

## Summary on BCT

- RT after lumpectomy reduces LR with a factor 3-4
- BCT = Lumpectomy PLUS radiotherapy is as safe as mastectomy, similar OS
- Boost of 16 Gy reduces LR with factor 2
- ***Still open questions:***
- What about the (young) high risk patients ?
  - More dose ? Young Boost Trial
- What can we do for low risk patients ?
  - Lower volume ? Partial breast RT ?
  - No RT at all, only hormonal treatment ?

## Design of the Young Boost trial accrual 2004-2011, N = 2400

Patients  $\leq 50$  years,  $T_{1-2}N_{0-2a}$  invasive breast ca

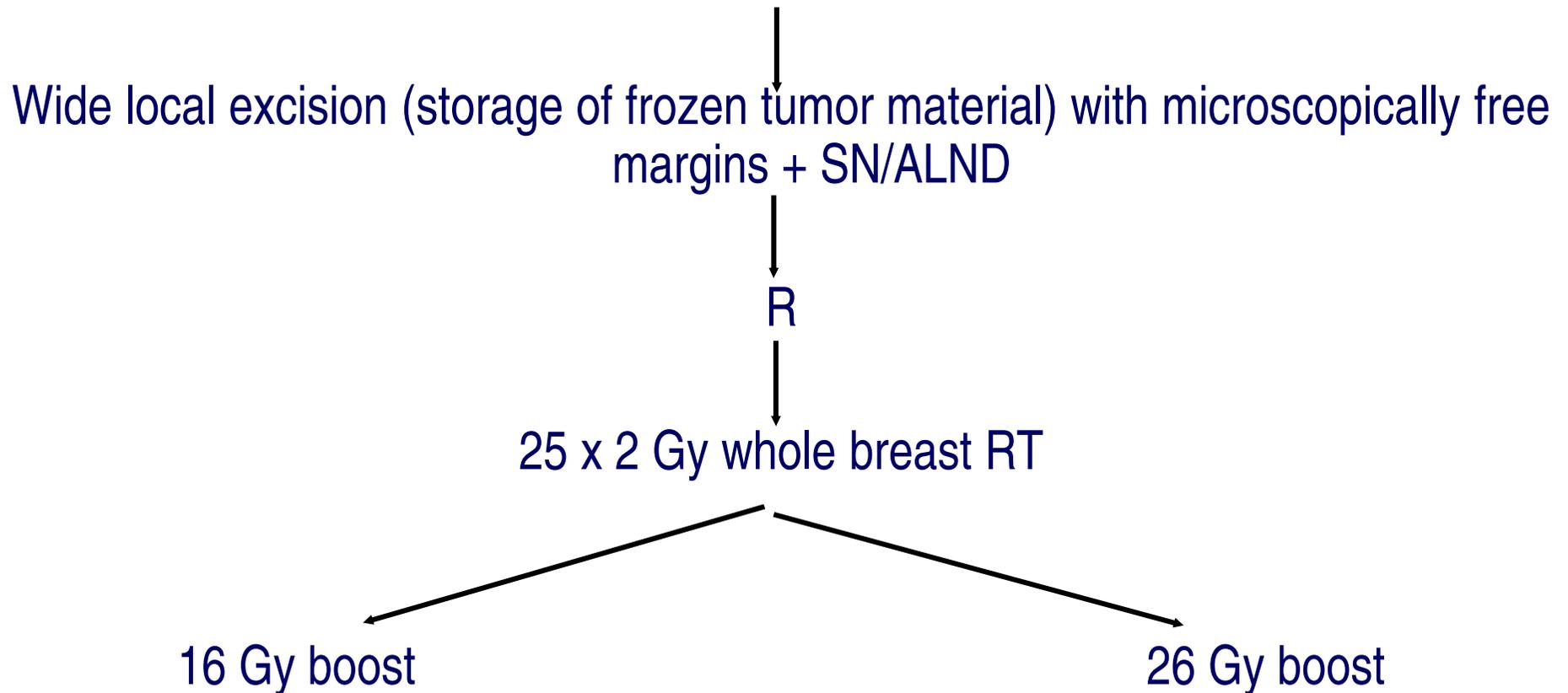
Wide local excision (storage of frozen tumor material) with microscopically free margins + SN/ALND

R

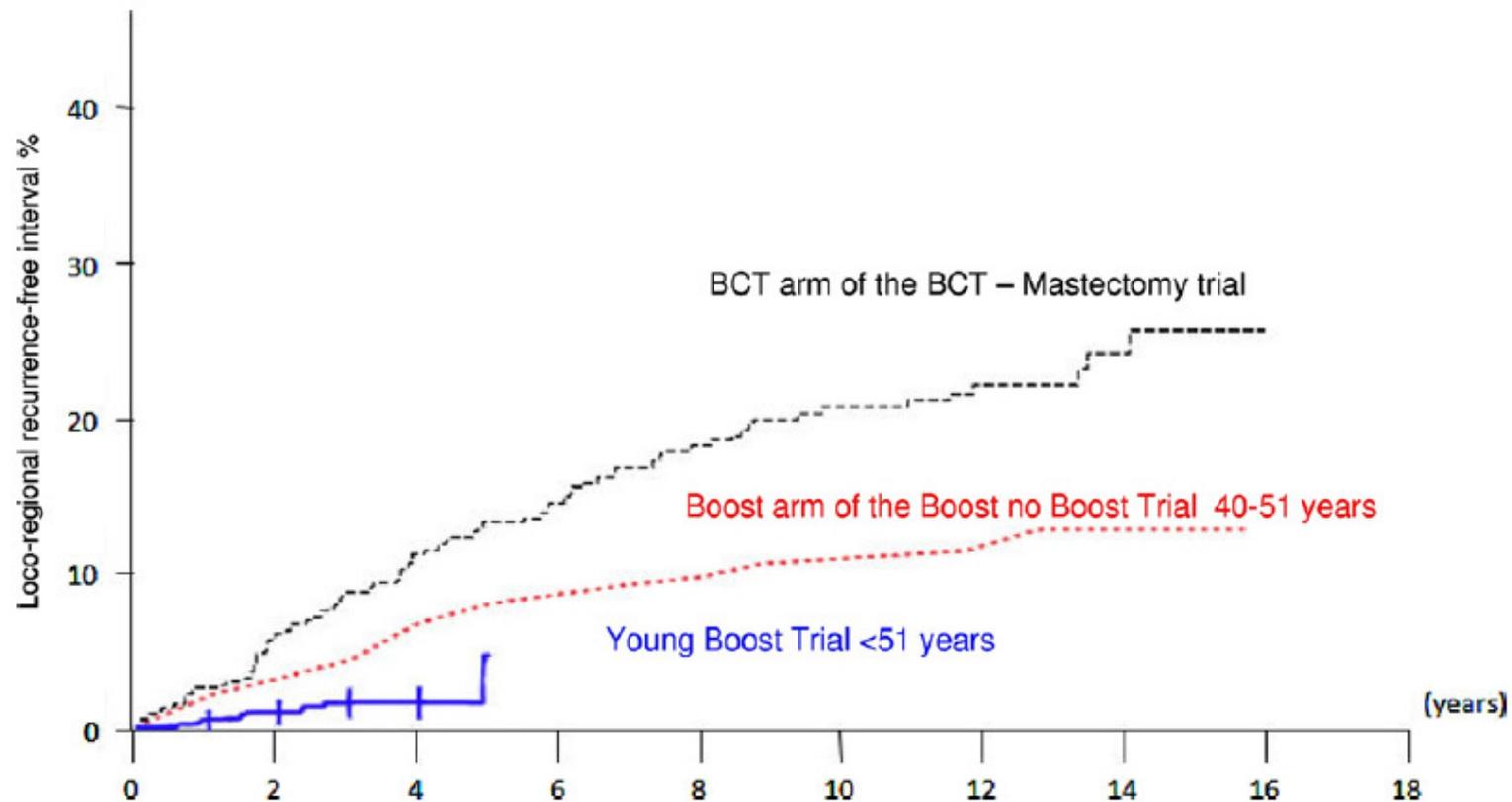
25 x 2 Gy whole breast RT

16 Gy boost

26 Gy boost



# Improving local recurrence rates over time



**Figure 4** The local recurrence rate in the consecutive EORTC 10801, EORTC 22881-10882, and the Young Boost trials.<sup>14</sup>

## Rationale for Accelerated Partial Breast Irradiation (APBI)

- Whole breast irradiation (16-33 fractions) is standard treatment in breast conserving therapy.
- However, most ipsilateral breast recurrences are mentioned to occur in same quadrant as the primary tumor.
- Partial breast irradiation: smaller target volume → allows to give a higher dose/fraction → less fractions → more convenient.

## Accelerated Partial Breast Irradiation

- Different techniques used:
  - Brachy: interstitial or mammosite
  - Intraoperative radiotherapy: 4-12 MeV electrons/50 kV photons
  - Postoperative external 3D Conformal RT
- Different doses used:
  - 10 x 3.4 Gy /5 days (brachy); 8 x 4 Gy ; 7 x 4.3 Gy
  - 1x 20 – 21 Gy (IORT)
  - 10 x 3.85 Gy/ 5 days (external)
- Only very limited results available for external partial breast RT; Many RCTs are currently testing APBI vs WBRT

## Current trials on APBI

Trial	Trial Characteristics			
	Target Accrual	No. of Arms	WBRT Fractionation	APBI Method
NSABP B39	4,300	Two	50 Gy in 25 fractions	3D-CRT, interstitial,* MammoSite†
RAPID	2,128	Two	50 Gy in 25 fractions	3D-CRT
IMPORT	2,100	Two	50 Gy in 25 fractions	3D-CRT
TROG	2,094	Three‡	50 Gy in 25 fractions or 42.5 Gy in 16 fractions	3D-CRT, interstitial,* MammoSite,† IORT
SHARE	2,796	3§	50 Gy in 25 fractions or 42.5 Gy in 16 fractions	3D-CRT
IRMA	3,302	2	50 Gy in 25 fractions	3D-CRT
GEC-ESTRO	1,170	2	50 Gy in 25 fractions	Brachytherapy

*In total data of > 17.000 pts should be available in 3 – 8 years !*

# Guidelines

## ASTRO consensus statement

Factor	<i>Suitable</i> Criterion	<i>Cautionary</i> Criterion	<i>Unsuitable</i> Criterion
<b>Patient factors</b>			
Age	≥60 y	50–59 y	<50 y
<i>BRCA1/2</i> mutation	Not present		Present
<b>Pathologic factors</b>			
Tumor size	≤2 cm*	2.1–3.0 cm*	>3 cm
T stage	T1	T0 or T2	T3–4
Margins	Negative by at least 2 mm	Close (<2 mm)	Positive
Grade	Any		
LVSI	No <sup>†</sup>	Limited/focal	Extensive
ER status	Positive	Negative <sup>†</sup>	
Multicentricity	Unicentric only		Present
Multifocality	Clinically unifocal with total size ≤2.0 cm <sup>‡</sup>	Clinically unifocal with total size 2.1–3.0 cm <sup>‡</sup>	If microscopically multifocal >3 cm in total size or if clinically multifocal
<b>Histology</b>	Invasive ductal or other favorable subtypes <sup>§</sup>	Invasive lobular	
Pure DCIS	Not allowed	≤3 cm	If >3 cm in size
EIC	Not allowed	≤3 cm	If >3 cm in size
Associated LCIS	Allowed		
<b>Nodal factors</b>			
N stage	pN0 (i <sup>-</sup> , i <sup>+</sup> )		pN1, pN2, pN3
Nodal surgery	SN Bx or ALND <sup>  </sup>		None performed
<b>Treatment factors</b>			
Neoadjuvant therapy	Not allowed		If used

# Guidelines

## GEC-ESTRO recommendations

GEC-ESTRO recommendations on patient selection for accelerated partial-breast irradiation.

Characteristic	A/low-risk group – good candidates for APBI	B/intermediate-risk group – possible candidates for APBI	C/high-risk group – contraindication for APBI
Patient age	>50 years	>40–50 years	≤40 years
Histology	IDC, mucinous, tubular, medullary, and colloid cc.	IDC, ILC, mucinous, tubular, medullary, and colloid cc	–
ILC	Not allowed	Allowed	–
Associated LCIS	Allowed	Allowed	–
DCIS	Not allowed	Allowed	–
HG	Any	Any	–
Tumour size	pT1–2 (≤30 mm)	pT1–2 (≤30 mm)	pT2 (>30 mm), pT3, pT4
Surgical margins	Negative (≥2 mm)	Negative, but close (<2 mm)	Positive
Multicentricity	Unicentric	Unicentric	Multicentric
Multifocality	Unifocal	Multifocal (limited within 2 cm of the index lesion)	Multifocal (>2 cm from the index lesion)
EIC	Not allowed	Not allowed	Present
LVI	Not allowed	Not allowed	Present
ER, PR status	Any	Any	–
Nodal status	pN0 (by SLNB or ALND <sup>a</sup> )	pN1mi, pN1a (by ALND <sup>a</sup> )	pNx; ≥pN2a (4 or more positive nodes)
Neoadjuvant chemotherapy	Not allowed	Not allowed	If used

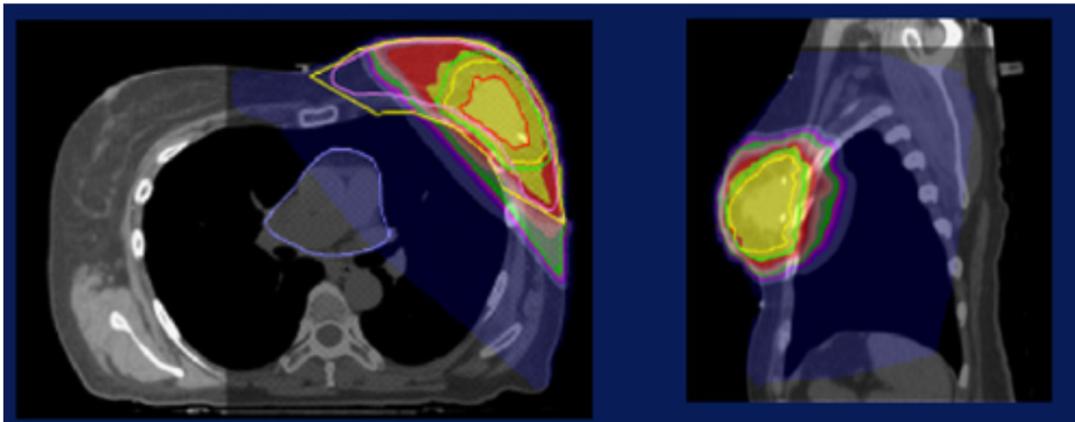
## Evidence after 2010; Real life experience

ELIOT out-trial, n = 1822 (= selection)

Risk group	% of pts	5y LR rate
ASTRO +	16%	1.5%
ASTRO +/-	38%	4.4%
<del>ASTRO -</del>	<del>45%</del>	<del>8.8%</del>
GEC-ESTRO +	31%	1.9%
<del>GEC-ESTRO +/-</del>	<del>15%</del>	<del>7.1%</del>
<del>GEC-ESTRO -</del>	<del>53%</del>	<del>7.8%</del>

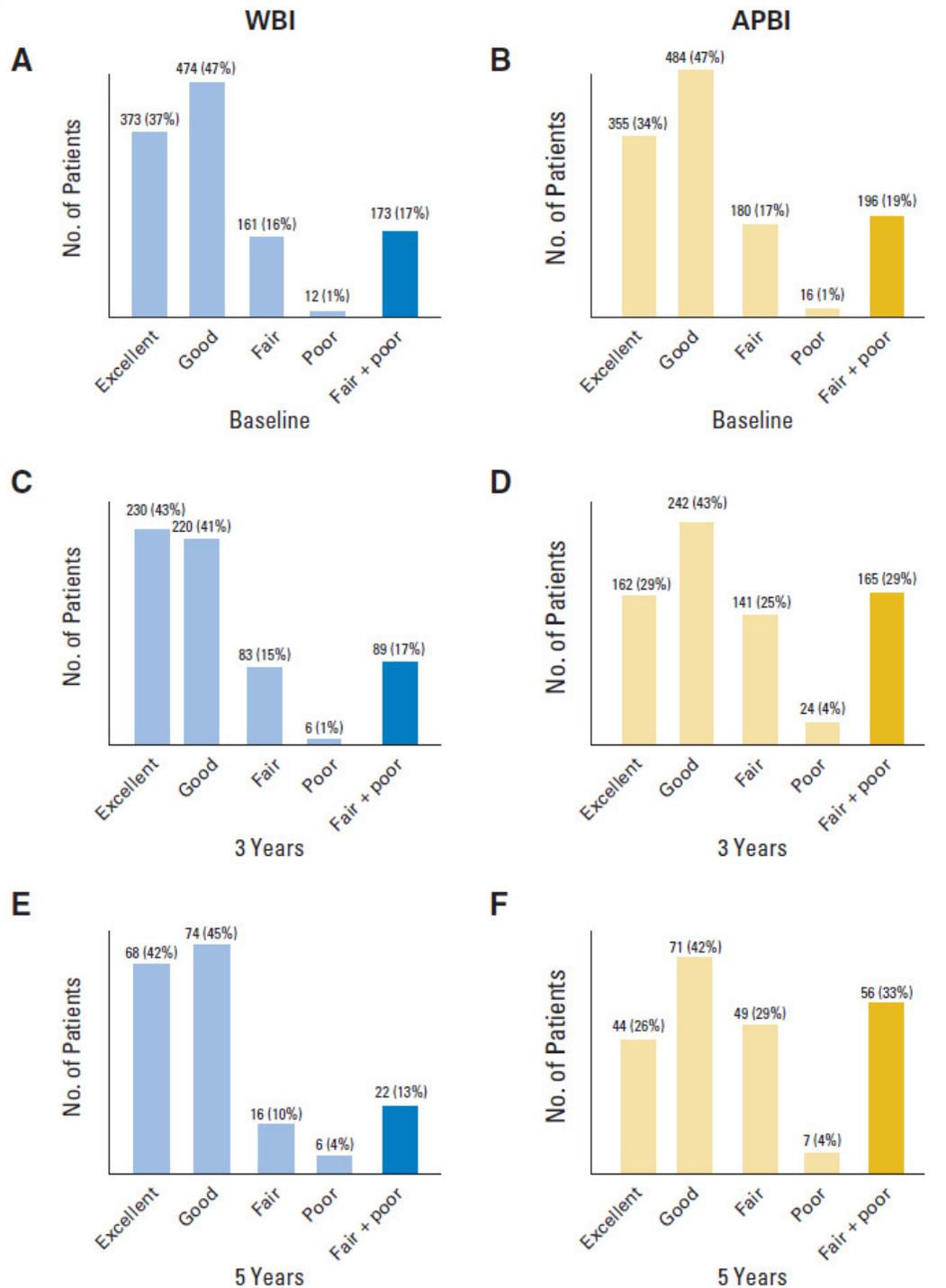
## Evidence after 2010: Side effects

### UNACCEPTABLE COSMESIS IN A PROTOCOL INVESTIGATING INTENSITY-MODULATED RADIOTHERAPY WITH ACTIVE BREATHING CONTROL FOR ACCELERATED PARTIAL-BREAST IRRADIATION

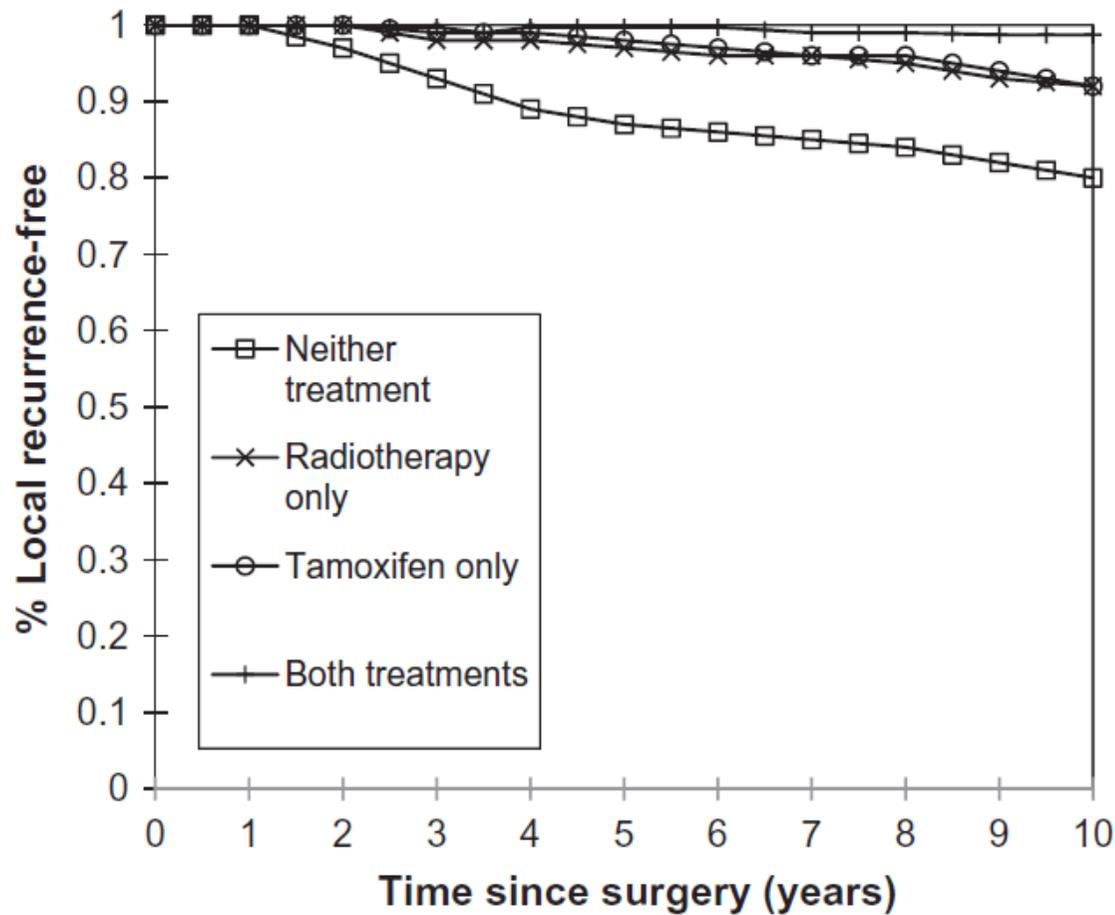


# RAPID trial, External APBI

- N = 2135
- APBI 10 x 3.85 Gy bid vs WBRT
- Median f-up 3 yr

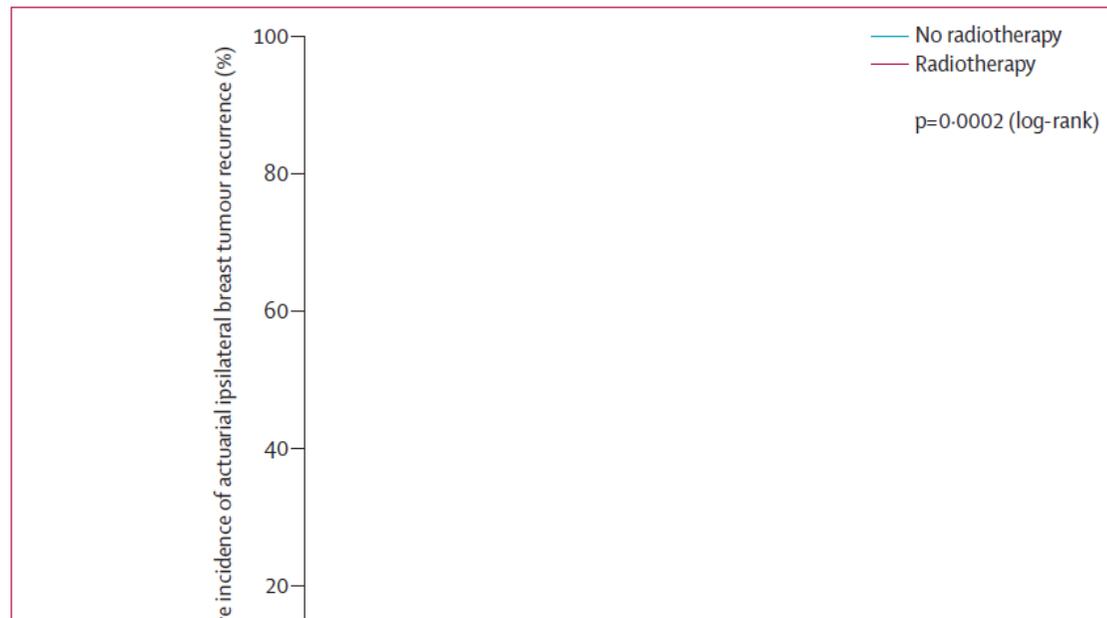


# Is less treatment safe ? BASO II trial



- N = 1135
- pT1N0
- Grade 1
- Clear margins
- Median f-up 121 mths

# PRIME-II study



- N = 1326
- Tumor < 3 cm, LVI or G3 allowed
- > 65 yr
- Clear margins
- Adjuvant hormonal Rx
- Median f-up 5 yr

**Interpretation** Postoperative whole-breast radiotherapy after breast-conserving surgery and adjuvant endocrine treatment resulted in a significant but modest reduction in local control for women aged 65 years or older with early breast cancer 5 years after randomisation. However, the 5-year rate of ipsilateral breast tumour recurrence is probably low enough for omission of radiotherapy to be considered for some patients.

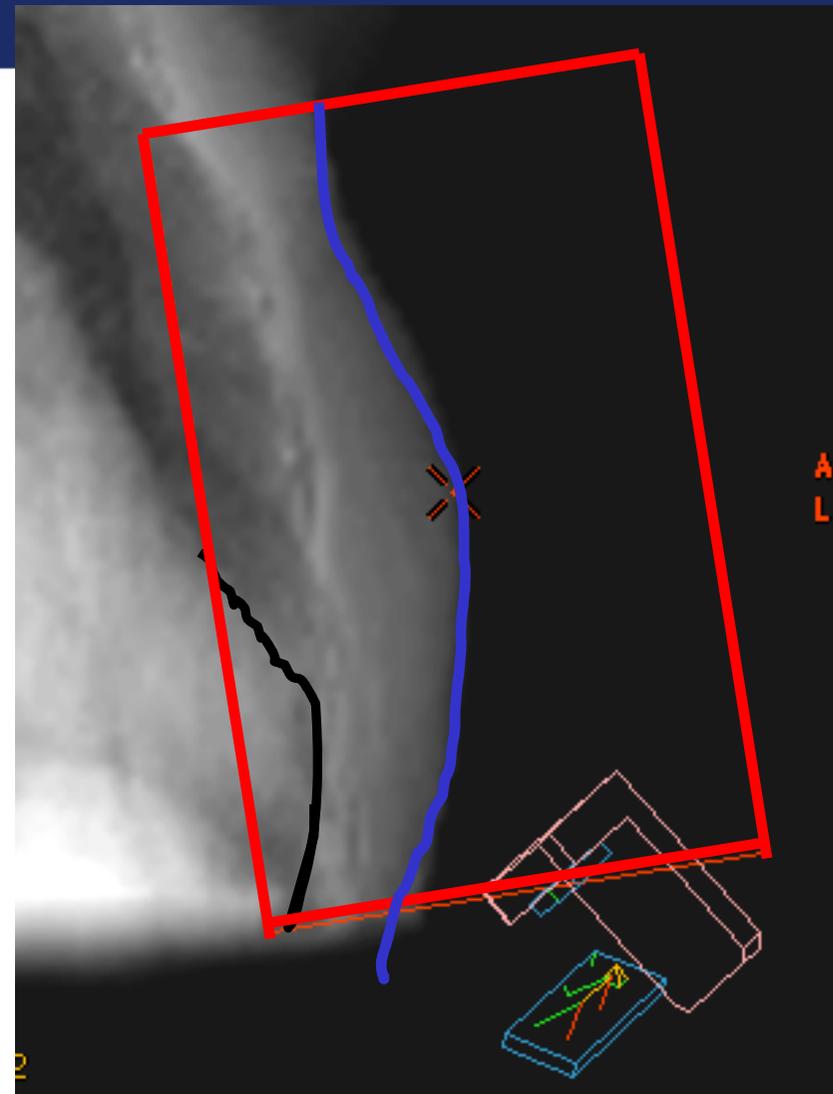
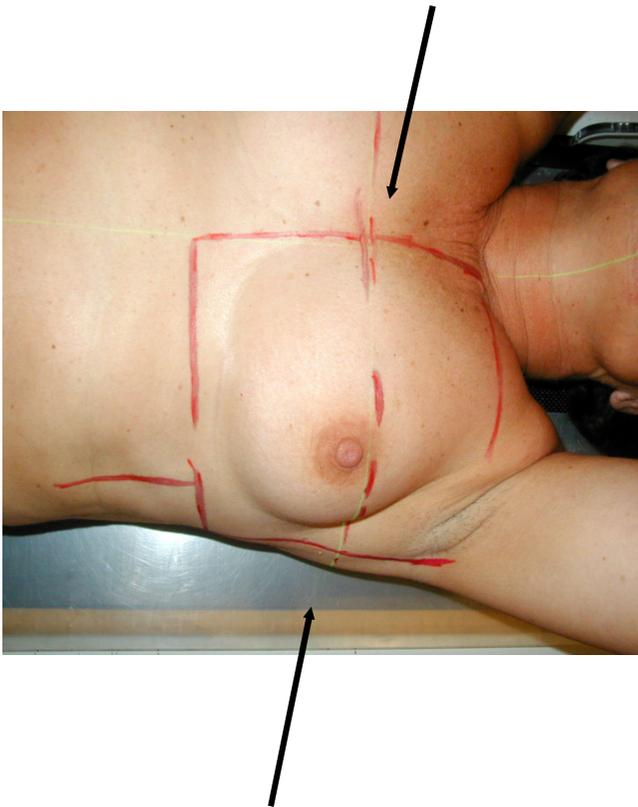
No radiotherapy	Entering interval	668	643	607	560	464	311
	Events	1	9	6	5	2	(3)
Radiotherapy	Entering interval	658	631	597	551	472	324
	Events	0	0	1	2	2	(0)

Figure 2: Time to actuarial ipsilateral breast tumour recurrence

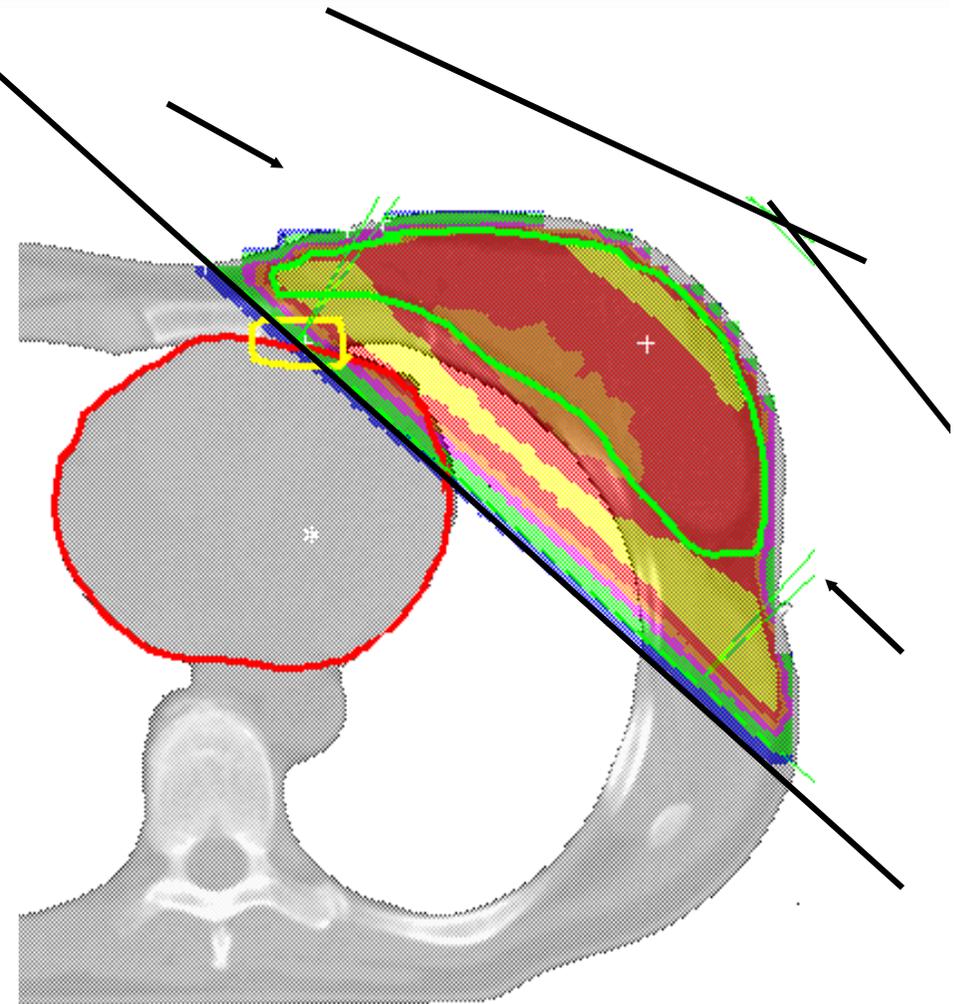
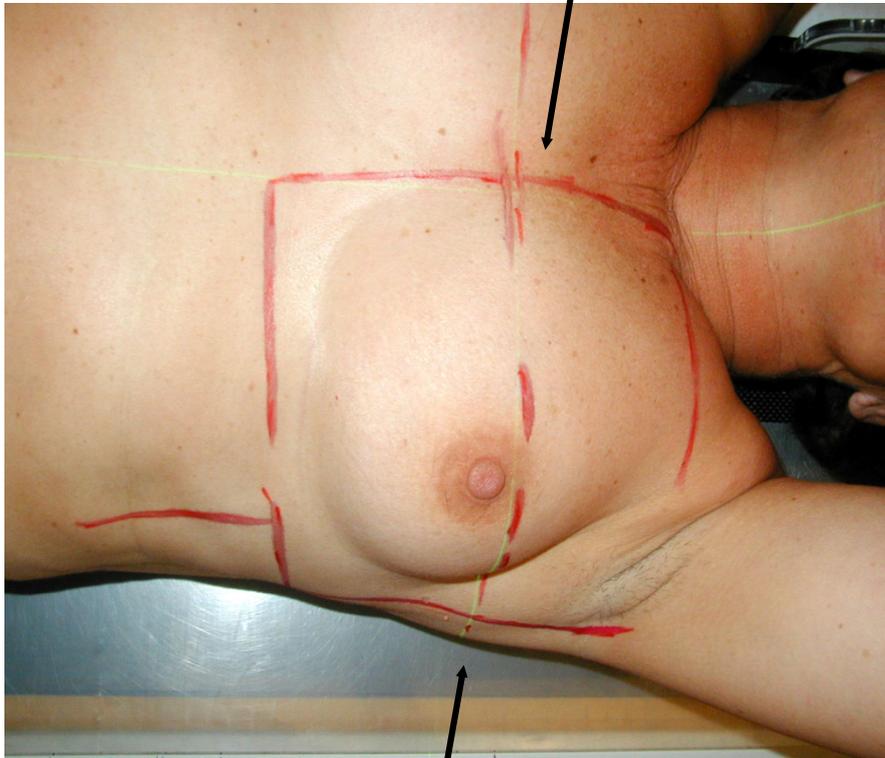
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  - Effect on Local control and or survival ?
  - Specific issues:
    - Indication for RT in pN1 disease
    - Axillary – regional treatment ?
  - History of BCT
    - Less treatment in low risk BC ?
- From conventional simulation to state of the art techniques
- ESTRO delineation guidelines

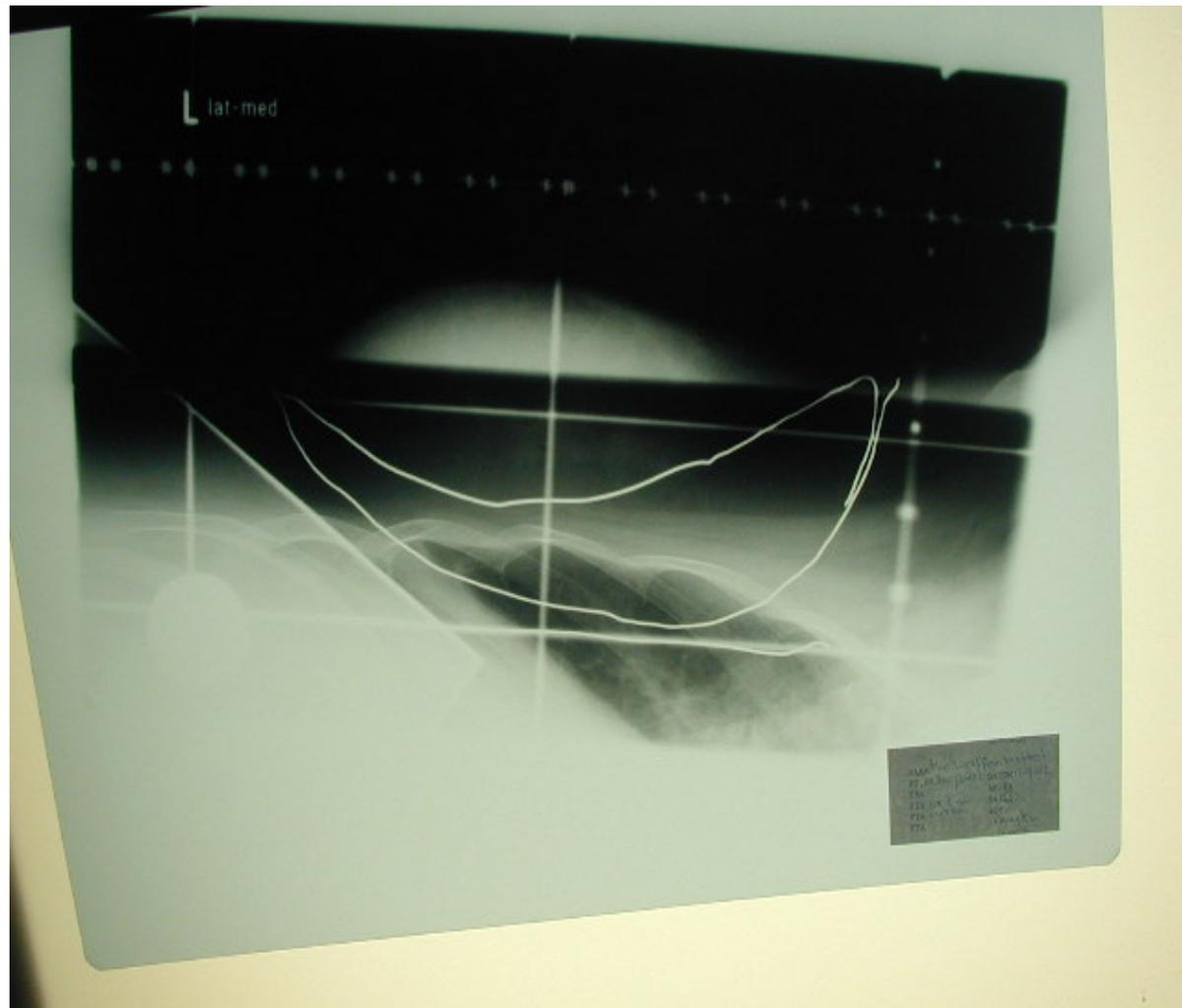
# Beam's eye view of medial tangential field



# Tangential fields in breast irradiation- inhomogeneous dose distributions

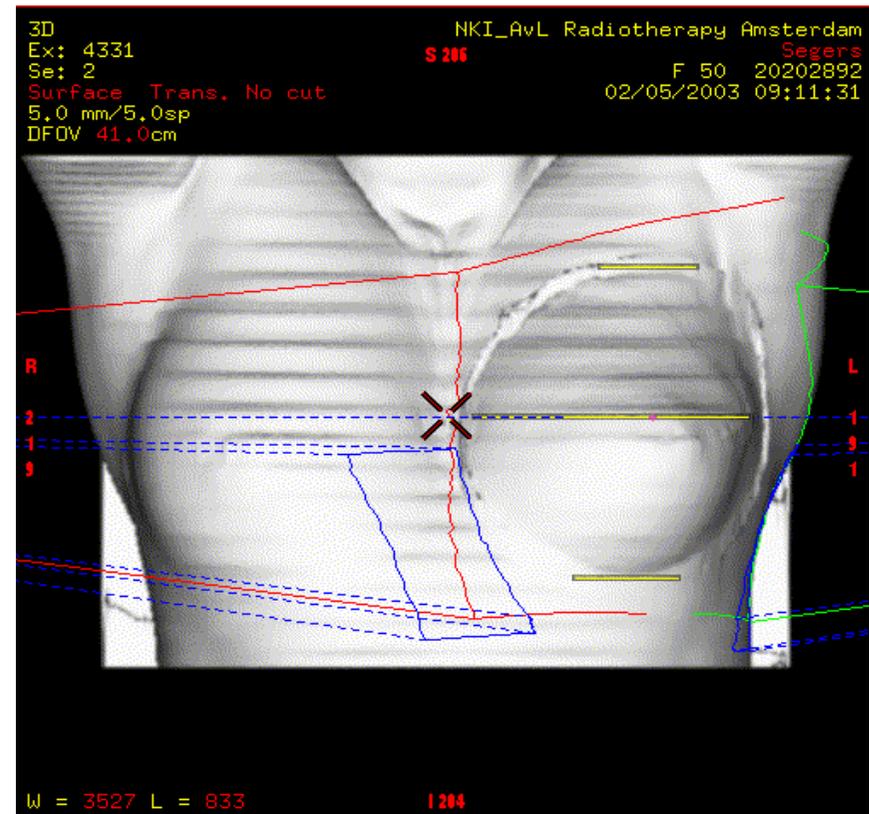
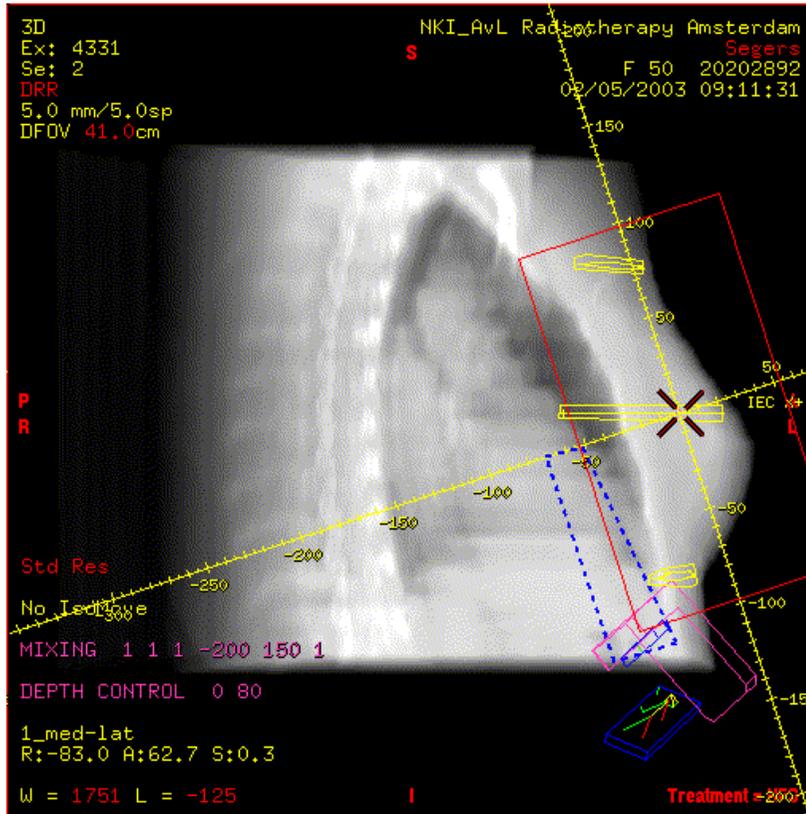


# Conformal radiotherapy use of heart block

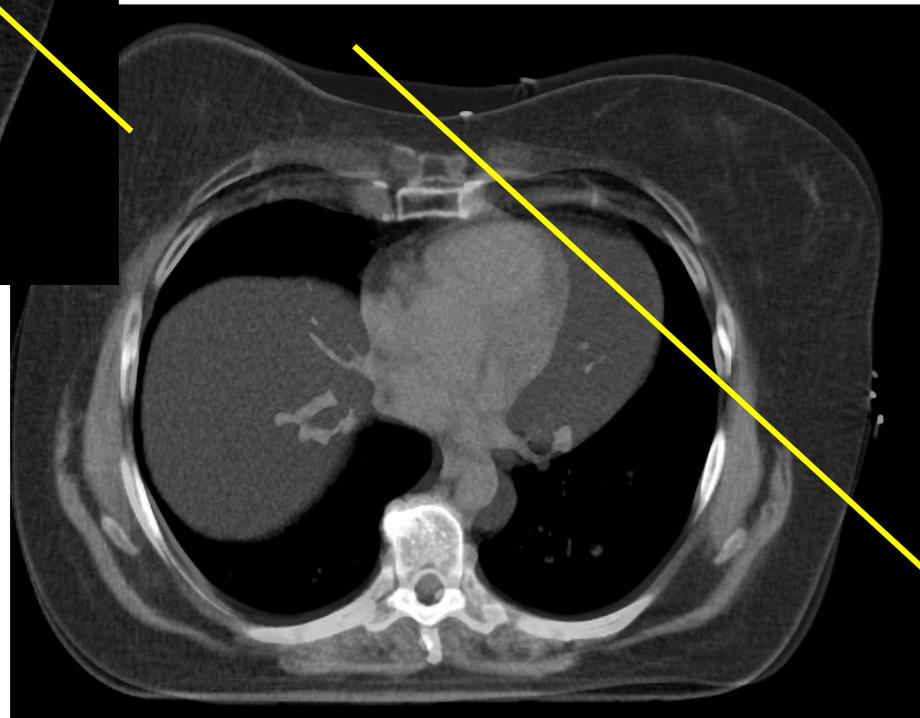
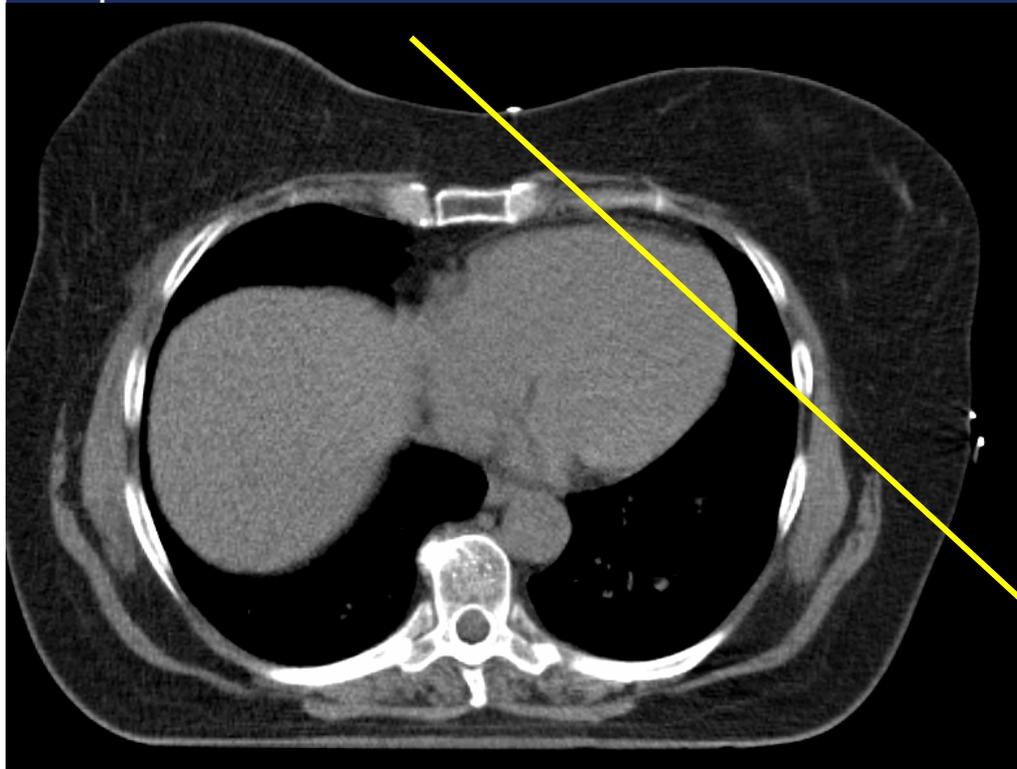


# 3D conformal radiotherapy

## Example of virtual simulated fields



# Breath hold to spare heart !



## What is IMRT: Intensity Modulated Radiotherapy ?

### Forward IMRT

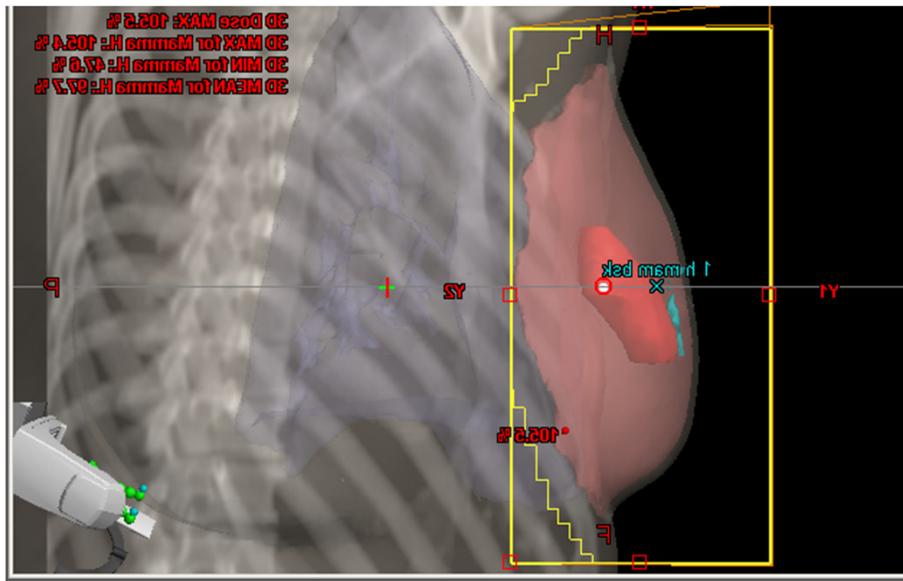
- Forward planning for dose homogeneity – field-in-field/electronic compensation
- Field arrangement as for standard 3D-CRT (basically tangents)

### Inverse-planned IMRT

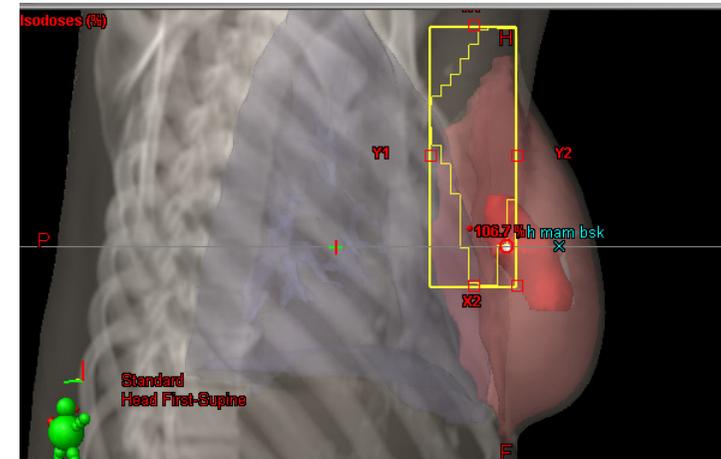
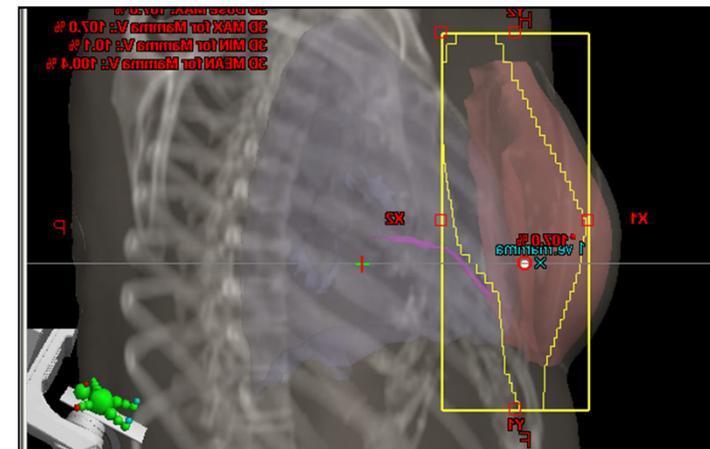
- Inverse planning with dosimetric constraints
- Extended field arrangement, including non-coplanar fields and non-tangent angles

*Slide courtesy M.A. Aznar, ESTRO teaching course*

# Forward planning - field-in-field



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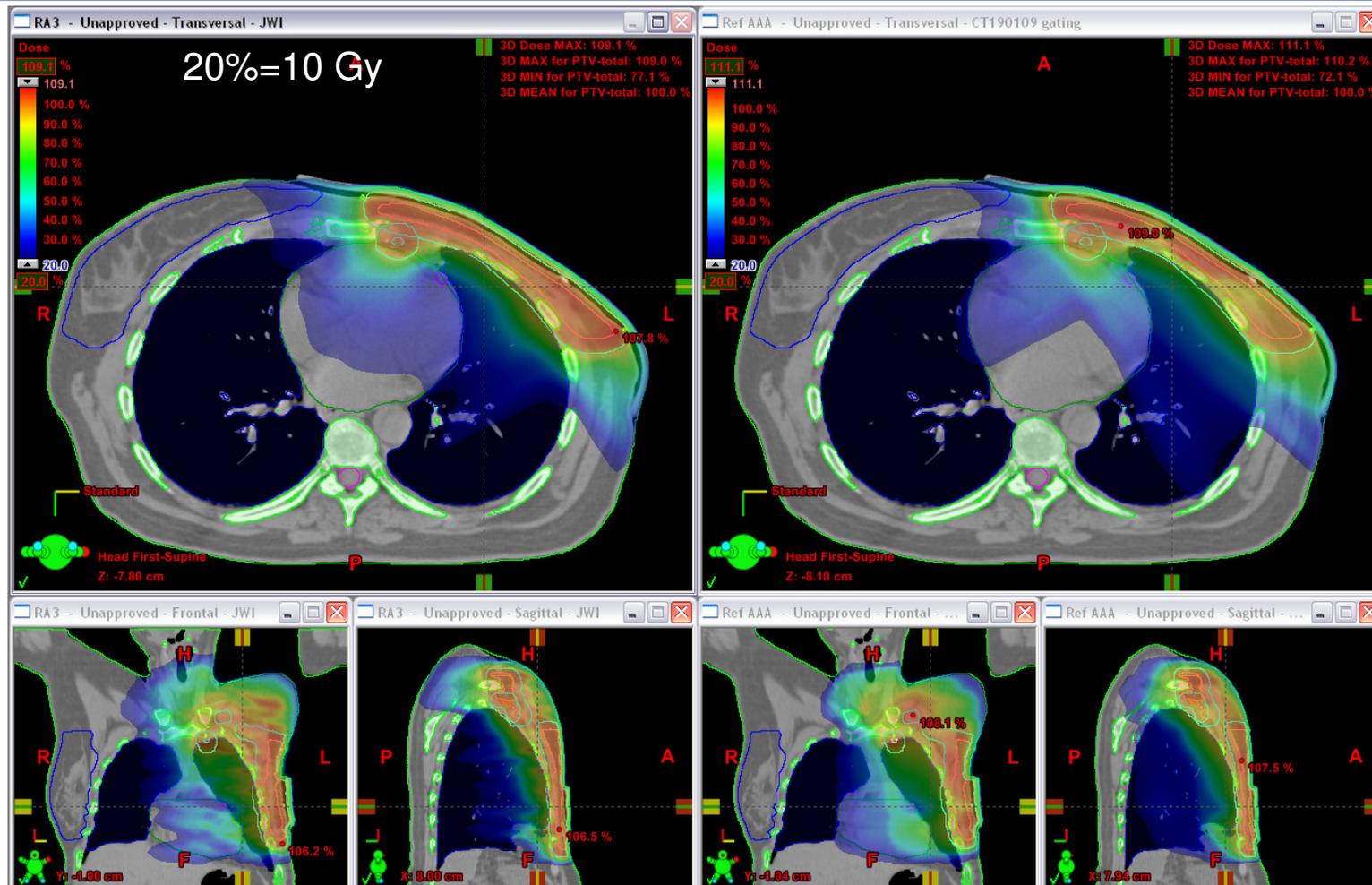


Slide courtesy M.A. Aznar, ESTRO teaching course

# Dose bath to healthy tissue

RA

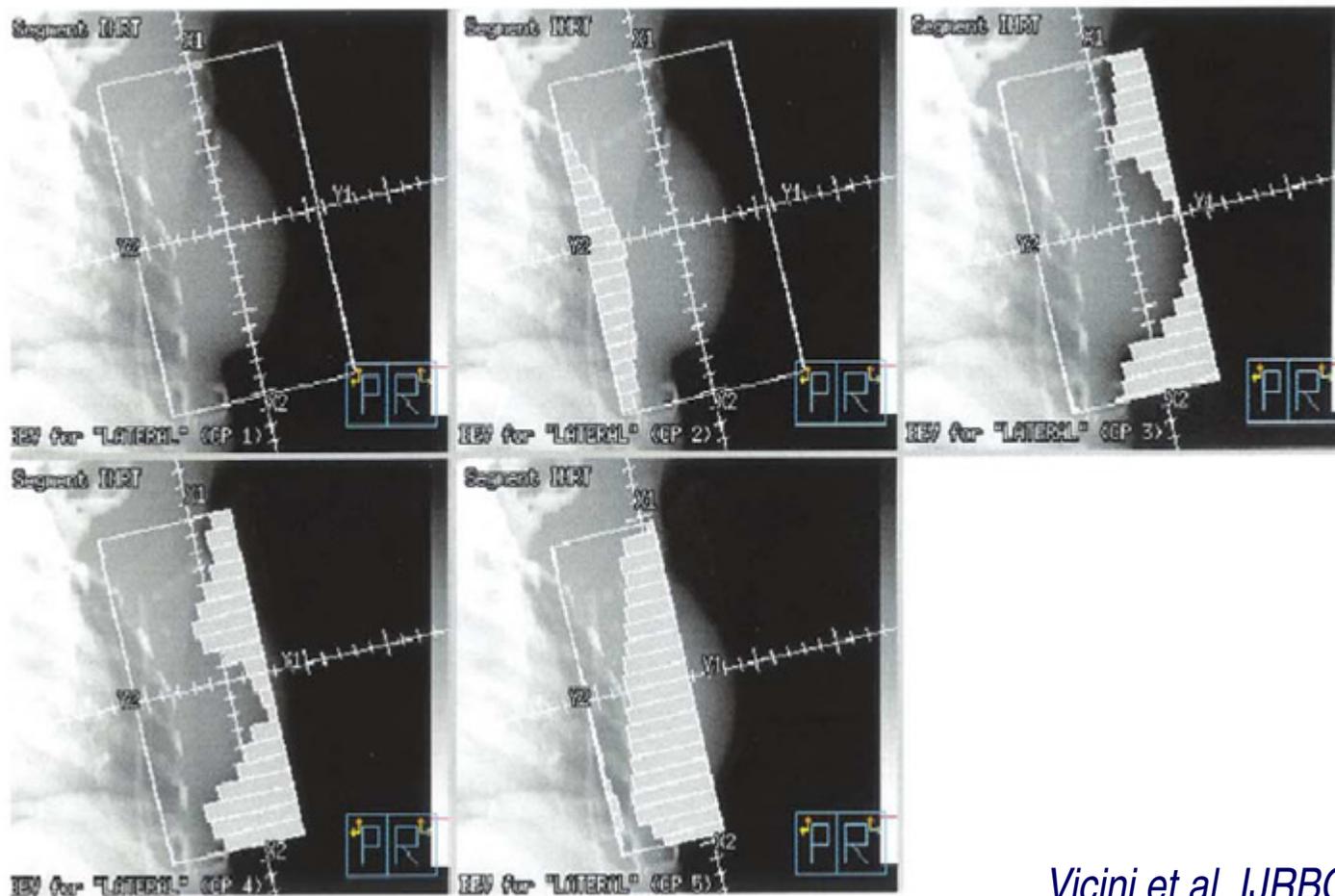
5f-IMRT



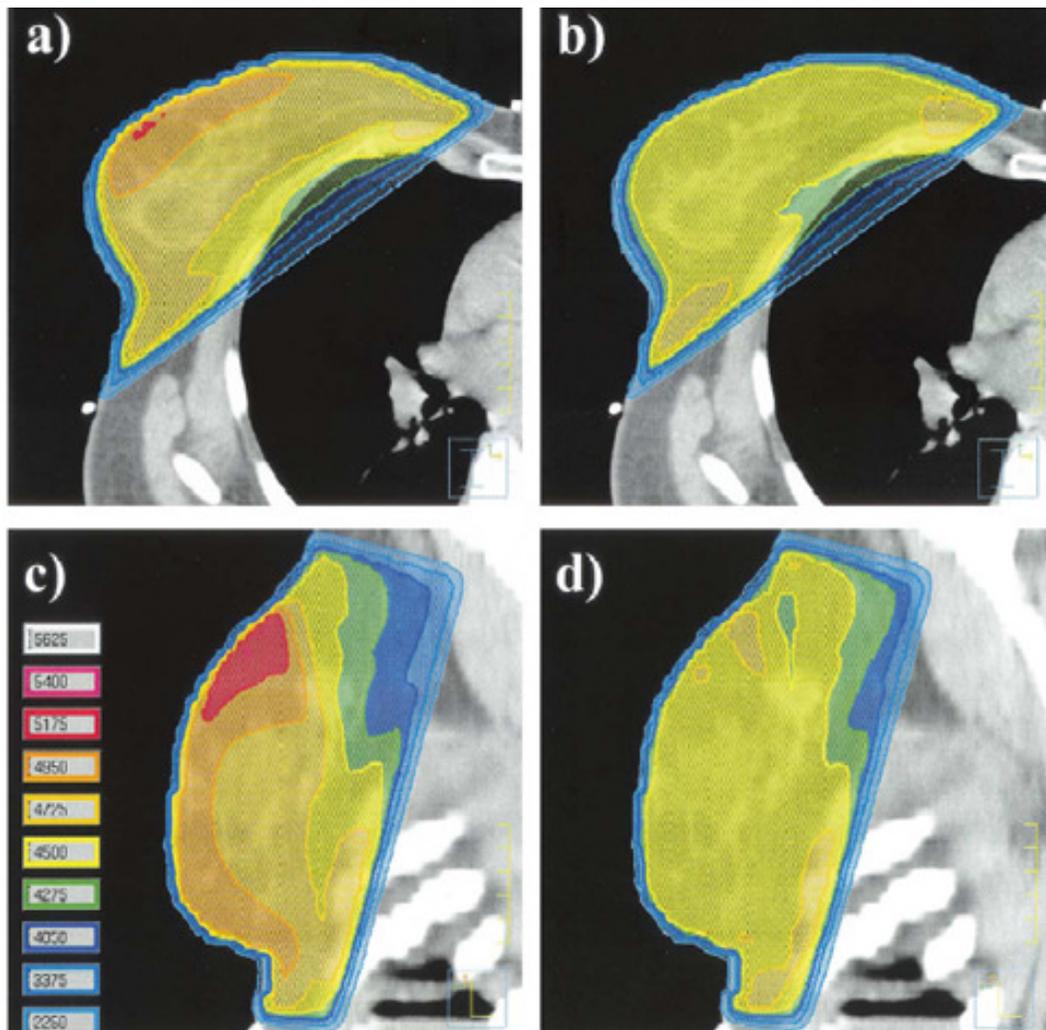
*Courtesy of Johan Wiren, Rigshospitalet*

# Use of IMRT for RT of the breast 2 tangents, conform segments to isodose surfaces

## a) Lateral IMRT Segments



## Use of IMRT for RT of the breast 2 tangents, conform segments to isodose surfaces



## Whole breast irradiation: Why CT-based delineation and planning ?

- Delineation of a PTV is very helpful in IMRT
- 3 RCTs have been published comparing IMRT (i.e. a more homogeneous dose distribution) with conventional 2D planning:
  - Donovan et al (Royal Marsden), R&O 2007: better cosmesis
  - Pignol et al, JCO 2008: less acute dermatitis ( < 6 weeks after end RT)
  - Barnett et al (Cambridge Breast IMRT trial), IJROBP 2011:
    - No difference in acute tox ( @ 3 wks after start RT) and shrinkage
    - Less telangiectasia @ 2 yrs
    - If good surgical cosmesis: trend for less deterioration after IMRT

# Cambridge Breast IMRT Trial, no effect on PROMS

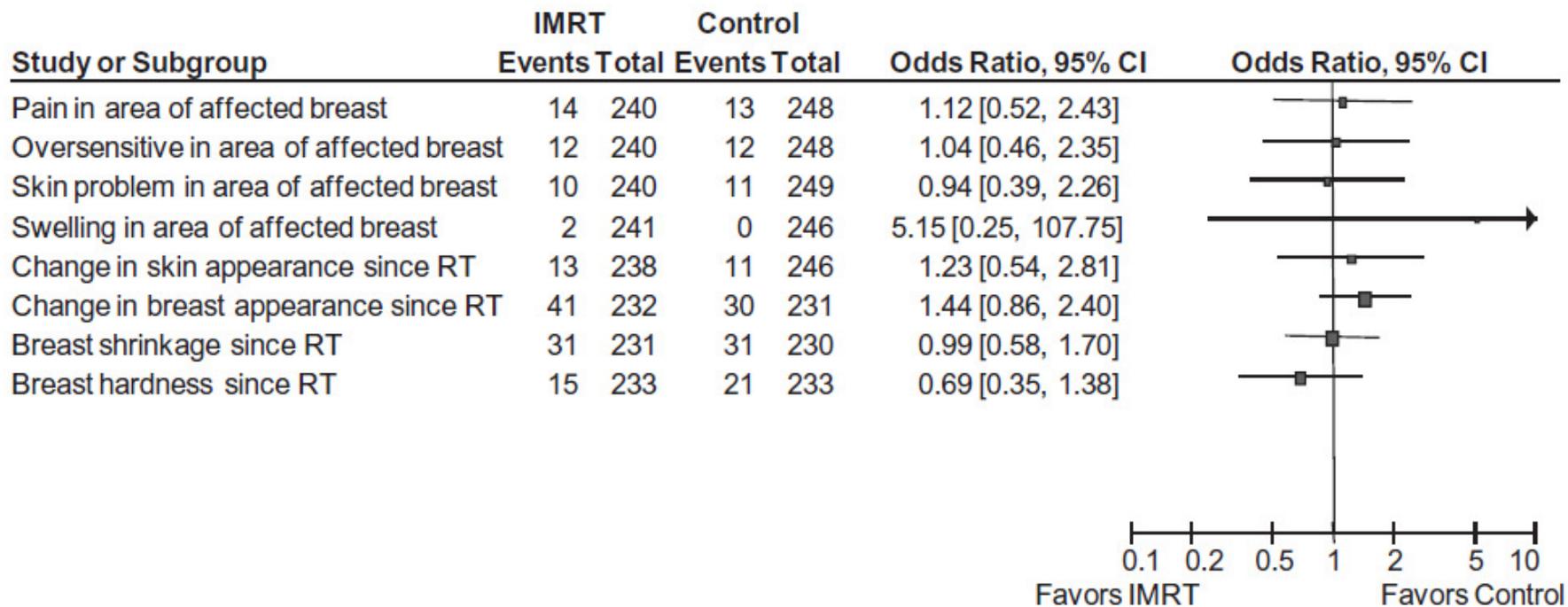


Fig. 1. Forrest Plot of moderate–severe toxicity assessed by patients at five years comparing standard radiotherapy (control) with simple IMRT.

## Summary IMRT

- Forward planned IMRT can provide target dose homogeneity, and potentially some sparing of organs at risk
- Effect documented in at least 2 clinical trials
- Inverse planned IMRT has not yet been proven to be advantageous for breast cancer
  - Patient-specific; field angles cannot be standardised.
  - Clear dosimetric advantage in very complex cases
  - Organ motion?

*Slide courtesy M.A. Aznar, ESTRO teaching course*

# Whole breast irradiation: Specifications for WBRT used in MAASTRO clinic

- Homogeneous dose in DTV.

**Table 3.** Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI) <sup>†</sup> % increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (-2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

0 2 4 6 8 10 12 14 16 18 20  
Mean Dose of Radiation to Heart (Gy)

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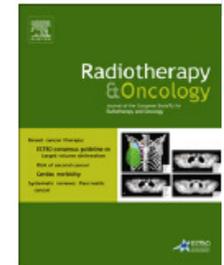


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## ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer

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## Breast Cancer Target Volume Delineation project

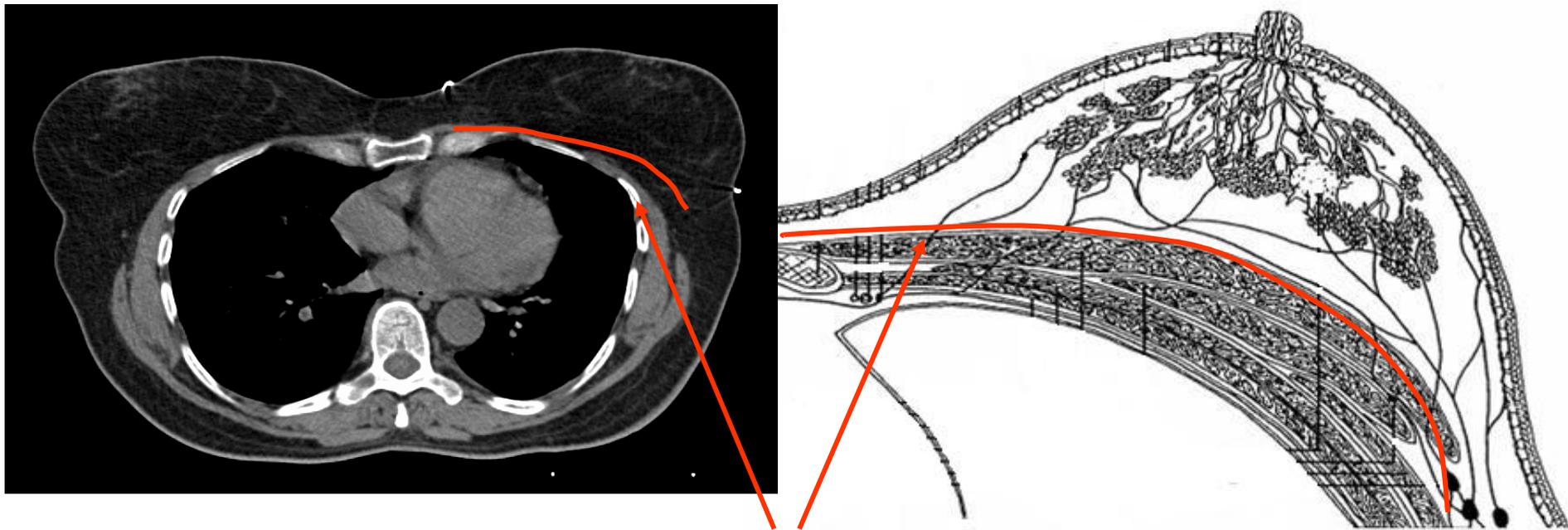
- ESTRO breast cancer course since 2009; later on also online courses using FALCON platform
- Delineation exercises, lots of discussion →
- Project started, aimed at
  - → preparing guidelines
  - → pan European agreement and endorsement
  - → atlas in major European languages

## Delineation of the CTV breast using CT: CTV breast = “whole glandular breast tissue” ?

But:

Glandular breast tissue is often not clearly visible on the planning CT.

No clear anatomical borders visible, apart from dorsal side.



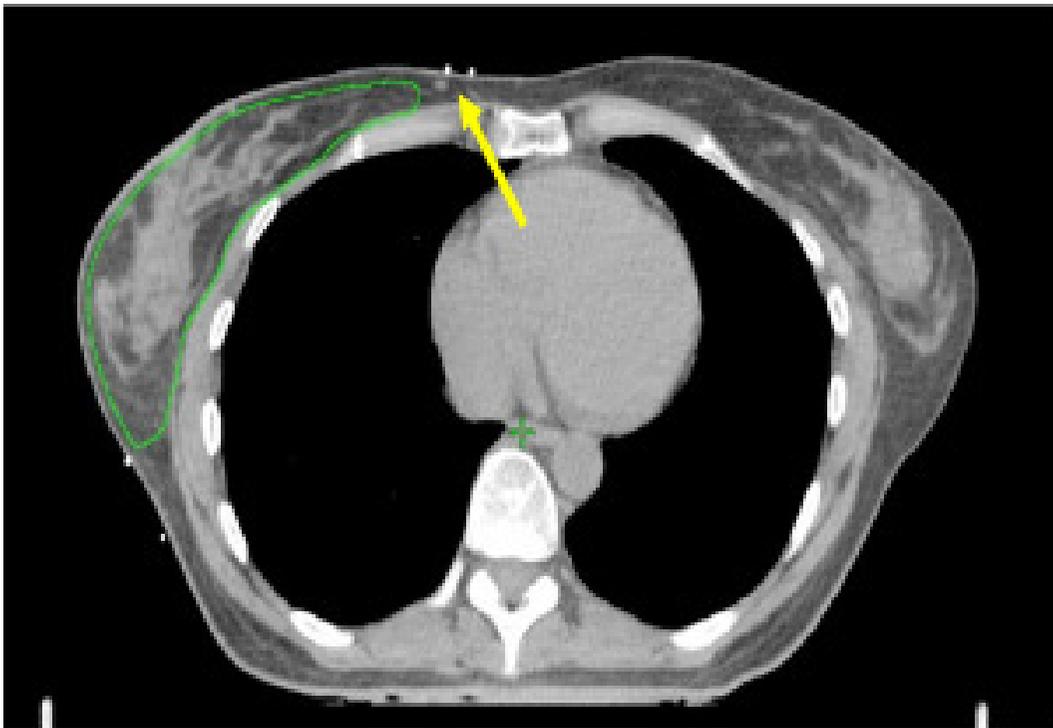
superficial pectoral fascia

## Delineation of the CTV breast

- Use of radio-opaque wire to mark the palpable breast tissue.
- Use of guidelines, e.g.:
  - Medial border of the CTV does not extend beyond the lateral edge of the sternum.
  - Cranial border of the CTV does not extend above the sterno-clavicular joint.
  - CTV does not extend within 0.5 cm of the skin.
  - Take visible breast tissue into account.



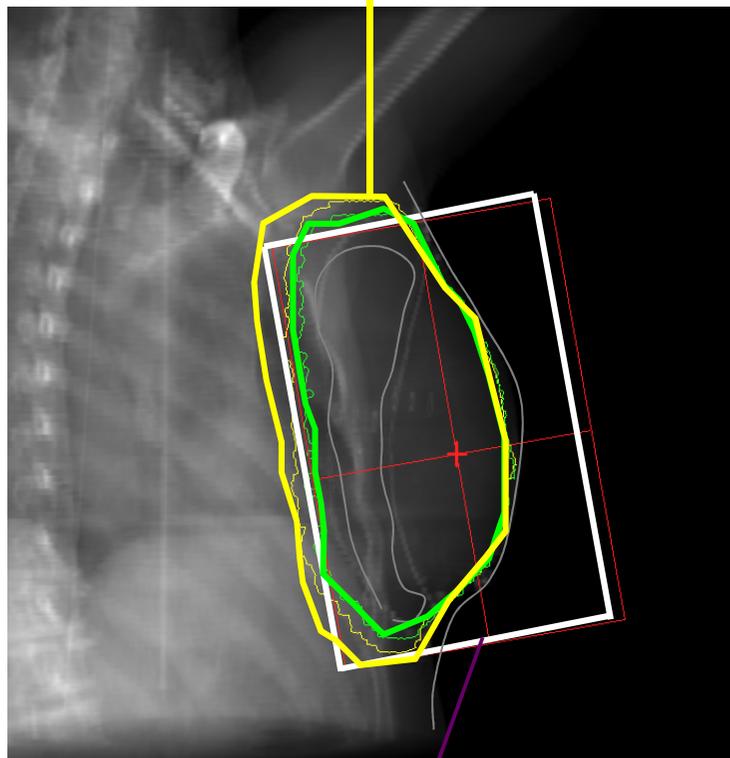
## Delineation of CTVp\_breast, using guidelines



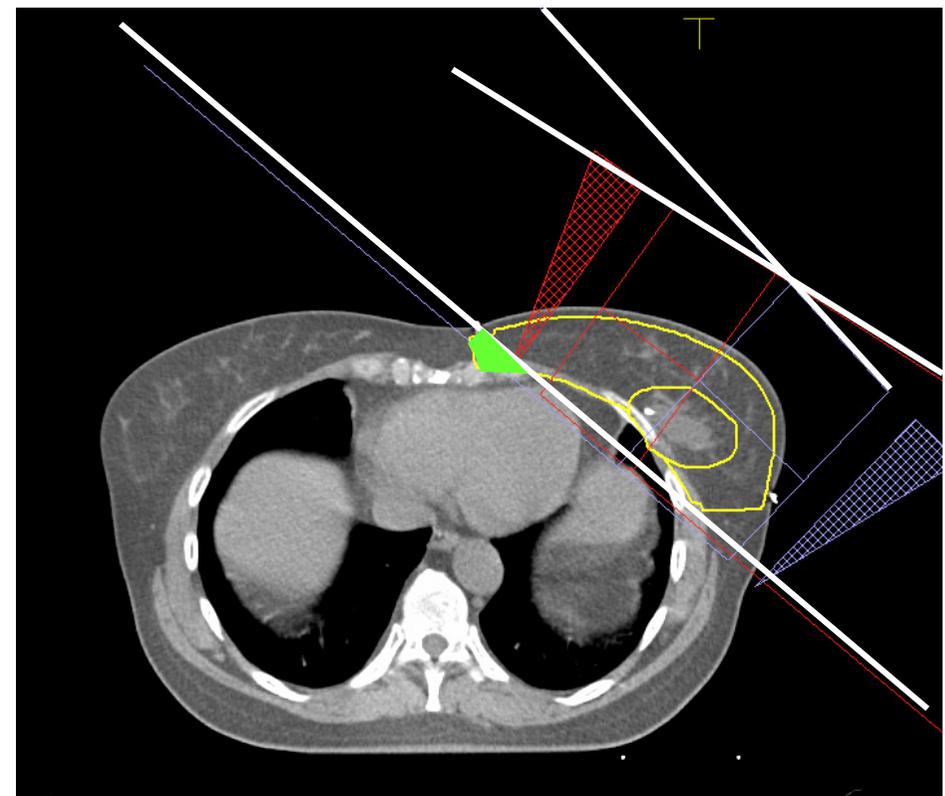


# Conventional RT fields are often too small for delineated PTVs

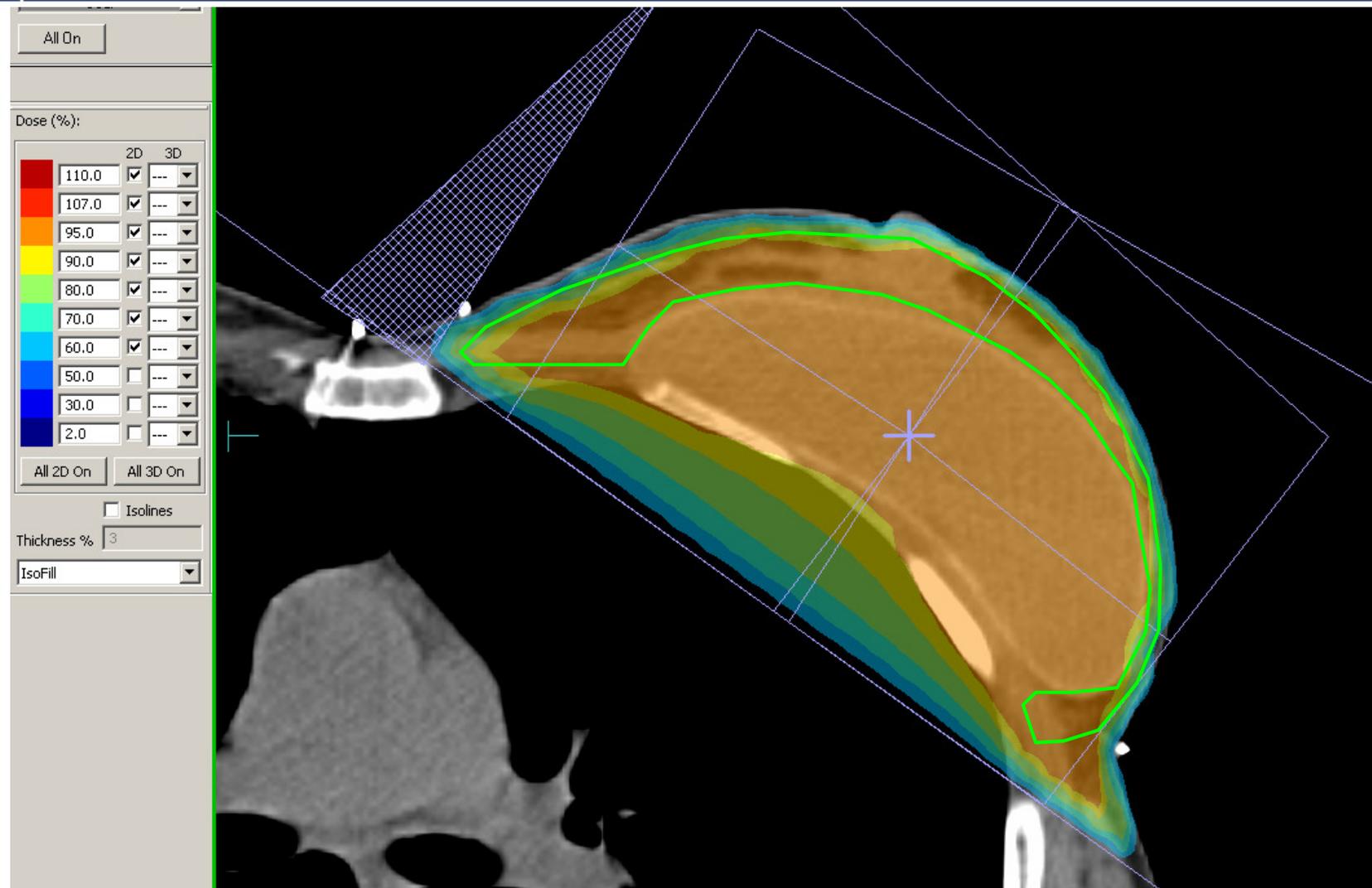
Delineated PTV<sub>breast</sub>



Conventional tangential field



How to deal with a subpectoral tissue expander/permanent implant ?  
Use bolus during part of /complete RT series ?

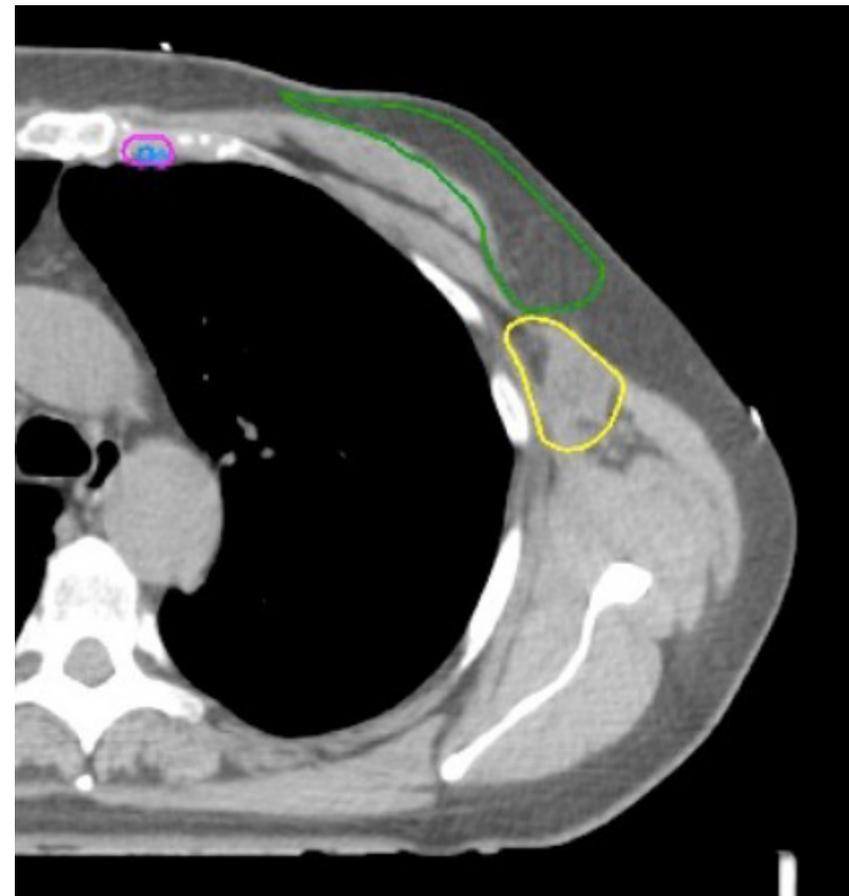


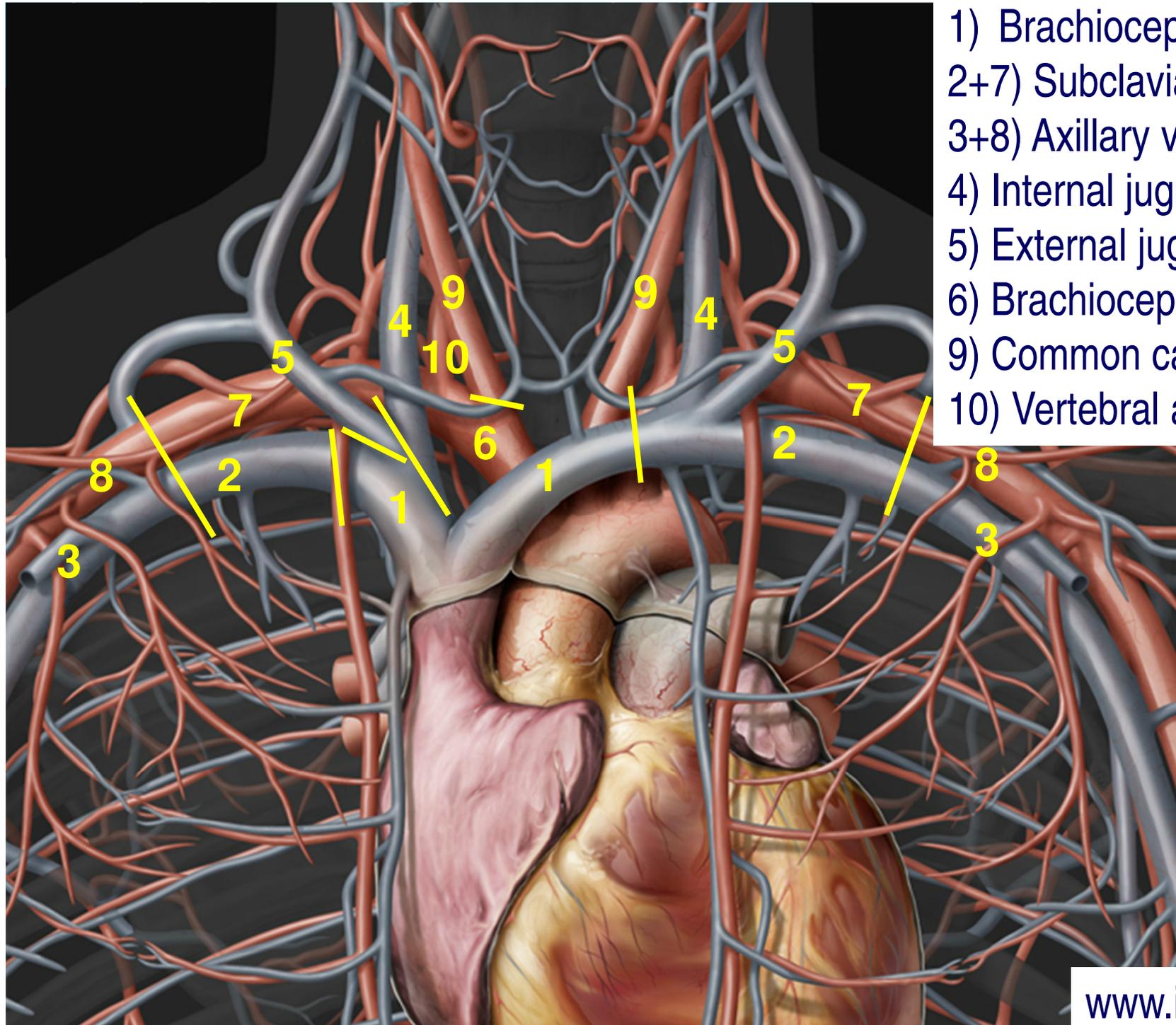
## Delineation of the thoracic wall

- All borders of the CTV thoracic wall are usually considered to be identical to the CTV breast.

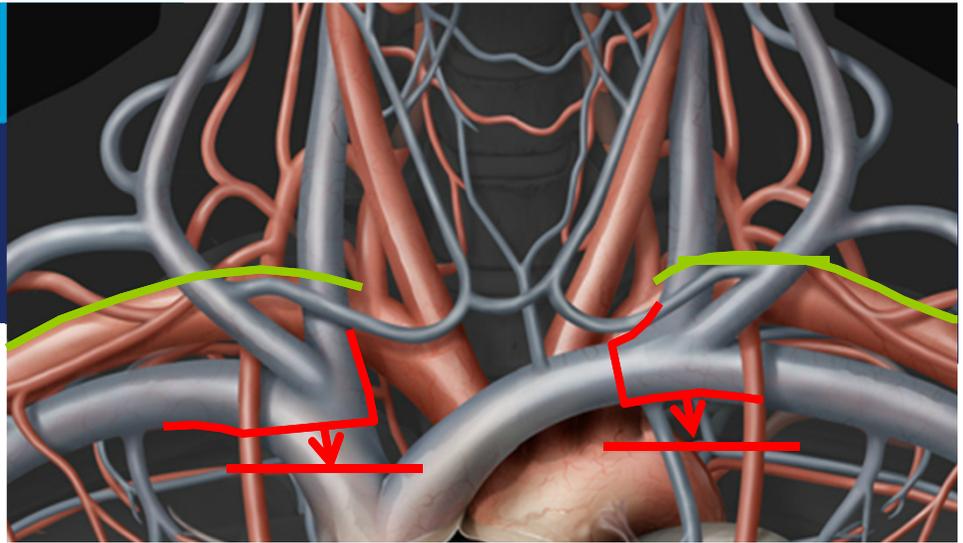
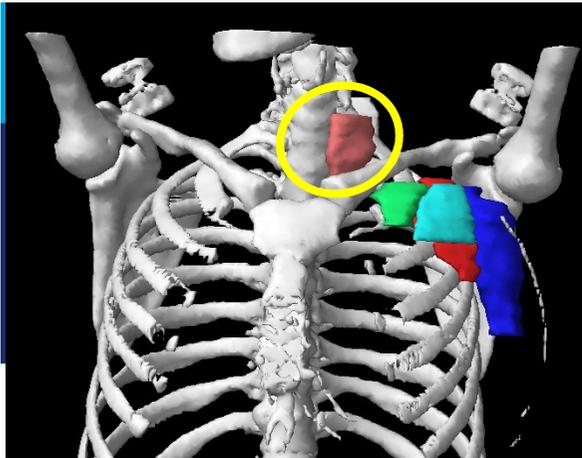
In case of an extremely thin thoracic wall, omission of the first 5 mm beneath the skin may result in no CTV at all.

In that case, do extend the CTV into the skin, and consequently use bolus.





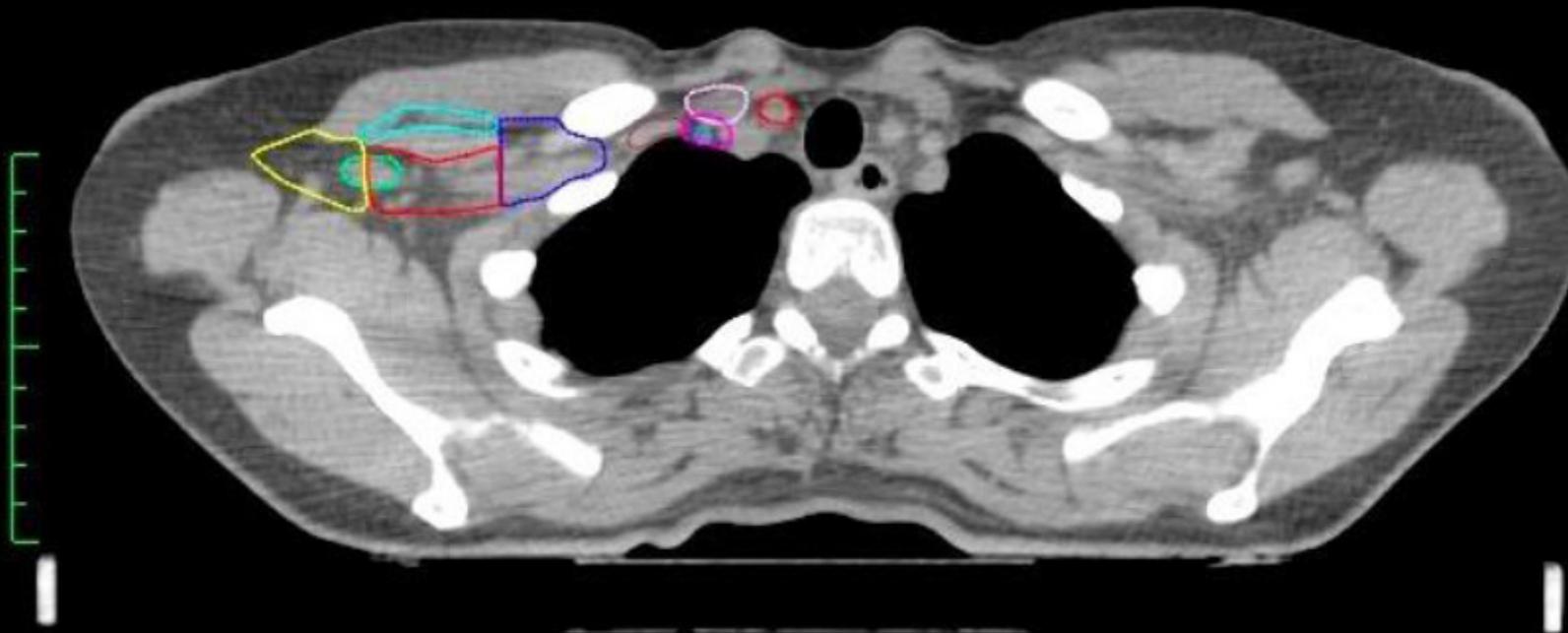
- 1) Brachiocephalic vein
- 2+7) Subclavian vessels
- 3+8) Axillary vessels
- 4) Internal jugular vein
- 5) External jugular vein
- 6) Brachiocephalic trunk
- 9) Common carotid artery
- 10) Vertebral artery



## Supraclavicular LN area, CTVn\_L4:

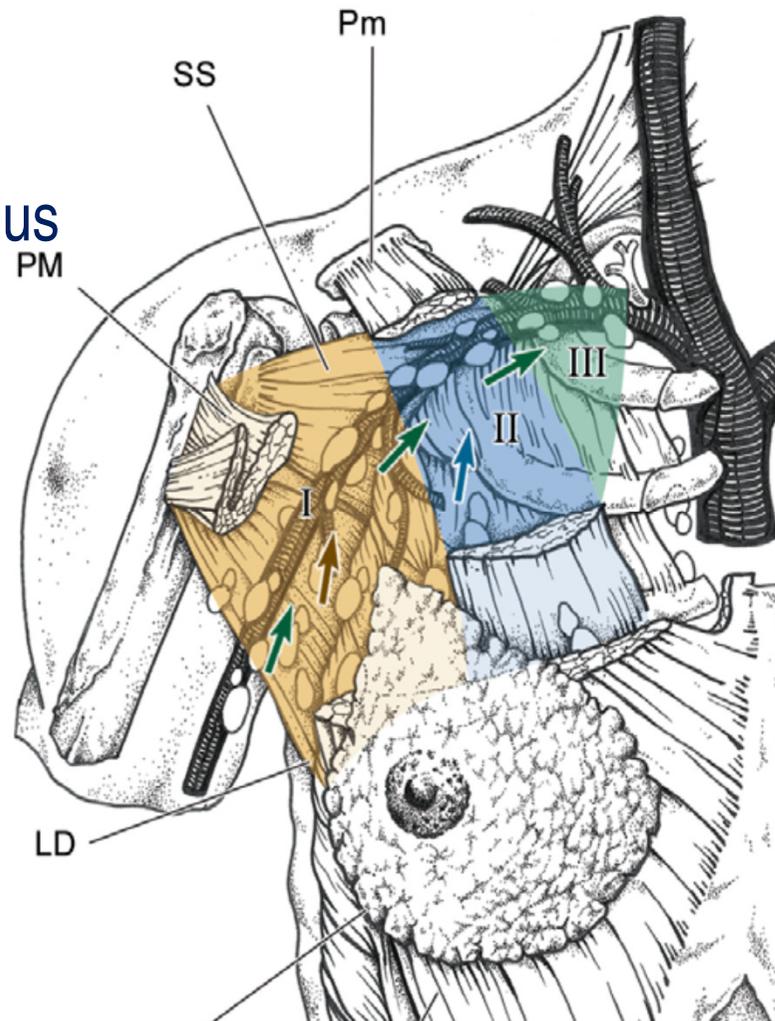
- ✓ Superior border: upper limit of subclavian artery
- ✓ Caudal border: 5mm caudal from junction of subclavian and internal jugular veins
- ✓ Ventral border: sternocleidomastoideus muscle, clavicle
- ✓ Dorsal border: Pleura
- ✓ Medial border: including the jugular vein without margin; excluding the thyroid gland and the common carotid artery
- ✓ Lateral border: includes the anterior scalene muscle, and connects to medial border CTVn L3

CTVn\_L4 = orange



# Global anatomy of axillary lymph nodes regions

Pm: pectoralis minor  
 Insertion: proc. coracoideus



Level I

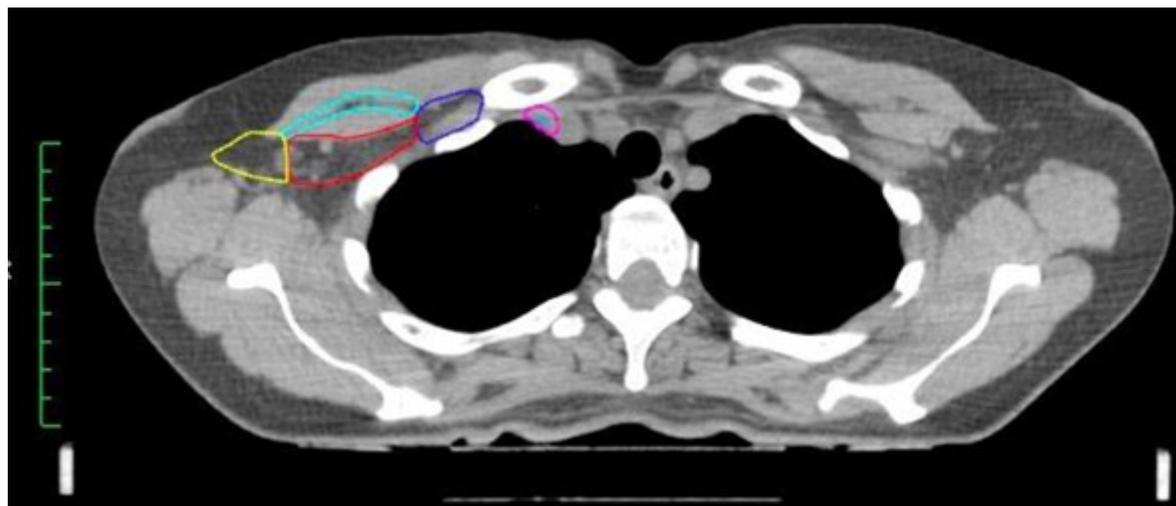
Level II

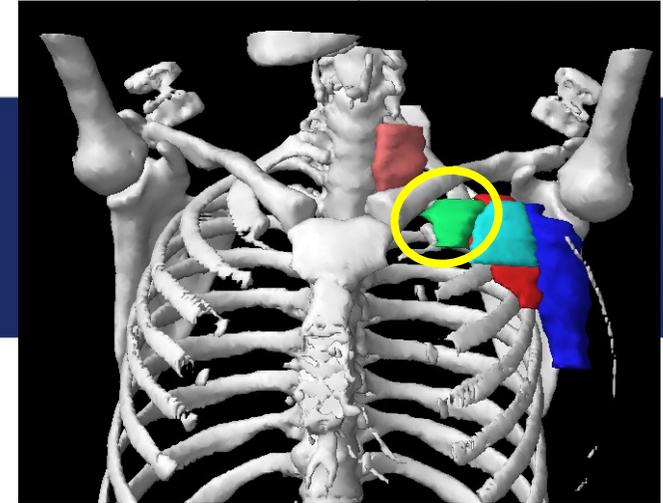
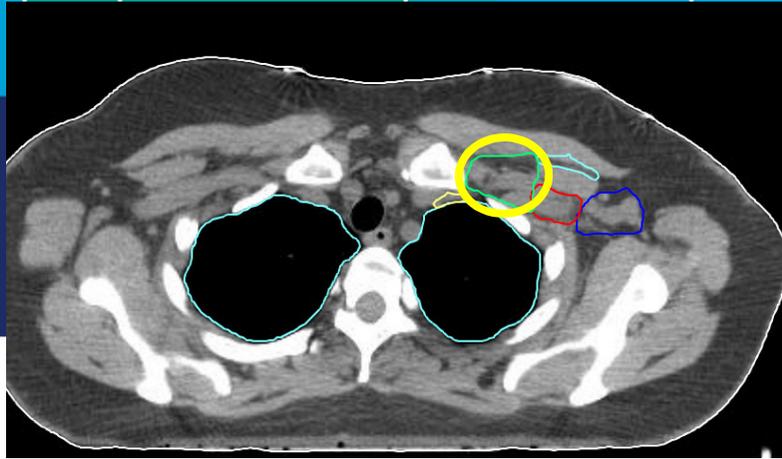
Level III

## Axillary lymph node areas

Traditionally → subdivided into 3 subregions:

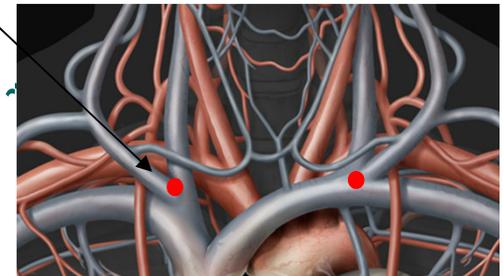
- **level 1** caudally from lower border of major pectoral muscle
- **level 2** posterior to minor pectoral muscle
- **level 3** located medio-cranially from the pectoral muscles
- + **Rotter** located between minor and major pectoral muscle



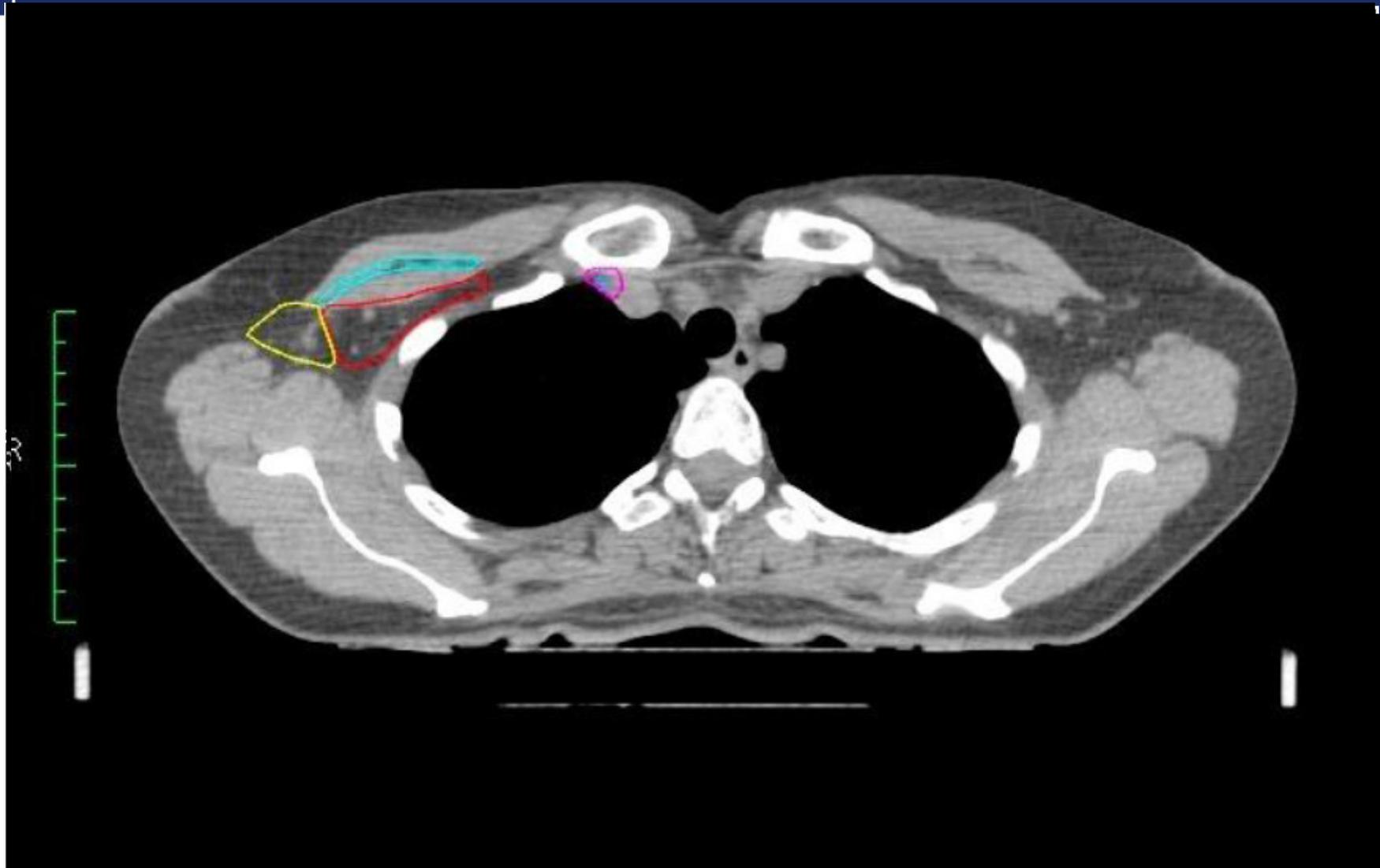


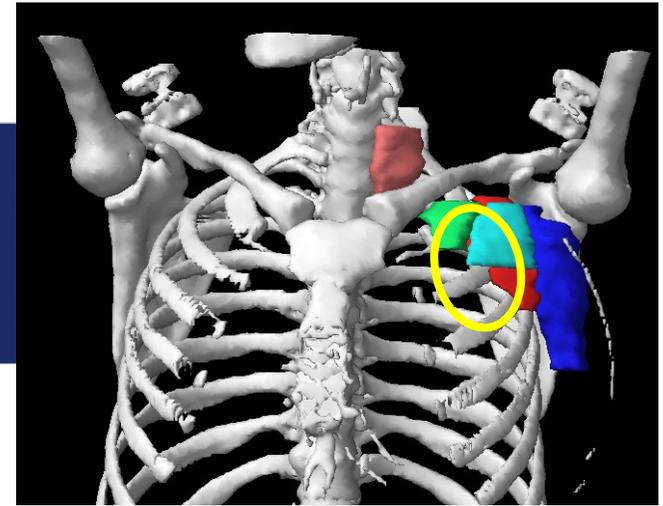
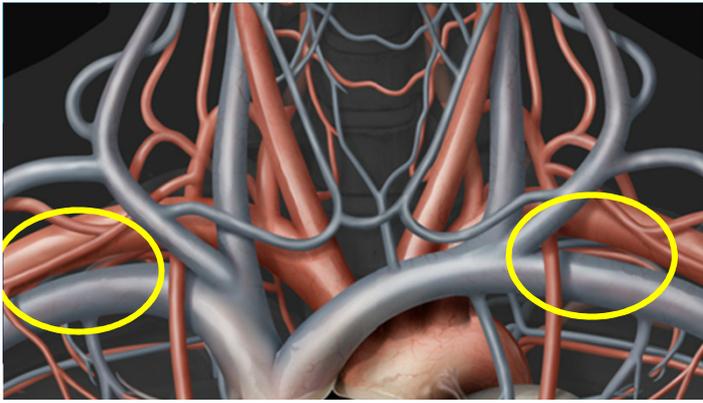
### Axilla level 3 (infraclavicular) – CTVn\_L3:

- ✓ Cranial border: 5mm cranial of the subclavian vein. More medially it is the clavicle
- ✓ Caudal border: 5mm below the subclavian vein
- ✓ Lateral border: medial side of the pectoralis minor muscle
- ✓ Medial border: junction of subclavian and jugular vein
- ✓ Ventral border: pectoralis major muscle
- ✓ Dorsal border: up to 5mm post. of subclavian/axillary vein



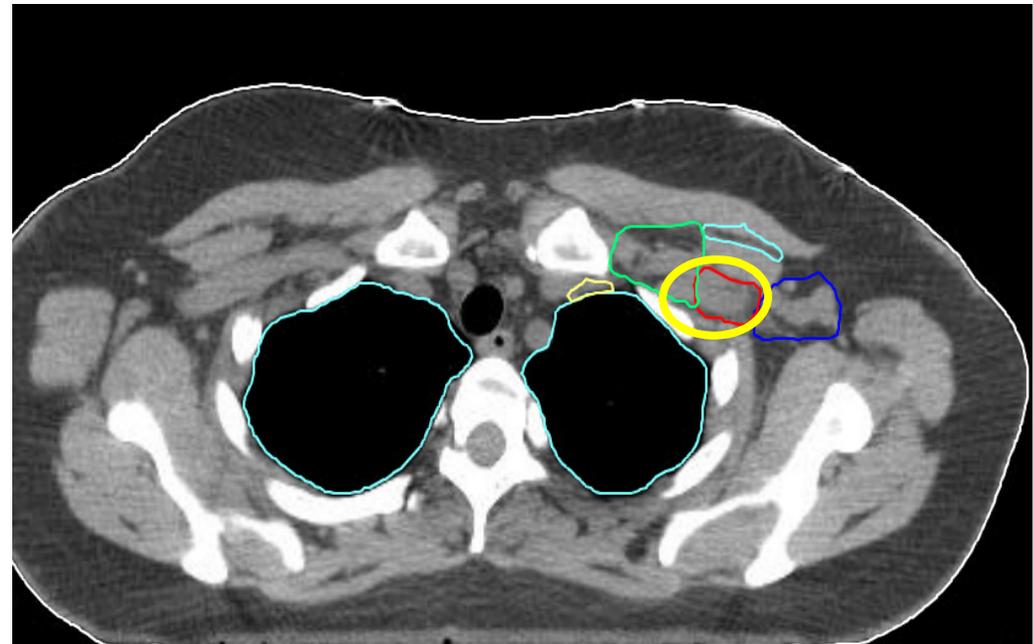
CTVn\_L3 = dark blue



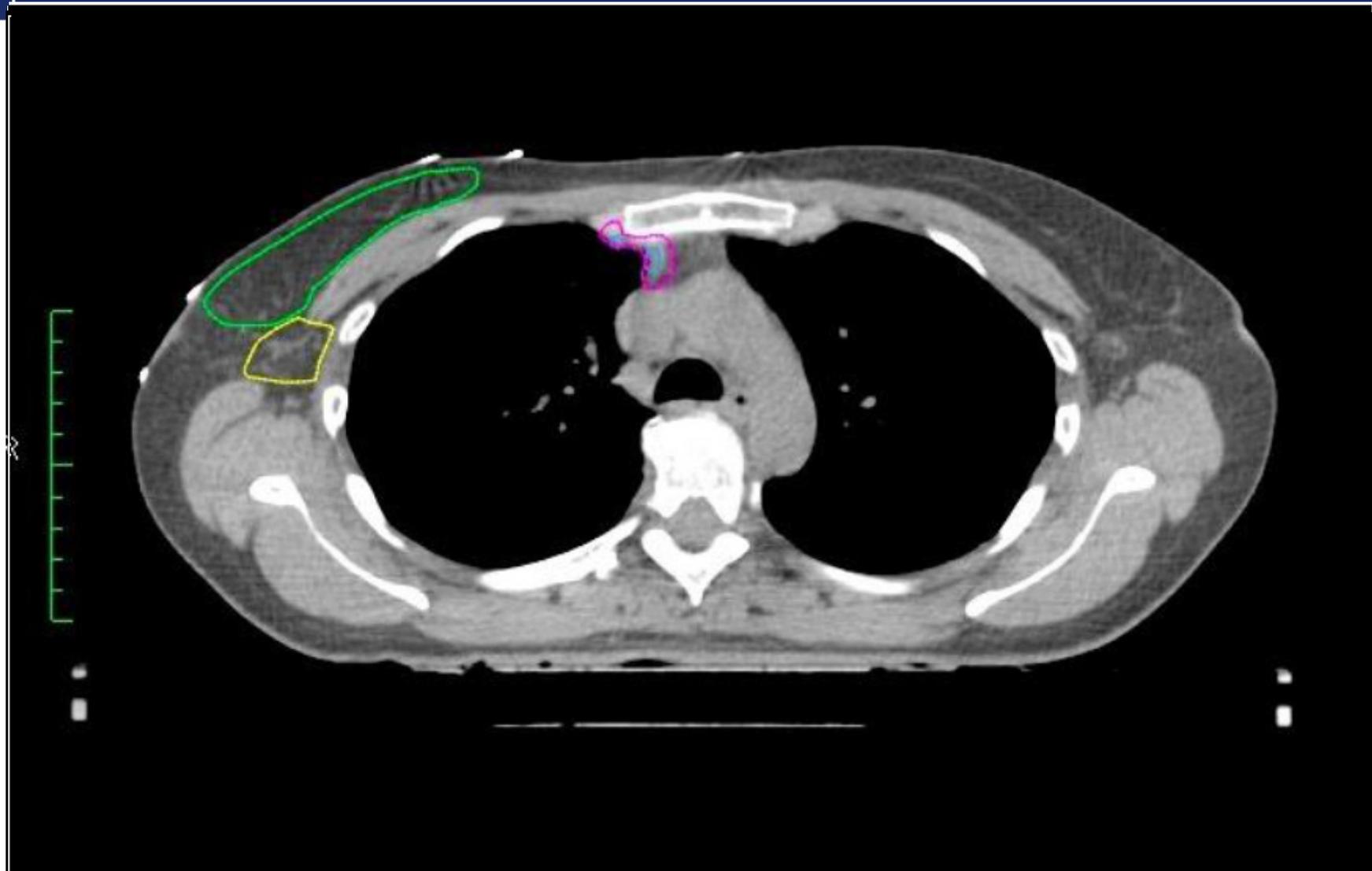


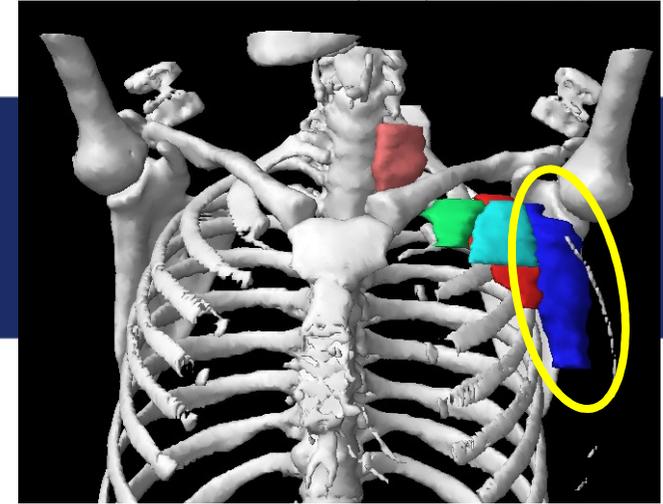
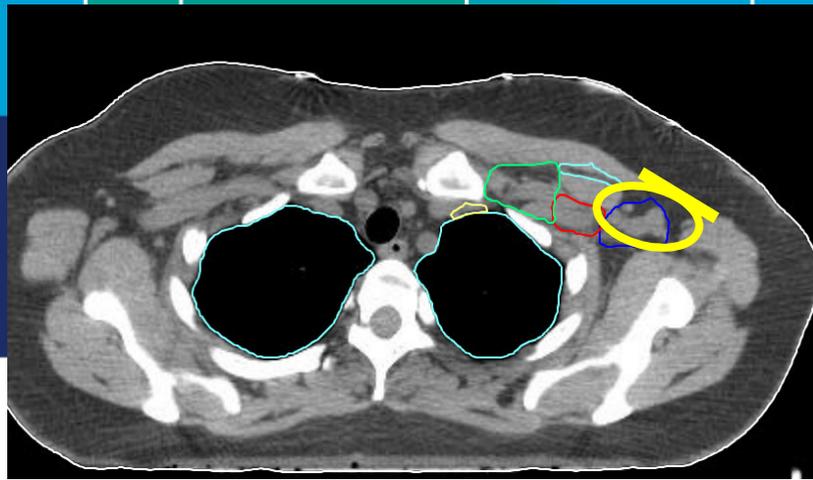
## Axilla level 2 – CTVn\_L2

- ✓ In between levels 1 and 3
- ✓ Dorsal of minor pectoral muscle
- ✓ Cranial/Dorsal: 5 mm around axillary vein
- ✓ Caudal: dorsal of minor pectoral muscle



CTVn\_L2 = red  
Rotter/ Interpectoral nodes = light blue





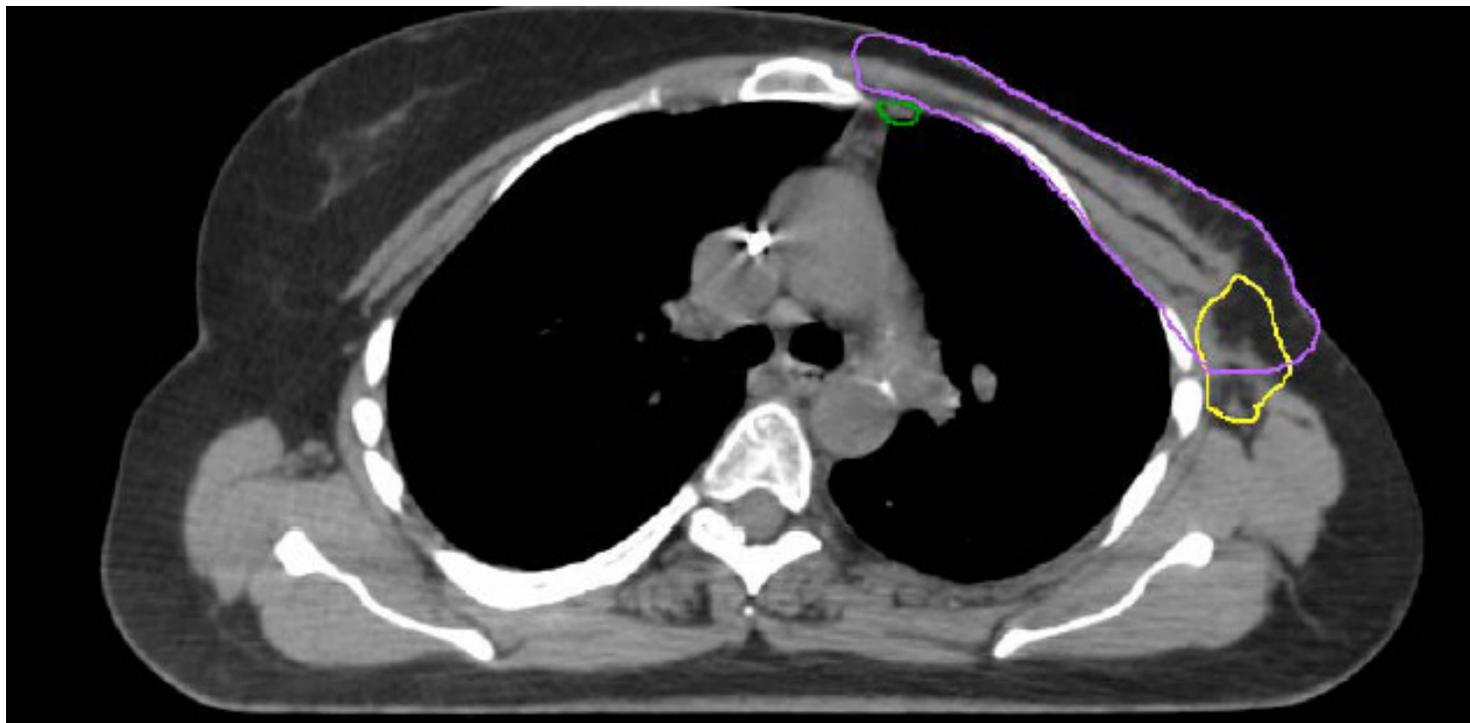
## Axilla level 1- CTVn\_L1:

- ✓ General: use surgical effects to guide
- ✓ Cranio-medial: lateral limit of level 2/ interpectoral nodes
- ✓ Cranio-lateral: up to 1 cm below and following edge of caput humeri, OR where axillary vein crosses the minor pectoral muscle; 5mm around axillary vein
- ✓ Caudal border: between the level of ribs 4 – 5
- ✓ Lateral border: up to superficial part of muscles (**line**)
- ✓ Medial border: level 2 and thoracic wall
- ✓ Ventral border: pectoralis major & minor muscles
- ✓ Dorsal border: up to the posterior blood vessels

CTVn\_L1 = yellow

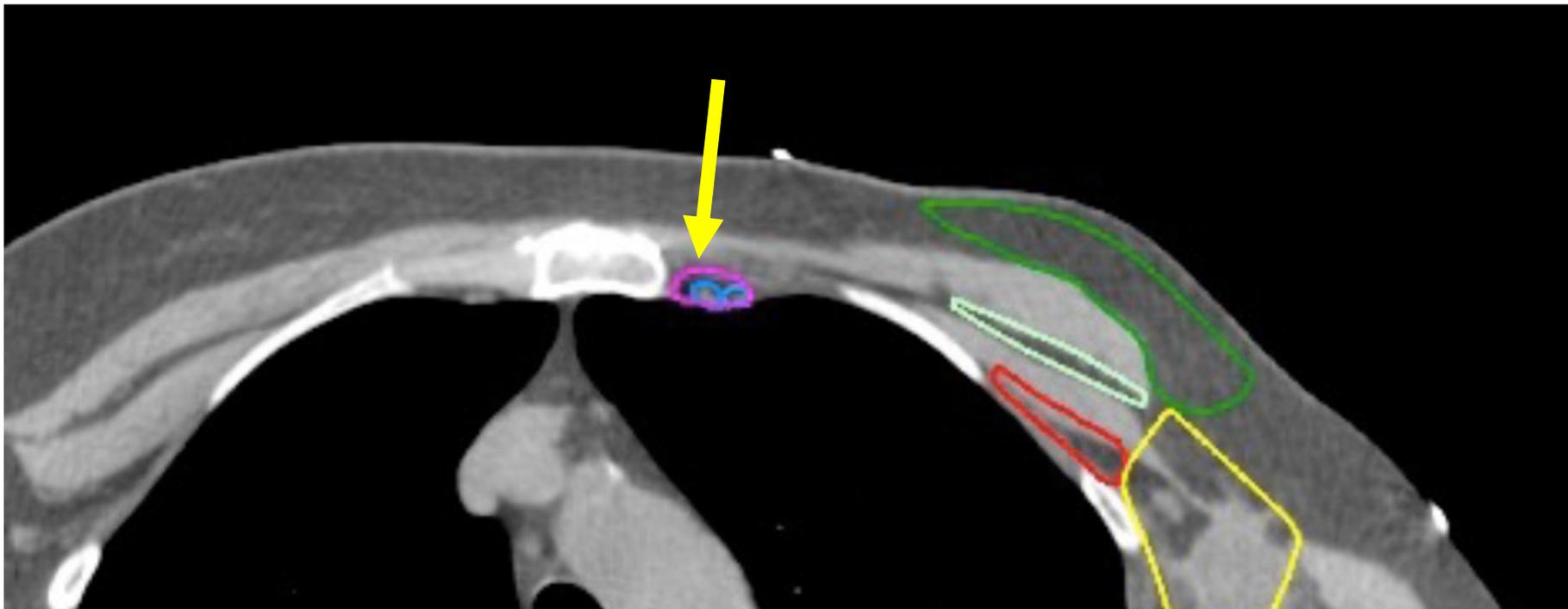


- RTOG atlas axilla level 1: different dorsal border of level 1 & different dorsal border of thoracic wall...



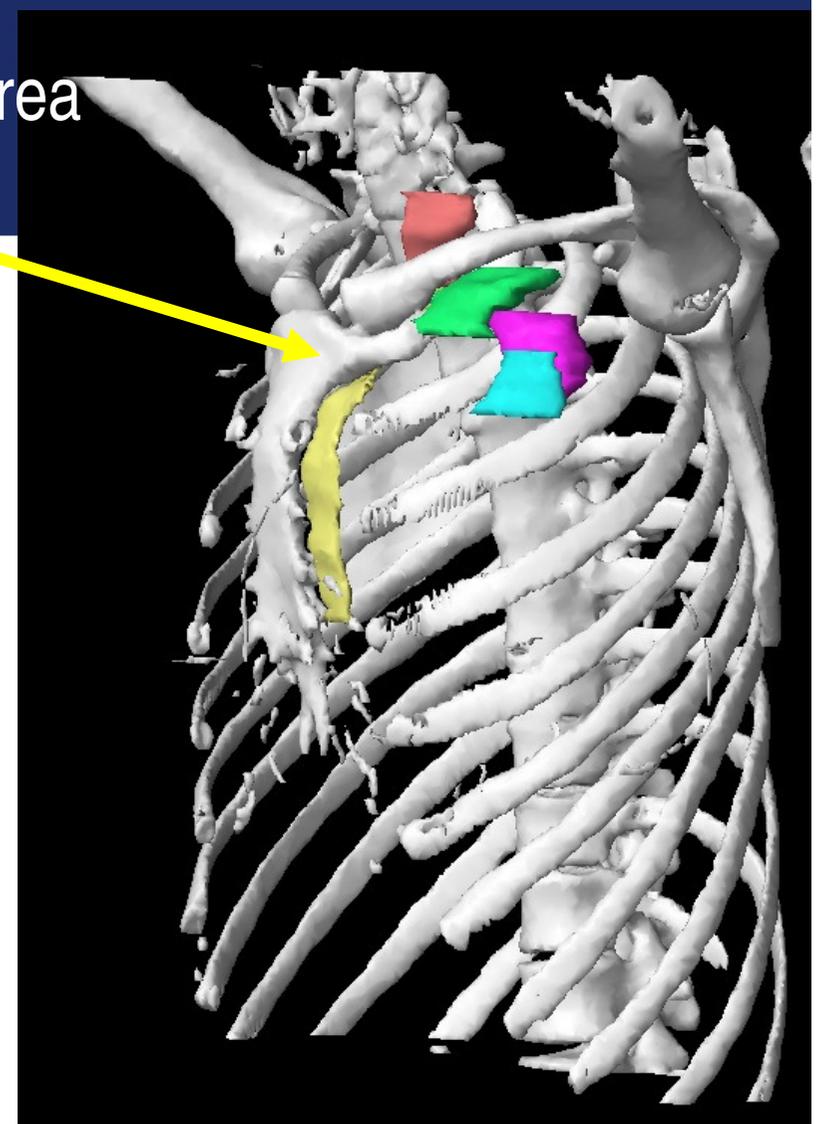
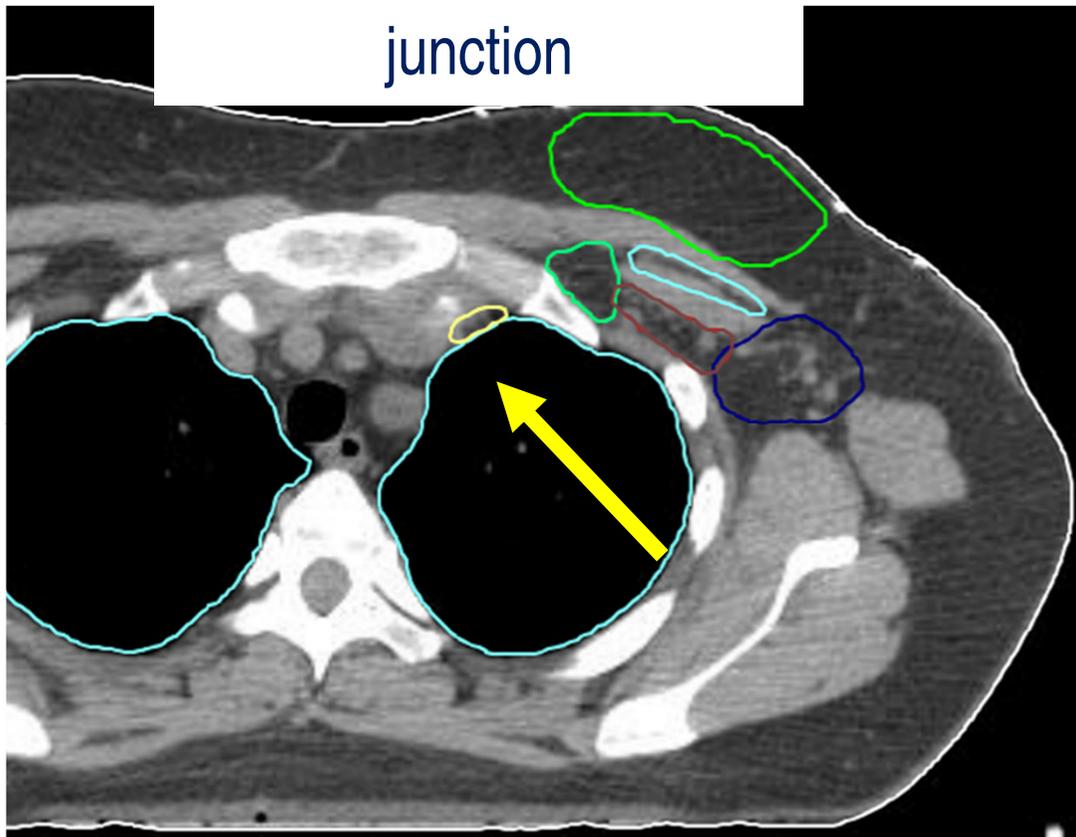
## CTV of internal mammary lymph node area

- ✓ Cranial: junction of subclavian and internal jugular veins → L4
- ✓ Caudal: superior side of the 4th rib
- ✓ Ventral: anterior limit of the vascular area
- ✓ Medial: 5 mm medial of vein; edge of the sternal bone
- ✓ Dorsal: pleura
- ✓ Lateral: 5 mm lateral of vein



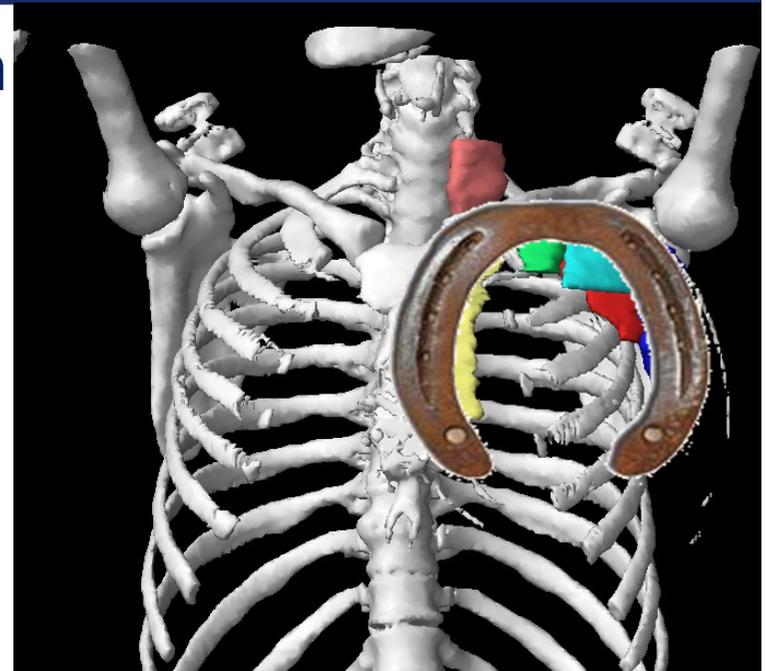
# CTV of internal mammary lymph node area

Critical area just behind the sternoclavicular junction



## General considerations

- General rule for LN areas: veins+ 5mm margin
- IV contrast → facilitates → for learning but not required.
- Normal anatomy atlas = more than helpful.
- Lymph node regions should all interconnect.
- Some discussion points left:
  - Are we ready to leave a gap between PTVs of primary tumor and LN areas ?



The DICOM files can be downloaded for free on <https://estro.box.com/s/wloruionfvbuf3twk8bx>.

## General considerations

- We don't have clinical reason to increase field size compared to the old standard fields.
  - ➔ mind resulting field size/including OAR!
  - ➔ a margin of 5 mm from CTV to PTV should be sufficient (if adequate fixation as well as a carefully designed IGRT procedure are used)

## Take Home Messages

- In general, RT reduces LR rate in breast cancer with factor 3-4.
- With contemporary chemotherapy and RT, preventing LRs also improves OS, in patients with intermediate and high risk.
- LR after BCT is very currently extremely low (< 2-3% at 5 yrs).
- Further studies (SELECTION!) are needed to find out which patients need more and which patients need less treatment.
- Delineation guidelines should not lead to larger RT -fields .

Thanks for you attention !

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