Breast cancer

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MD

Plan of the seminar:

→ Presentation
→ General information
→ Risk factors
→ Prognostic factors
→ Diagnostics and staging system
→ Treatment
-> Follow up

General information

Breast cancer

- Most masses we can find in breast are **benign (fibroadenomas)**
- Cancer of the breast can be detected by **screening**
- Around 200000 new cases of invasive breast ca / year in EU (around 2000 in men).
- Crude incidence around 110/100000 females; mortality 38.4/100000

RISK FACTORS

What are the risk factors ?

- **Sex**

→ The most common cancer among women

→ Women 100 times more often than men (men are at low risk)

- **Age**

→ Breast cancer incidence (look below) and death rates increase with age

<0,4% when 30-40 yr

3,7% when 60-70 yr

What are the risk factors ?

- **Reproductive factors**

→ Long menstrual history:
early menarche (before 12 yr),
late menopause (after 55 yr)

→ Never having children
(in contrary: breastfeeding is a protective factor)

→ Having first child after 30 yr

- **Race**

→ White women: higher incidence of breast ca. than African women but… after 40 yr

→ In contrary African women: higher incidence of breast ca. before 40 yr; also more likely to die because of breast ca. than White women (any age).

What are the risk factors ?

- **Breast cancer in relatives**

→ First-degree relative (sister, mother, daughter) with b.c. increases the risk of developing b.c.

→ Second-degree relatives in case of their premenopausal diagnosis

- **Genetic changes**

→ 5-10% of b.c are connected to genetic disorders:

→ BRCA1 and BRCA2 (present in less than 1% - no screening tests recommended) → around 70% lifetime risk (!)

→ p53, CHEK2, Rb-1, C-Myc

→ genetic disease: Li-Fraumeni or Cowden syndrome,

What are the risk factors ?

- **Benign breast diseases**

→ Ductal hyperplasia

→ Atypical ductal hyperplasia

(especially when with family history)

- **Previous irradiation**

→ Mantle radiation for HD

What are the risk factors ?

- **Previous breast cancer**

- **Other risk factors (dependent on life style):**

  Postmenopausal hormone therapy
  (estrogen+ progesteron)
  Oral contraceptives
  No physical activity
  Diet (being overweight, alcohol consumptio

What are the risk factors ?

- **High risk :**

- BRCA1/2 gene mutation or first-degree relative with a BRCA1/2
A lifetime risk of b.c. > 20% (based mainly on a family history)
- History of radiation therapy (between 10 ys and 30 yr)
- Some genetic disease (Li-Fraumeni syndrome)

- **Increased risk :**

- A lifetime risk of breast cancer 15 - 20%,
- Personal history of breast cancer, ductal or lobular carcinoma in situ, atypical ductal or lobular hyperplasia
- Extremely dense breasts (shown by mammogram)

Question

You examined a 3,5 cm mass in your 31-year old patient's left breast. A biopsy (fine needle aspiration) revealed carcinoma cells. You know that the patient has a sister (33-year old) with a history of breast cancer. Which risk factor is the most likely to be responsible for this cancer?

A. BRCA1 or 2 mutation

B. Prior intraductal papilloma

C. Early menarche

D. Diet rich in fats

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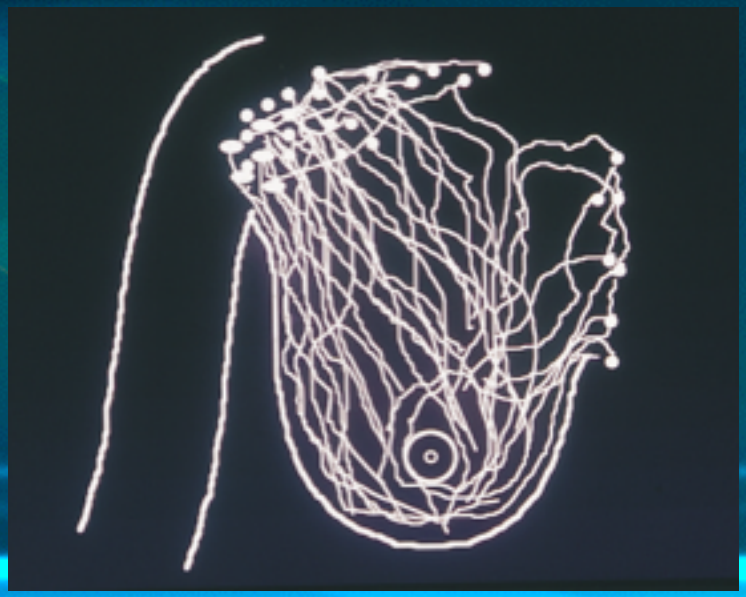
PROGNOSTIC FACTORS

What are the prognostic factors ?

- **Size of the tumor**
- **Lymph nodes involvement**
- **Histological type**
- **Grading**



What are the prognostic factors ?

- **Resections margins status**

→ Resection of the breast tumor with an approximately 1cm-thick rim of surrounding tissue with the expectation that this will yield a microscopic margin of at least 1 to 5 mm on pathologic analysis.

→ In general, a microscopic margin of at least 1-2 mm seems to insure reasonable likelihood that that local failure rates will be less than 5 % at 5 years.

- **Vessel invasion**

- **HER-2 receptor overexpression or amplification**

- **(Estrogen and progesterone receptor expression)**

Predictive factors

Triple negative b.c- tumor with negative receptors for HER-2, ER and PR (10-15%)

What are the prognostic factors ?

HER-2 receptor

Human Epidermal growth factor Receptor 2

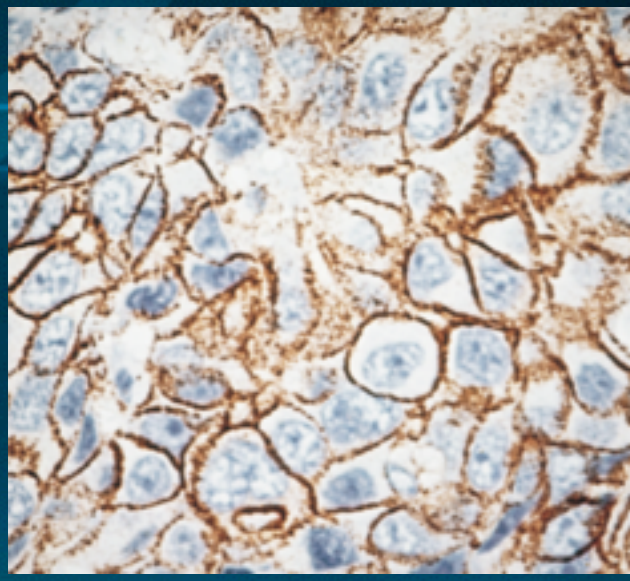
→ CD340, erbB2, HER2/neu

→ Transmembrane oncoprotein

→ Belongs to EGF receptors family

→ Orphan receptor

→ Acts as a dimer



Question

Which of the following you would considered to be a good prognostic factor for breast cancer?

A. HER2 receptor overexpression
B. Well differentiated tumor
C. >4 lymph nodes involved in ca process
D. Vessel invasion

Question

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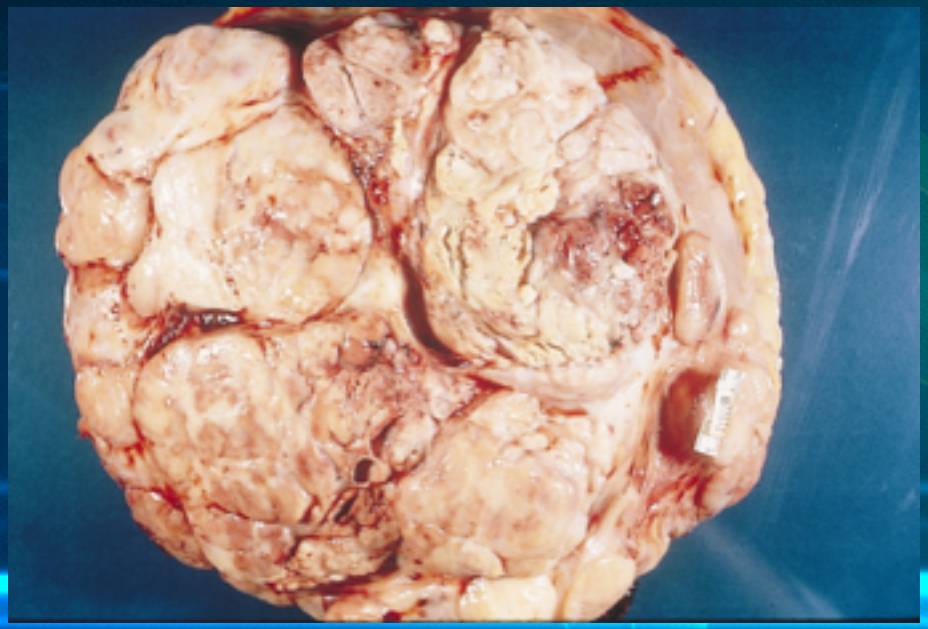
Histology

- Usualy ‘benign’ tumors:

→ Phyllodes tumor

→ Intraductal papilloma



Histology

- Carcinoma in situ:

→ Ductal DCIS

No invasion of the basement membrane of the breast ducts

→ Lobular LCIS

Benign-appearing proliferation of terminal ductules,

Often multifocal and bilateral

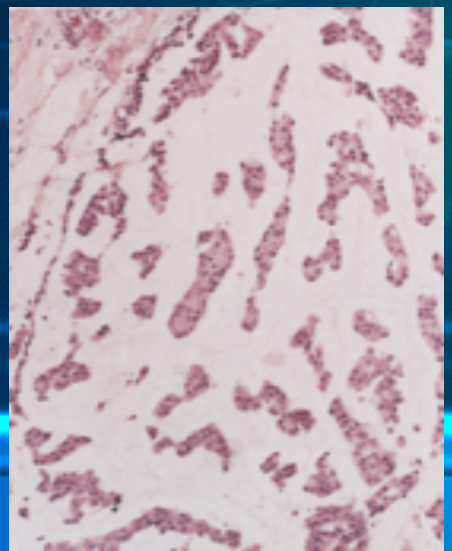
Cribriform DCIS with central necrosis (x400).

Histology

- Infiltrating ca:

→ Ductal (NOS)

- The most common breast cancer (around 75%)
- Scirrhous; Medullary; Mucinous
- Paget disease is a subtype in which malignant ductal cells extend intraepithelially to the skin of the nipple.



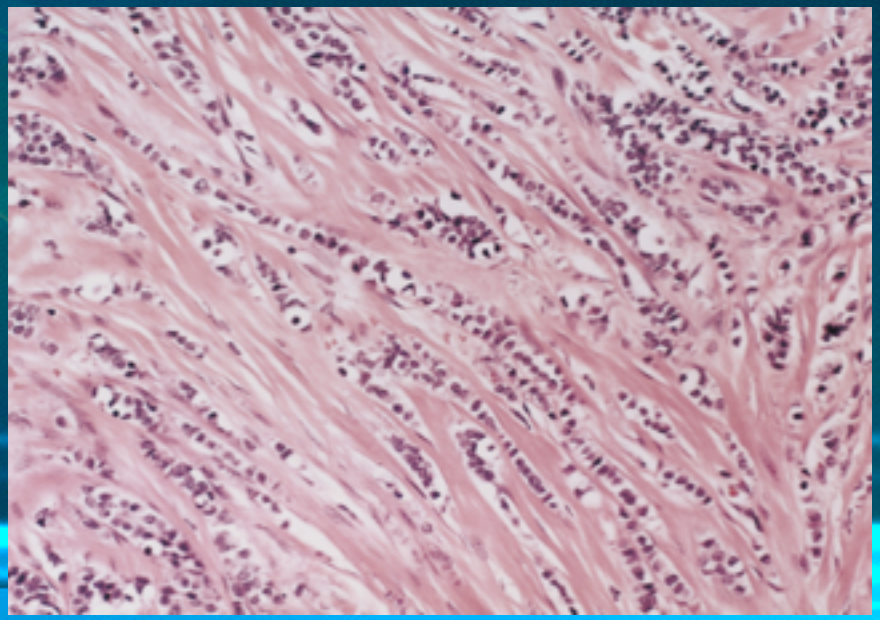
Mucinous carcinoma
Clusters of tumor cells float in a pool of extracellular mucin

Histology

- Infiltrating ca:

→ Lobular

- About 10% of breast cancers
- Arises from terminal ductules of the lobules
- Often multicentric
- Often bilateral (20%)

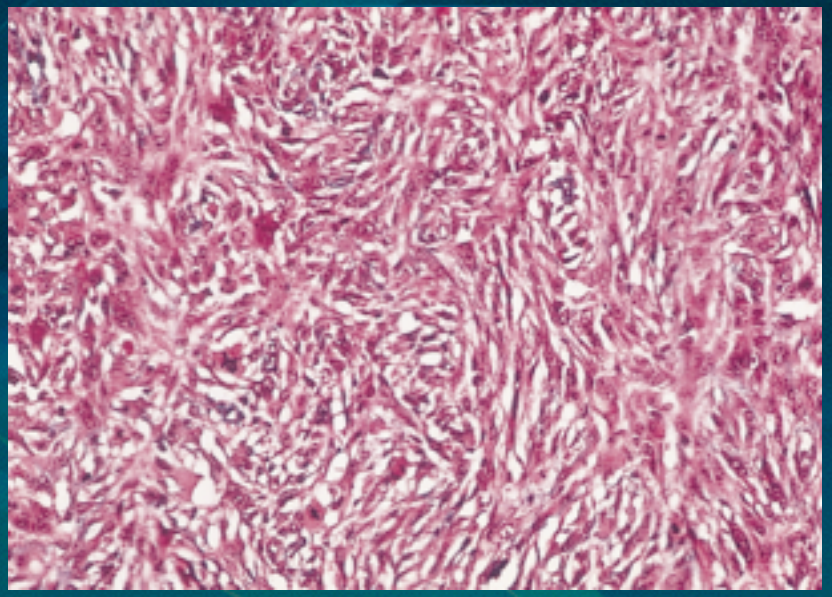


Infiltrating lobular carcinoma.
The tumor cells infiltrate in typical linear files

Histology

- Other rare tumors

→ Sarcoma



High grade sarcoma

→ Lymphoma

Question

Which of the following connections is false?

A. Phyllodes tumor → usually behaves as benign change
B. LCIS → often multifocal
C. Infiltrating ductal ca.→ the most common breast ca.
D. Paget disease → a type of Infiltrating lobular ca.

Question

Which of the following connections is false?

A. Phyllodes tumor → usually behaves as benign change
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DIAGNOSIS

How do we diagnose breast cancer ?

- Physical examination:

→ Women in their 20s and 30s - a clinical breast exam (CBE) every 3 years performed by a health professional

→ Women after 40 yr- CBE every 1 year performed by a health professional

→ Breast self-examination (BSE) – every month

! Don't forget to check if there is nipple discharge !
! Breast cancer occurs most often in the upper outer quadrant of the breast !

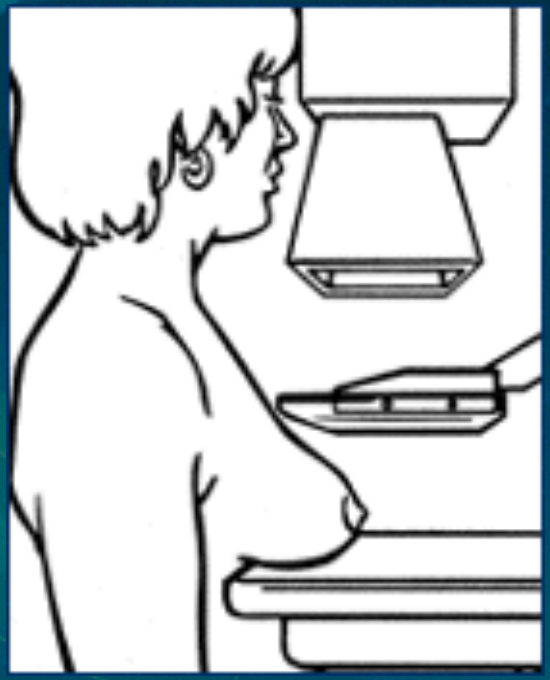
Picture taken from www.mammoscan.com

movie

How do we diagnose breast cancer ?

- Mammogram - an x-ray exam of the breast

→ Once a year for every woman > 40yr
who has no symptoms
BILATERAL MAMMOGRAPHY
Usually 2 x-ray pictures of each breast



- **USG**
- **MRI**

(in addition to, not instead of mammogram)

Women at high risk should get an MRI and a mammogram every year starting from 30 yr

Women at moderately increased risk should have additional MRI screening considered and should have a mammogram every year starting from 30 yr

How do we diagnose breast cancer ?

What do we look for on mammograms?

→ Calcifications

→ Macrocalcifications: usually related to non-cancerous conditions (also usually do not require a biopsy). They are found in about 1/2 of all women > 50 yr, and in 1/10 women < 50 yr.

→ Microcalcifications: tiny specks of calcium, alone or in clusters. If a suspicious look and pattern→ a biopsy

→ A mass: may be just cysts or non-cancerous solid tumors but also may be a cancer (usually masses should be biopsied if they are not cysts)

A mammogram it cannot prove that an abnormal area is a cancer

Histopathological assesment (a needle biopsy or an open surgical biopsy) is needed

Mammogram reports

The American College of Radiology has developed a standard system of describing mammograms which is called the Breast Imaging Reporting and Data System (BI-RADS).

Picture taken from www.cancer.org

Question

The best evidence for a mortality benefit for mammography is in women aged:

A. 30 to 39 years
B. 40 to 49 years
C. 50 to 69 years
D. 70 to 89 years

Question

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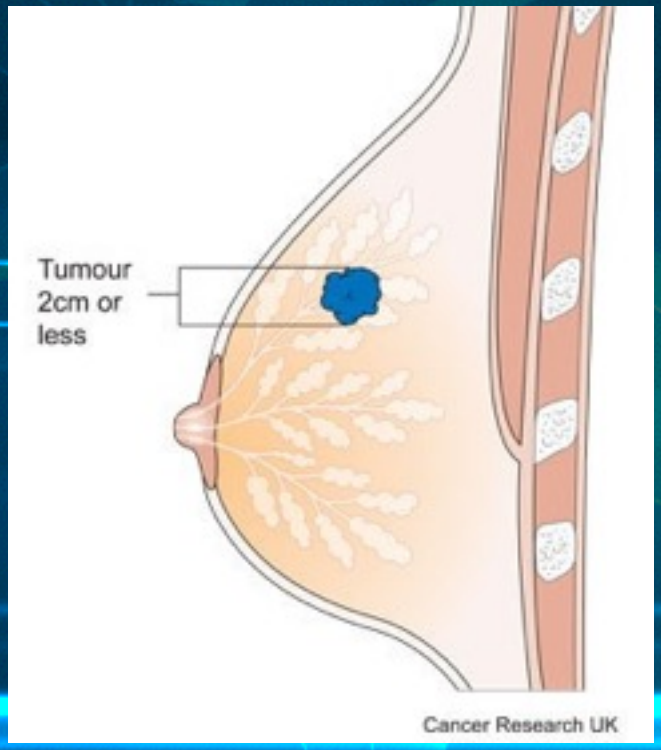
What else should we do (after receiving a histopathological report) before treatment?

- Blood tests (full blood counts) and routine chemistry
- Chest X-Ray, CT
- Liver USG
- Bone scan
- Ca 15.3

STAGING

TNM staging

TX means that the tumour size cannot be assessed
Tis means DCIS
T1 – The tumour is 2 centimetres (cm) across or less

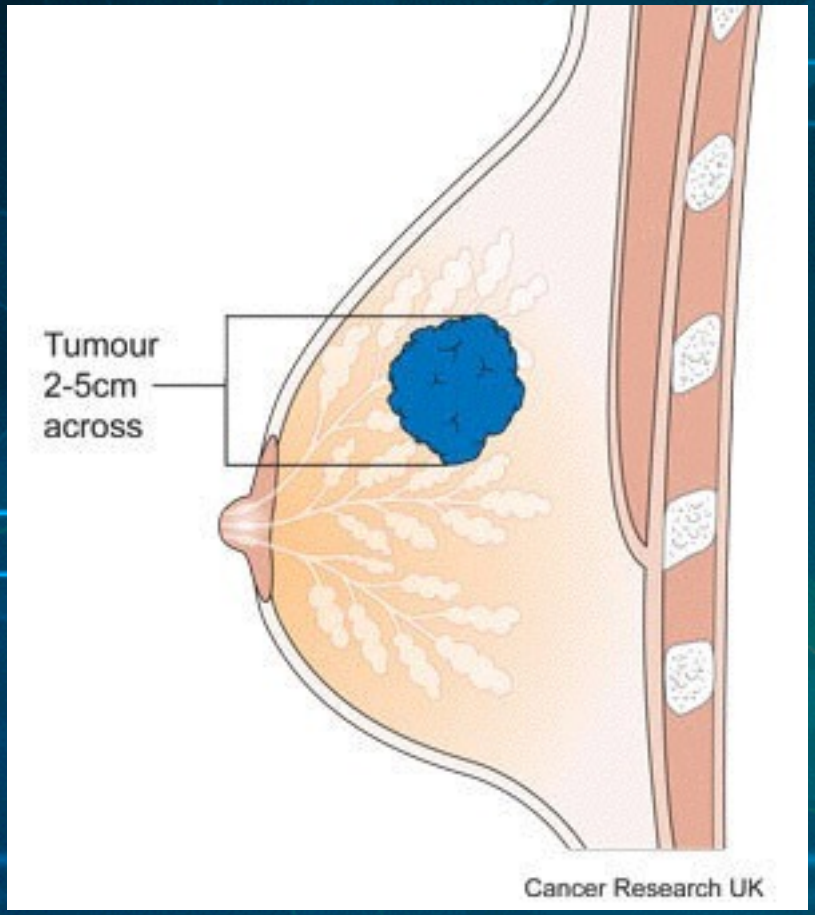


TNM T

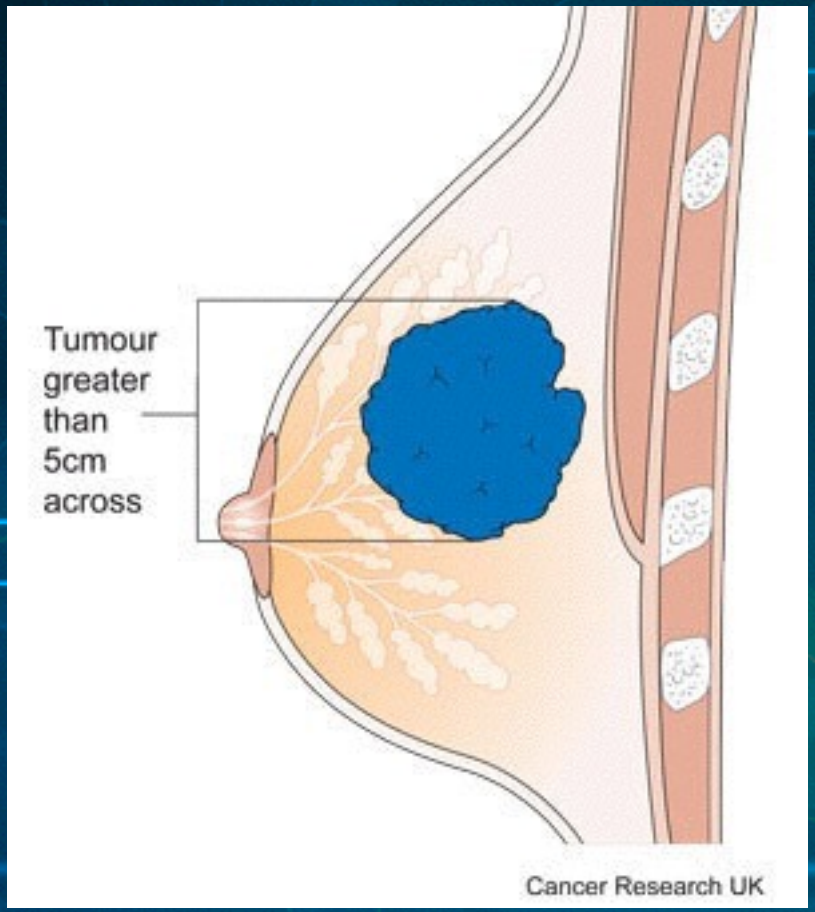
T1 is further divided into 4 groups

- T1mi – the tumour is 0.1cm across or less
- T1a – the tumour is more than 0.1 cm but not more than 0.5 cm
- T1b – the tumour is more than 0.5 cm but not more than 1 cm
- T1c – the tumour is more than 1 cm but not more than 2 cm

T2 – The tumour is more than 2 centimetres, but no more than 5 centimetres across



T3 – The tumour is bigger than 5 centimetres across



TNM T

T4 is divided into 4 groups

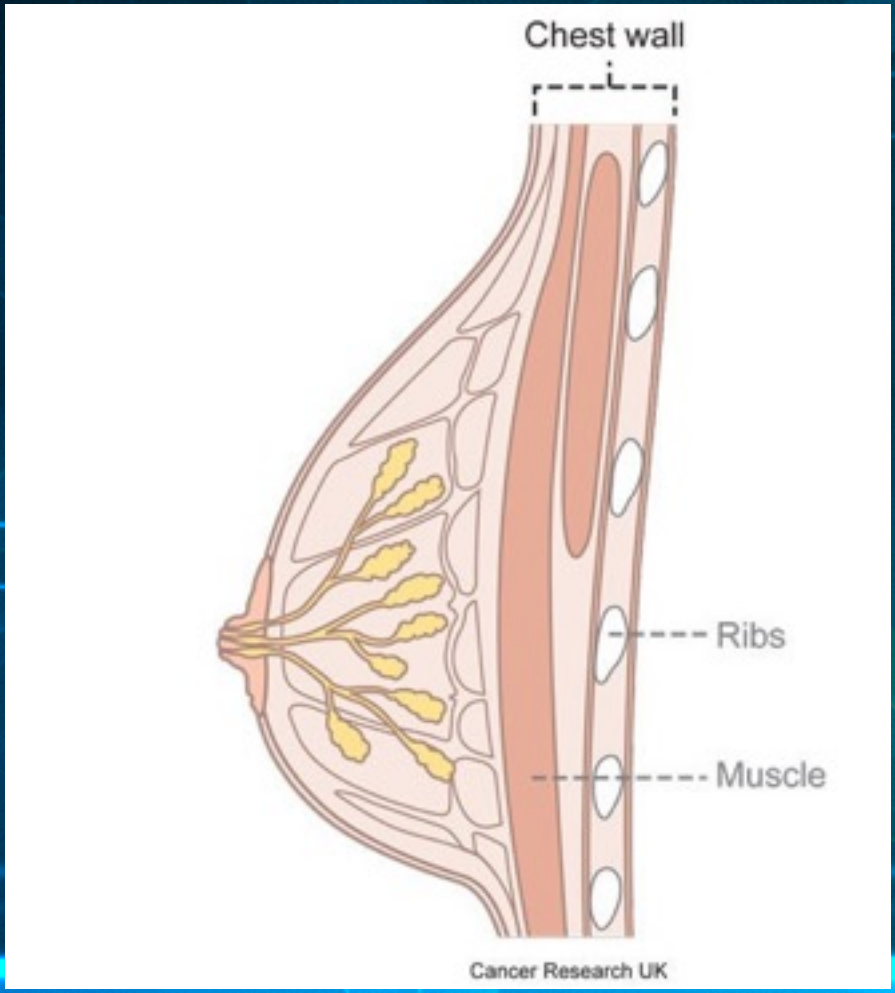
T4a – The tumour has spread into the chest wall

T4b – The tumour has spread into the skin and the breast may be swollen

T4c – The tumour has spread to both the skin and the chest wall

T4d – Inflammatory carcinoma – this is a cancer in which the overlying skin is red, swollen and painful to the touch

T4



N staging

NX means that the lymph nodes cannot be assessed (for example, if they were previously removed)

N0 – No cancer cells found in any nearby nodes
Isolated tumour cells (ITCs) are small clusters of cancer cells less than 0.2 mm across, or a single tumour cell, or a cluster of fewer than 200 cells in one area of a lymph node. Lymph nodes containing only isolated tumour cells are not counted as positive lymph nodes

N1 – Cancer cells are in the lymph nodes in the armpit but the nodes are not stuck to surrounding tissues

pN1mi – One or more lymph nodes contain areas of cancer cells called micrometastases that are larger than 0.2mm **or** contain more than 200 cancer cells but are less than 2mm

N staging

N2 is divided into 2 groups

N2a – there are cancer cells in the lymph nodes in the armpit, which are stuck to each other and to other structures

N2b – there are cancer cells in the internal mammary nodes(behind breast bone) which have either been seen on a scan or felt by the doctor. There is no evidence of cancer in lymph nodes in the armpit

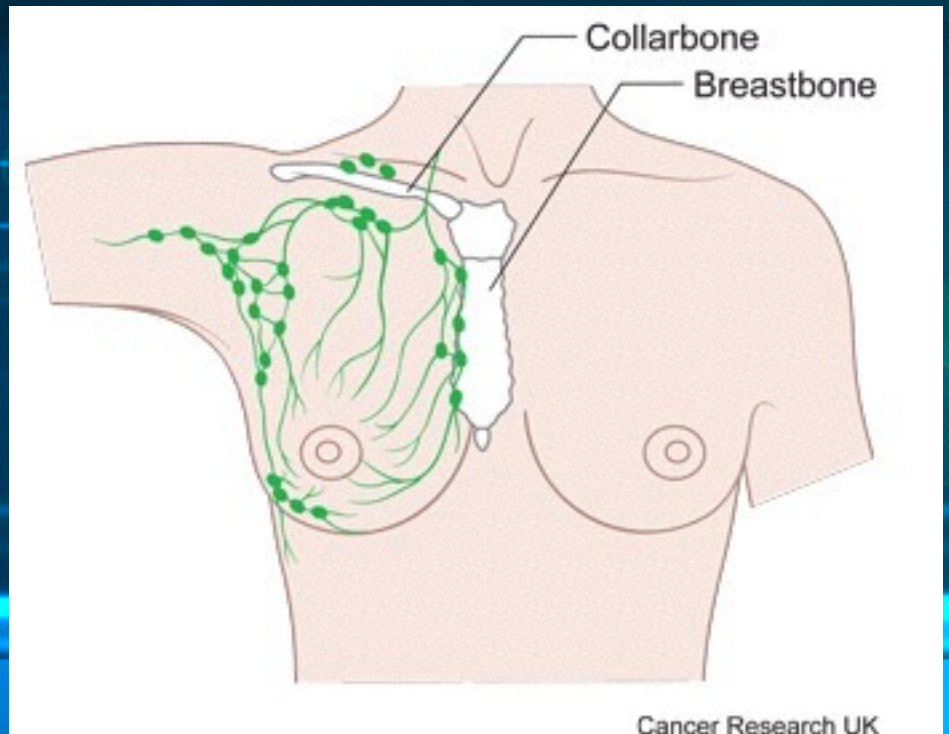
N staging

N3 is divided into 3 groups

N3a – there are cancer cells in lymph nodes below the collarbone

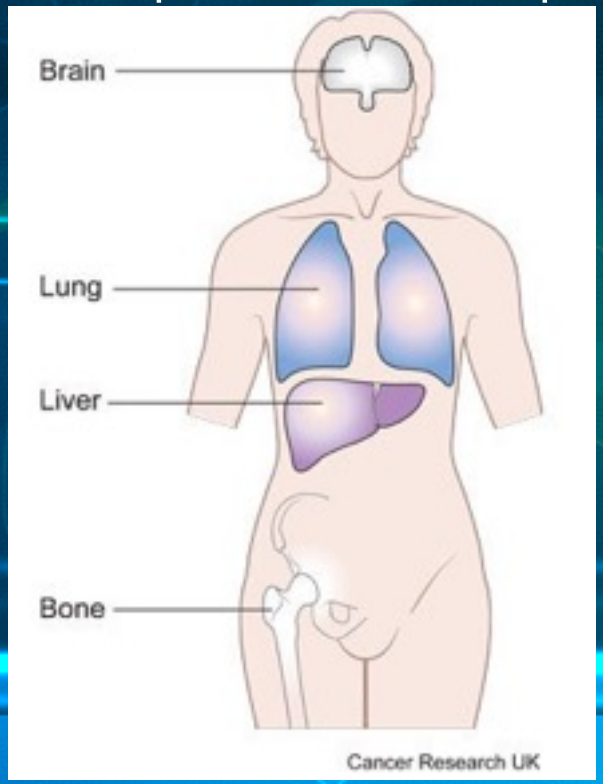
N3b – there are cancer cells in lymph nodes in the armpit and behind the breast bone

N3c – there are cancer cells in lymph nodes above the collarbone



The M stages (metastases)

M0 means that there is no sign of cancer spread
cMo(i+) means there is no sign of the cancer on physical examination, scans or X-rays but cancer cells are present in blood, bone marrow, or lymph nodes far away from the breast cancer – the cells are found by laboratory tests
M1 – means the cancer has spread to another part of the body




Bones
Lungs
Brain
Metastatic disease
Liver
Breast
....
Ovary
Skin

TNM-staging

0		Tis N0 M0	
I		T1 N0 M0	98% 5-yr survival
II	A	T0/1 N1 M0 or T2 N0 M0	A 88% 5-yr survival
	B	T2 N1 M0 or T3 N0 M0	B 76% 5-yr survival
III	A	T0/1/2 N2 M0 or T3 N1/2 M0	A 56% 5-yr survival
	B	T4 Any N M0 or any T N3 M0	B 49% 5-yr survival
IV		Any T Any N M1	16% 5-yr survival

Treatment

Treatment

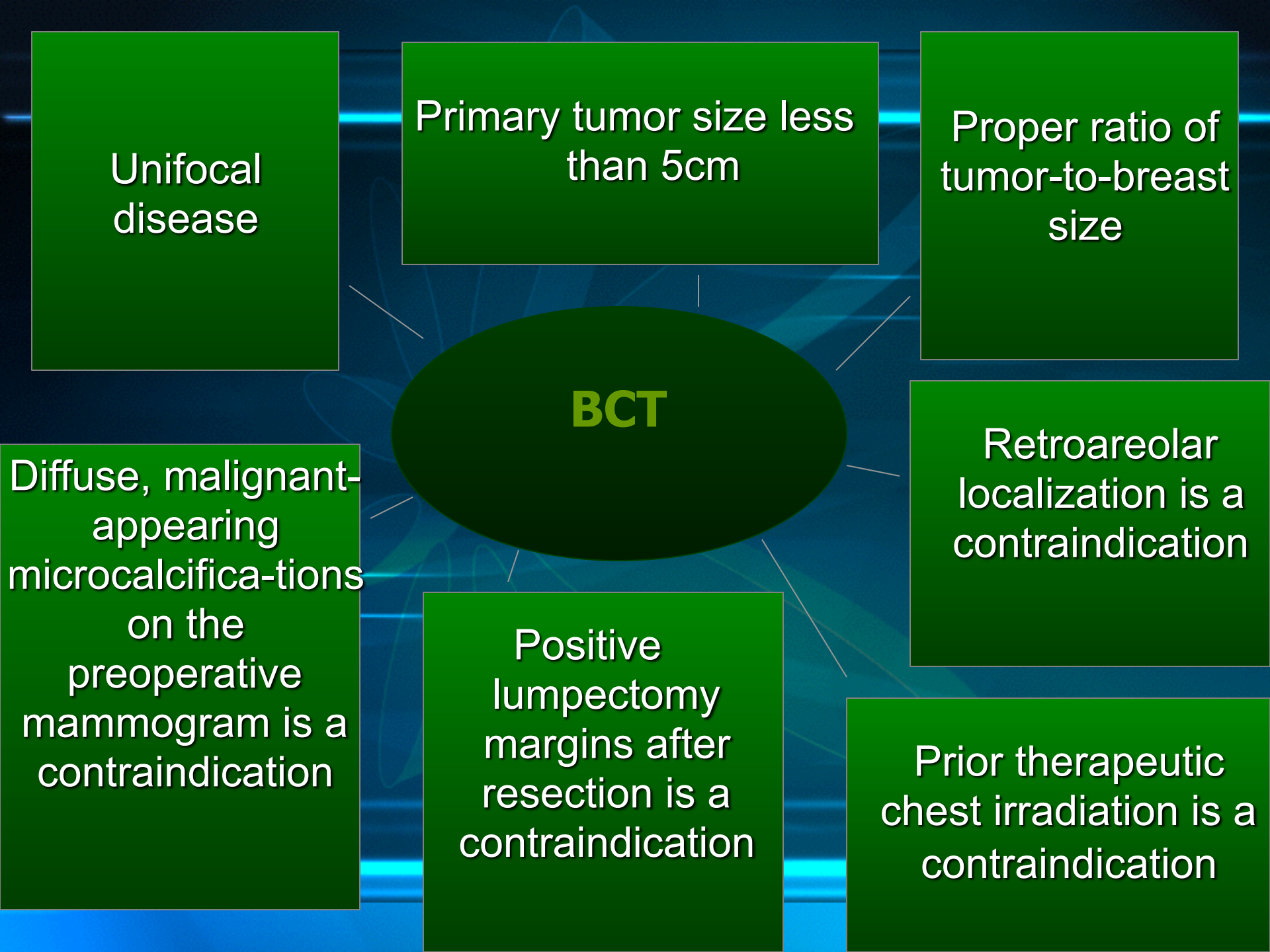
- à Surgery
- à Chemotherapy
- à Radiotherapy
- à Hormone therapy
- à Targeted therapy

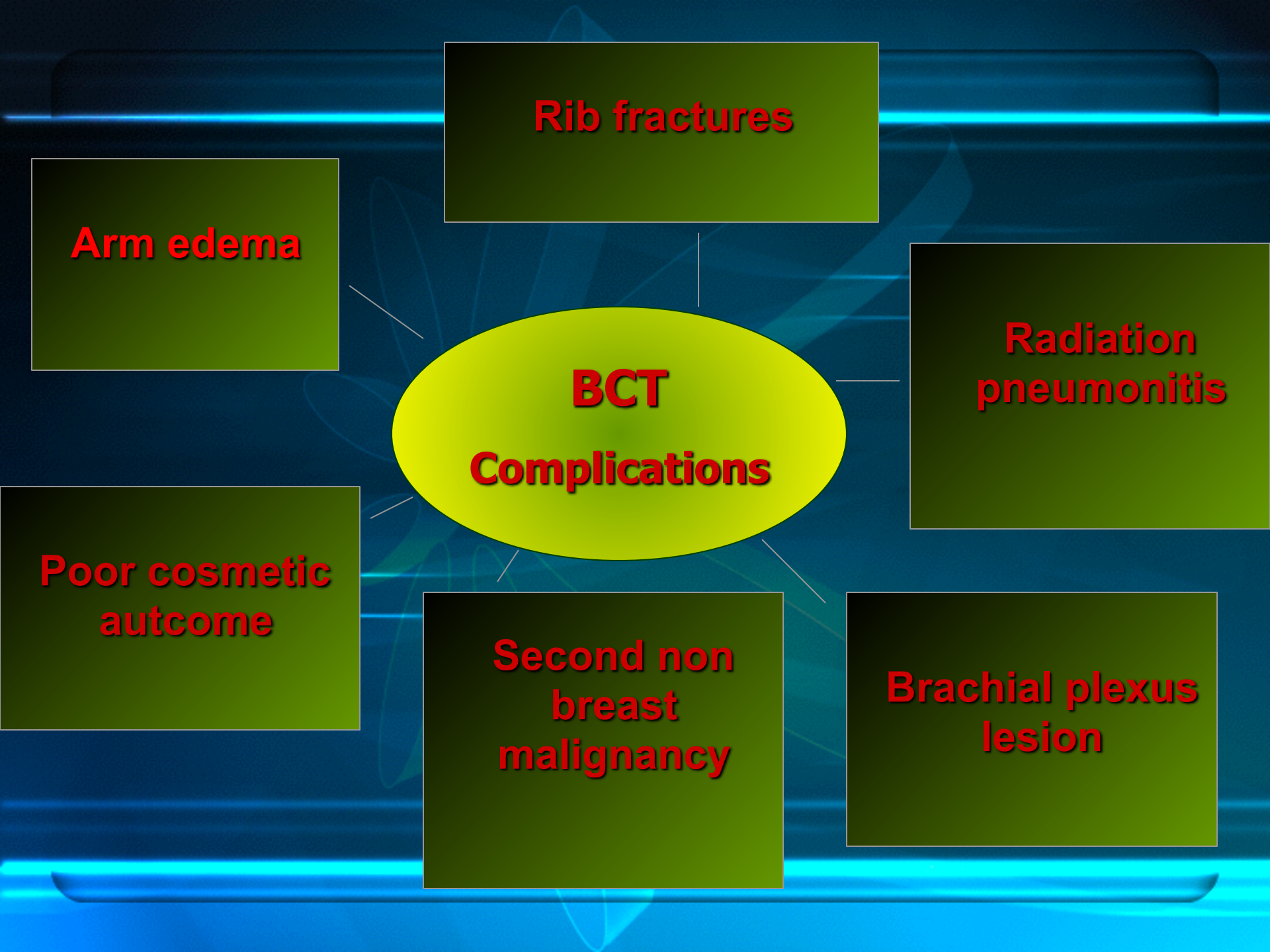
Surgery

- à Tumorectomy
- à Breast Conserving Therapy
- à Total mastectomy
- à Modified mastectomy
- à Reconstruction
- à Palliative operations

BCT: removing of tumor, sentinel lyph node followed by RTH
Radical treatment!

Pathologic diagnosis with fine needle aspiration (FNA) or core needle biopsy (CNB) should be obtained before any surgical procedure


Unifocal disease
Primary tumor size less than 5cm
Proper ratio of tumor-to-breast size
BCT
Diffuse, malignant-appearing microcalcifica-tions on the preoperative mammogram is a contraindication
Retroareolar localization is a contraindication
Positive lumpectomy margins after resection is a contraindication
Prior therapeutic chest irradiation is a contraindication


Rib fractures
Arm edema
BCT
Complications
Radiation pneumonitis
Poor cosmetic autcome
Second non breast malignancy
Brachial plexus lesion

Sentinel lymph node biopsy

A sentinel node

Theoreticaly, first lymph node collecting cancer cells that metastaze from the tumor

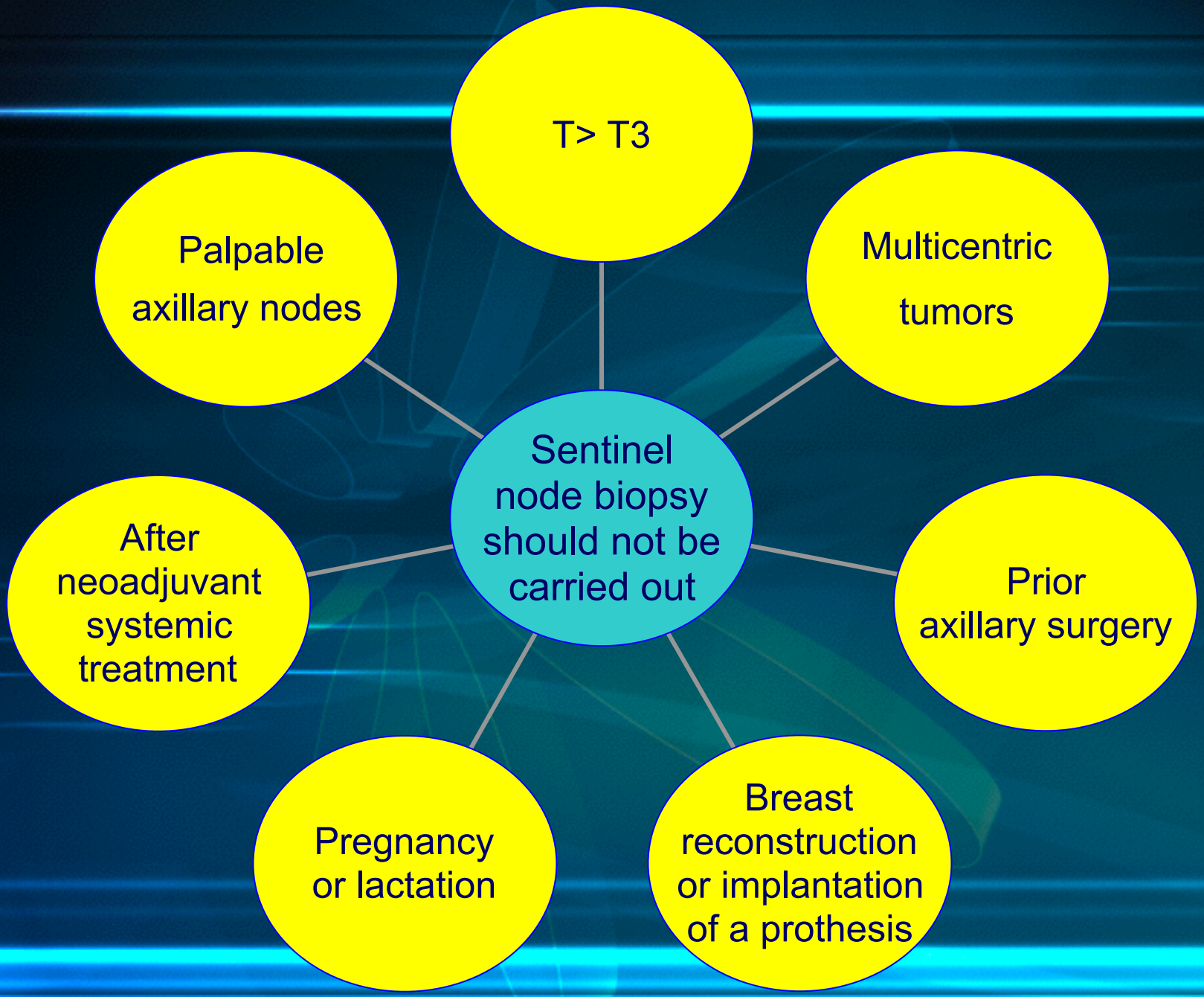
Procedure

An injection with a radionuclide near the tumor →

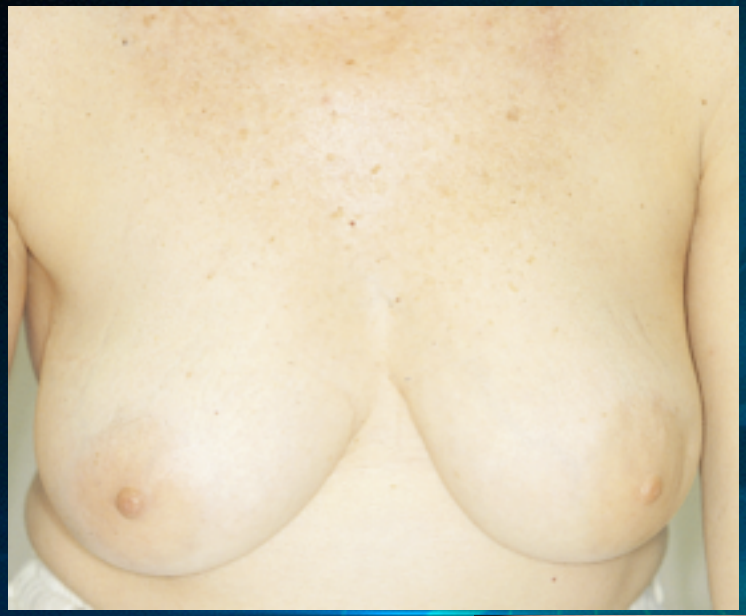
Scinctigraphic imaging →

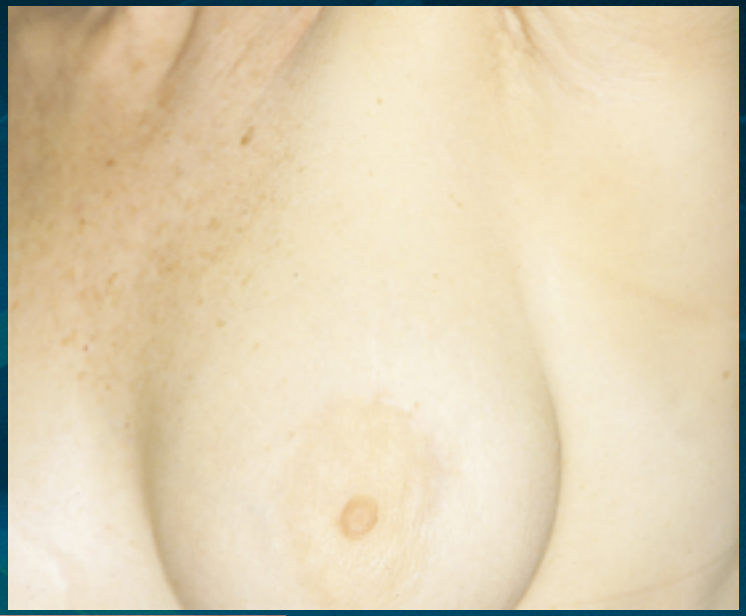
Just before the biopsy: injection of a blue dye →

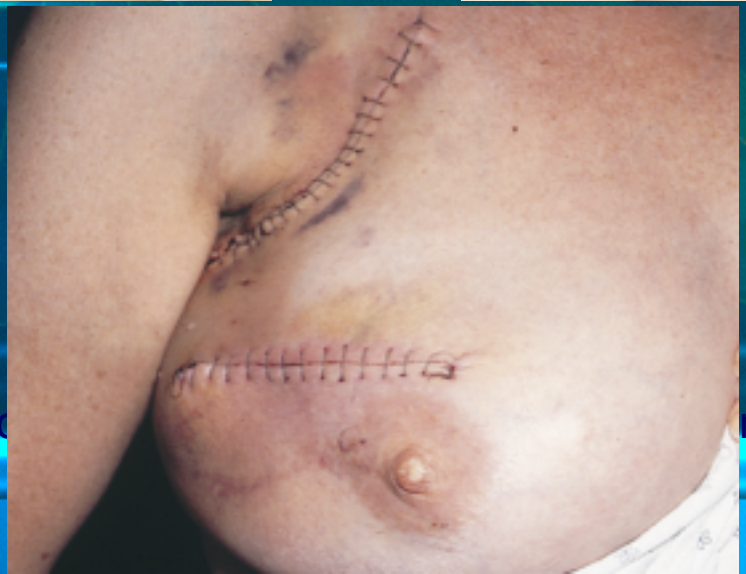
During the biopsy: visual detection+ radionuclide detection of a sentinel node


T> T3
Palpable axillary nodes
Multicentric tumors
Sentinel node biopsy should not be carried out
After neoadjuvant systemic treatment
Prior axillary surgery
Pregnancy or lactation
Breast reconstruction or implantation of a prothesis

Surgery



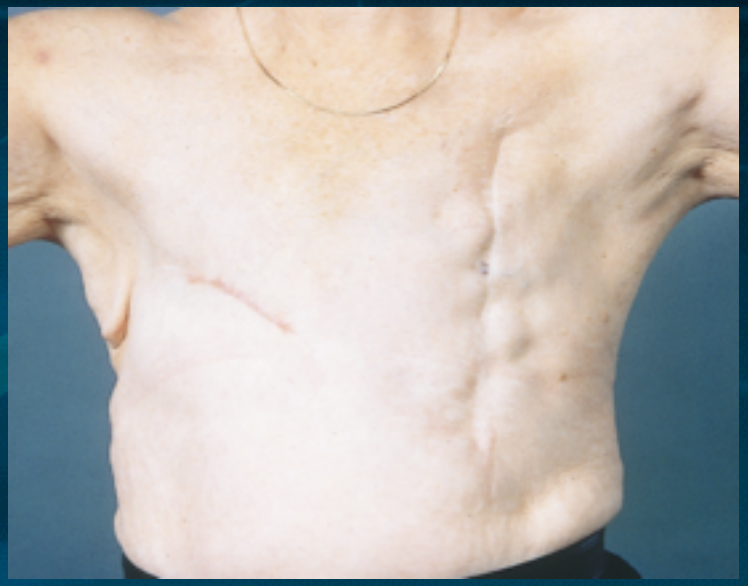




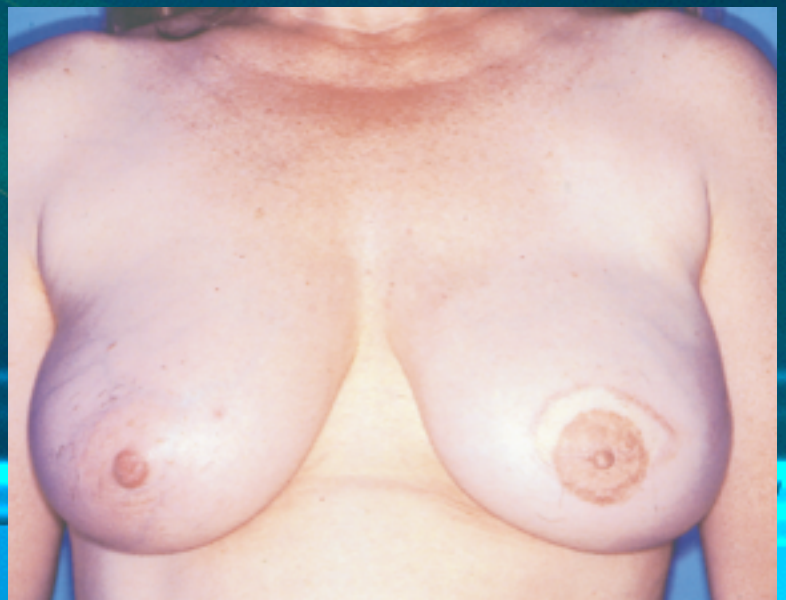
Poor cosmetic outc n size, and hematoma

Surgery

Metachronous bilateral breast cancers treated with radical mastectomy (left) and modified radical mastectomy (right).



Reconstruction of the breast



Systemic treatment

St. Gallen consensus

Table 1

Systemic Treatment Recommendations for Breast Cancer Subtypes

Subtype		Clinico-pathologic definition	Treatment
Luminal A		• ER and/or PgR positive • HER2 negative • Ki-67 low (<14%)	Endocrine therapy alone
Luminal B	HER2-	• ER and/or PgR positive • HER2 negative • Ki-67 high(≧14%)	Endocrine ± cytotoxic therapy
	HER2+	• ER and/or PgR positive • HER2 over-expressed or amplified • Any Ki-67	Cytotoxics + anti-HER2 + endocrine therapy
HER2+		• HER2 over-expressed or amplified • ER and PgR absent	Cytotoxics + anti-HER2
Triple-negative		• ER and PgR absent • HER2 negative	Cytotoxics

St Gallen International Expert Consensus 2011

Ki-67

- is a protein that in humans is encoded by the *MKI67* gene (antigen identified by monoclonal antibody Ki-67).

- is a cellular marker for proliferation.[5] It is strictly associated with cell proliferation. During interphase, the Ki-67 antigen can be exclusively detected within the cell nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. Ki-67 protein is present during all active phases of the cell cycle (G_1, S, G_2, and mitosis), but is absent from resting cells (G_0).

St. Gallen consensus(Ki67 20% - new borderline)

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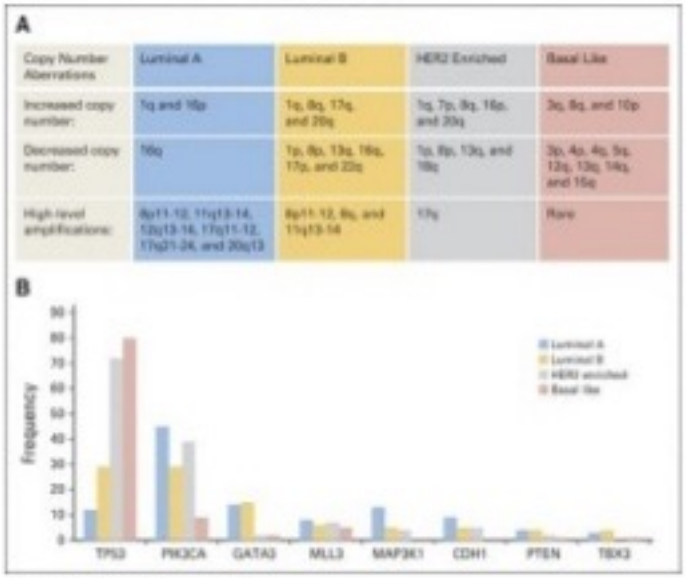
	HER2+	• ER and/or PgR positive • HER2 over-expressed or amplified • Any Ki-67	Cytotoxics + anti-HER2 + endocrine therapy
HER2+		• HER2 over-expressed or amplified • ER and PgR absent	Cytotoxics + anti-HER2
Triple-negative		• ER and PgR absent • HER2 negative	Cytotoxics

St Gallen International Expert Consensus 2011

St. Gallen 2013

INTRINSIC SUBTYPES

SOMATIC MUTATIONS AND MOLECULAR ALTERATIONS



A: *copy number alteration*

B: *most commonly mutated cancer-related genes*

Ades F, JCO 2014

SURROGATE DEFINITIONS OF INTRINSIC SUBTYPES

(St Gallen International Expert Consensus 2013)

Intrinsic subtype	Clinico-pathologic surrogate definition	Notes
Luminal A	**Luminal A-like** *all of:* ER and PgR + HER2 - Ki-67 'low'	Ki-67< 14% or 20% PgR ≥20%
Luminal B	**Luminal B-like (HER2 negative)** ER + HER2 - *and at least one of:* Ki-67 'high' PgR 'negative or low'	Ki-67 ≥ 14% or 20% PgR <20%
	Luminal B-like (HER2 positive) ER + HER2 + Any Ki-67, Any PgR	
Erb-B2 overexpression	**HER2 positive (non-luminal)** HER2 + ER and PgR absent	
Basal-like	**Triple negative (ductal)** ER and PgR absent HER2 -	There is an 80% overlap between 'triple-negative' and 'basal-like' subtype. TNBC also includes some special histological types

Goldhirsch A. Ann Oncol 2013

Adjuvant Chemotherapy in ER-negative disease:

Yes

- Triple negative tumor
- Patients receiving anti-HER2 treatment

No

- Rare phenotypes with N0 and no other signs of increased metastatic potential
- In T1a N0

Adjuvant Chemotherapy in ER-positive, HER2-negative disease:

Relative indications:

- High grading (3)
- Lower hormone receptors level
- > 4 lymph nodes involved
- Extensive peritumoral vascular invasion
- pT> 5cm (T3)
- Patient's preference

neoadjuvant treatment

» with locally advanced tumors cT3; N2+

Question

Which factor is a relative indication for adjuvant chemotherapy for patients with ER-positive and HER2-negative breast cancer?

A. Low grading (1)

B. > 2 lymph nodes involved

C. Lower hormone receptors level

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ADJUVANT SYSTEMIC Chemotherapy USED IN THE TREATMENT OF EARLY BREAST CANCER

Regimen		Frequency	**Drugs**
TAC		Every 21 days X 6 treatments	**Docetaksel** **Doxorubicin**
AC		Every 21 days x 4 treatments	**Cyclophosphamide** **Doxorubicin**
FEC		Every 21 days x 6 times	**5FU,Cyclophosphamide Epirubicin**
AC with Paclitaxel		Every 21 days x 4 treatments	**AC ->Paclitaxel**
AC with DTX		Every 21 days x 4 treatments	AC-> Docetaksel

Hormon therapies

Selective estrogen receptor modulators **(SERM)**	**tamoxifen**, toremifene
Luteinizing hormone-releasing hormone analogue (**GnRHA** – gonadotropin-releasing hormone analogue)	goserelin, luprorelin, triptorelin, buserelin
Third-generation aromatase inhibitors **(AI)**	anastrozole, letrozole
	exemesthane
Progestins	medroxyprogesterone acetate, megestrol acetate
Estrogen receptor down-regulator	fulvestrant

Adjuvant endocrine therapy:

- Applied in all pts whose tumors show evidence of endocrine responsiveness (the presence of ANY detectable estrogen receptor)

Question

Adjuvant endocrine therapy should be given to the patients :

A. whose tumors show the presence of any detectable estrogen receptor

B. whose tumors show presence the estrogen receptors in at least > 9% of tumor cells

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A woman with a 6-cm breast cancer (cT3) and clinically palpable immobile ipsilateral axillary nodes (cN2) would best be served by

A. surgery
B. neoadjuvant chemotherapy
C. adjuvant chemotherapy
D. radiation therapy

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Adjuvant endocrine therapy (ER+):

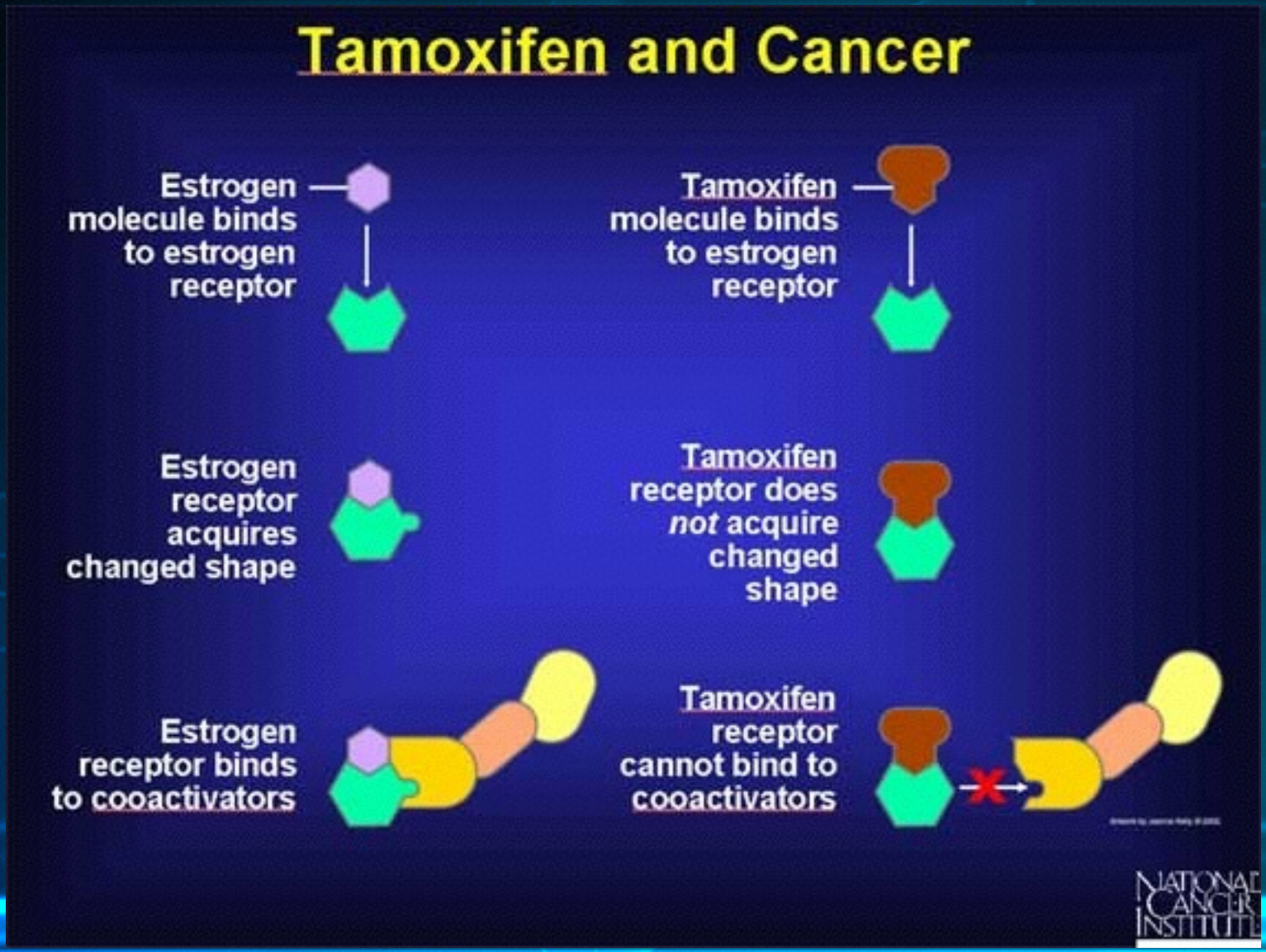
Premenopausal patients

- 1. Tamoxifen+ ovarian function suppression GnRHA
- Contraindicated: aromatase inhibitors!!!

Postmenopausal patients

1. Tamoxifen
2. Aromatase inhibitors

TAMOXIFEN


Tamoxifen and Cancer
Estrogen molecule binds to estrogen receptor
Tamoxifen molecule binds to estrogen receptor
Estrogen receptor acquires changed shape
Tamoxifen receptor does *not* acquire changed shape
Estrogen receptor binds to cooactivators
Tamoxifen receptor cannot bind to cooactivators
NATIONAL CANCER INSTITUTE

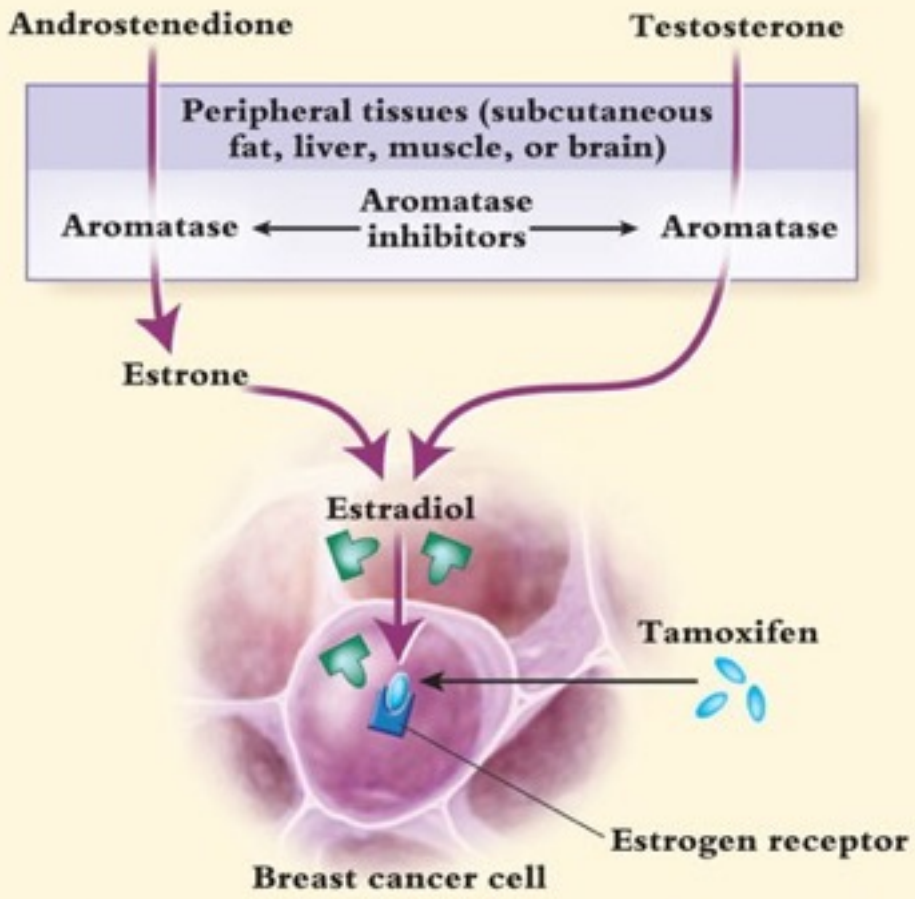
Tamoxifen

side effects therapy

- endometrial cancers
- thromboemboliae
- BUT improves bone mass

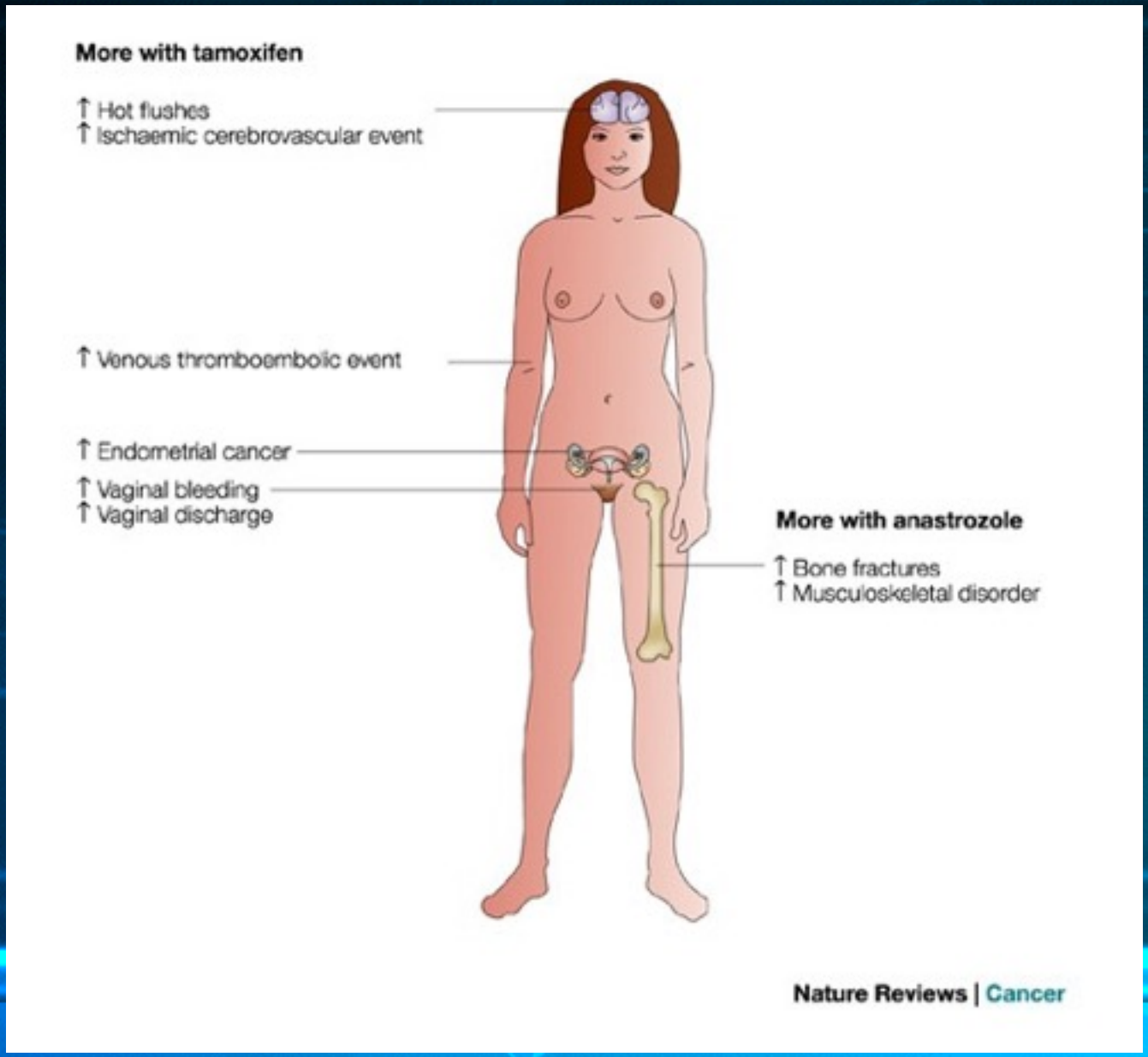
AI Aromatase Inhibitors

Figure 2. Mechanism of action of the aromatase inhibitors.



Source: Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med. *2003;348:2431-2442. Copyright © 2003 Massachusetts Medical Society. All rights reserved.*

Tamoxifen vs IA



Question

What kind of the adjuvant endocrine therapy is the best option for your premenopausal patients with breast cancer (ER+):

A. Tamoxifen + GnRH

B. Aromatase inhibitor alone

C Initial treatment with aromatase inhibitor and then Tamoxifen

Question

What kind of the adjuvant endocrine therapy is the best option for your premenopausal menstruating patients with breast cancer (ER+):

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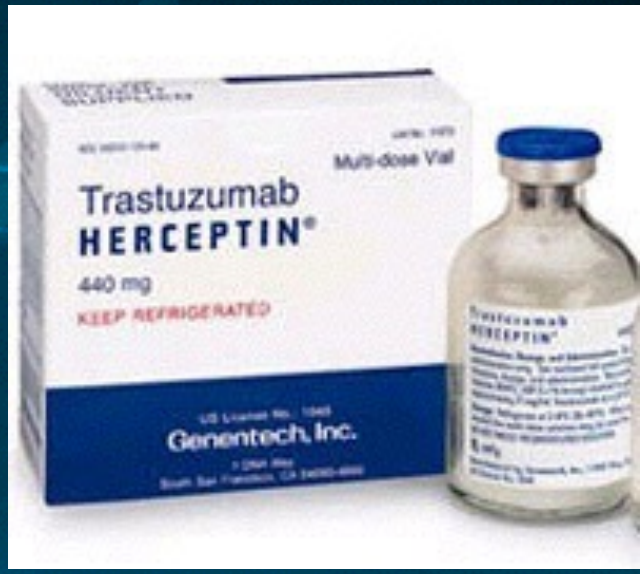
C Initial treatment with aromatase inhibitor and then Tamoxifen

Targeted Therapy

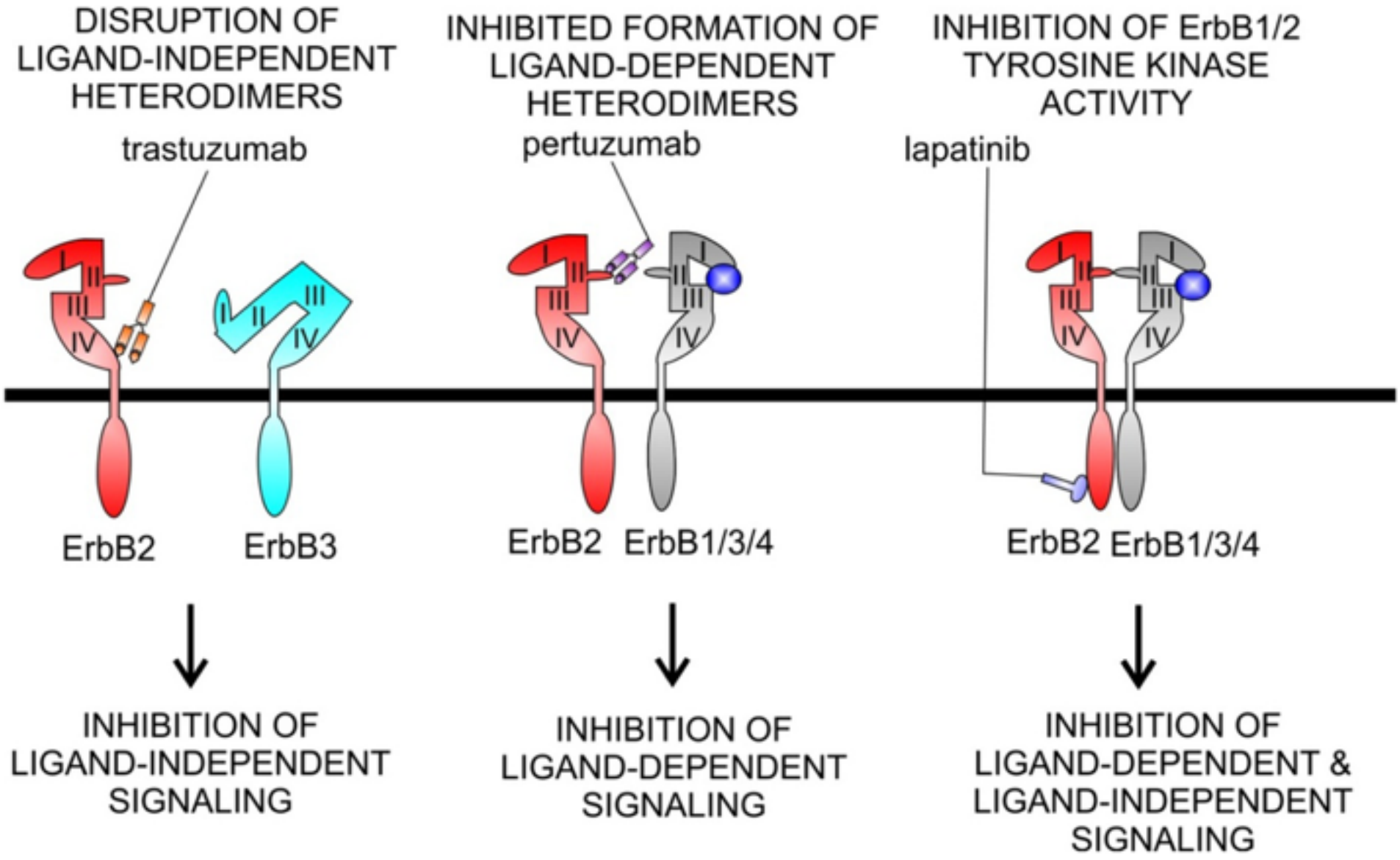
Herceptin - Trastuzumab



- à Humanized monoclonal antibody against HER2 receptor
- à Reduces cancer cells proliferation
- à Suppresses angiogenesis
- à Side effects: cardiotoxity (especially when given with antracyclines!); also weakness, nausea, vomiting- rare

Avastin – bevacizumab (anti VEGF)

movie


DISRUPTION OF LIGAND-INDEPENDENT HETERODIMERS
trastuzumab
I
II
III
IV
ErbB2
ErbB3
INHIBITED FORMATION OF LIGAND-DEPENDENT HETERODIMERS
pertuzumab
ErbB2
ErbB1/3/4
INHIBITION OF ErbB1/2 TYROSINE KINASE ACTIVITY
lapatinib
ErbB2
ErbB1/3/4
INHIBITION OF LIGAND-INDEPENDENT SIGNALING
INHIBITION OF LIGAND-DEPENDENT SIGNALING
INHIBITION OF LIGAND-DEPENDENT & LIGAND-INDEPENDENT SIGNALING

Anti-HER2 therapy in adjuvant:

- 1 year duration of trastuzumab therapy
- Anti-HER2 + chemotherapy
- Anti-HER2 + endocrine therapy
- No need if HER2+ if T<1cm and N0

Question

A 55-year-old woman noted a mass in her left breast 2 months ago. On examination: 2 to 3 cm mass in the upper outer quadrant, no palpable lymph nodes. BCT is performed. Cancer cells are negative for ER and PR, but positive for HER2. Which of the following additional treatment options is most likely to be effective in this case?

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B. Tamoxifen or anastrozol
C. Cefalosporins
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What is the recommended duration for the therapy with Transtuzumab (Herceptin) in patients with breast cancer HER2+?

A. 6 months

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C 5 years

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FOLLOW UP

Recommended breast cancer surveillance

MODE OF SURVEILLANCE	SUMMARY OF RECOMENDATION
History / physical examination	Every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annualy
Referral for genetic counseling	Criteria inculde: (1) Ashkenazi Jewish heritage, (2) History of ovarian cancer at any age in the patient or any first- or second-degree relatives, (3) Any first-degree relative with a history of breast cancer diagnosed before the age 50 years, (4) Two or more first- or second-degree relatives diagnosed with breast cancer at any age, (5) Patient or relative with diagnosis of bilateral breast cancer' (6) History of breast cancer in a male relative
Breast self-examination	All women should be counseled to perform monthly breast self-examinatin
Mammography	First post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis but no earlier than 6 months after definitive radiation therapy.
Pelvic examination	

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Pelvic examination	Regular gynecologic follow-up is recommended for all women. Patients who receive TAM should be advised to report any vaginal bleeding to their physicans.