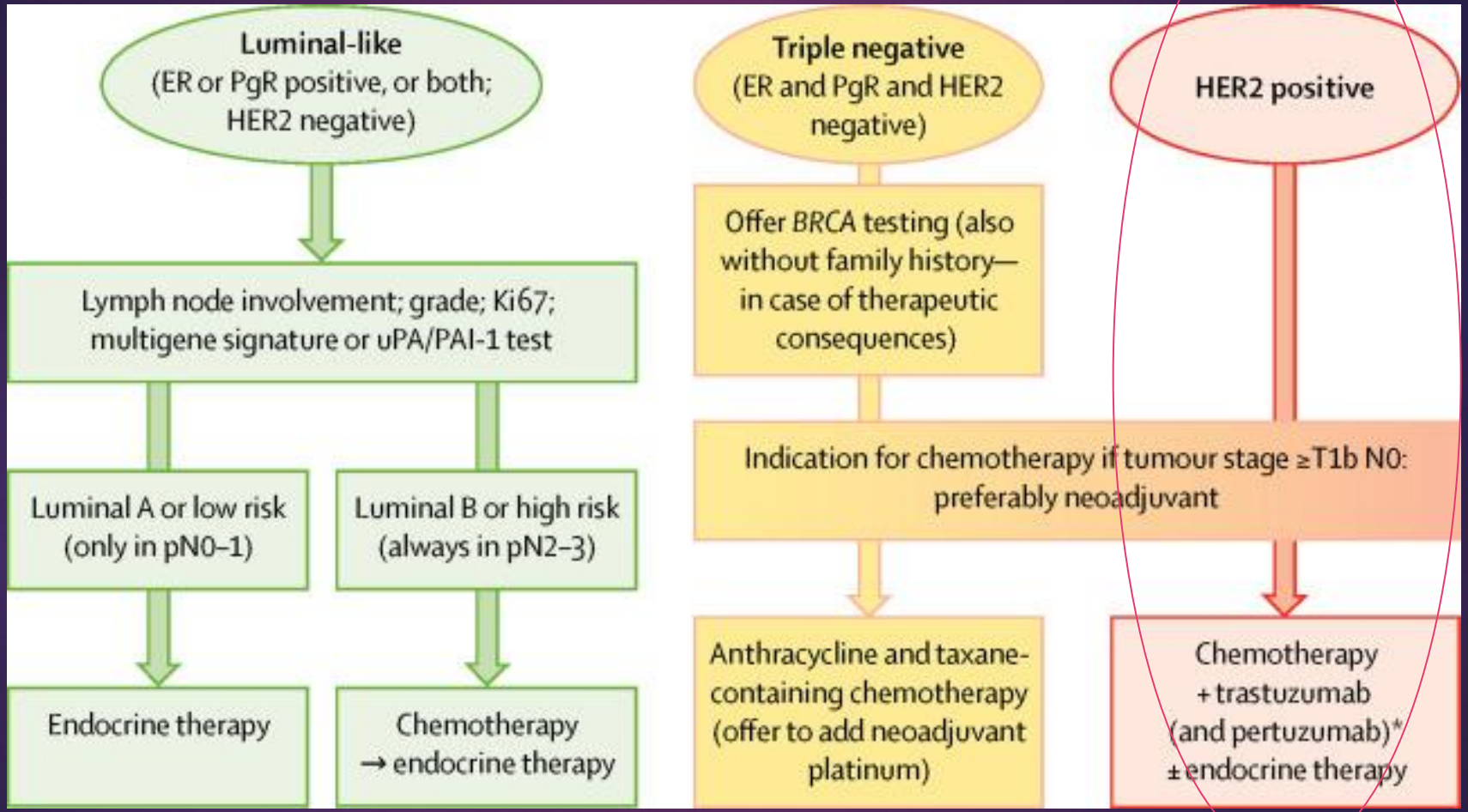
Smith IE, Dowsett M. N Engl J Med. 2003;348:2431-2442. Perez EA. *Ann Oncol*. 2007;18(supp 8): viii26–viii35. EBCTG . *Lancet*. 2015;386:1341-1352. Letrozole (Femara®) PI 2018 (www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files /Femara.pdf). Anastrozole (Arimidex®) PI 2018 (https://dailymed.nlm.nih.gov/dailymed/drugInfo. cfm?setid=acbfaaa9-503c-4691-9828-76a7146ed6de). Exemestane (Aromasin®) PI 2018 (http://labeling.pfizer.com/ ShowLabeling. aspx?id=523). Tamoxifen (Soltamox) PI 2012. (http://soltamox.com/wp-content/uploads/2016/07/Soltamox-FDA-Approved-Package-Insert.pdf)

FISH hybridization test for HER 2+



Identification of Her-2-positive breast cancer samples by FISH. The specimens with 2+ immunostaining scores were identified as Her-2-positive if the Her-2 (red arrow): CEP17 (green arrow) ratio was greater than or equal to 2 according to fluorescence in situ hybridization.

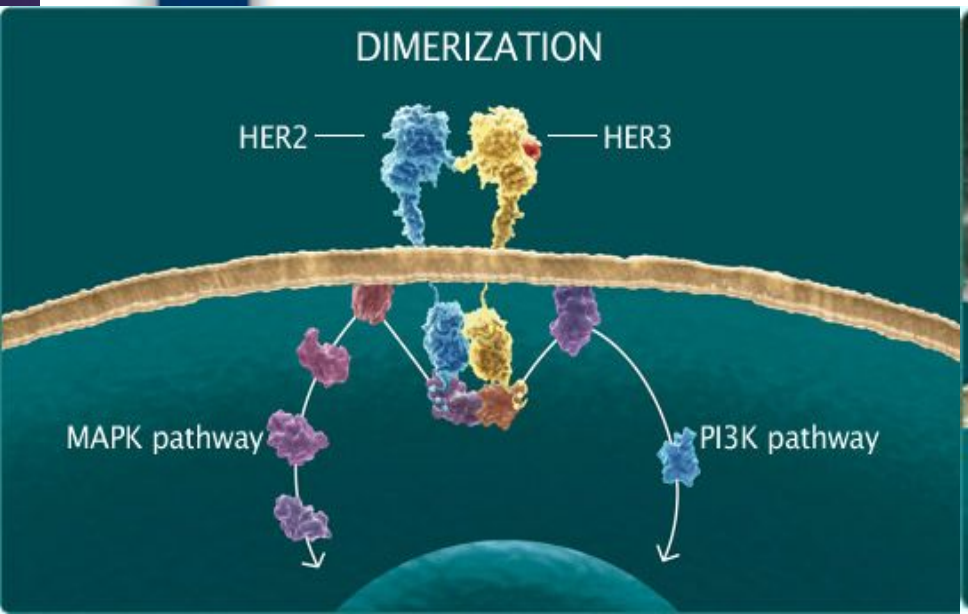
APPROACH TO BC MEDICAL TREATMENT

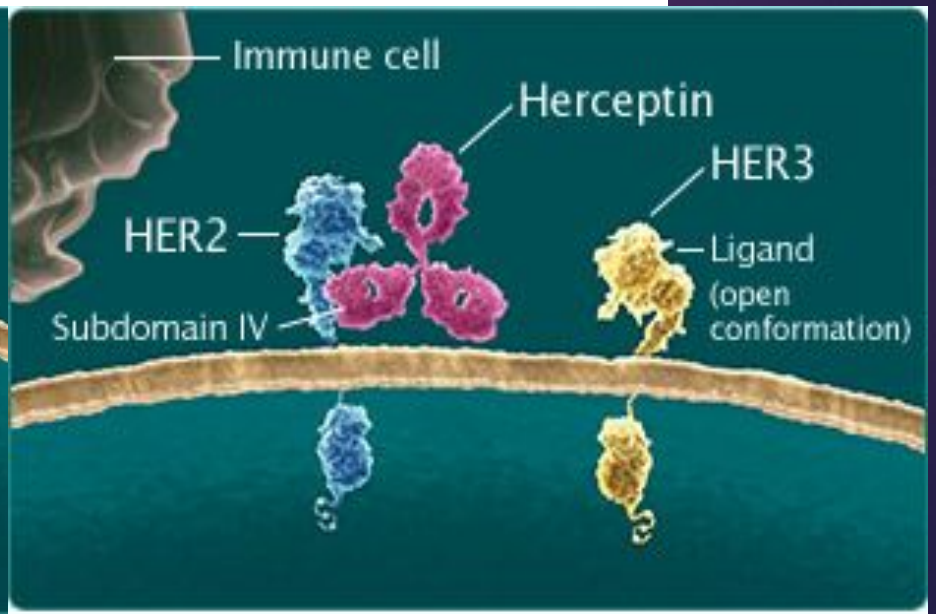


Monoclonal antibodies

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)

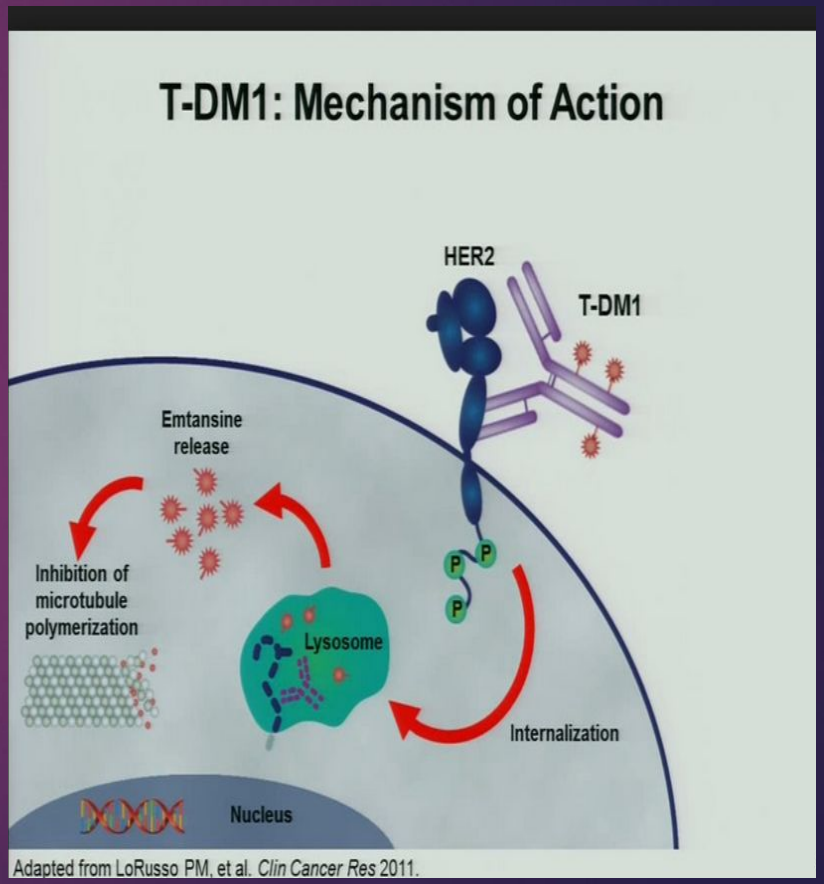




Trastuzumab emtansine (TDM1= KADCYLA)

- Her 2 pos BC

- Trastuzumab emtansine
- Conjugant therapy



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?

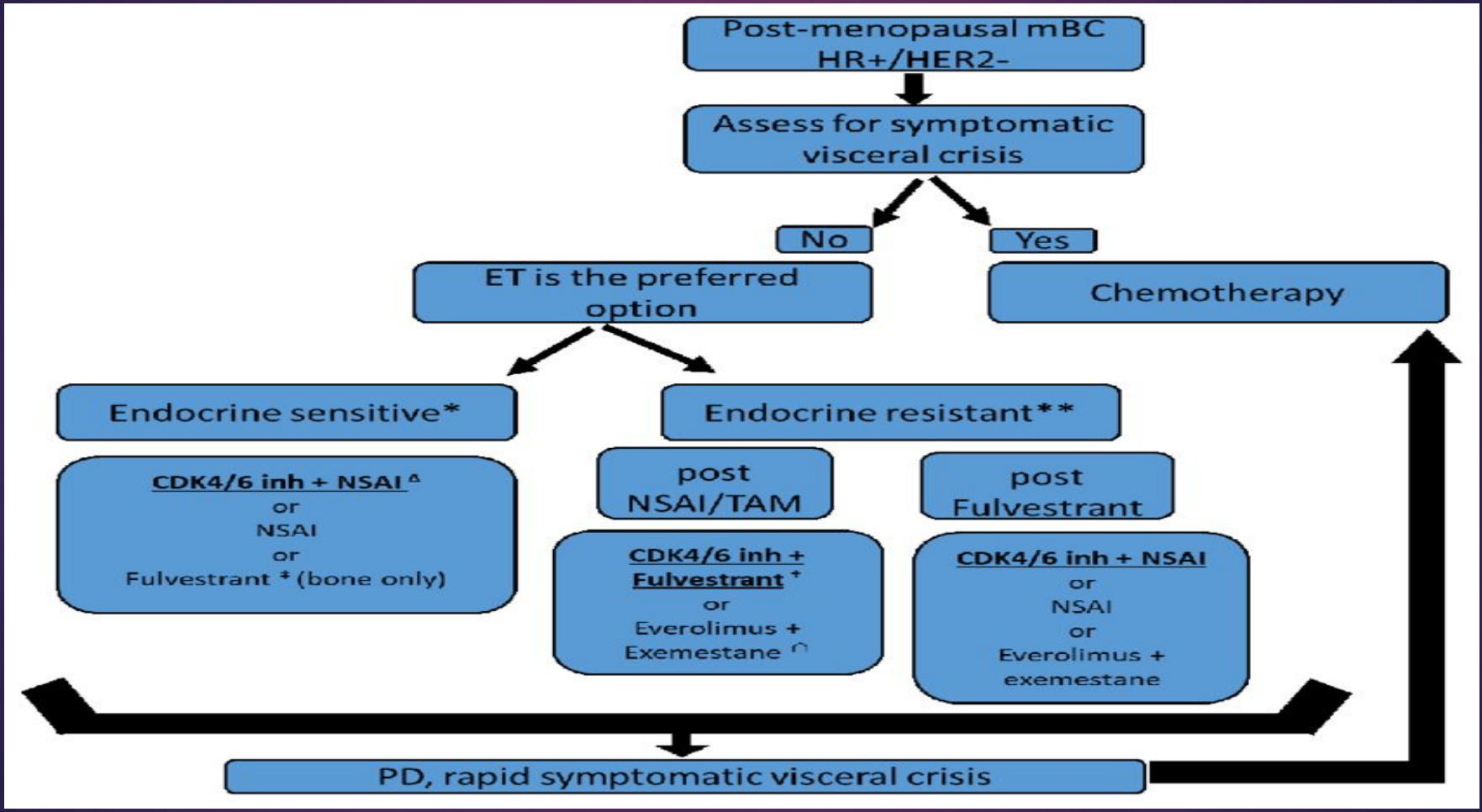
mBC

- 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

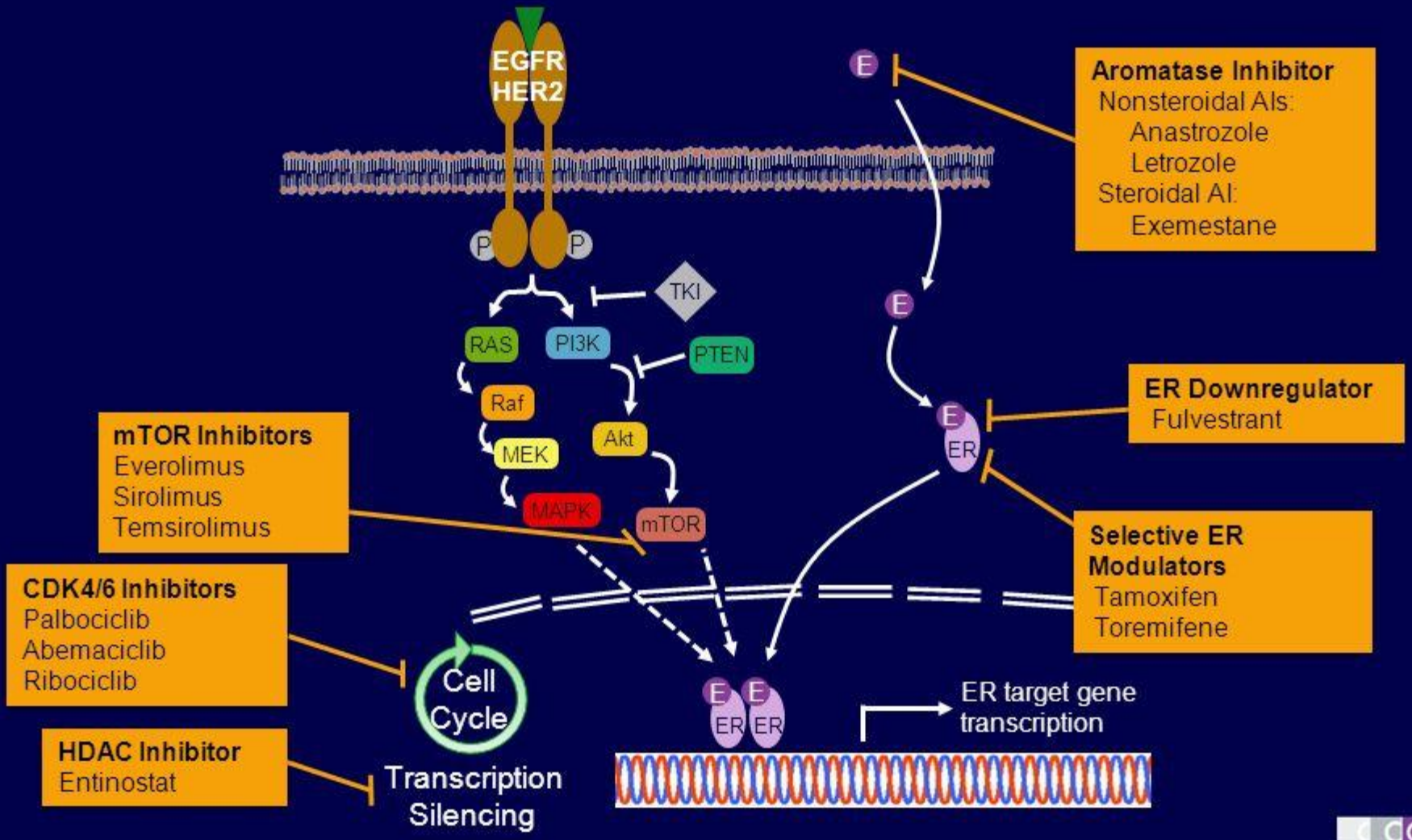
THERAPEUTIC ENDPOINTS

- **OVERALL SURVIVAL**
- **QUALITY OF LIFE**
- RESPONSE RATE
- TIME TO PROGRESSION
- TIME TO TREATMENT FAILURE
- SAFETY PROFILE

mBC approach(example)



Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer



Johnston SR. Clin Cancer Res. 2010;16:1979-1987.

Slide credit: clinicaloptions.com

Triple Negative Breast Cancer:

- Triple negative breast cancer (TNBC) is clinically characterized by the lack of expression of estrogen, progesterone and HER2 hormone receptors.
- Comprises about 10-20% of breast cancers: more than one out of every 10.
- Does not respond to current hormonal therapy (such as tamoxifen or aromatase inhibitors) or therapies that target HER2 receptors, such as Herceptin (trastuzumab). Women diagnosed with TNBC generally face a poorer prognosis.
- Treatments that target other processes may be helpful in treating triple negative breast cancer when combined with chemotherapy:
  - **Avastin:** interferes with VEGF (vascular endothelial growth factor), inhibiting the growth of new blood vessels at the tumor site.
  - **Erbitux**: interferes with EGFR (epidermal growth factor receptor), which is often overexpressed in triple negative cancer.
  - **PARP inhibitors:** inhibit poly (ADP-ribose) polymerase, an enzyme used by cancer cells to repair DNA damage. In BRCA

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
  - In combination with capecitabine

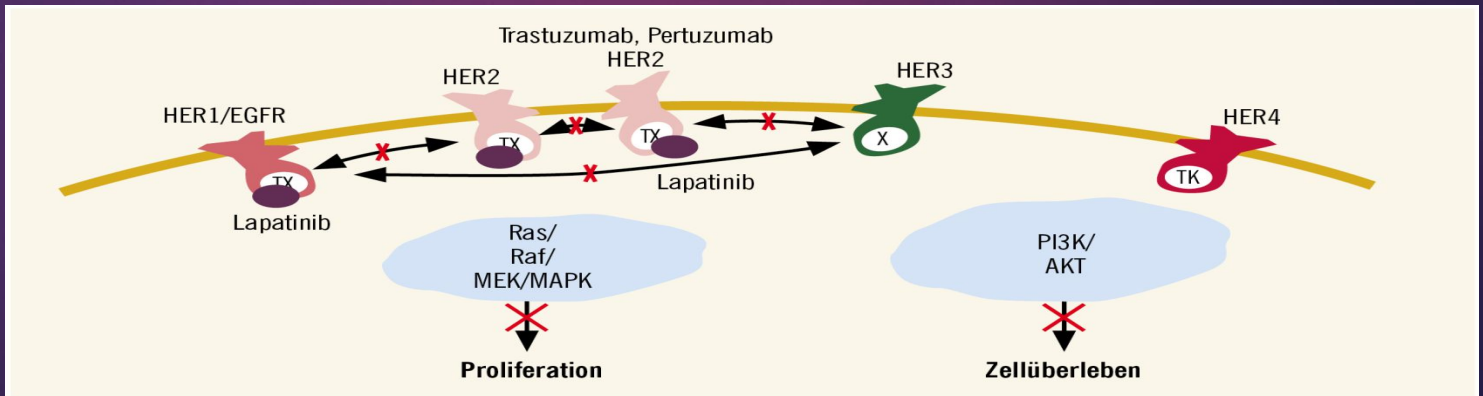
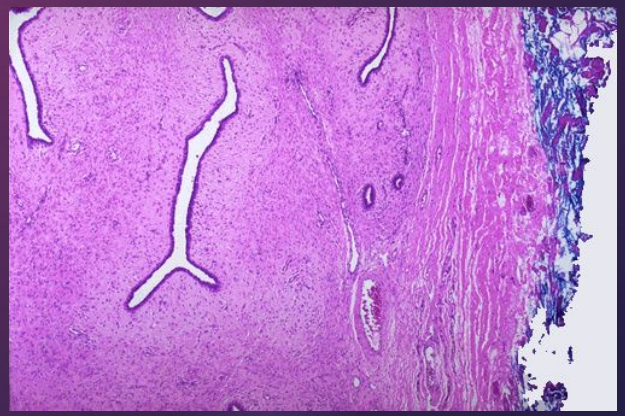


Abb. 3: Mit Lapatinib die Resistenz gegen Anti-HER2-Therapien überwinden

Other breast cancers

- Phyllodes tumor
  - <1% of breast tumors
  - Age 30-45
  - Similar in appearance to fibroadenoma
  - 4% recurrence after excision
  - 0.9% axillary spread
  - Radiation, chemotherapy, tamoxifen ??

Phyllodes



Fibroaden

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 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).

Angiosarcoma

- Risk factors
  - Radiation
  - Lymphedema
- Treatment
  - Excision, radiation

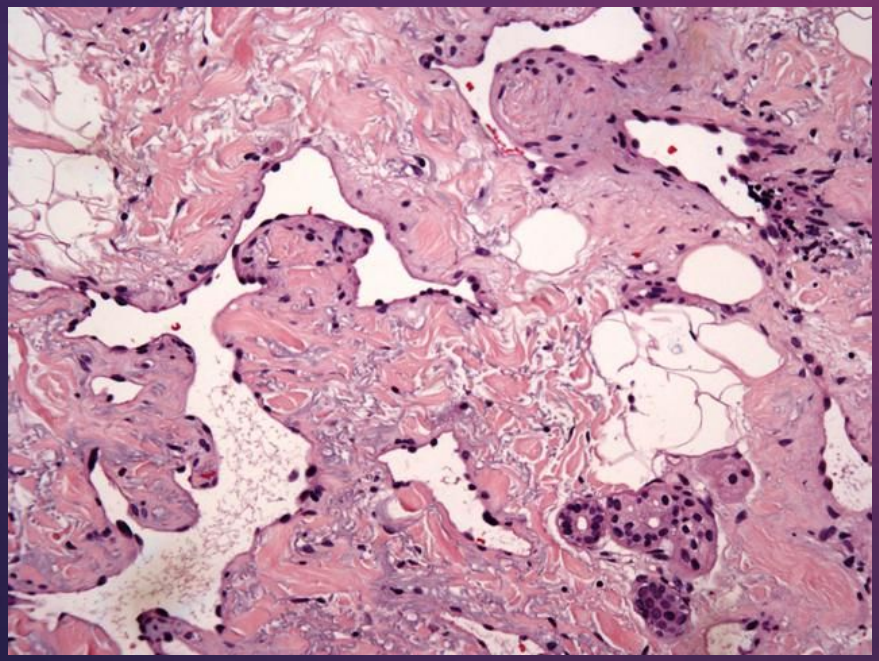


Figura 1 - Notar mastectomia e linfedema no membro superior esquerdo ipsilateral, associado à lesão vinhosa no terço superior.

Male breast cancer

- 90% are invasive at time of diagnosis
- 80% ER+, 75% PR+, 30% *HER2/neu*
- More invade into pectoralis
- Treatment same as for female ca

CASE 1

03.2021 Diagnosis

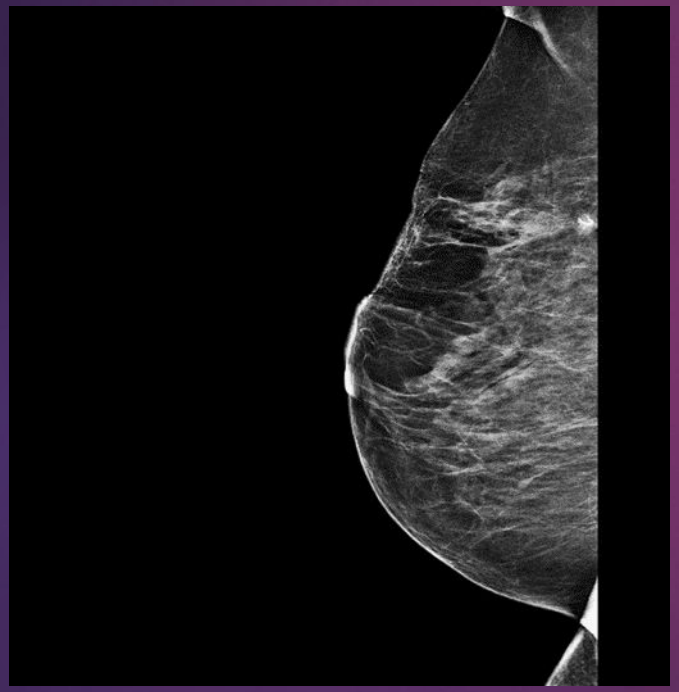
INCIDENTAL IMAGING TEST

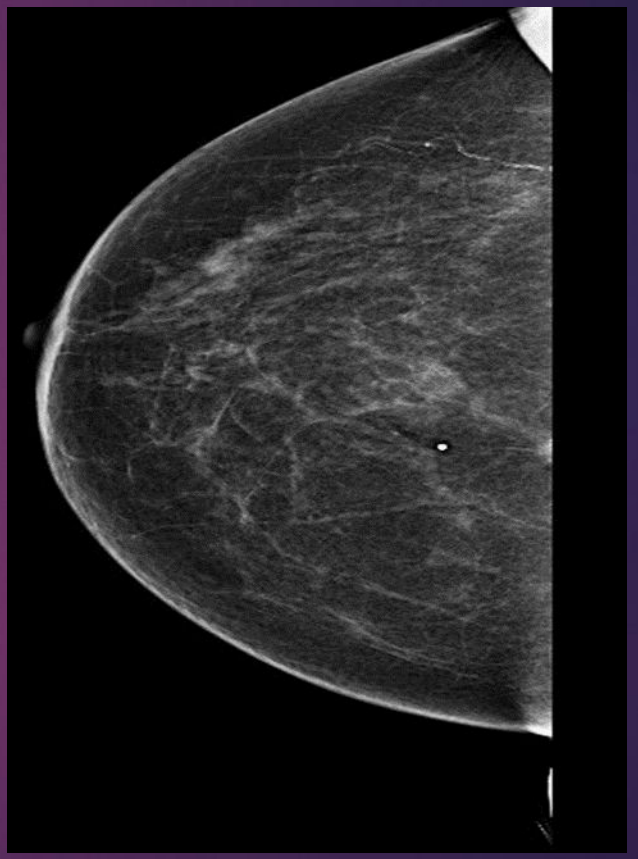
CT CHEST

AGE-76 Y.O.

FNL BY US –clip and tumor

RT BREAST MAMMOGRAPHY



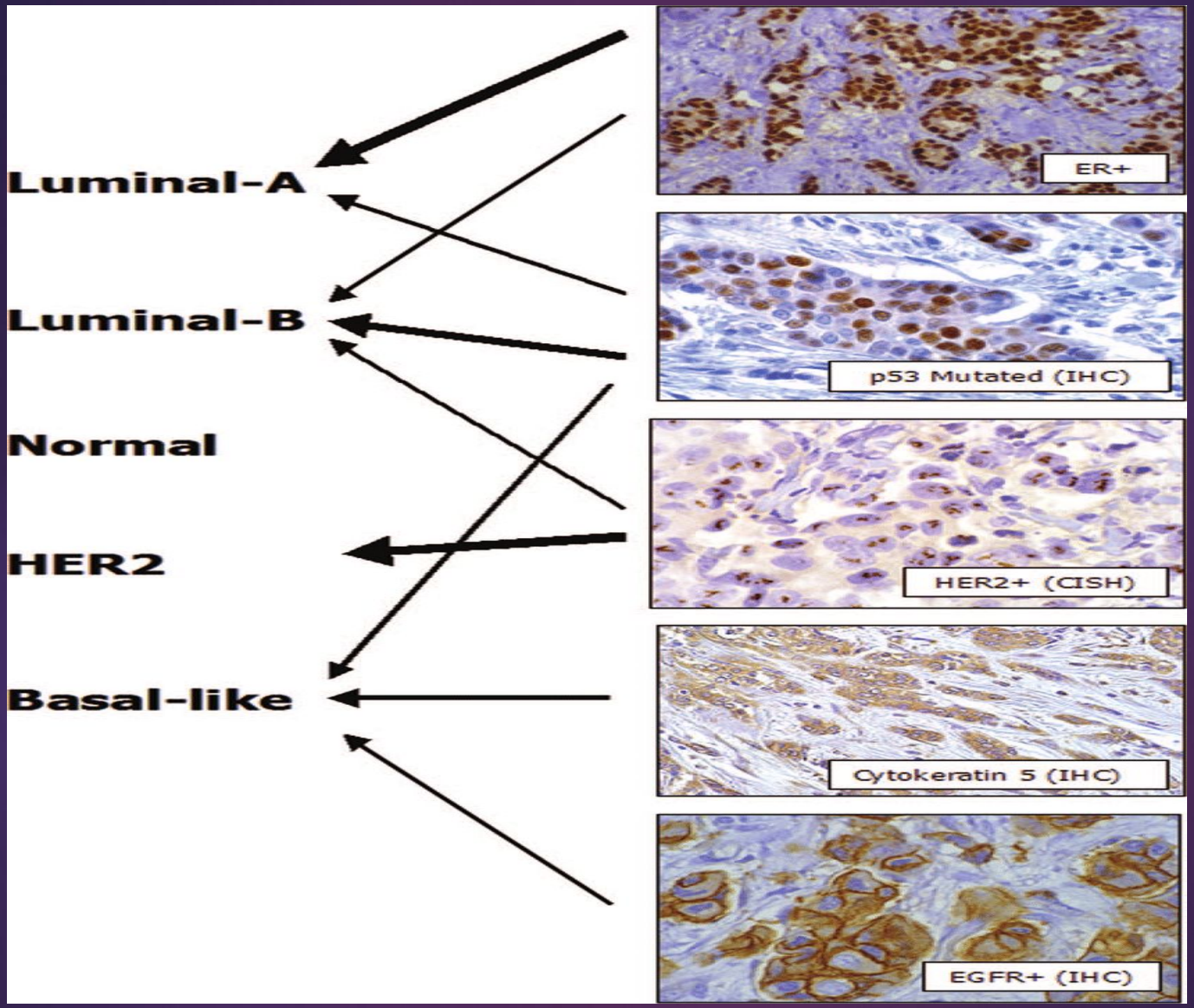


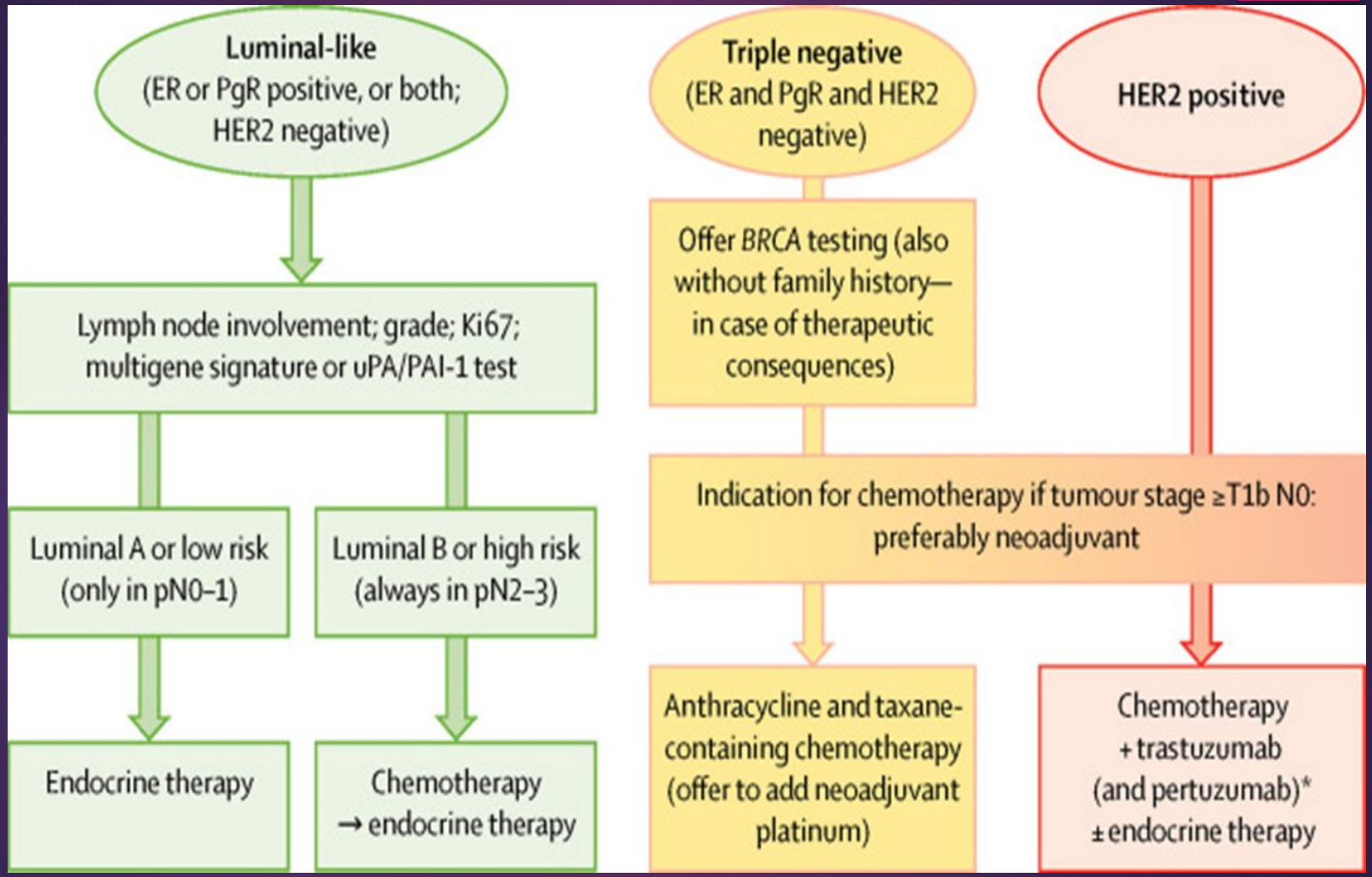
PATHOLOGICAL TEST

- INVASIVE BREAST CARCINOMA STAGE I
- G1 0.8 CM 0/2 LN NO PNI OR LVI 0.6 FROM POSTERIOR MARGINS
- ER-95%PR 3-5% KI 67-1-2%
- HER2 POSITIVE BY FISH

STAGE?

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


Luminal-A
Luminal-B
Normal
HER2
Basal-like
ER+
p53 Mutated (IHC)
HER2+ (CISH)
Cytokeratin 5 (IHC)
EGFR+ (IHC)

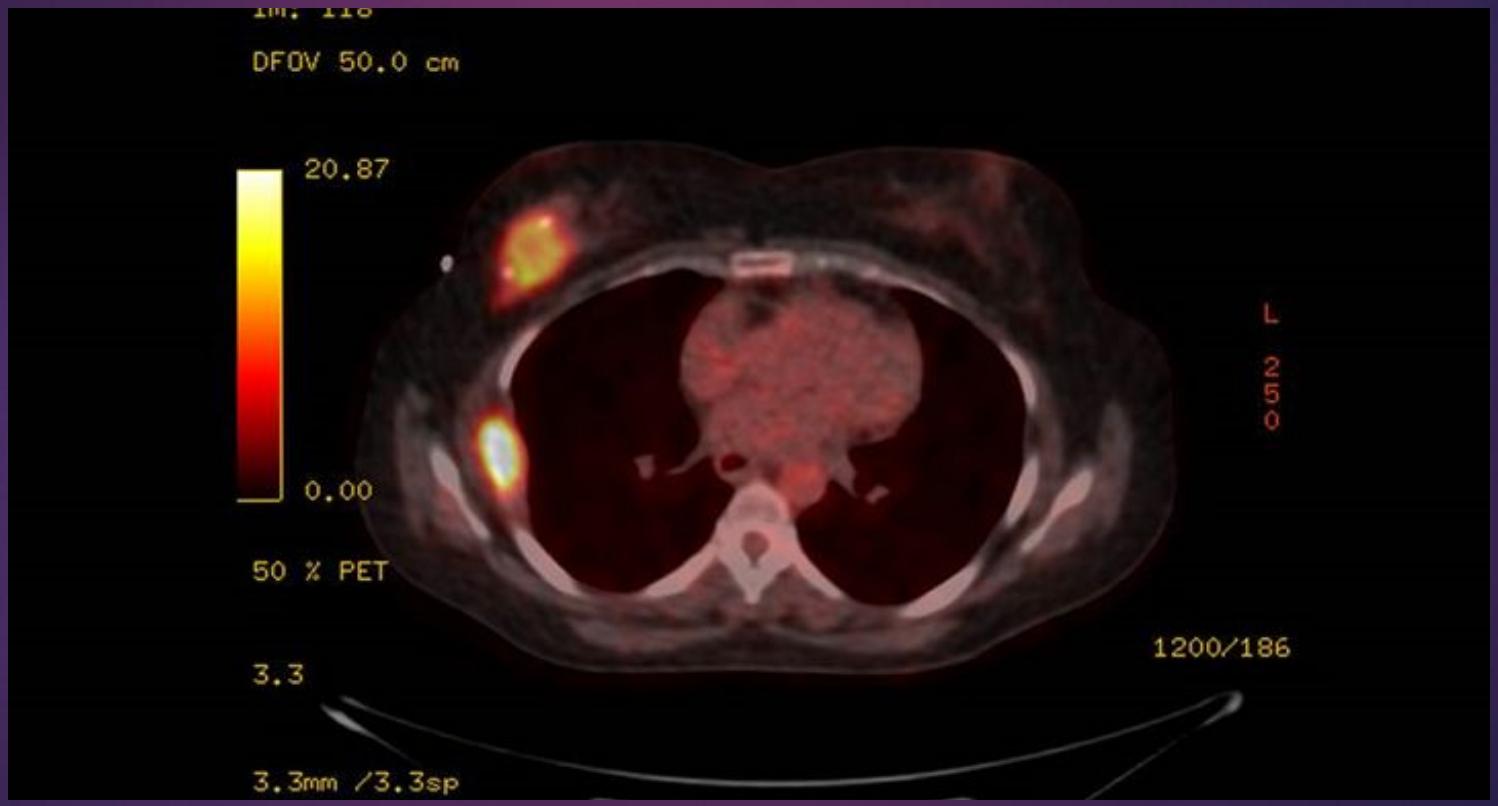

Luminal-like
(ER or PgR positive, or both; HER2 negative)
Lymph node involvement; grade; Ki67; multigene signature or uPA/PAI-1 test
Luminal A or low risk (only in pN0–1)
Luminal B or high risk (always in pN2–3)
Endocrine therapy
Chemotherapy → endocrine therapy
Triple negative
(ER and PgR and HER2 negative)
Offer BRCA testing (also without family history—in case of therapeutic consequences)
HER2 positive
Indication for chemotherapy if tumour stage ≥T1b N0: preferably neoadjuvant
Anthracycline and taxane-containing chemotherapy (offer to add neoadjuvant platinum)
Chemotherapy + trastuzumab (and pertuzumab)* ± endocrine therapy

CT CHEST- DD?

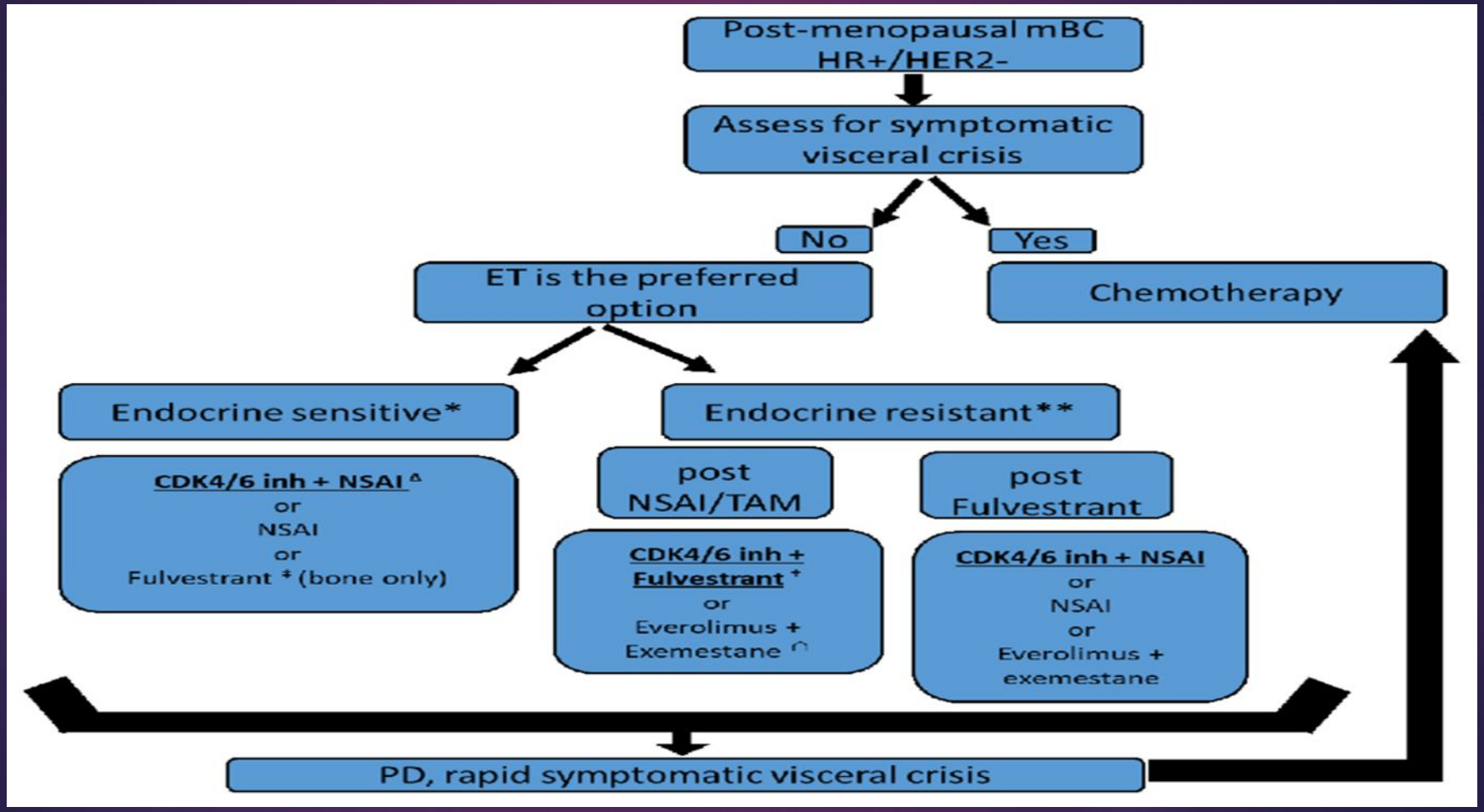
CASE 2

- AGE -48
- SELF EXAMINATION- BREAST TUMOR

AFTER LN POS. TEST AND BREAST IMAJING



- RT BREAST CA WITH RIB5 OLIGPMTS- STAGE IV



TREATMENT ONGOING

- 01.09.2021 PALBO+LETROZOL
- G4 ALT ELEVATION , G2 AST ELEVATION HEPATITIS PROFILE NEGATIVE
- 10.2021- STOPPED PALBO +LETROZOLE FOR 3 WEEKS
- PET CT 21.10.21-2 LESIONS IN RIBS, 1 LUNG LESION , less SUV in rt breast axilla and 5th rib
- 11.10.21 BIOPSY APPROVED BREAST MTS IN 5TH RIB LESION
- 11.2021- LETROZOLE ONLY
- AST 43 ALT 115 11.11.2021 CA15-3-49.7
- 18.11.2021- ALT-52
- TMB 18.11.21-RECHALLENGE PALBO DR TO 75 MG/D +LETROZOL
- FOLLOW UP LAB TEST WEEKLY