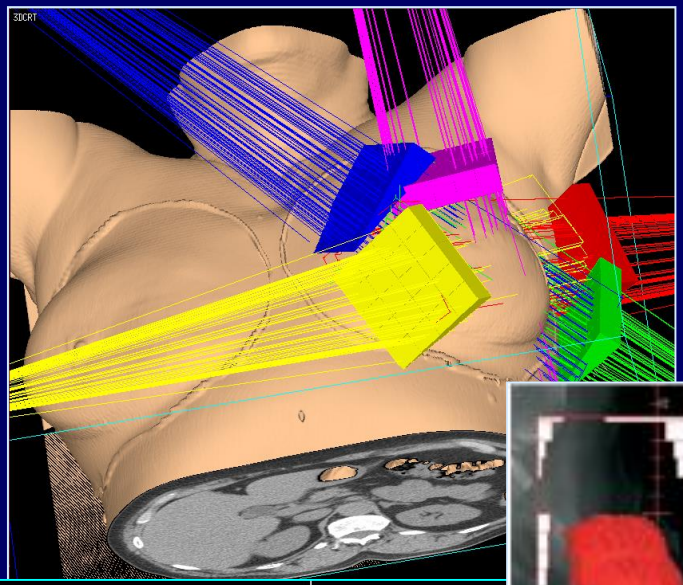
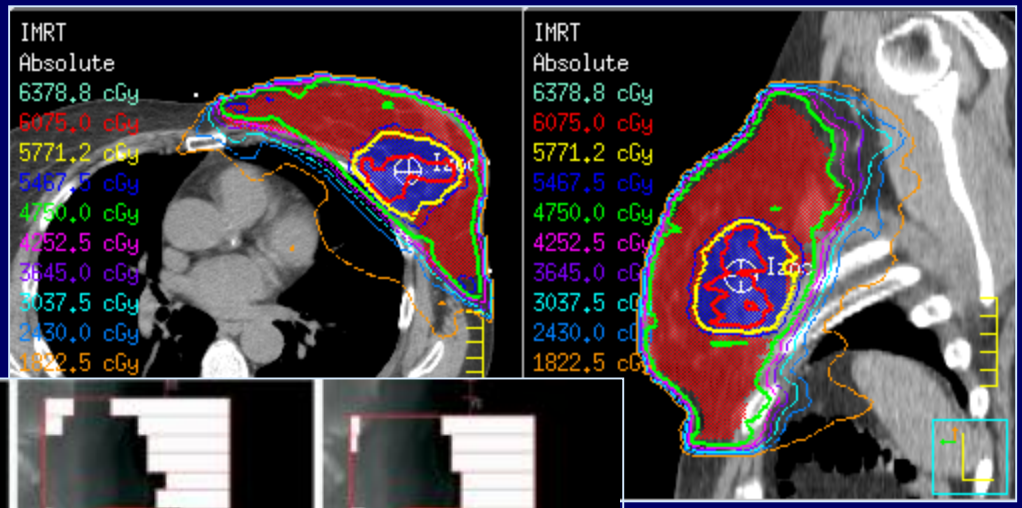
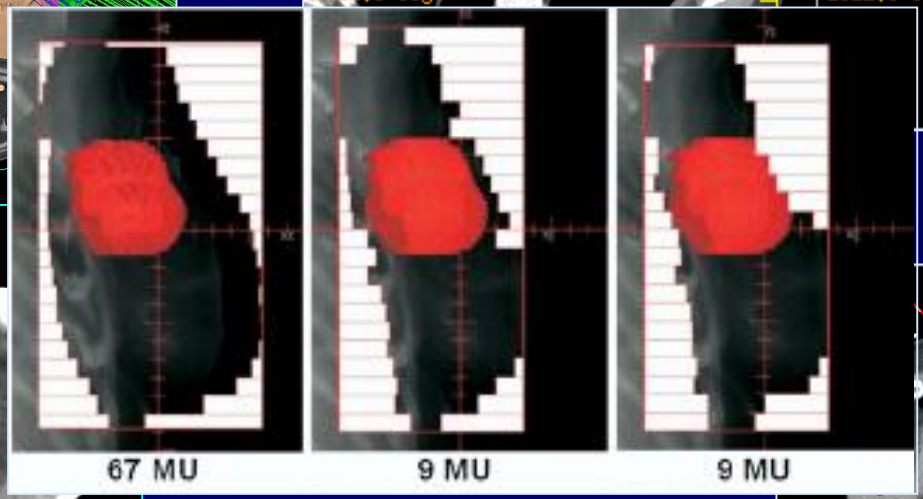
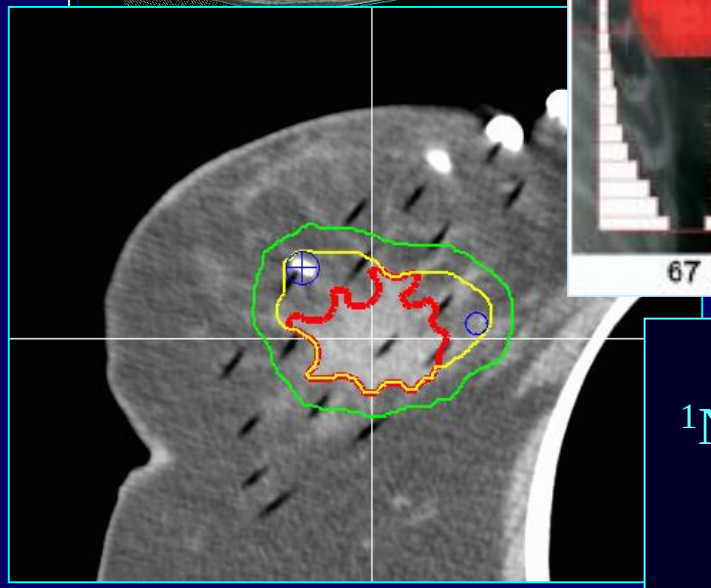
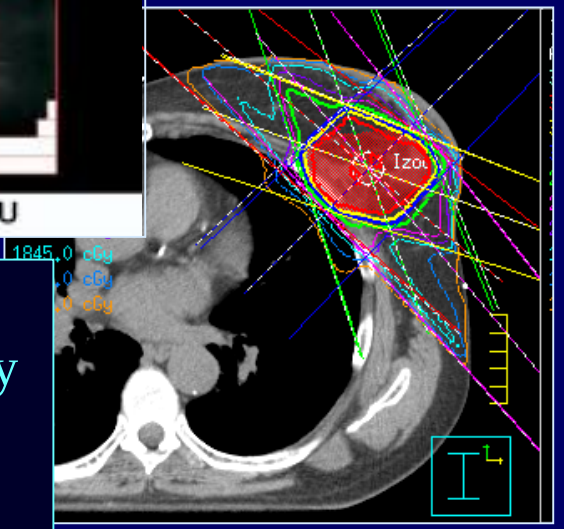
Multidisciplinary management of breast cancer











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Incidence of breast cancer in Hungary 2014
Female population

1.	Breast	7911 (21%)
2.	Colorectal	4852 (13%)
3.	Lung & trachea	4610 (12%)
…		
All:		37830

Emlőrákos halálozás Magyarországon 2014

1.	Lung & trachea	3277 (22%)
2.	Colorectal	2202 (15%)
3.	Breast	2107 (14%)
…		
All:		14985

Etiology of breast cancer

- 90% - Sporadic
- 10% - Hereditary gene mutation (BRCA 1 & 2)

- Etiological factors
  - Oestrogen hormones:
    - Early first mutation
    - Late menopause
    - Hormonal contraceptives
    - Menopausal hormone supplementation
    - High-fat containing diat
    - Alcohol consumtion
  - Preventive factors:
    - Childbirth at young age
    - Physical activity

Histology of breast tumours

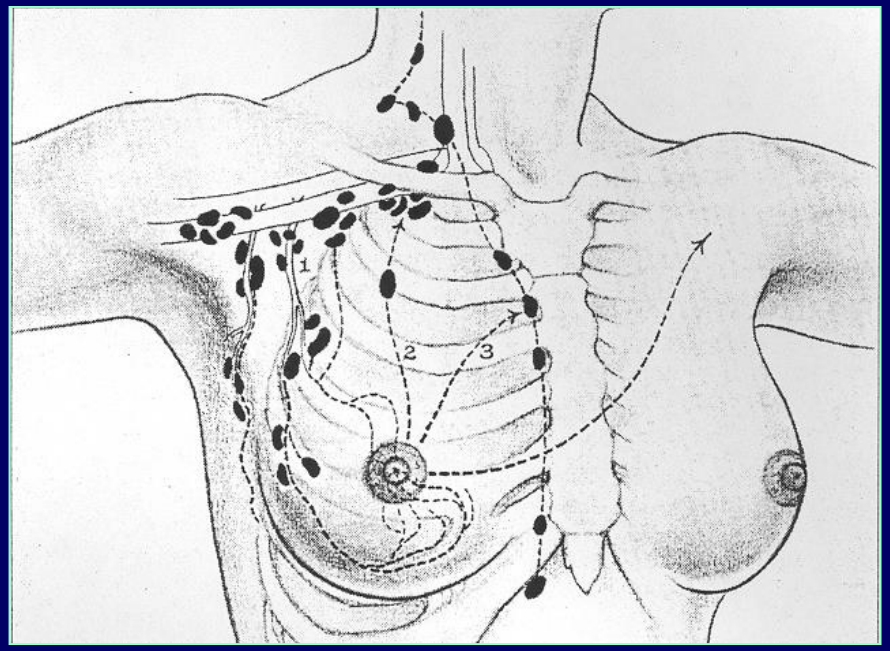
- Adenocarcinoma arising from glandular breast tissue(>95%)

The most common histological types of breast cancer	
In situ cancers	Lobular carcinoma in situ (LCIS)
	Ductal carcinoma in situ (DCIS)
	Paget's disease of the nipple
Invasive cancers	Invasive ductal carcinoma (IDC)
	Invasive lobular carcinoma (ILC)
	Papillary cancer
	Tubular cancer
	Mucinous cancer
	Medullary cancer

- Rare breast tumours:
  - Breast sarcomas
  - Primary breast lymphomas

Lymphatic pathways of breast cancer:

1. Axillary LNs
2. Supraclavicular LNs
3. Parasternal LNs



Haematogen, distant metastases:

- Liver
- Lung
- Bones
- Brain

TNM classification of breast cancer

- T
  - Tis: Carcinoma in situ
  - T1: ≤ 20 mm
  - T2: 21-50 mm
  - T3: > 50 mm
  - T4: thoracic wall, skin, mastitis carcinomatosa
- N
  - N0: No LN met.
  - N1: mobile ipsilateral axillary LN mets.
  - N2: fixed axillary LN or parasternal LN mets.
  - N3: supraclavicular LN met.
- M
  - M0: No distant met.
  - M1: Presence of distant mets.

Early breast ca

Locoregionally advanced breast ca

Metastatic breast ca

Stage:

0: Tis N0 M0
I: T1 N0 M0
II: T1-2 N1 M0;
T2-3 N0 M0

III: T3 N1 M0;
All N2-3 M0;
All T4 M0

IV: M1

pTNM classification of breast cancer

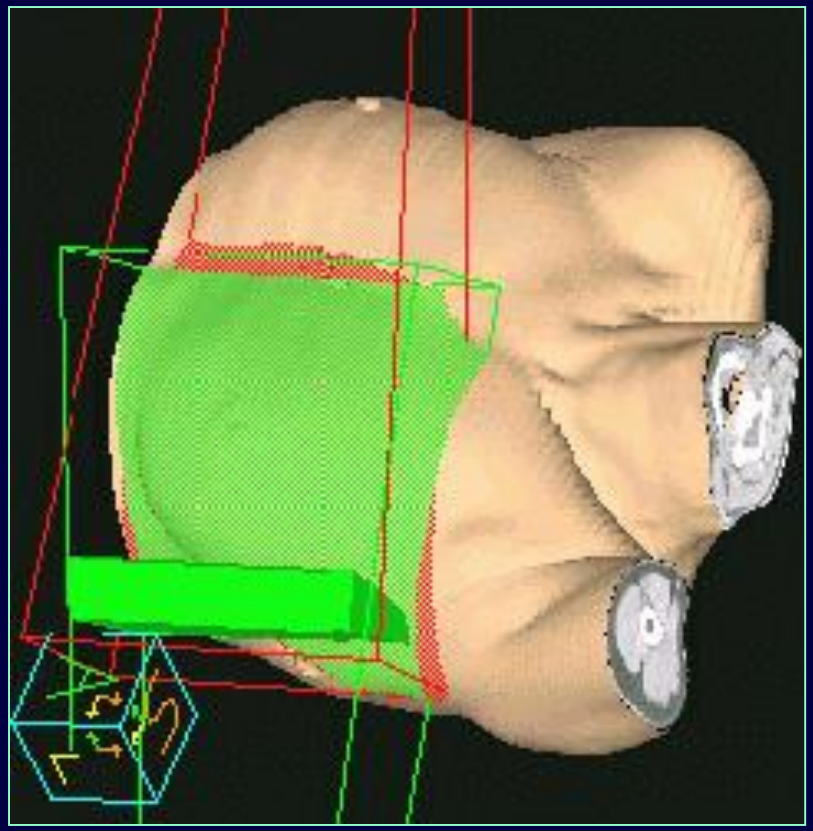
- pT
  - pTis: Carcinoma in situ
  - pT1: ≤20 mm
    - pT1mic: ≤1 mm
    - pT1a: >1-5 mm
    - pT1b: >5-10 mm
    - pT1c: >10-20 mm
  - pT2: >20-50 mm
  - pT3: > 50 mm
  - pT4: thoracic wall, skin, mastitis carcinomatosa
- pN
  - pN0: No LN met.
  - pN1mi: axillary micrometastasis (≤2 mm)
  - pN1a: 1-3 axillary LN mets. (>2 mm)
  - pN2a: 4-9 axillary LN mets.
  - pN2b: parasternal LN met.
  - pN3a: ≥10 axillary LN mets.
  - pN3c: supraclaviculari LN met.
- pM
  - pM0: No distant met
  - pM1: Histologically proven distant met.

Breast cancer - Symptoms, diagnosis and staging

- Asymptomatic in early stages
- Palpable mass
  - Breast
  - Ipsilateral axillary nodes
  - Ipsilateral supraclavicular nodes
- Exulceration, fixation to chest wall
- Mastitis carcinomatosa
- Staging:
  - Mammography and breast and LN US
  - Fine-needle aspiration cytology or core biopsy
  - Chest X-ray/CT
  - Abdominal US/CT
  - Bone-scan
  - PET-CT ($\geq$ Stage III)

Multidisciplinary management of breast cancer

- Surgery
  - Breast conserving surgery = BCS (quadrantectomy, wide excision)
  - Modified radical mastectomy
  - Axillary dissection
  - Sentinel LN biopsy
- Radiotherapy = RT
  - Postoperative
  - Preoperative
  - Definitive
  - Palliative
- Systemic treatments
  - Neoadjuvant, adjuvant, palliative
  - Chemotherapy = CT
  - Hormonal therapy = HT
  - Targeted biological treatment



Basic principles of the management of breast cancer

- Main factors of treatment decisions
  - Primary tumour size (T-status)
  - Status of regional LNs (N-status)
  - Presence or absence of distant mets. (M-status)
  - Histological type and tumour charecteristics:
    - Differenciation (Grade 1-3)
    - Hormone receptor status (ER & PgR)
    - HER-2 status
    - Lympho-vascular invasion (LVI)
    - Status of surgical margins (R1, R0, close)
    - Patients' age, comormidities, ECOG performance status
- Early stages (St. 0-I-II):
  - Local treatments (Surgery + RT) ± adjuvant systemic treatments
- Locoregionally advanced breast ca. (St. III)
  - Neoadjuvant CT/biolgical therapy + surgery + RT
- Metastatic breast ca. (St. IV)
  - Palliative systemic drug treatments + palliative RT

Surgical management

- Breast conserving surgery
  - Quadrantectomy (excision with a margin of 2 cm + skin above tumour and pectoral fascia)
  - Wide excision (excision with a margin of 2 cm, wo. the skin and fascia)
- Mastectomy
- Axillary LN biopsy (>2 pos. LNs → Axillary dissection)
- Axillary dissection

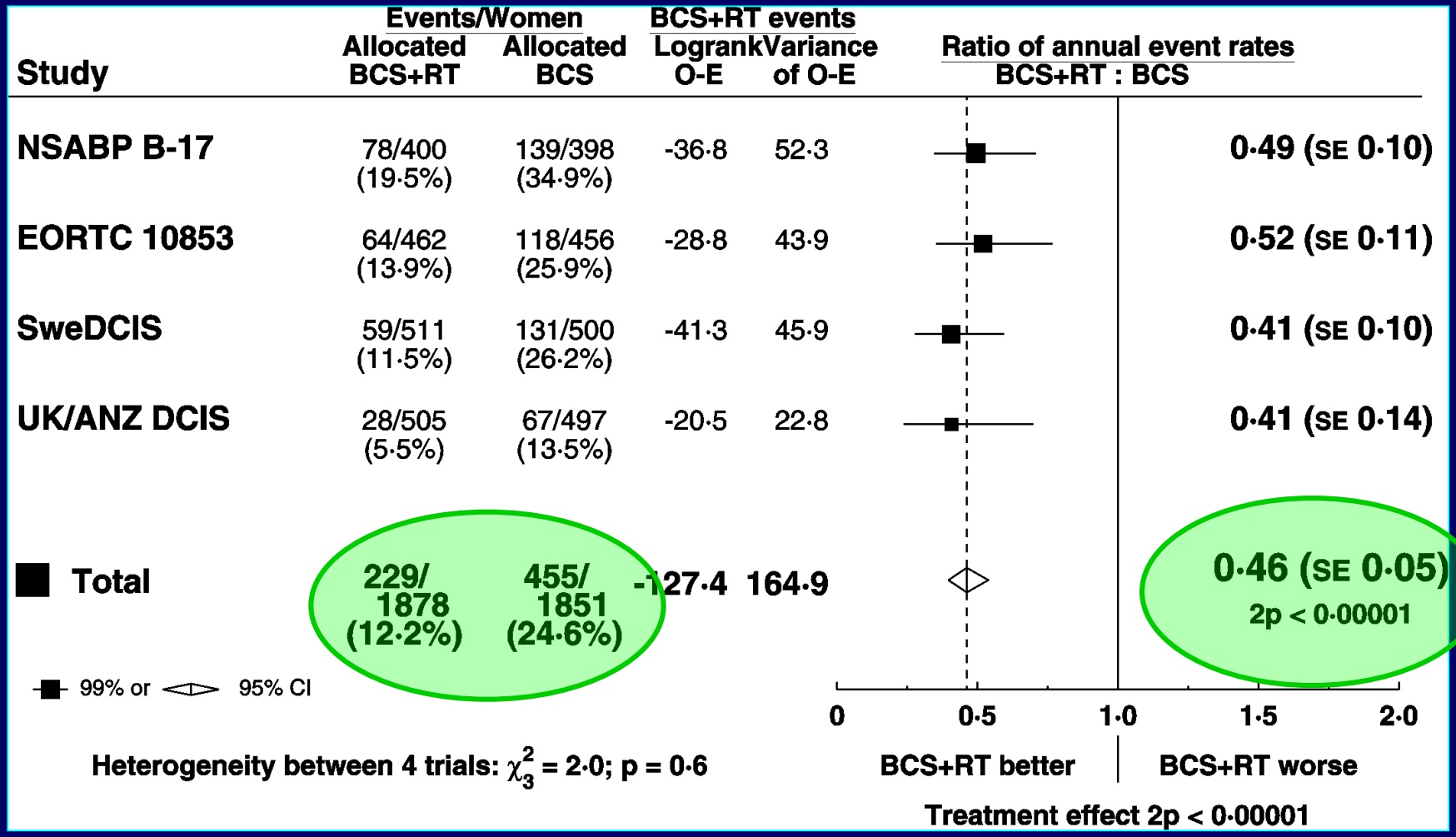
Figure II.8.-1:
Patient after left-sided breast conserving surgery

Figure II.8.-2:
Patient after right-sided total mastectomy

Radiotherapy of breast cancer

- Early stages (St. 0-I-II)
  - Postoperative RT
    - After BCS – irradiation of the remaining breast tissue
    - After mastectomy – irradiation of the chest wall
    - Irradiation of the regional LNs
- Locoregionally advanced breast ca. (St. III)
  - Neoadjuvant CT
  - Resectable: Postoperative RT
  - Non resectable: Preoperative or definitive RT
- Irradiation of distant mets. (St. IV)
  - Palliative RT

DCIS: BCS + RT versus BCS alone
Ipsilateral breast tumour recurrence according to RT



RT decreases the risk of local recurrence by 50-60%

Radiotherapy guidelines– Carcinoma in situ

- **Lobular carcinoma in situ (LCIS) – after BCS**
- RT is not indicated

- **In situ ductalis carcinoma (DCIS) – emlőmegtartó műtét után**
- Whole breast RT is indicated

- **DCIS – after mastectomy**
- RT is not indicated

Early invasive breast cancer - Local recurrence and overall survivval according to RT

Level I evidence – 6 randomized studies

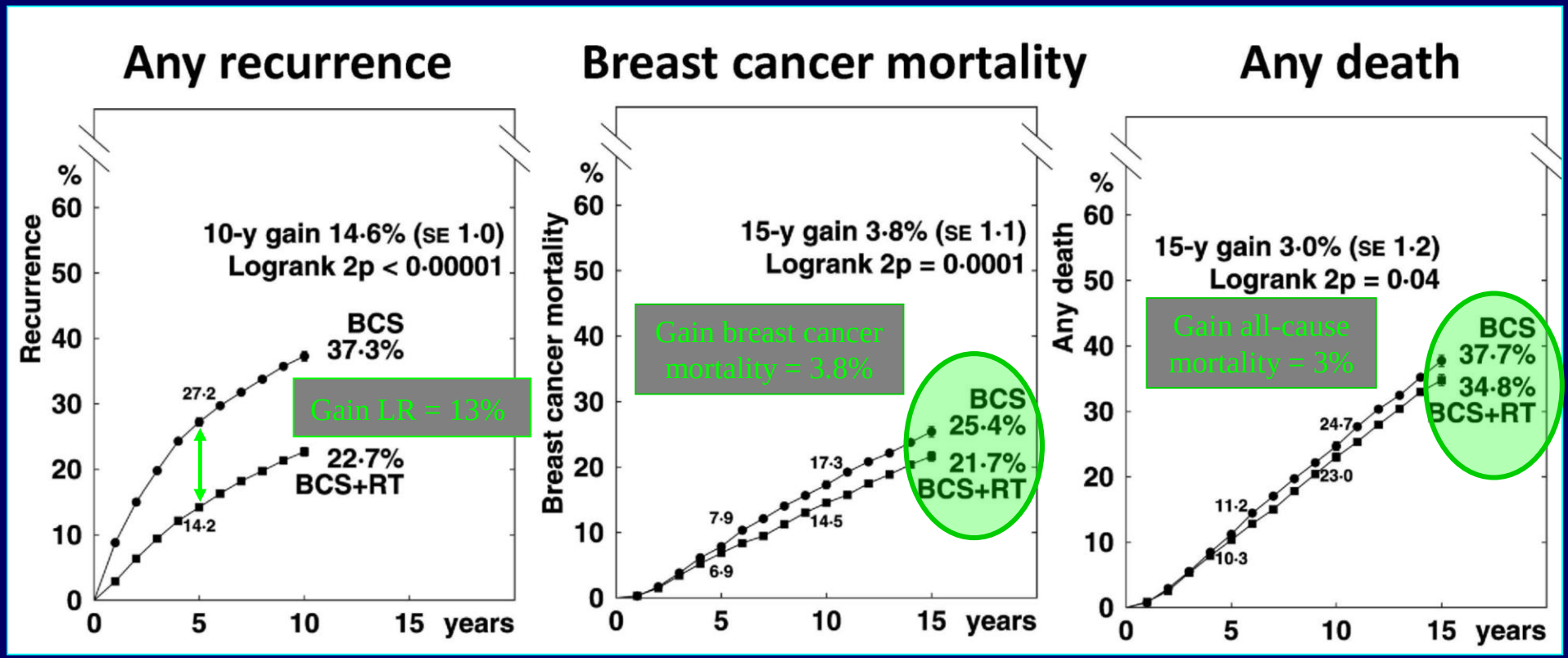
Study	FUP	BCS LR%	BCS + RT LR%	BCS OS%	BCS + RT OS%
NSABP-B-06	20 év	39%	14%	46%	46%
Milan III	9 ys	24%	6%	77%	82%
Ontario	8 ys	35%	11%	77%	79%
Uppsala	9 ys	24%	8%	78%	78%
Scottish	6 ys	25%	6%	83%	83%
London	14 ys	50%	29%	57%	60%

LR risk withour RT: 3-4 x ⇑

EBCTCG meta-analysis 2010: Effect of radiotherapy after BCS on the rate of recurrence, breast cancer mortality, and overall survival

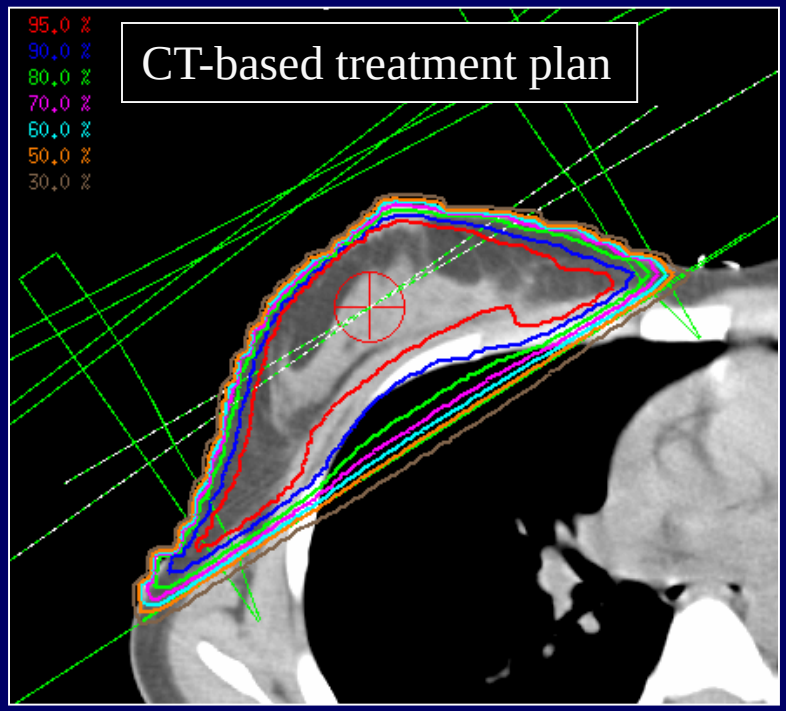
11.000 pts.

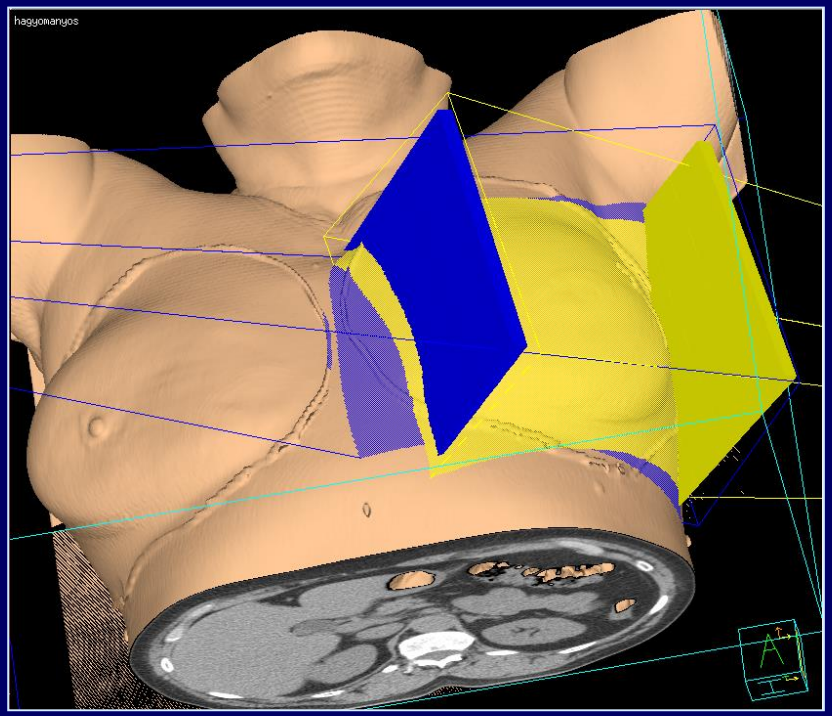
”One-to-Four Rule”

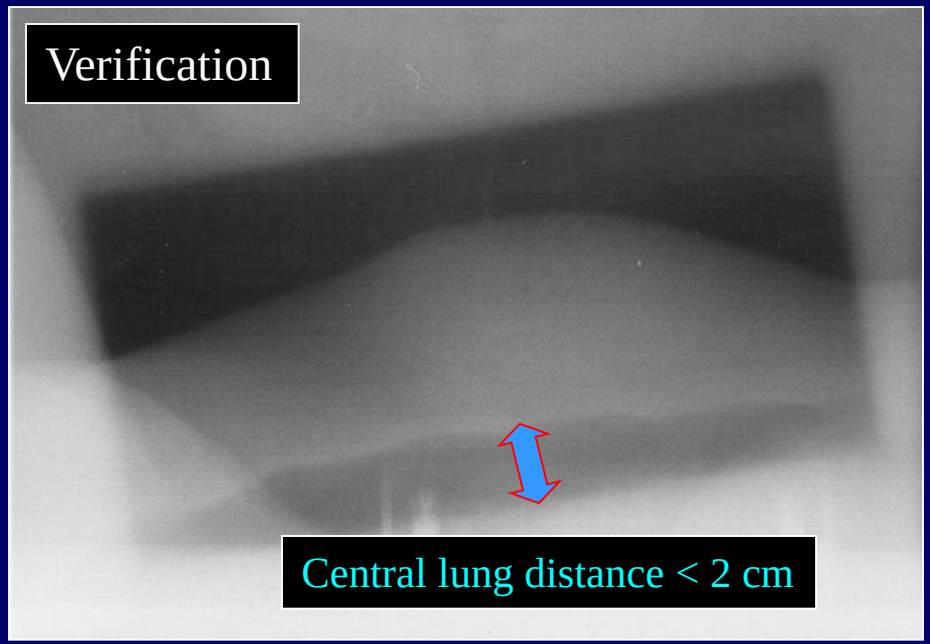


Standard RT technique after BCS - Whole Breast Irradiation (WBI)

Two opposed tangential 4-9 MV photon fields
CT-based treatment planning
Target volume: whole breast + chest-wall
Total dose: 50 Gy (25x2 Gy/5 weeks) or
40 Gy (15x2.67 Gy/3 weeks)



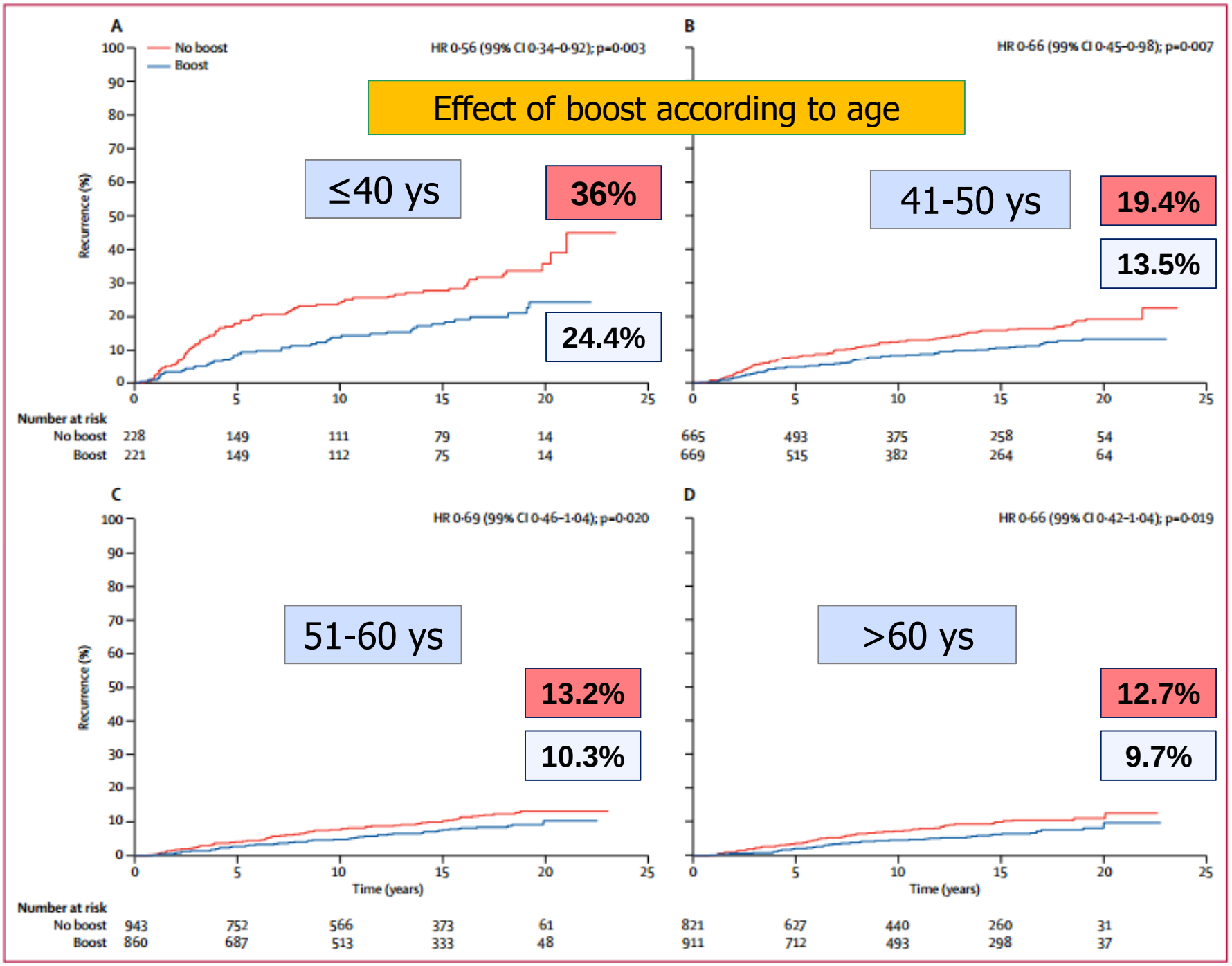




Effect of tumour bed boost irradiation on local recurrence rate

3 randomized study

Study	N	Boost dose (Gy)	Median FUP	5-year LR%	20-year LR%	Relative Risk
EORTC	5318	15-16	10.8 ys	4.3 vs 7.3	12 vs 16.4	0.65
Lyon	1024	10	3.3 ys	3.6 vs 4.5	NA	0.34
NIO, Budapest	621	12-16	5 ys	6.3 vs 13.3	NA	0.42


Effect of boost according to age
A
No boost
Boost
HR 0·56 (99% CI 0·34–0·92); p=0·003
≤40 ys
36%
24.4%
Recurrence (%)
B
HR 0·66 (99% CI 0·45–0·98); p=0·007
41-50 ys
19.4%
13.5%
Number at risk
No boost 228 149 111 79 14
Boost 221 149 112 75 14
665 493 375 258 54
669 515 382 264 64
C
HR 0·69 (99% CI 0·46–1·04); p=0·020
51-60 ys
13.2%
10.3%
Time (years)
D
HR 0·66 (99% CI 0·42–1·04); p=0·019
>60 ys
12.7%
9.7%
Number at risk
No boost 943 752 566 373 61
Boost 860 687 513 333 48
821 627 440 260 31
911 712 493 298 37

Radiotherapy guidelines – Early stage breast ca.

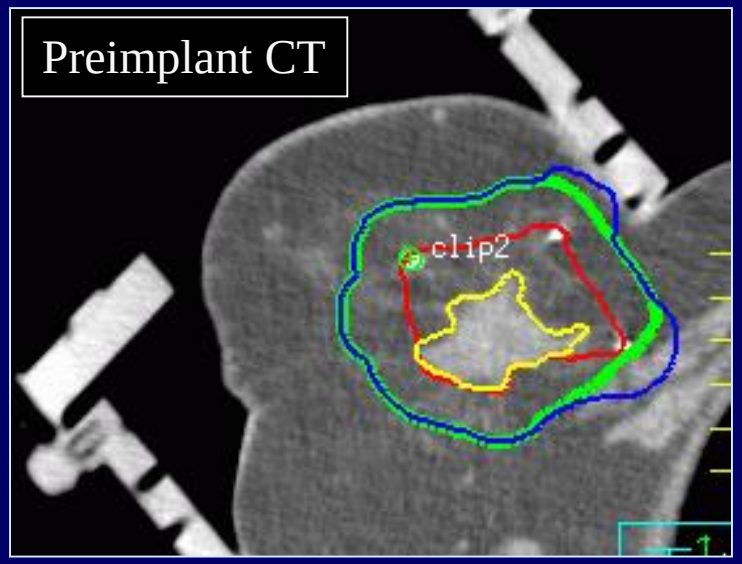
- After BCS and WBI

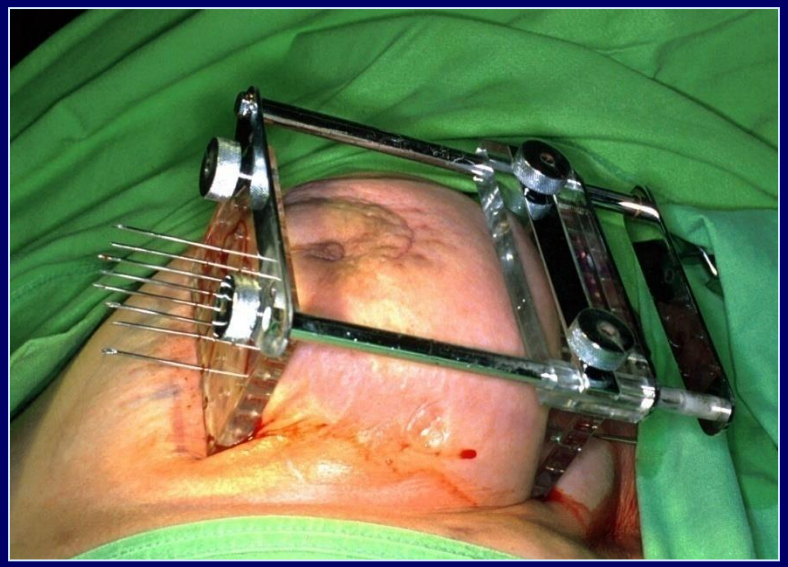
- Indications of tumour bed boost:

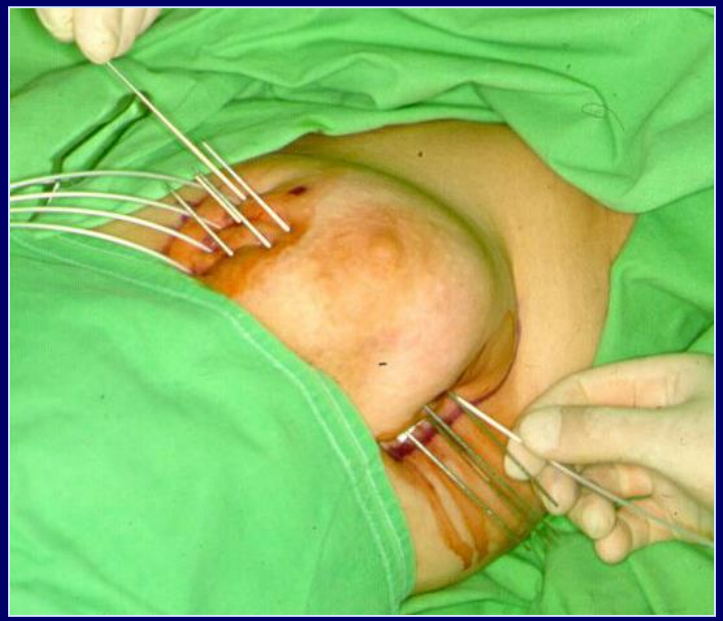
- Absolute indication:
- ≤50 years of age
- Microscopically involved surgical matgin (if reexcision is omitted)
- Close surgical margins (tumour free margin <2 mm)
- Extensive intraductal component (EIC)

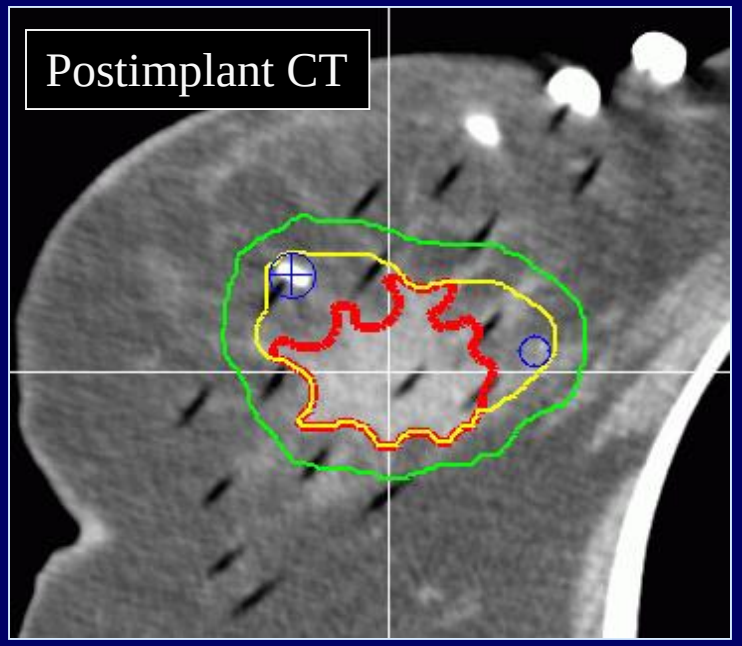
- Relative indication:
- LVI
- Poorly differentiated (grade 3) tumour
- Tumour size > 30 mm

New RT option after BCS-
Accelerated partial breast irradiation (APBI)



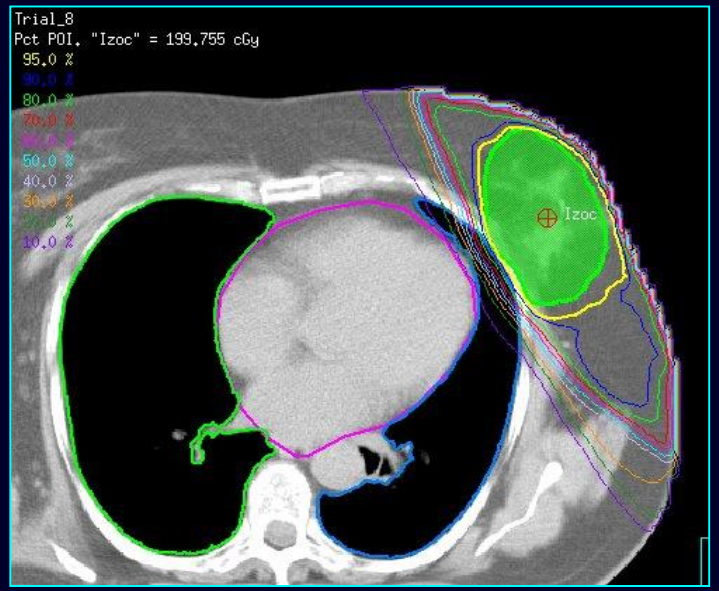






Accelerated Partial Breast Irradiation (APBI)

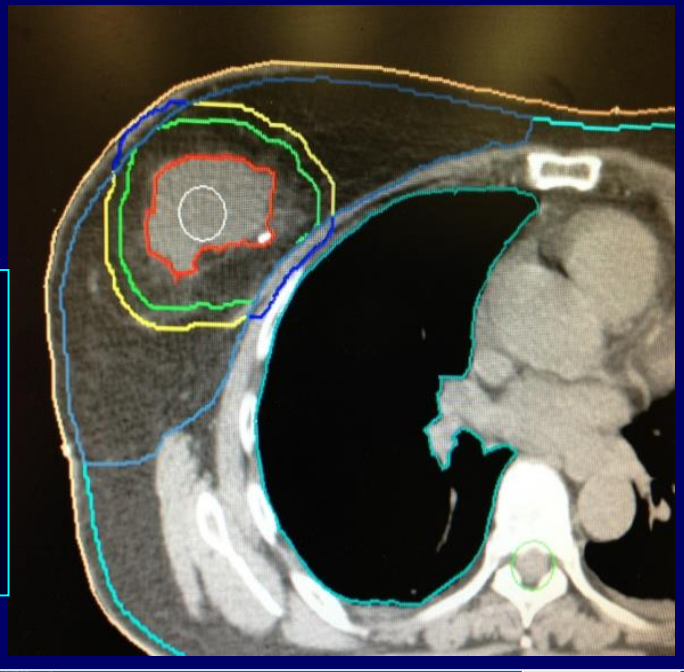
- Reduction of treatment volume:
  - Target volume = excision cavity + 1-2 cm
- Reduction of treatment time (from 5-6 weeks to 1-5 days)
  - Increase dose/fraction (from 1.8-2 Gy to 3.4-6 Gy)
  - Decrease number of fractions (from 25-30 to 5-10 fractions)
- Patient selection
  - Age > 50 years; pT1-2 (< 3 cm); clear surgical margins, pN0, no EIC

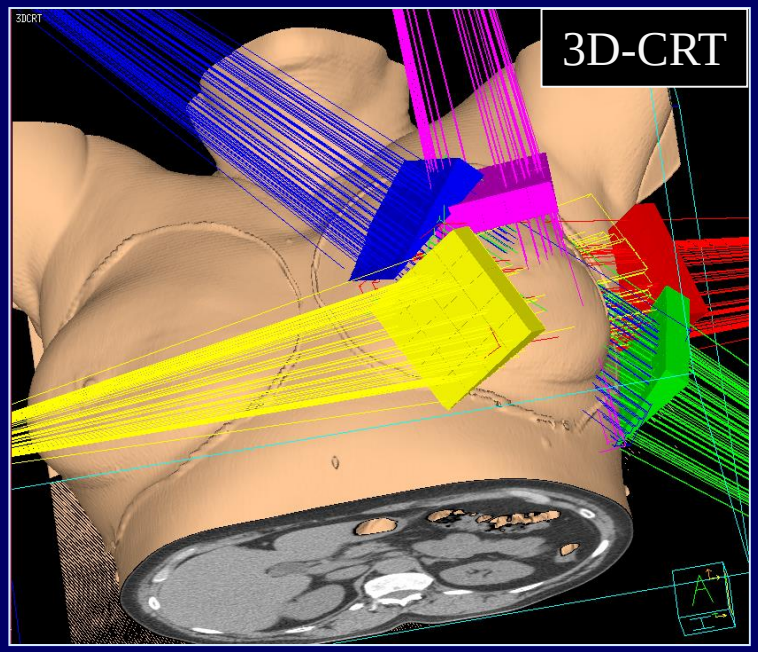


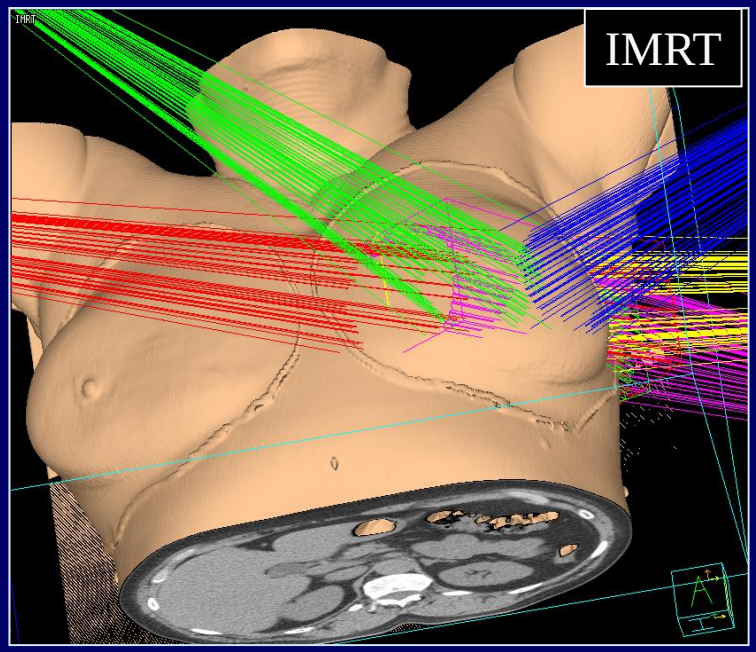
APBI with external beam irradiation

- 3D-CRT
- IMRT + IGRT

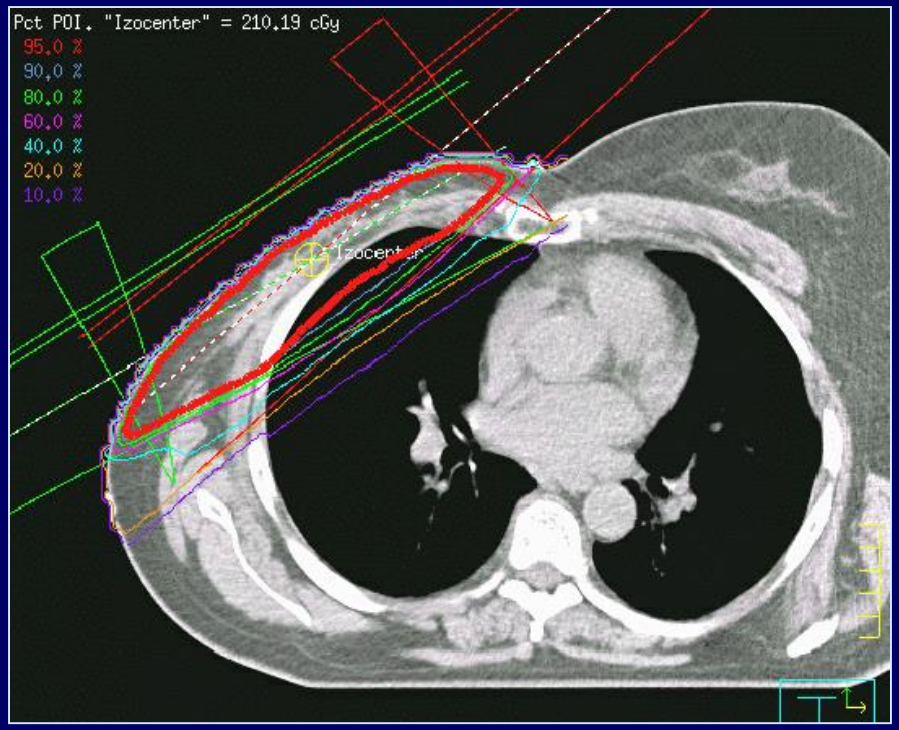
- Dose: 36.9 Gy (9 x 4.1 Gy/5 days)
- CTV = tumor bed + 2 cm – free surgical margin
- PTV = CTV + 5 mm



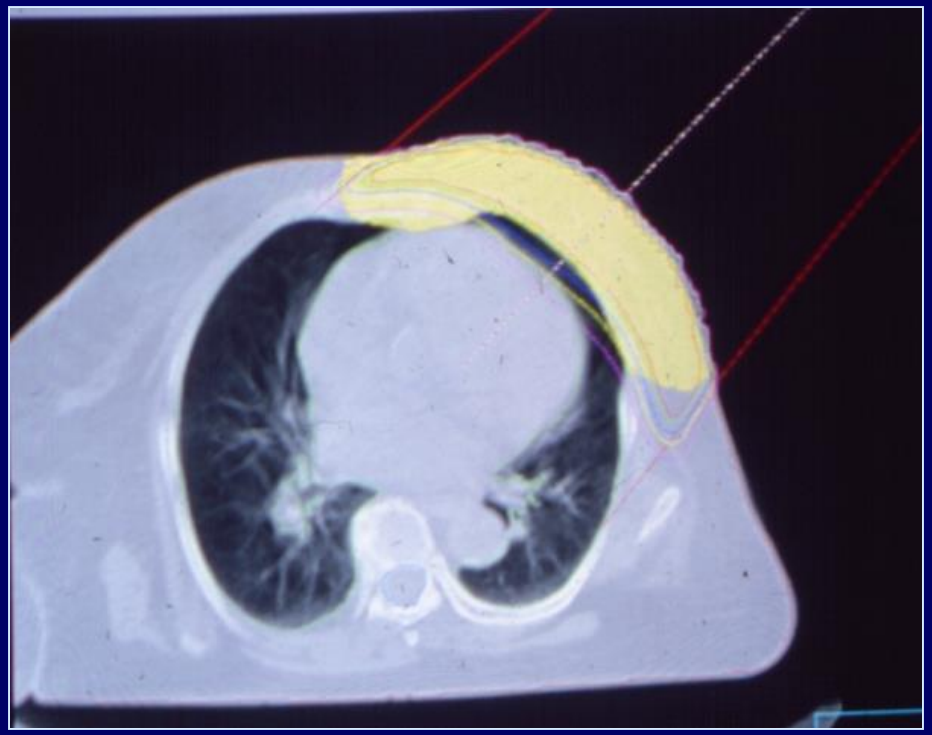




Irradiation of the chest wall after mastectomy



Tangential photon fields

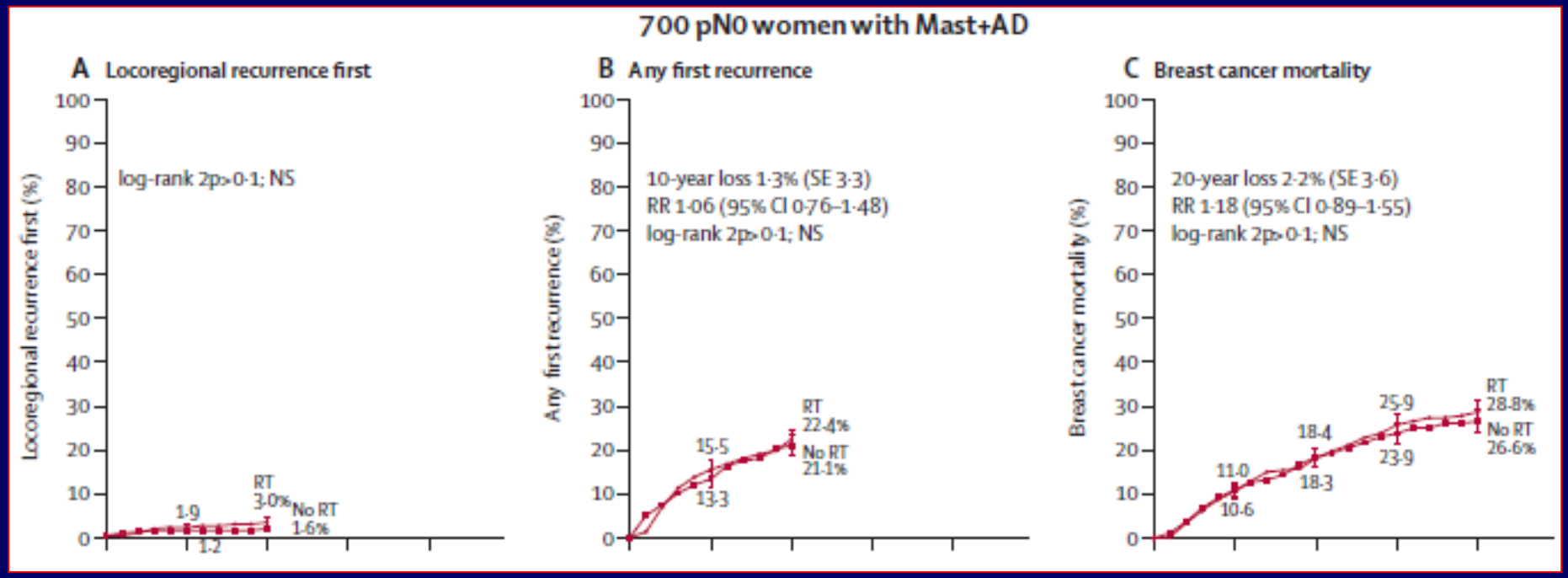


Direct electron field

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

Lancet 2014; 383: 2127–35

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*



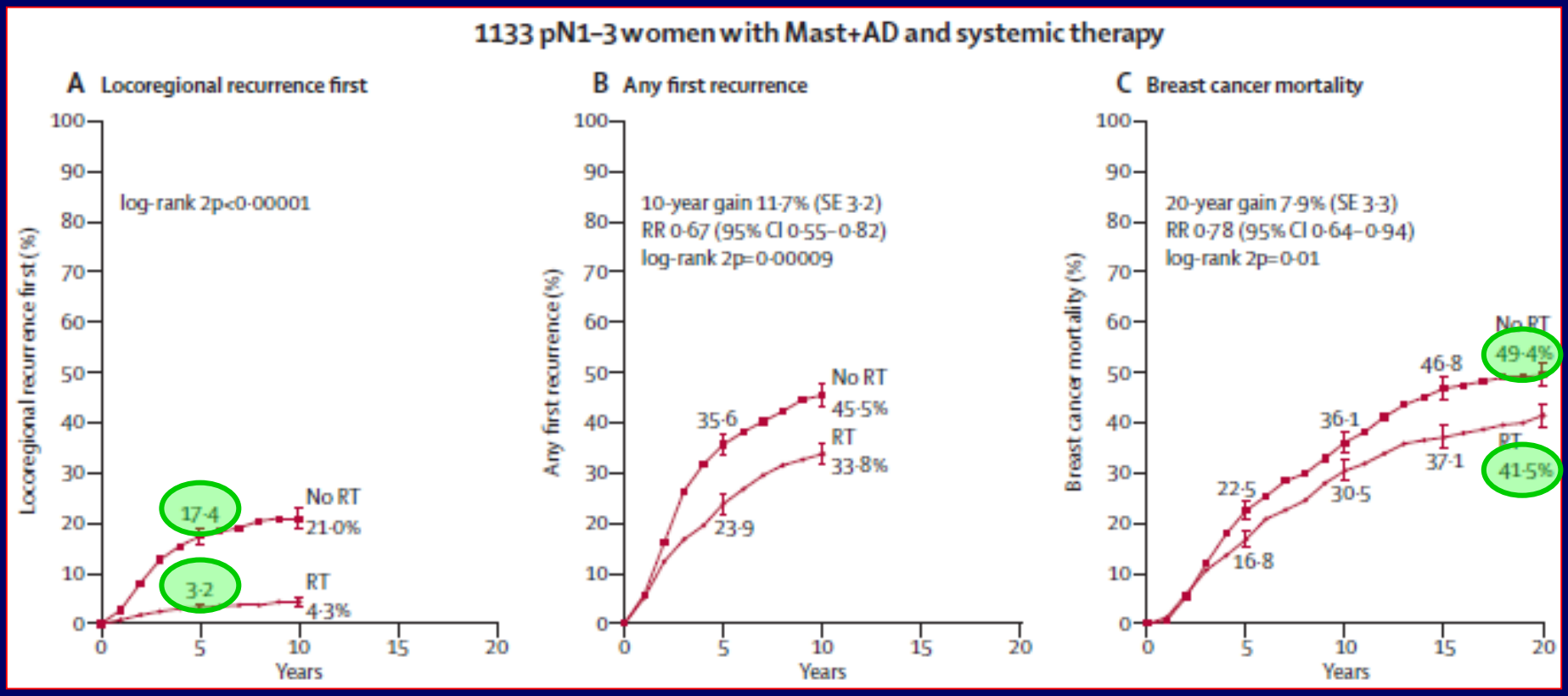
RT is not indicated in pT1-2 pN0 status!

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

Lancet 2014; 383: 2127–35

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

"1-to-1.5 rule"



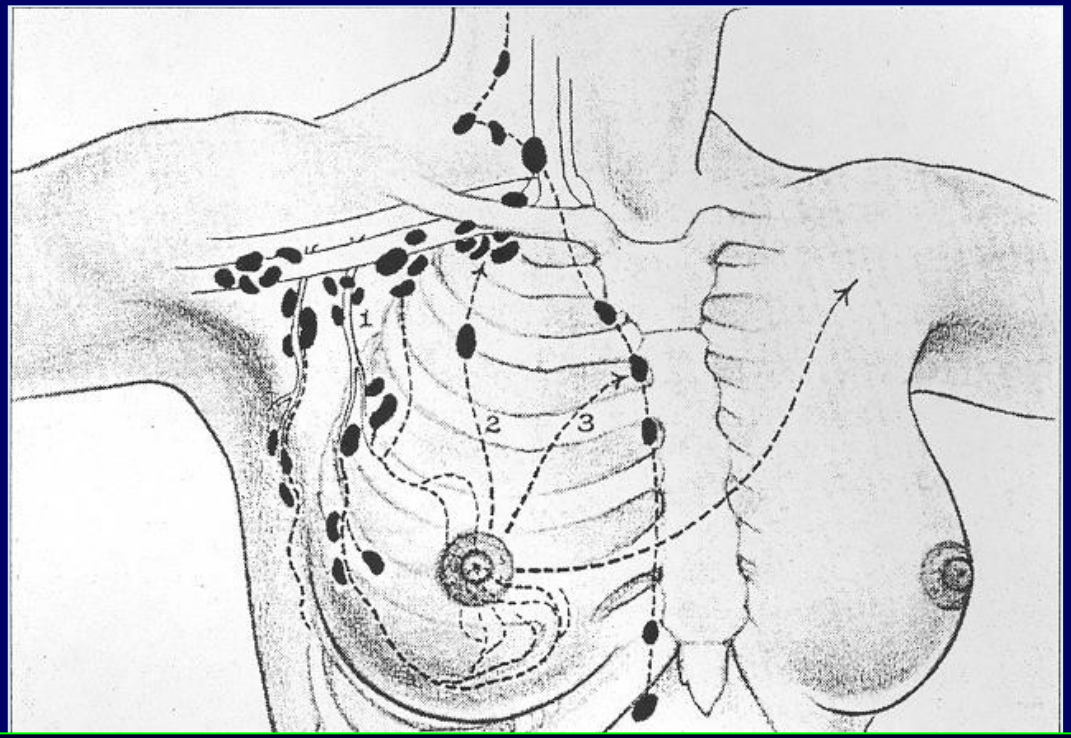
In pT1-2 pN1 status RT significantly increases locoregional tumour control and overall survival!

Radiotherapy guidelines – Early stage breast cancer

- **Irradiation of the chest wall after mastectomy:**
- *pT1-2 pN0-1mi:* RT is not indicated after R0 resection.
- *pT3 pN0:* Chest wall RT is indicated.
- *pT1-2 pN1a-2a-3a:* Locoregional RT is indicated:

  RT decreases the 5-year rate of locoregional recurrence by 15% and improves 20-year breast cancer specific survival by 8-10%.

Lymphatic pathways of breast cancer

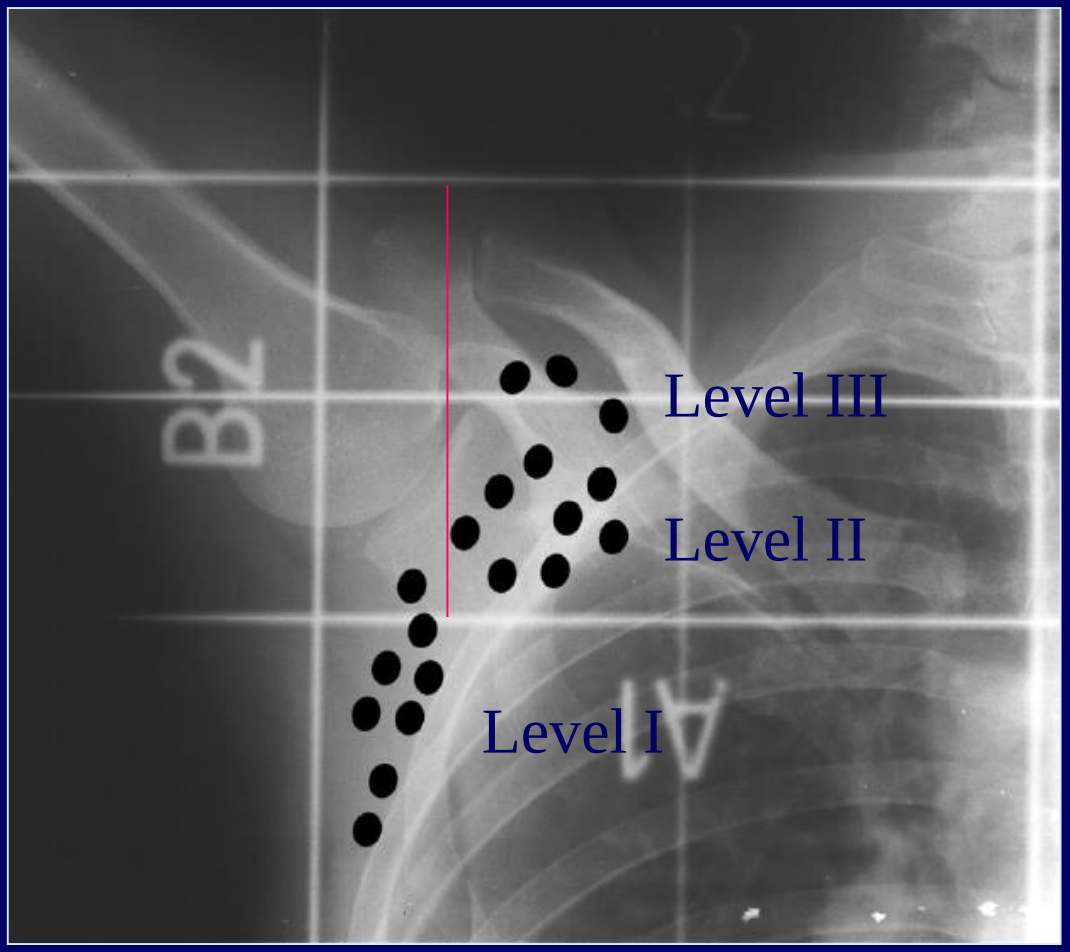


1. Axillary LNs 2. Supraclavicular LNs; 3. Parasternal LNs

Incidence of regional recurrences:

- Rate of axillary recurrence: 0-3%
- Rate supraclavicular recurrence: 6-12%
- Rate of parasternal recurrence: < 1%

Irradiation of axilla and supraclavicular fossa



Radiotherapy guidelines – Early stage breast cancer

- **RT of axillary-supraclavicular region after sentinel LN biopsy:**
- *pN0-1mi(sn):* RT is not indicated.
- *pN1a(sn):* In case of completion axillary lymph node dissection (ALND) RT of the supraclavicular fossa and level III of the axillary tail is indicated. RT of the lower axilla (level I-II) is not indicated.

  If ALND is omitted: RT of the whole axillary-supraclavicular region is indicated.

Radiotherapy guidelines – Early stage breast cancer

- **RT of axillary-supraclavicular region after ALND:**
- *pN0-1mi:* RT is not indicated.
- *pN1a, 2a, 3a, 3c:* RT of the supraclavicular fossa and level III of the axillary tail is indicated.

Radiotherapy guidelines–
Timing of RT and systemic therapies

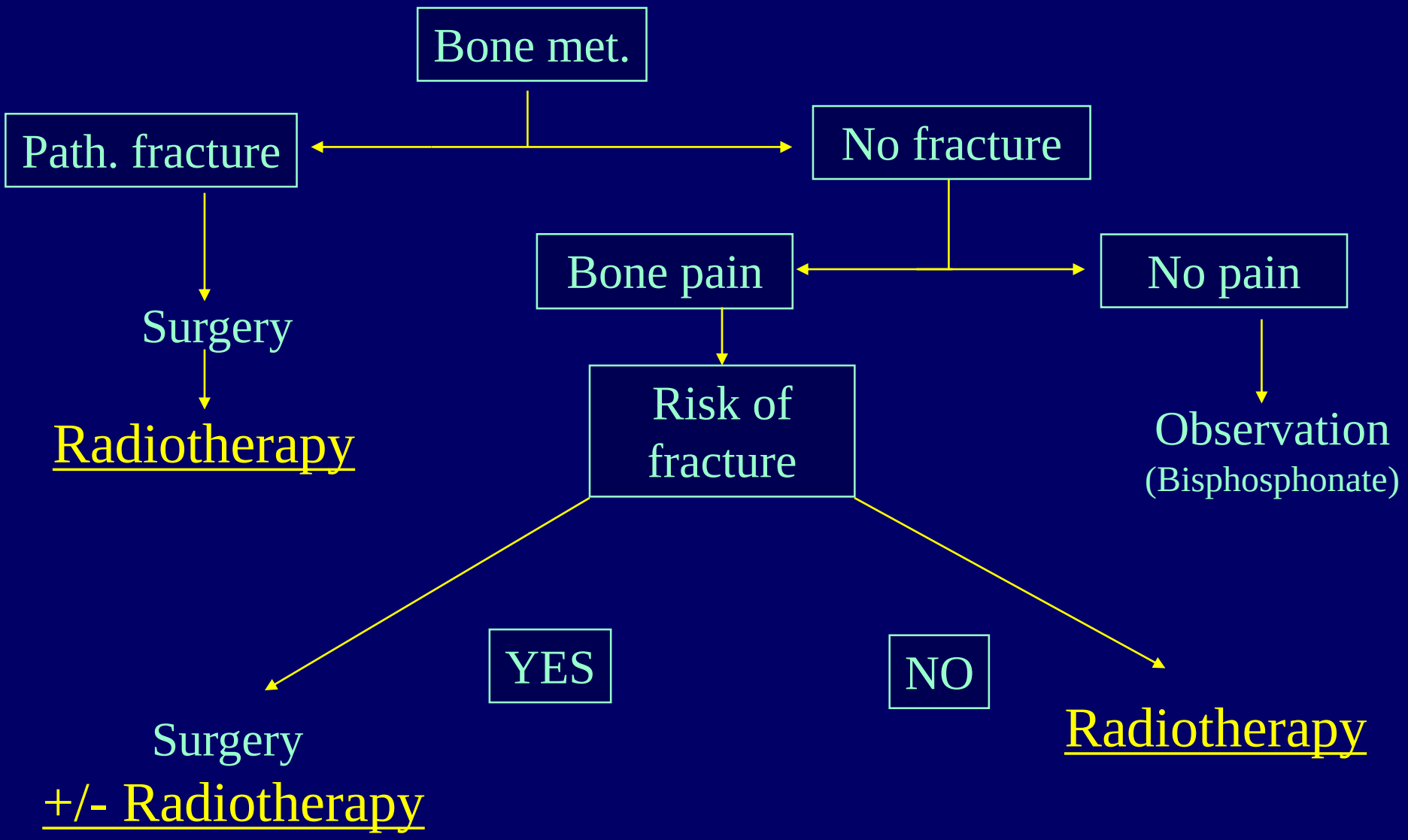
- RT should be started within 12 weeks (ideally 4-6 weeks) after surgery.
- In case of adjuvant CT, RT should be started 3 weeks after the last CT cycle.
- RT is given after CT, however RT should be completed within 7 months after surgery.
- Herceptin can be given concurrently with RT.
- Hormonal therapy can be given concurrently with RT.

Radiotherapy guidelines – Irradiation of distant metastases

- In case of solitary or oligometstatic brain metastases (2 to 4 mets.) stereotactic radiosurgery (15-20 Gy) is indicated.
- Multiplex (>4) brain mets. → Whole brain RT is indicated.

- Bone mets.: 1 x 8 Gy, 5 x 4 Gy, 10 x 3 Gy
- Brain mets.: 10 x 3 Gy WBRT or stereotactic focal RT
- Vena Cava Superior (VCS) syndrome: 5 x 4 Gy, 10 x 3 Gy

Local management of bone metastases



Systemic drug treatment of breast cancer

- **Early stages (St. I-II) – adjuvant systemic drug therapy**
- **Advanced breast ca.**
  - **Locoregionally advanced breast ca. (St. III) – neoadjuvant CT**
  - **Metastatic breast ca. (Distant mets. – St. IV) – palliative drug treatment**
- **Effective drugs:**
  - **Chemotherapy (CT)**
  - **Hormonal therapy (HT)**
  - **Targeted biological therapies (Herceptin)**

Systemic treatment of eraly stage breast cancer

Risk group characteristics that determine whether adjuvant drug treatment is required	
Low-risk	– no lymph node metastases – tumour grade I, mature tumour – tumour with favourable biological behaviour (low mitotic rate) – no vascular or perineural invasion – patient is older than 35 years
High-risk	lymph node metastases are present – tumour is HER2 positive, biologically aggressive, has a high mitotic rate – triple negative tumour (ER, PgR, and HER2 negativity) patient is young (≤35 years) or breast cancer occurs during pregnancy

- **Hormone receptor (ER, PgR) +: anti-oestrogen therapy (± CT)**
- **Hormone receptor -: CT**
- **HER-2 +: CT + targeted biological therapy (Herceptin)**

Drug treatment of breast cancer

- **HT:**
  - **Premenopause: tamoxifen (Zitazonium) + LHRH analoge (Zoladex)**
  - **Postmenospause: aromatase inhibitors (letrosole, anastrasole, examestane)**
- **CT:**
  - **Left ventricle EF > 50% (cardiotoxicity)**
  - **Combined CT**
  - **Antracyclin and/or taxane containing regimens + 5FU, cyclophosphamid**
  - **Triple negative (ER-, PgR-, HER-2 -) breast ca.: Platin containing CT**
- **Targeted biological therapy:**
  - **HER-2+: CT + Herceptin**

Drug treatment of locoregionally advanced breast cancer

- **Neoadjuvant CT**
- **HER2+: CT + Herceptin**

- **Adequate tumour response: Surgery**

- **Postoperative RT;**
- **ER/PgR+: additional HT**

Drug treatment of metastatic breast cancer

The risk factors of metastatic breast canceri		
Risk factor	**Low risk**	**High risk**
Hormone receptor (ER, PR)	positive	negative
HER2 status	negative	positive
Tumour-free survival	>2 years	<2 years
Number of metastases	limited	extensive
Site of metastases	bone and soft tissue	visceral
Adjuvant treatment	not received	received
Treatment of metastases	not received	received

Factors to be considered during the treatment of metastatic breast cancer	
"Aggressive" treatment not indicated	**"Aggressive" treatment indicated**
Slowly progressing disease	Rapidly progressing/ life-threatening disease
Visceral involvement is minimal, bone, soft tissue, lymph node metastases are present	Symptomatic patient
Combined chemotherapy is required, but the patient is not in a suitable condition	Strong visceral involvement
Asymptomatic patient in good general condition	Patient is in suitable condition for combined chemotherapy – and it serves a legitimate purpose

Goal: Long-term survival with good quality of life!

Drug treatment of metastatic breast cancer

- **No life-threatening disease and ER/PgR+:**
  - **HT (AI, tamoxifen)**
  - **Progression: 2nd. line HT (switch to Faslodex)**
  - **Combination with m-TOR inhibitors (everolimus) OR**
  - **CDK 4,6-inhibitoras (palbociklib)**
  - **Postmenospause: aromatase inhibitors (letrosole, anastrasole, examestane)**
  - **Further progression: CT**

- **High-risk, life-threatening disease, ER/PgR-:**
  - **Antracyclin- or taxane-based combined CT**

- **HER2 pozitive:**
  - **CT + Herceptin**

Thank you for your attention!