GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ESMO Preceptorship Programme

Breast Cancer

Multidisciplinary management, standards of care, therapeutic targets and future perspectives

Lisbon, Portugal

16-17 September 2016

Principles of breast radiation therapy

Philip Poortmans, MD, PhD

16 September 2016

Past-President

ESTRO
European Society for
RADIOTHERAPY
& ONCOLOGY

Department of
Radiation Oncology

Radboudumc

Principles of breast radiation therapy

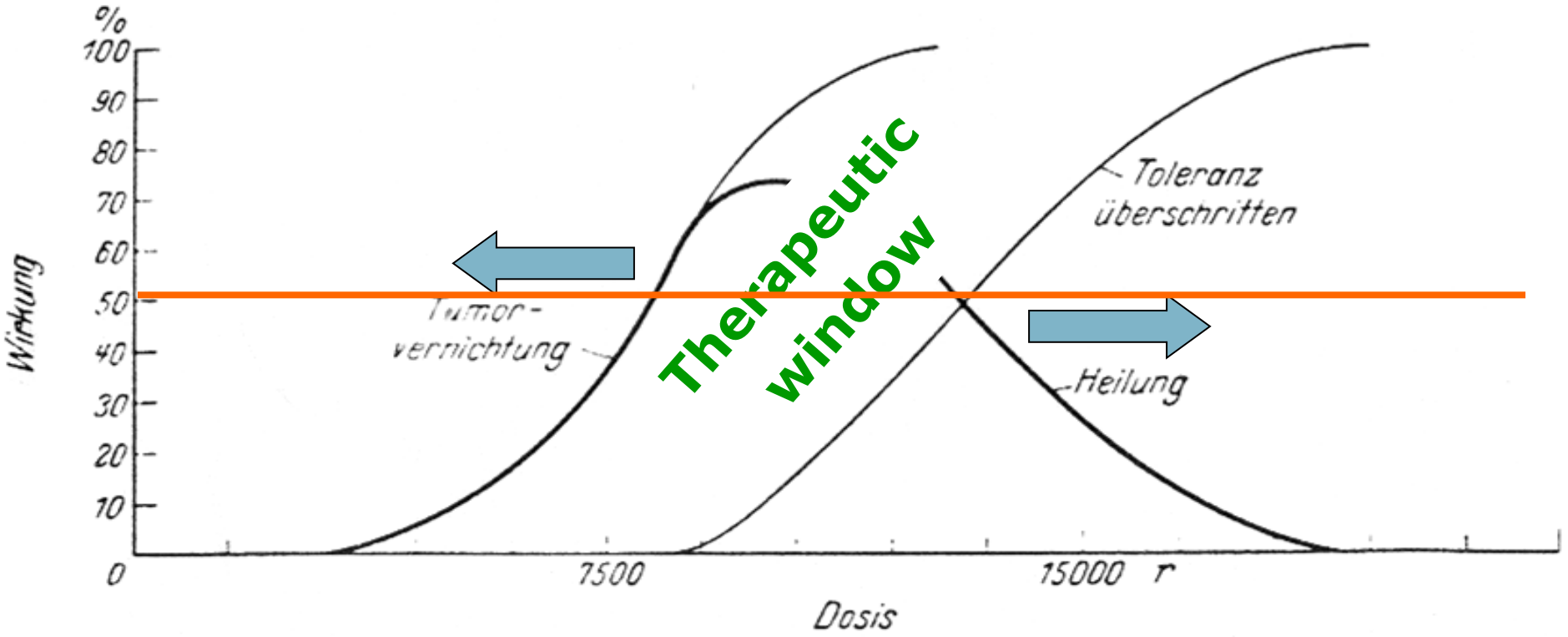
- Introduction
- Tasks of the radiation oncologist
- Indications
- Side-effects
- New developments
- The future

Introduction

Erfahrungen über die Verträglichkeitsgrenze für Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden*).

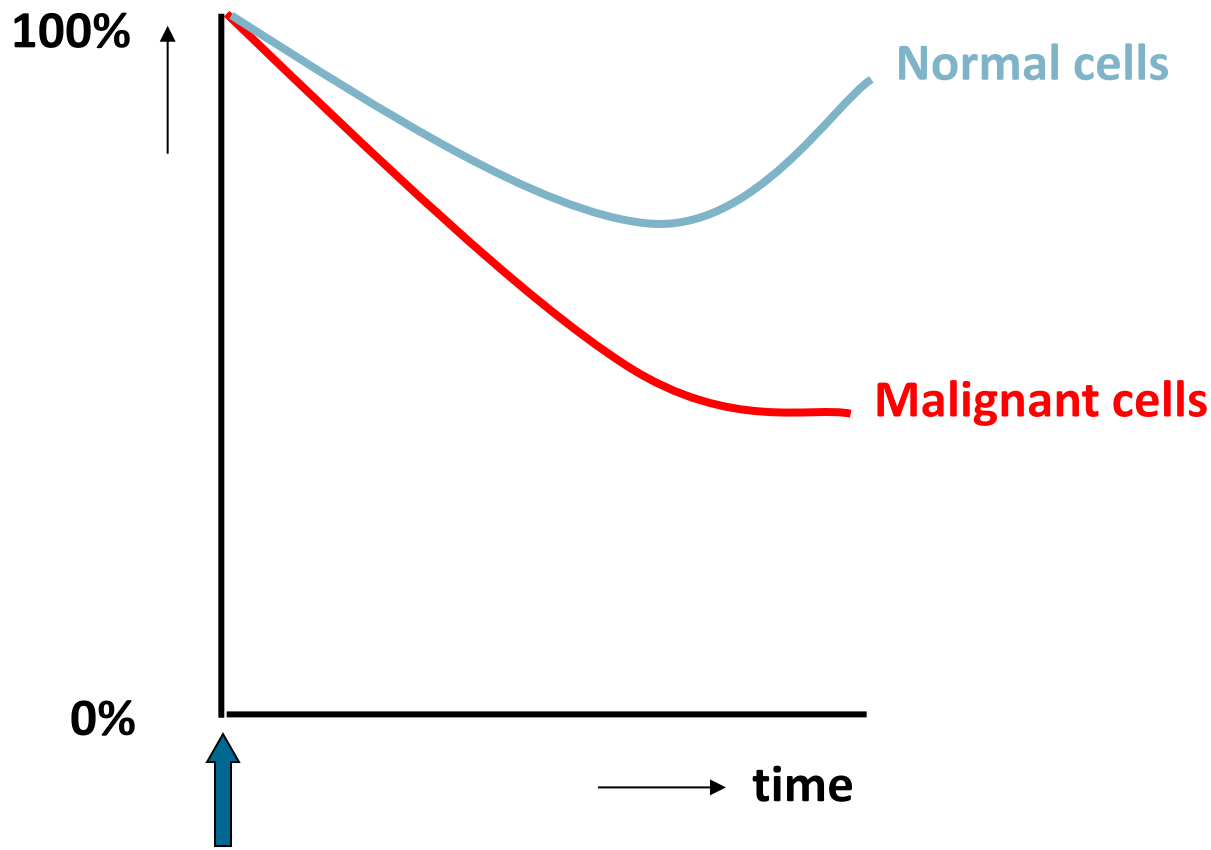
Von

H. Holthusen, Hamburg.



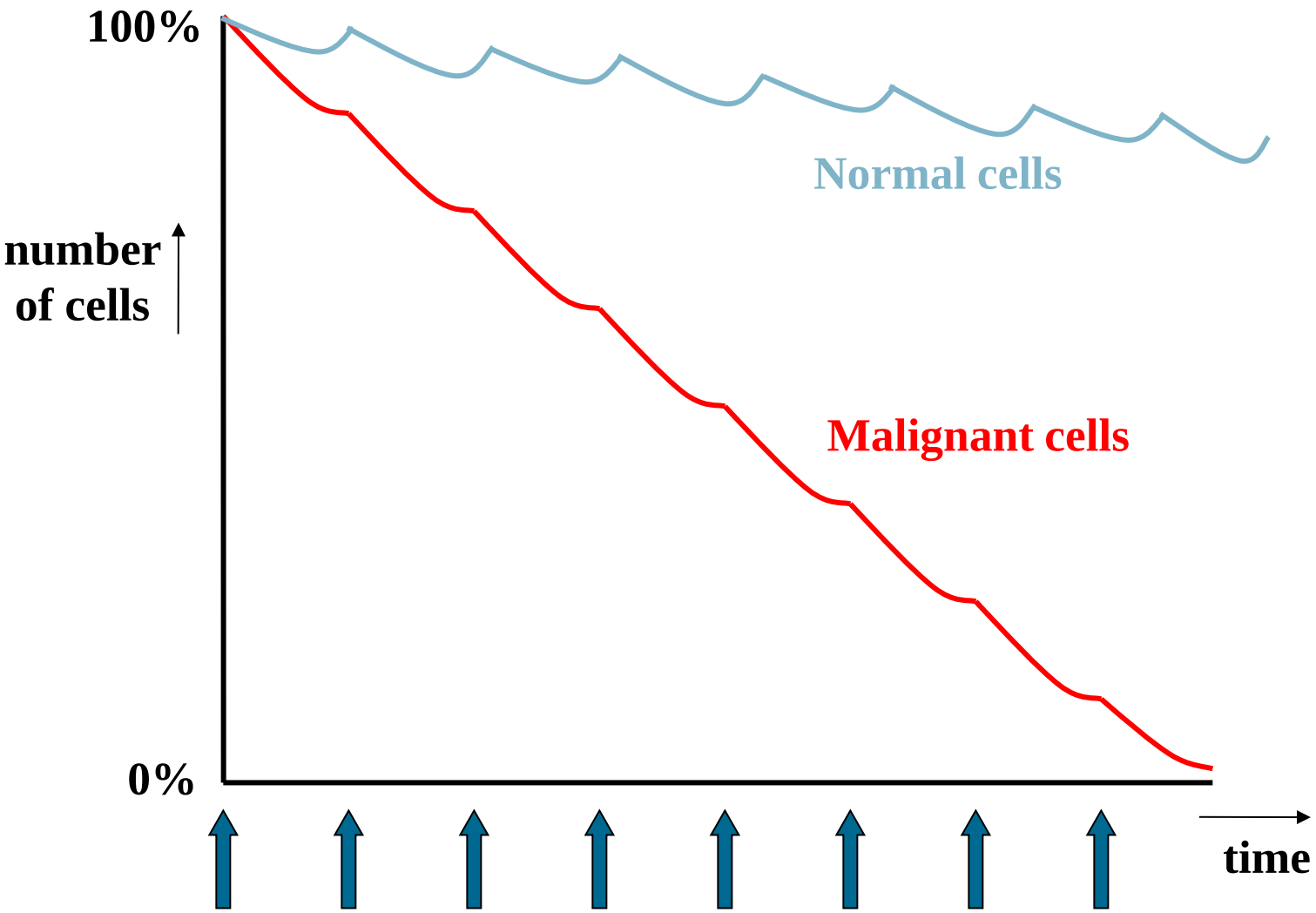
*) Vortrag vor der Deutschen Röntgengesellschaft am 24. April 1936

Introduction

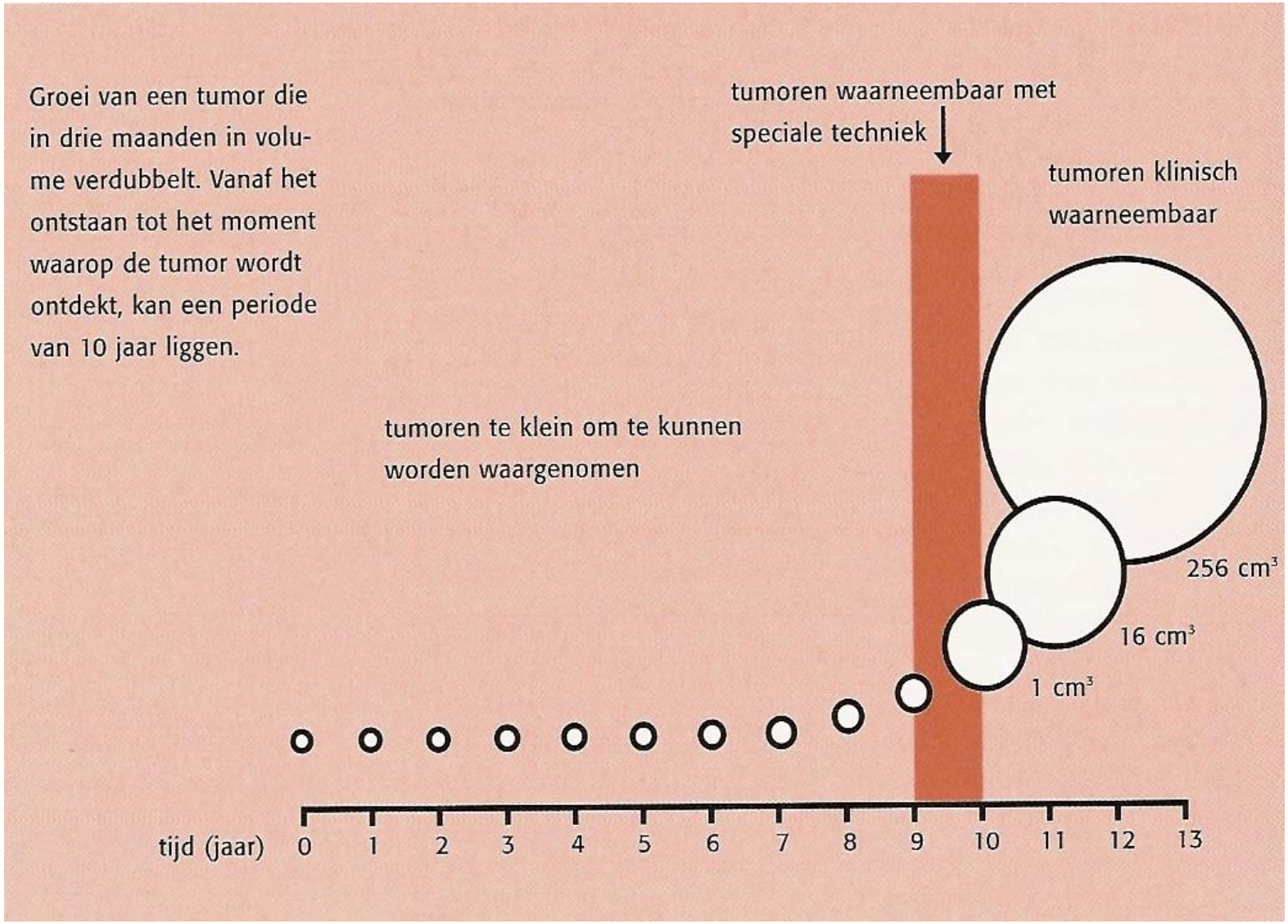


➔ *Delivery of the total dose in several small fractions*

Introduction



Introduction



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Tasks of the radiation oncologist

J.B. Murphy

1857 - 1916

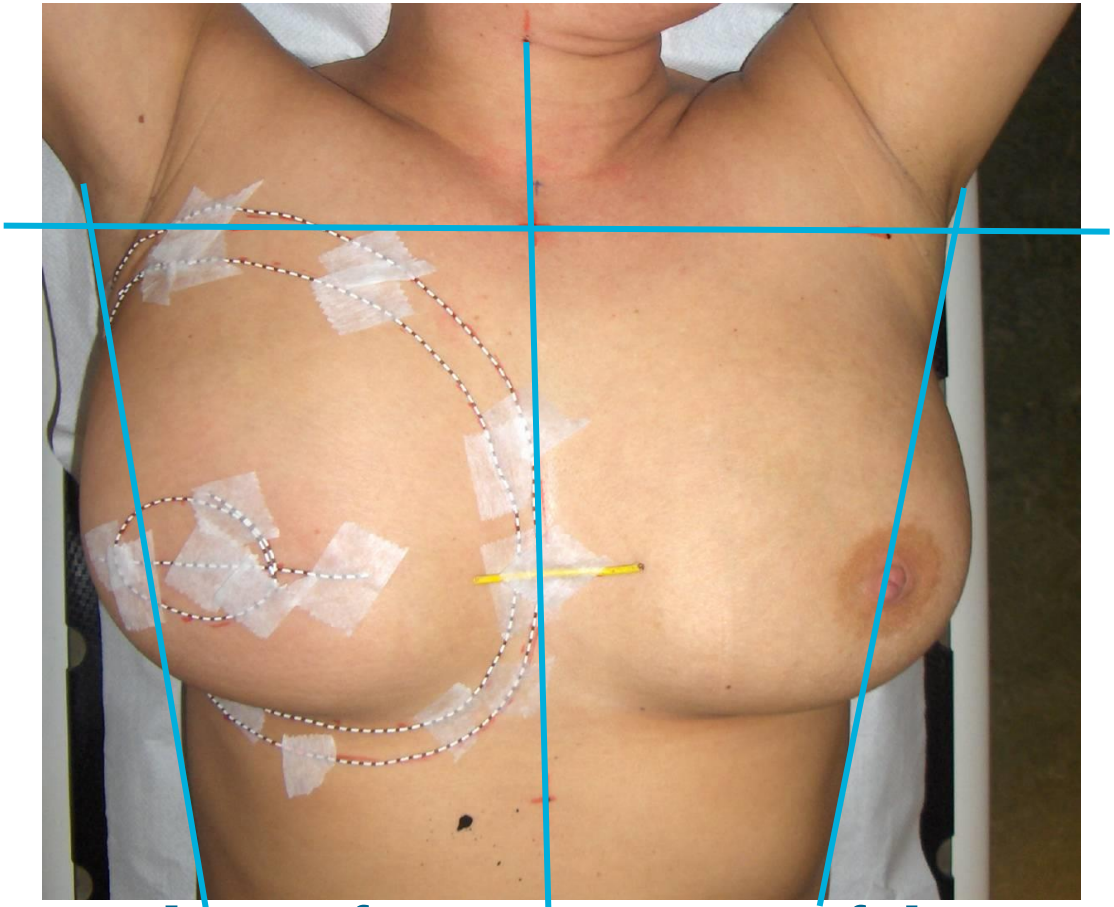
The patient is the centre of the medical universe around which all our work revolves and towards which all our efforts tend.

Tasks of the radiation oncologist

The CT scan enables the making of an individualised treatment plan.

Tasks of the radiation oncologist

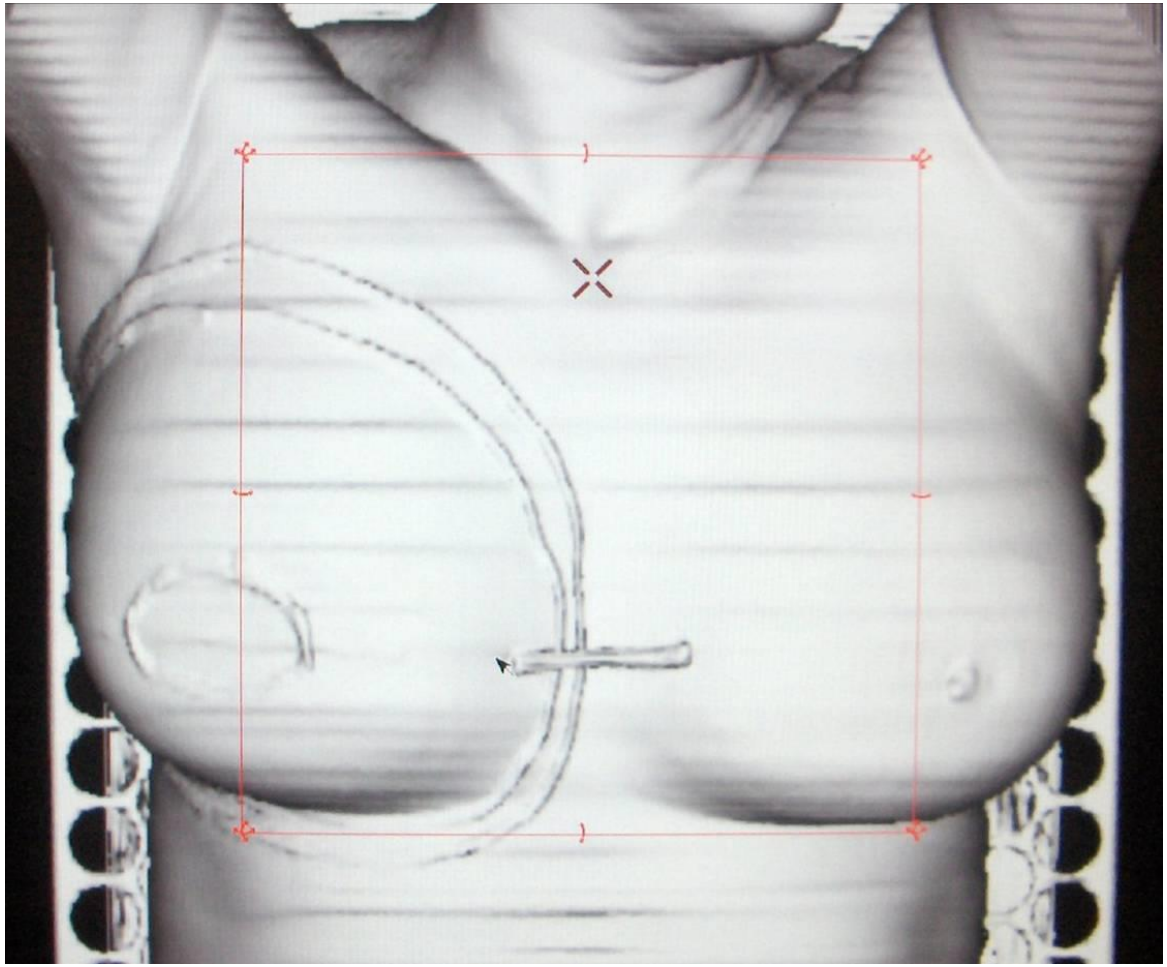
CT scan: positioning

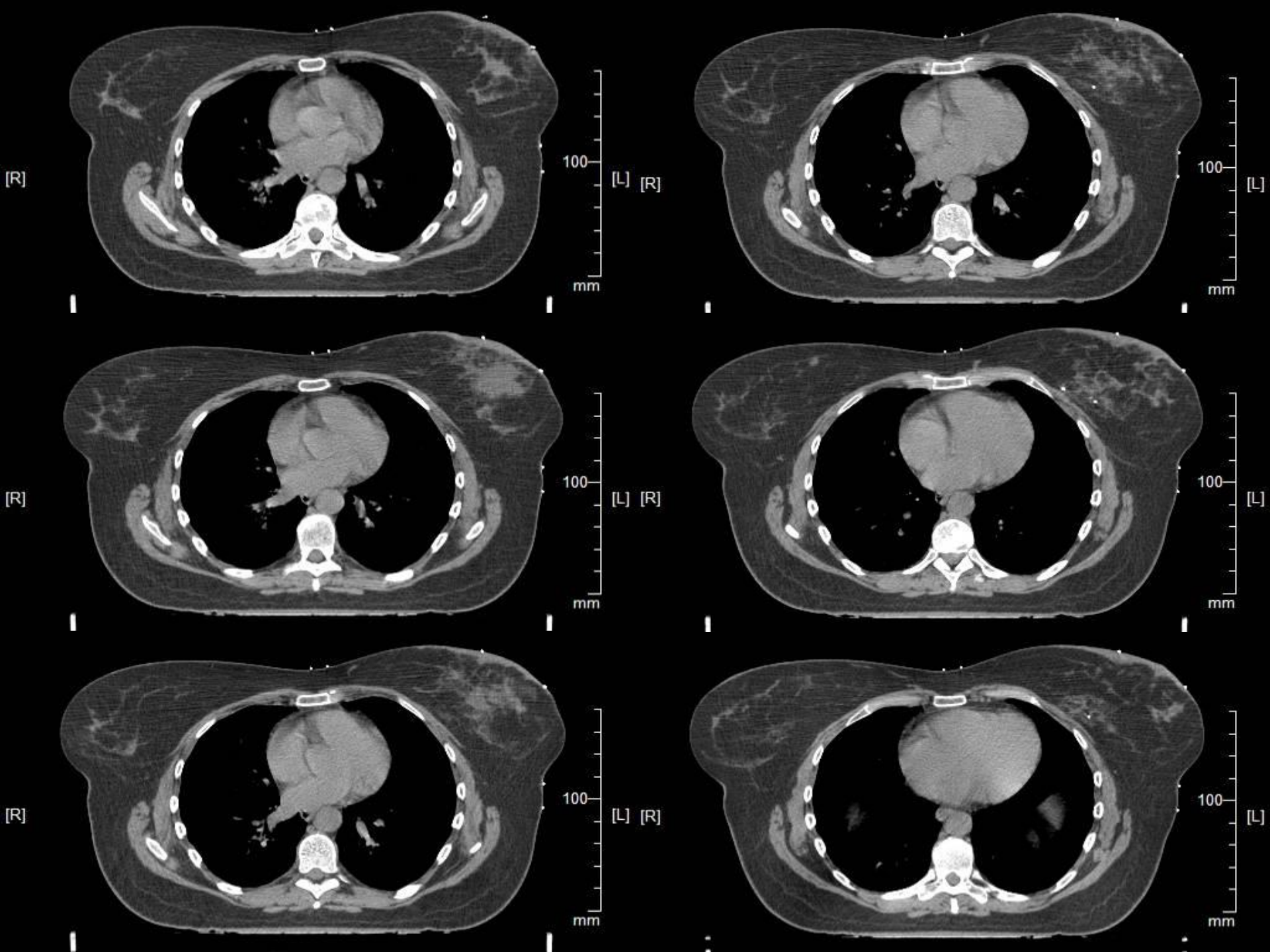


LASER limes for positioning of the patient.

Tasks of the radiation oncologist

CT scan: positioning

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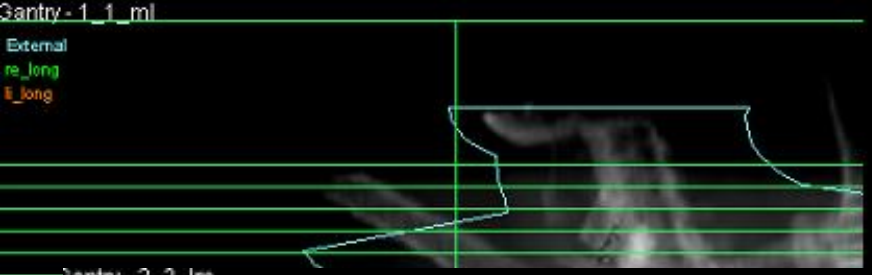
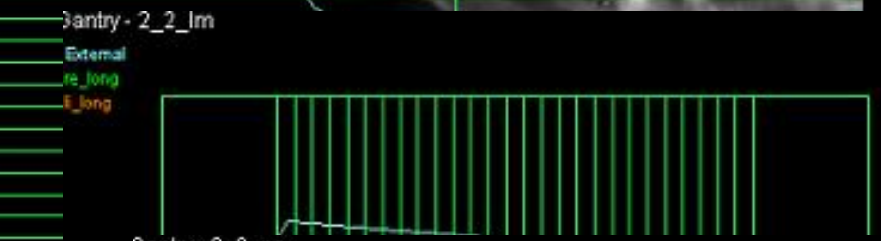
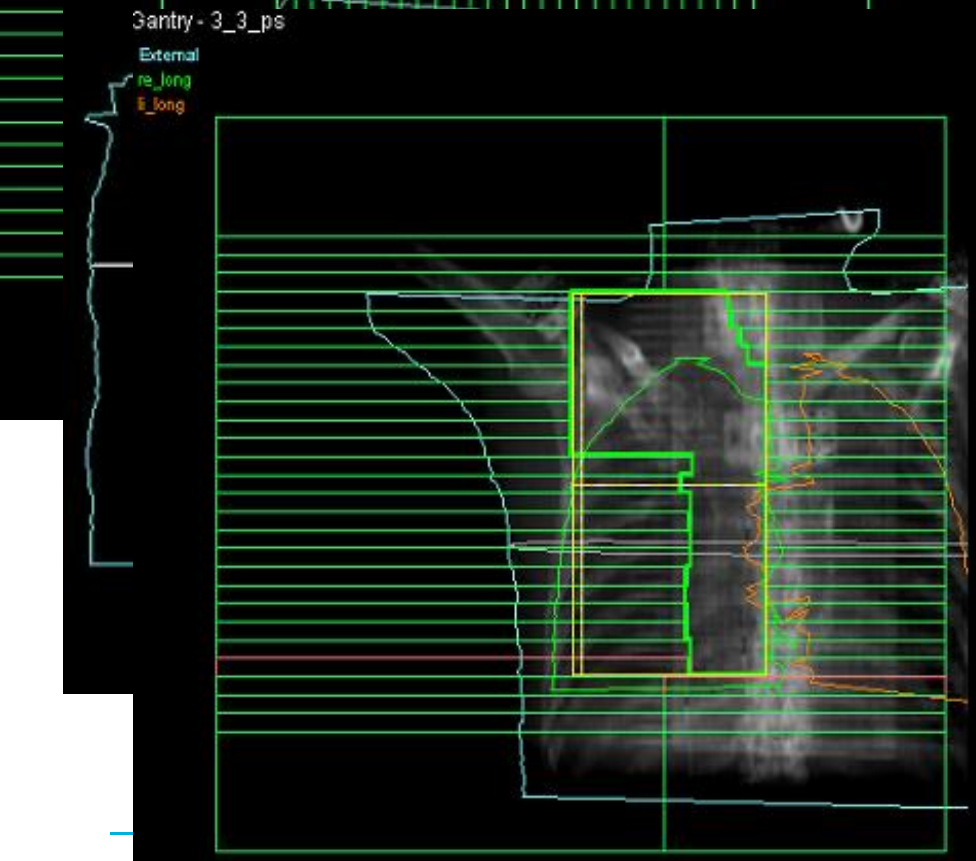
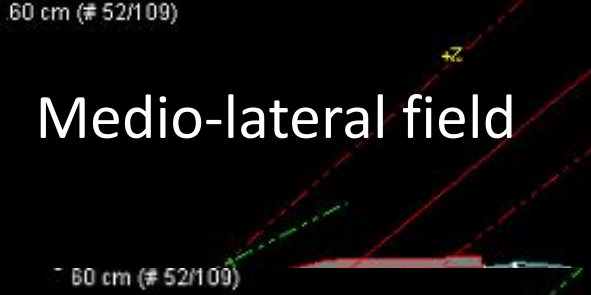
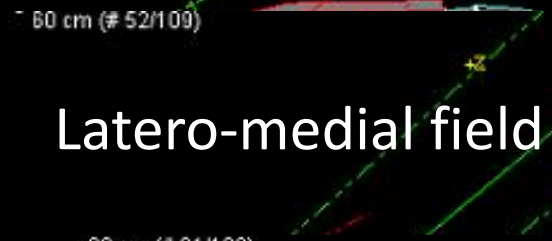




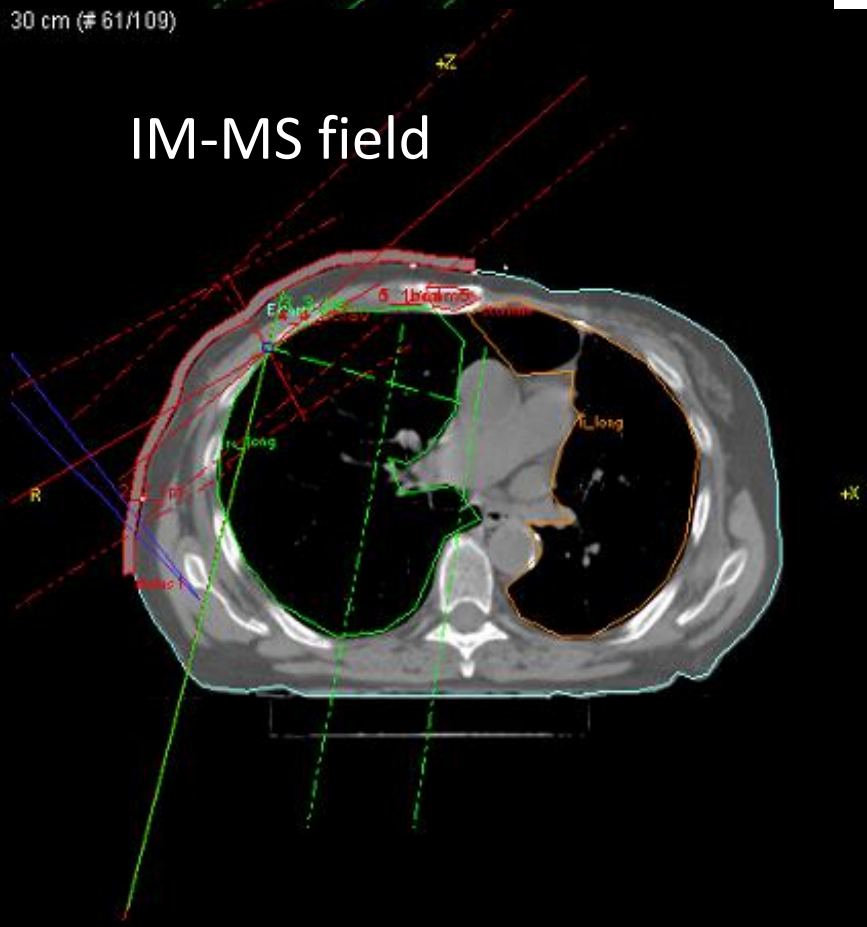




Medio-lateral field



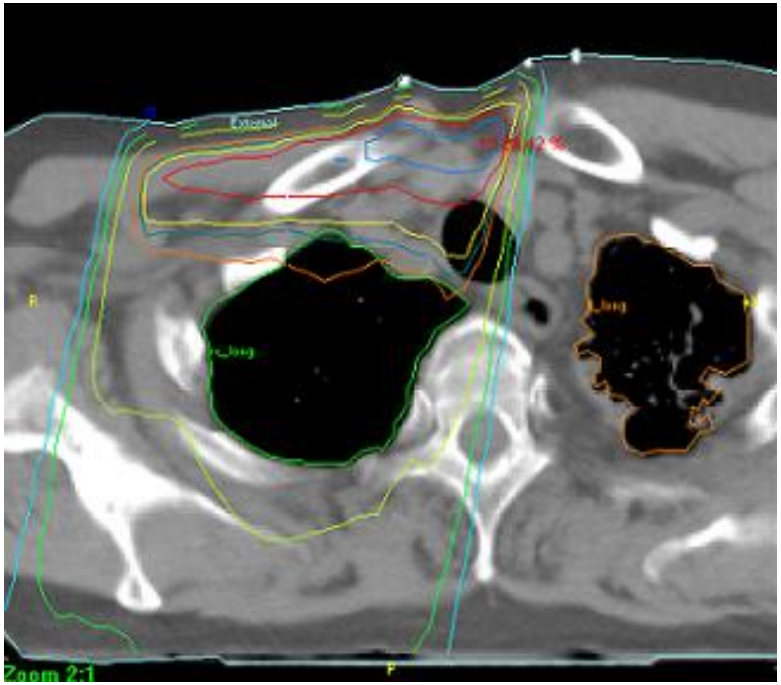
Latero-medial field



IM-MS field

Projection: 100.00 cm

Tasks of the radiation oncologist



Supraclavicular

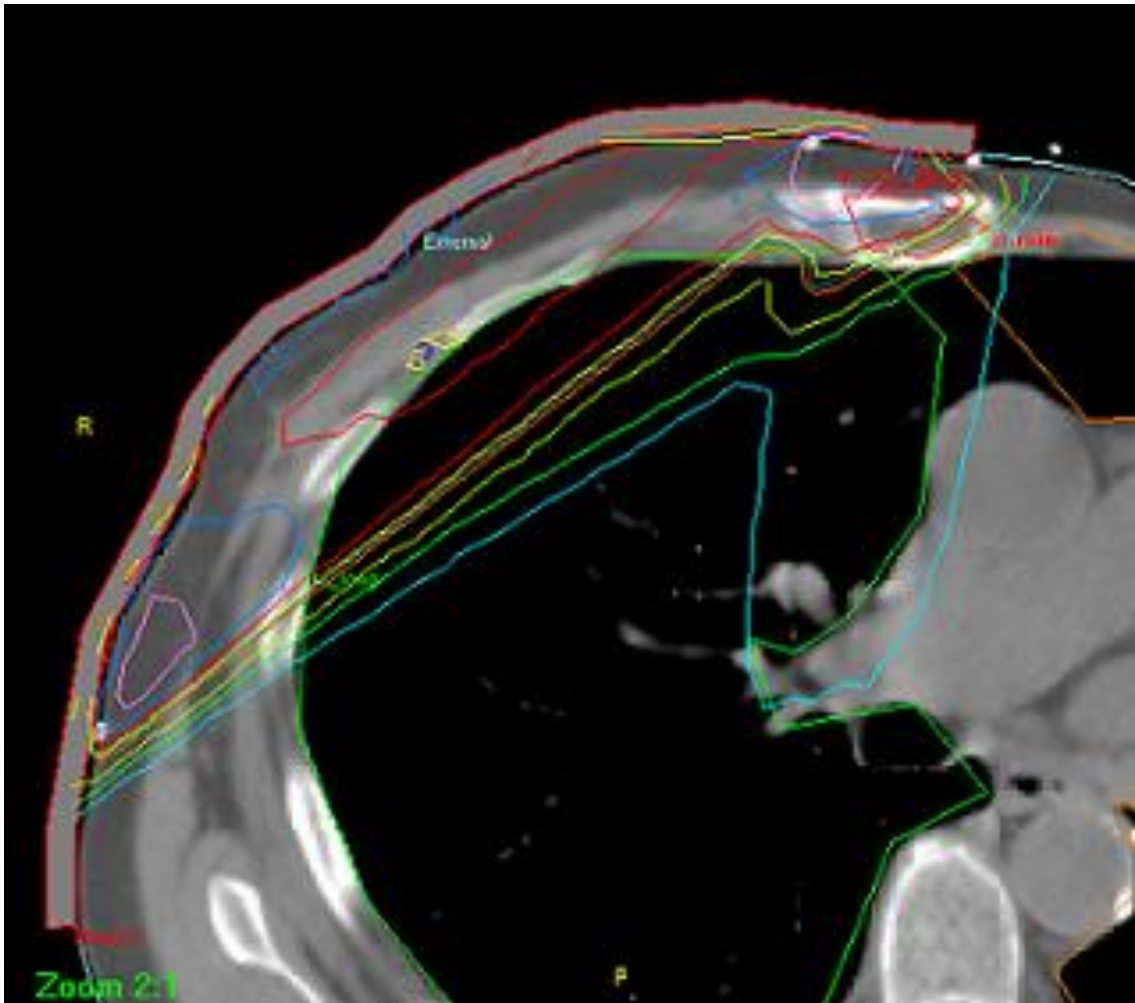
±

axilla

Chest wall

&

IMC



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Indications: breast conserving therapy

	5-year local recurrence risk (%) in trials of: (a) RT after BCS (node-negative)	
	RT versus control	Absolute reduction (SE)
Age (years)		
<50	11 *vs* 33	22 (2)
50–59	7 *vs* 23	16 (2)
60–69	4 *vs* 16	12 (1)
⩾70	3 *vs* 13	11 (2)
Tumour grade		
Well differentiated	4 *vs* 14	10 (2)
Moderately differentiated	9 *vs* 26	17 (2)
Poorly differentiated	12 *vs* 34	22 (3)
Tumour size (T category)		
1–20 mm (T1)	5 *vs* 20	15 (1)
21–50 mm (T2)	14 *vs* 35	21 (3)
>50 mm (T3 or T4*)	..	..
ER status		
ER-poor	12 *vs* 30	18 (3)
ER-positive	6 *vs* 25	19 (2)
Number of involved nodes		
1–3	..	..
⩾4	..	..
All women	7 *vs* 23	**16 (1)**

LR - 70%

EBCTCG Lancet 2005; 366: 2087–2106

Indications: breast conserving therapy

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2011; 378: 1707–16

Indications: breast conserving therapy

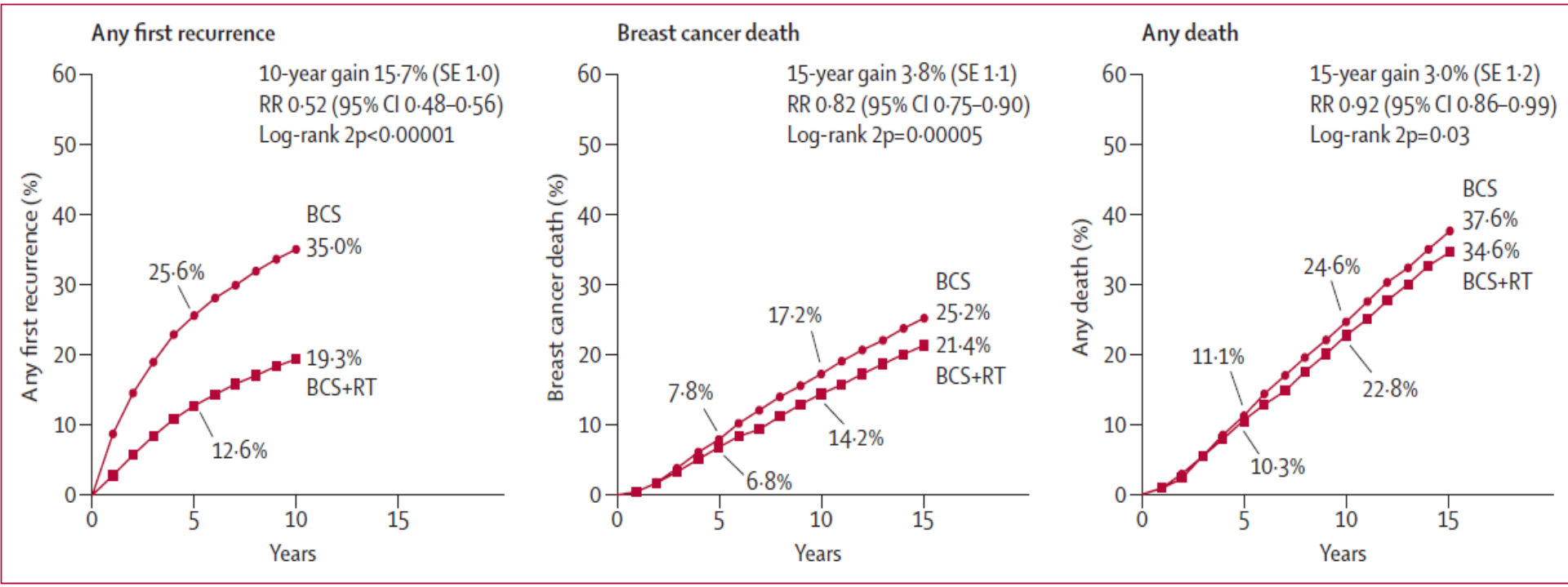

Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials
Further details are in webappendix p 5. RR=rate ratio. Rate ratios in this figure include all available years of follow-up.

EBCTCG Lancet 2011; 378: 1707–1716

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Indications: breast conserving therapy

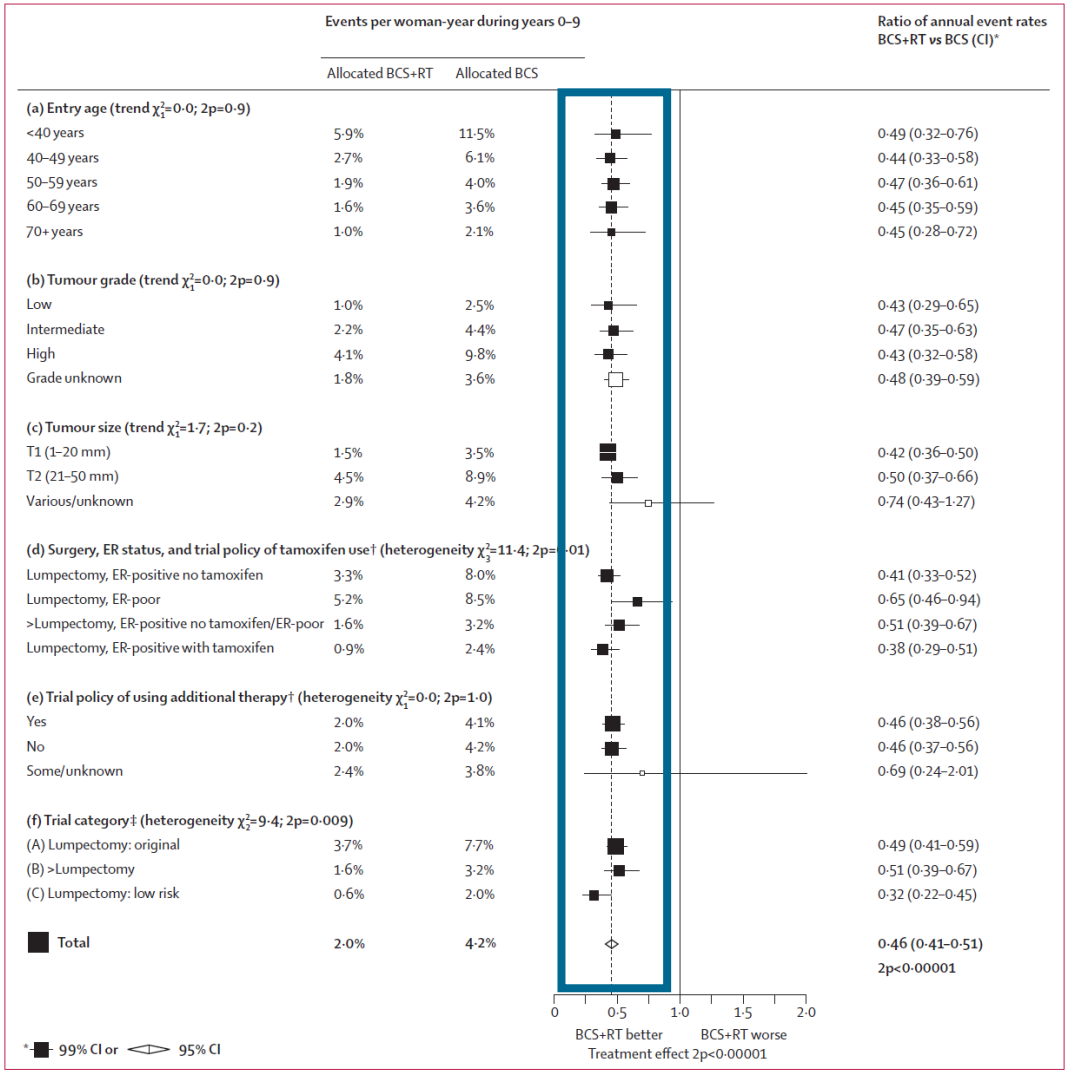

Figure 3: Event rates for any (locoregional or distant) first recurrence (% per year) and recurrence rate ratios for various factors, considered separately, during years 0–9 in women with pathologically node-negative disease (n=7287)

Any event - 54%

EBCTCG Lancet 2011; 378: 1707–1716

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Indications: breast conserving therapy

	Number allocated BCS+RT/BCS	10-year risk of a locoregional or distant recurrence (%)			Test for trend/heterogeneity in absolute reduction	
		BCS+RT	BCS	Absolute reduction with RT (95% CI)	2p unadjusted*	2p adjusted*
(a) Entry age (years)					<0·00001	0·0002
<40	189/174	36·1	60·7	24·6 (13·2 to 36·0)		
40–49	576/582	20·8	41·4	20·6 (15·1 to 26·1)		
50–59	1093/1028	15·0	29·7	14·7 (10·8 to 18·6)		
60–69	1138/1167	14·2	28·3	14·1 (10·4 to 17·8)		
70+	679/661	8·8	17·7	8·9 (4·0 to 13·8)		
(b) Tumour grade					<0·00001	<0·00001
Low	750/757	11·0	22·4	11·4 (6·3 to 16·5)		
Intermediate	816/843	16·4	31·6	15·3 (10·4 to 20·2)		
High	448/431	28·6	53·3	24·7 (17·6 to 31·8)		
Grade unknown	1661/1581	14·7	28·2	13·5 (10·4 to 16·6)		
(c) Tumour size					0·02	0·06
T1 (1–20 mm)	2942/2920	12·4	27·5	15·1 (12·7 to 17·5)		
T2 (21–50 mm)	513/487	30·7	50·0	19·3 (12·6 to 26·0)		
Various/unknown	220/205	24·9	32·6	7·6 (–1·8 to 17·0)		
(d) ER status and trial policy of tamoxifen use†					<0·00001	0·003
ER-poor	448/427	28·9	43·8	14·9 (8·0 to 21·8)		
ER-positive no tamoxifen	1686/1626	18·6	36·0	17·4 (14·3 to 20·5)		
ER-positive with tamoxifen	1541/1559	8·7	22·0	13·3 (10·0 to 16·6)		
(e) Trial policy of using additional therapy†					0·06	0·45
No	1498/1471	15·8	31·6	15·8 (12·7 to 18·9)		
Yes	2127/2085	16·1	31·8	15·6 (12·3 to 18·9)		
Some/unknown	50/56	..	..	..		
(f) Trial category‡					<0·00001 (A *vs* C); 0·90 (A+C *vs* B)	0·16 (A *vs* C); 0·00003 (A+C *vs* B)
(A) Lumpectomy: original	1223/1197	27·8	47·9	20·1 (16·0 to 24·2)		
(B) >Lumpectomy	986/970	14·3	25·9	11·6 (7·9 to 15·3)		
(C) Lumpectomy: low risk	1466/1445	6·3	19·9	13·6 (9·7 to 17·5)		
Total	3675/3612	15·6	31·0	15·4 (13·2 to 17·6)		

***Table 2:* Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence in women with pathologically node-negative disease (n=7287), subdivided by patient and trial characteristics**

Any event – 24,6

…

Any event – 8,9

EBCTCG Lancet 2011; 378: 1707–1716

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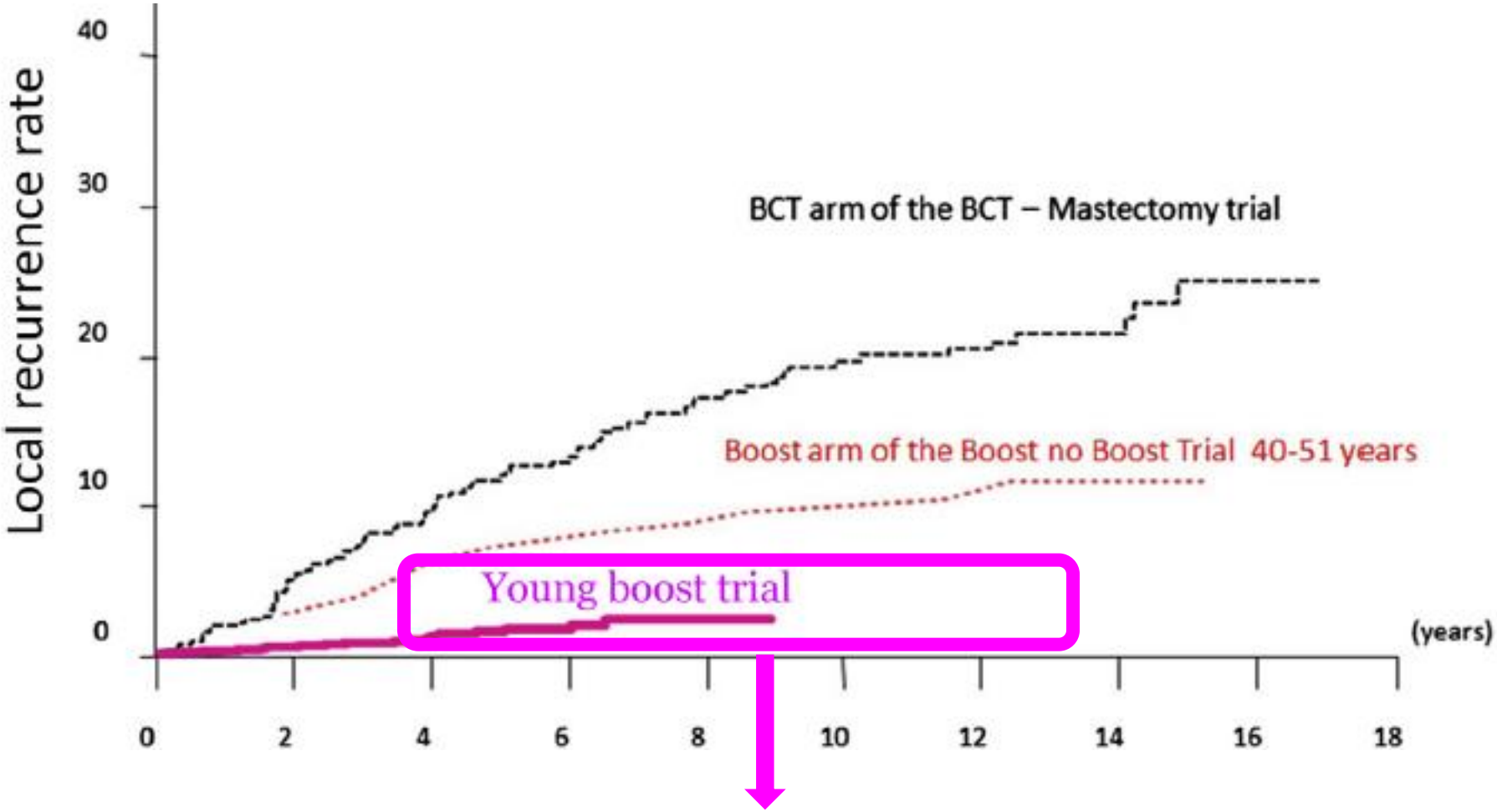
Indications: breast conserving therapy

We did improve BCT rates!



Poortmans P, et al. The Breast 2016; in press.

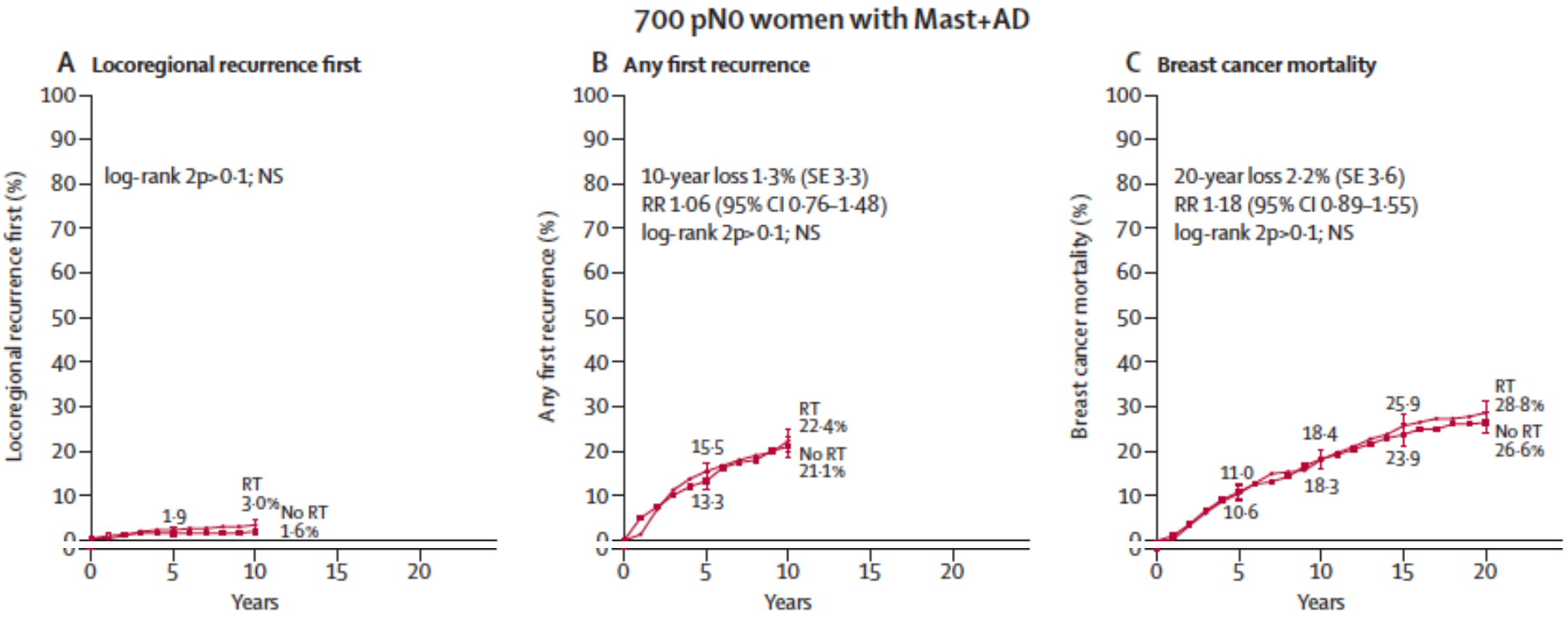
Indications: mastectomy

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

*EBCTCG (Early Breast Cancer Trialists' Collaborative Group)**

EBCTCG: Lancet 2014;383:2127–35

Indications: mastectomy



EBCTCG: Lancet 2014;383:2127–35

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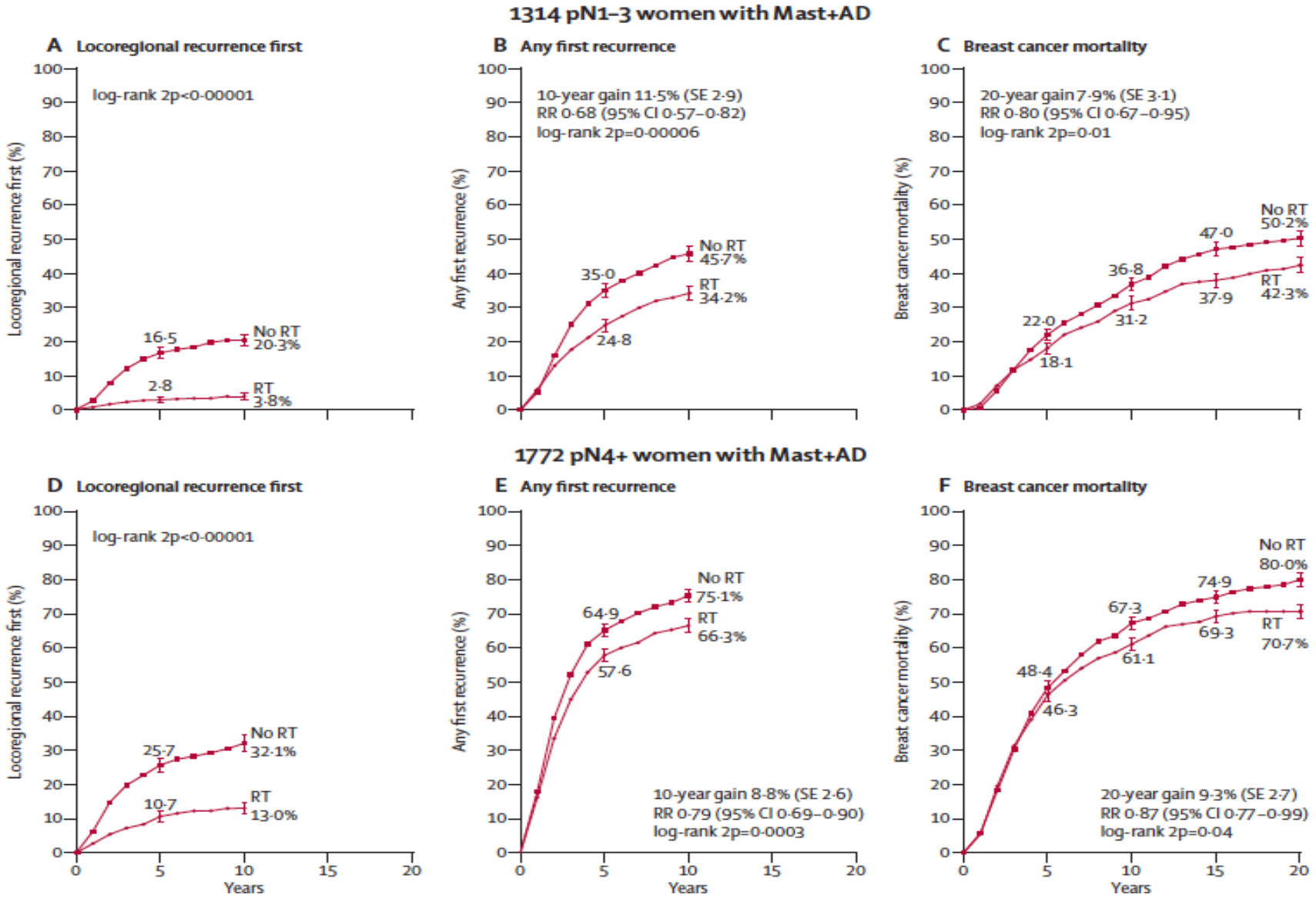
Indications: mastectomy



EBCTCG: Lancet 2014;383:2127–35

Radboudumc

Indications: general

- “Always” as part of breast conserving therapy
- After mastectomy based on risk factors: tumour size; grade; lymph node involvement; resection margens; tumour type; vasculair invasion
- Local control en survival last decennia even better after BCT!
- Dose and target volumes depending on tumour-, patient- and other treatment-characteristics
- On-going research in de-escalation in patients with a favourable prognosis!

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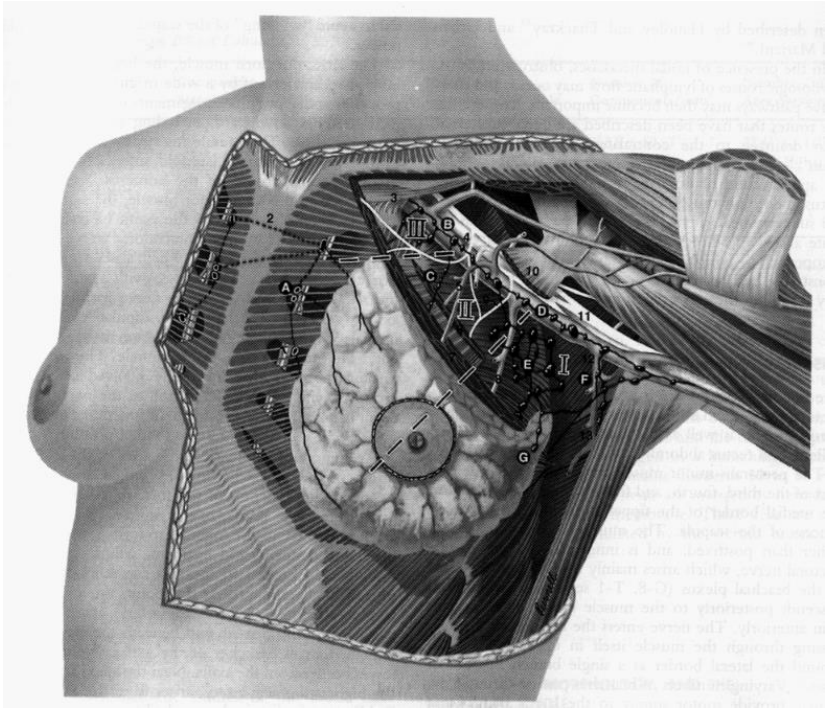
Side-effects

- Arm edema
- Impairment of shoulder movement
- Brachial plexus damage
- Telangiectasia
- Change in breast appearance
- Subcutaneous fibrosis
- Pneumonitis and lung fibrosis
- Ischemic heart disease
- Secondary malignancy



Side-effects: grading: *fibrosis*

- Grade 0 = none
- Grade 1 = barely palpable
- Grade 2 = definite increased density & firmness
- Grade 3 = marked density, retraction & fixation

LENT SOMA. R&O 1995;35:17–60. Harris JR. IJROBP 1979;5:257–61.

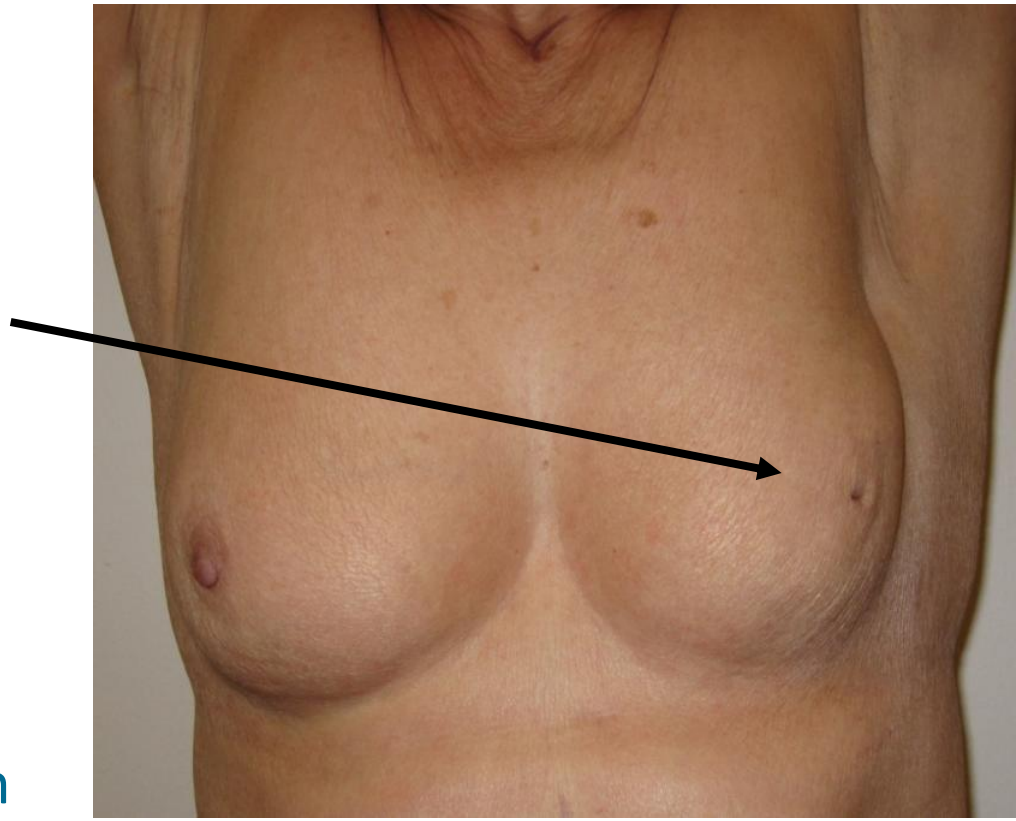
Side-effects: grading: *skin colour*

0 No difference in colour between the breasts, neither on skin nor areola/nipple

1 Nipple/areola or skin darker/lighter on treated side compared to untreated side

2 Both nipple/areola and skin darker/lighter on treated side compared to untreated side

3 Marked difference in colour between treated and untreated breast, either in skin or nipple/areola or both



LENT SOMA. R&O 1995;35:17–60. Harris JR. IJROBP 1979;5:257–61.

Side-effects: grading: *telangiectasia*

Small dilated vessels

0 = none

1 = <1/cm^2

2 = 1-4/cm^2

3 = >4/cm^2

LENT SOMA. R&O 1995;35:17–60. Harris JR. IJROBP 1979;5:257–61.

Side-effects: influencing factors

- ✓ Radiation therapy
- ✓ Surgery
- ✓ Systemic therapy
- ✓ Comorbidity
- ✓ Individual radiosensitivity: genetics
- ✓ Unknown

Side-effects: factors: *radiation therapy*

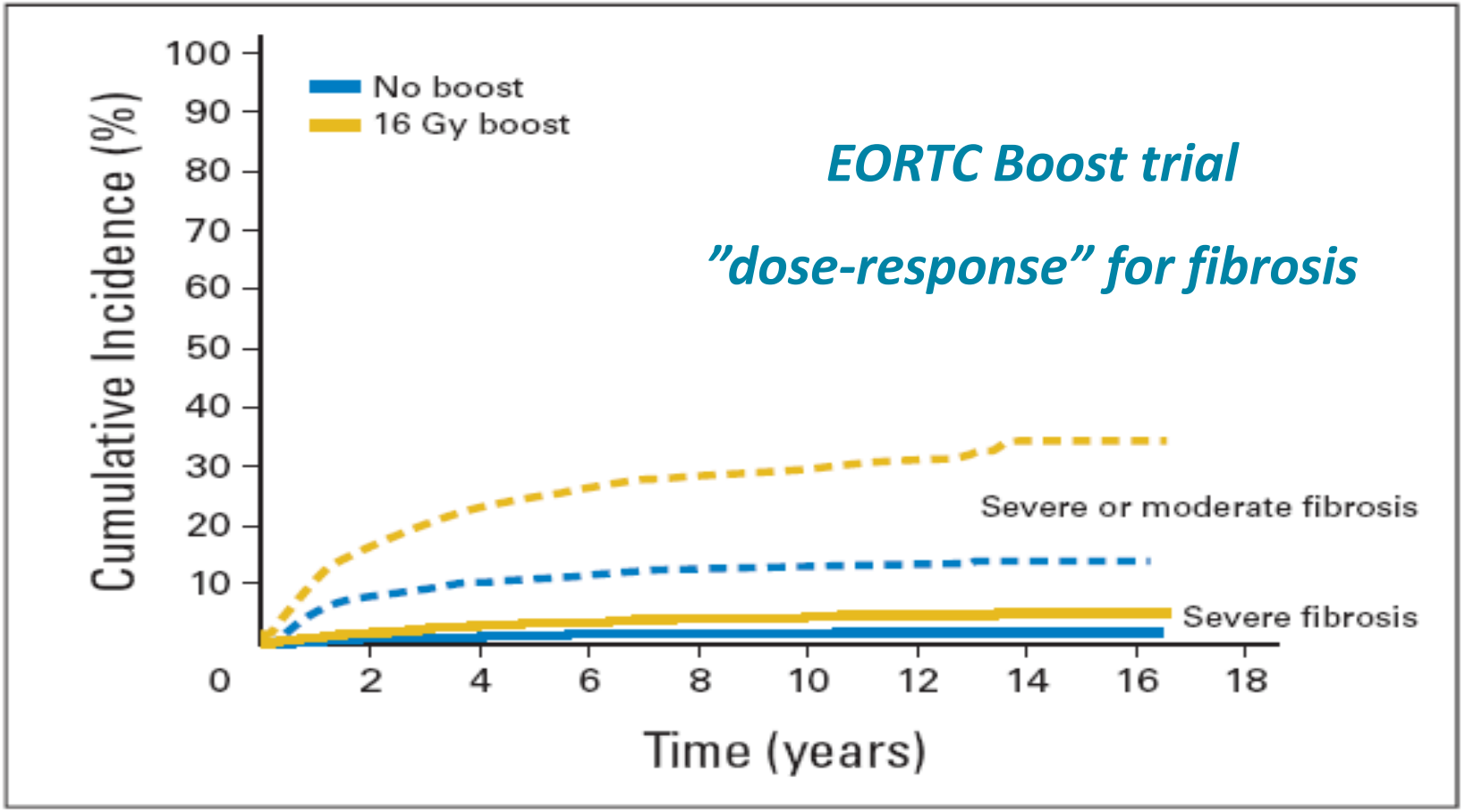
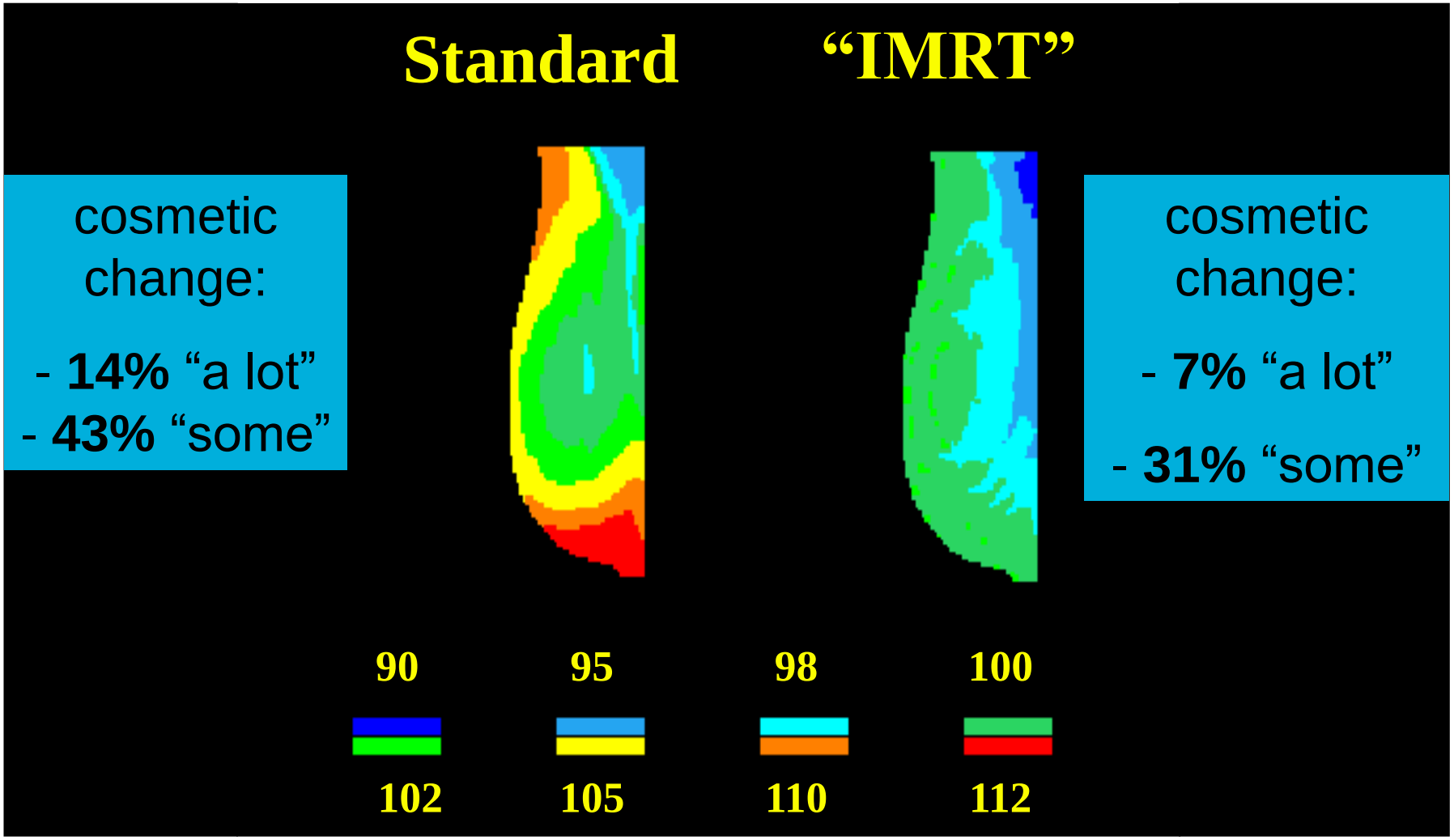


Fig 4. Cumulative incidence of moderate or severe fibrosis after 50 Gy irradiation or 50 Gy irradiation and a boost of 16 Gy.

Bartelink et al. JCO 2007

Side-effects: factors: *radiation therapy*

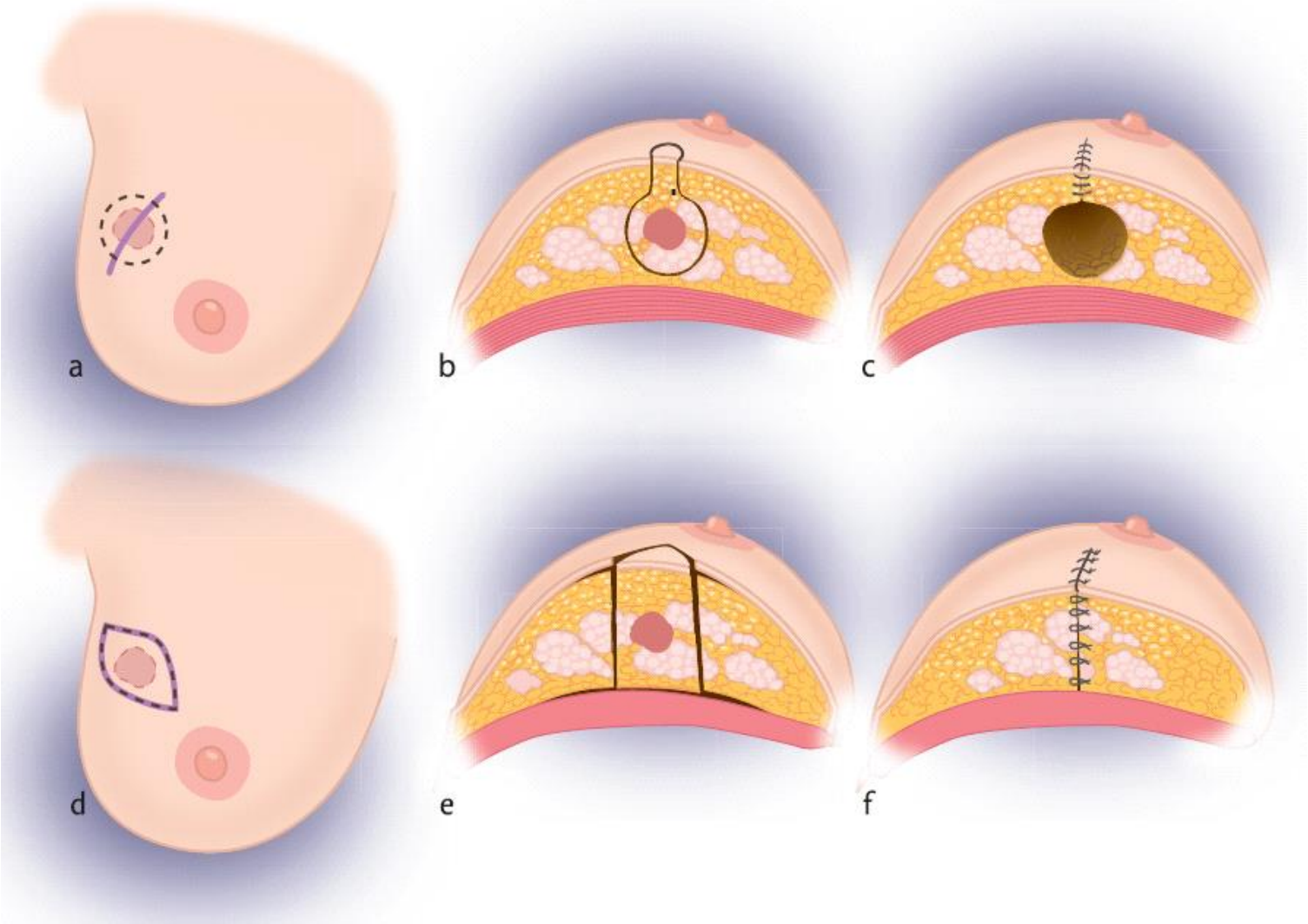


Donovan, Yarnold et al. Radiother Oncol 2007

Side-effects: factors: *surgery*

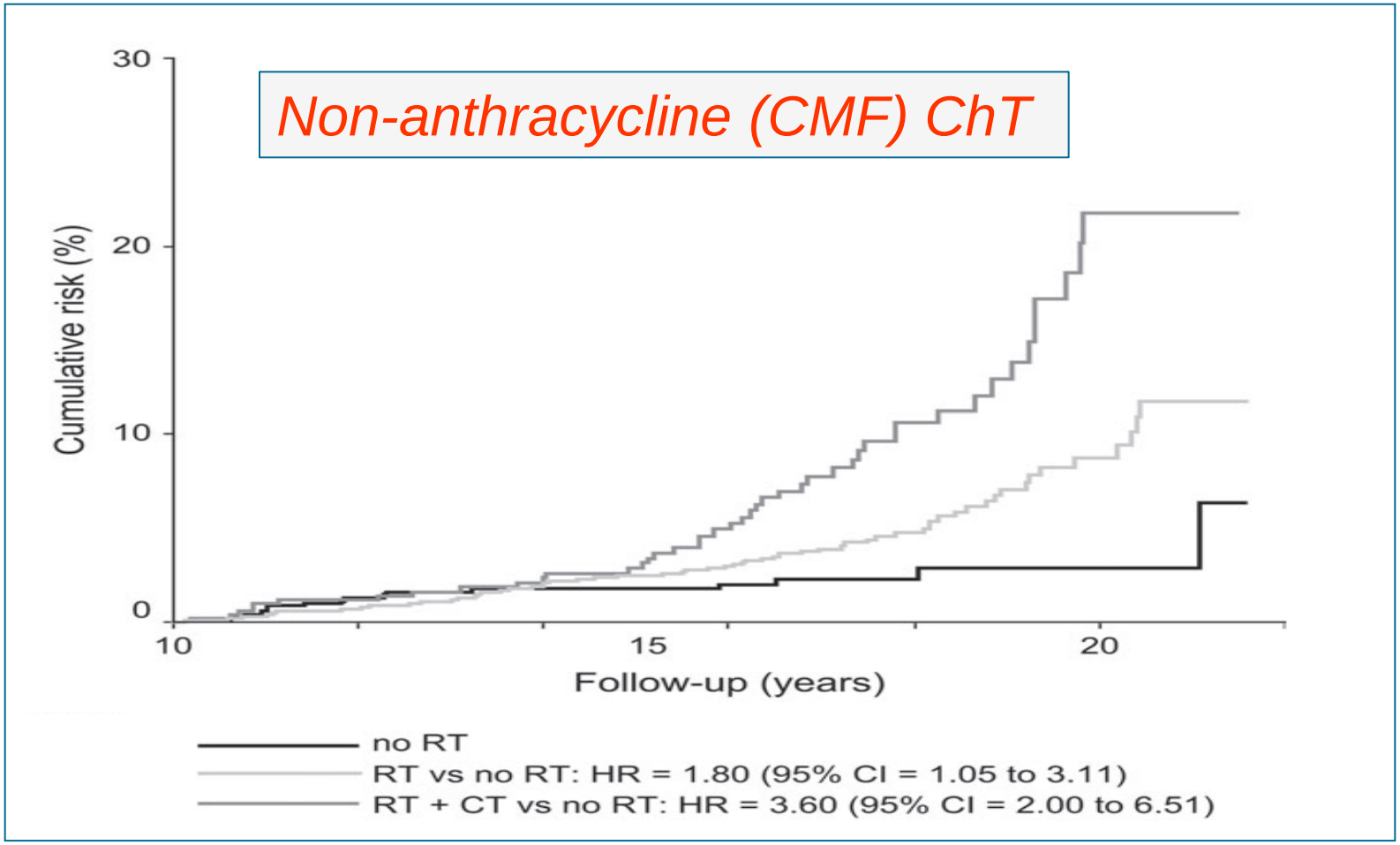
Past

Present



Menke et al, NTVG 2007

Side-effects: factors: *systemic therapy*



Congestive heart failure risk

Hooning, JNCI 2007

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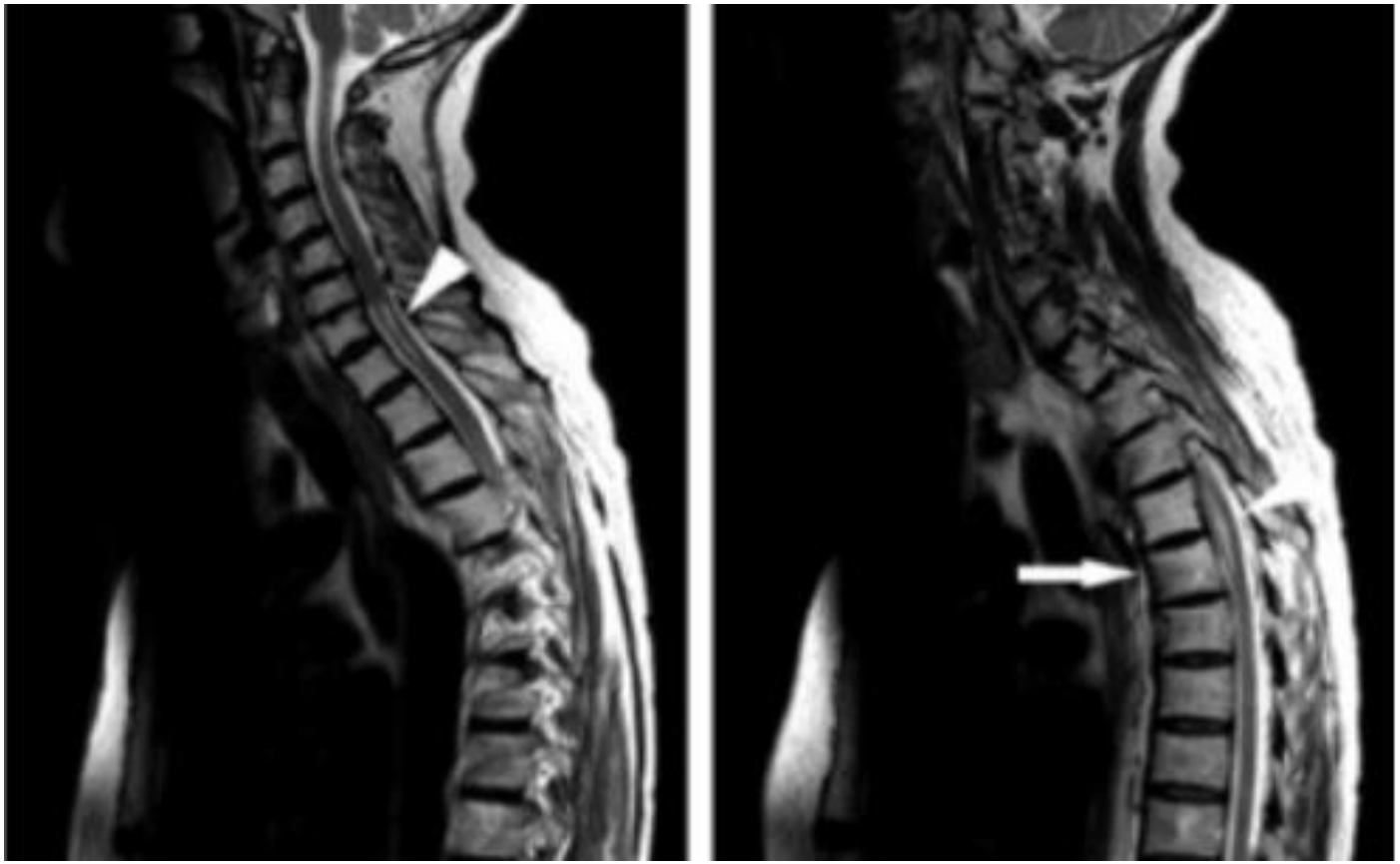
Side-effects: factors: *systemic therapy*

Radiation myelitis after 28 Gy concurrent with trastuzumab



New treatments ➔ new risks!

Law, Breast Care 2009

Side-effects: factors: *comorbidity*

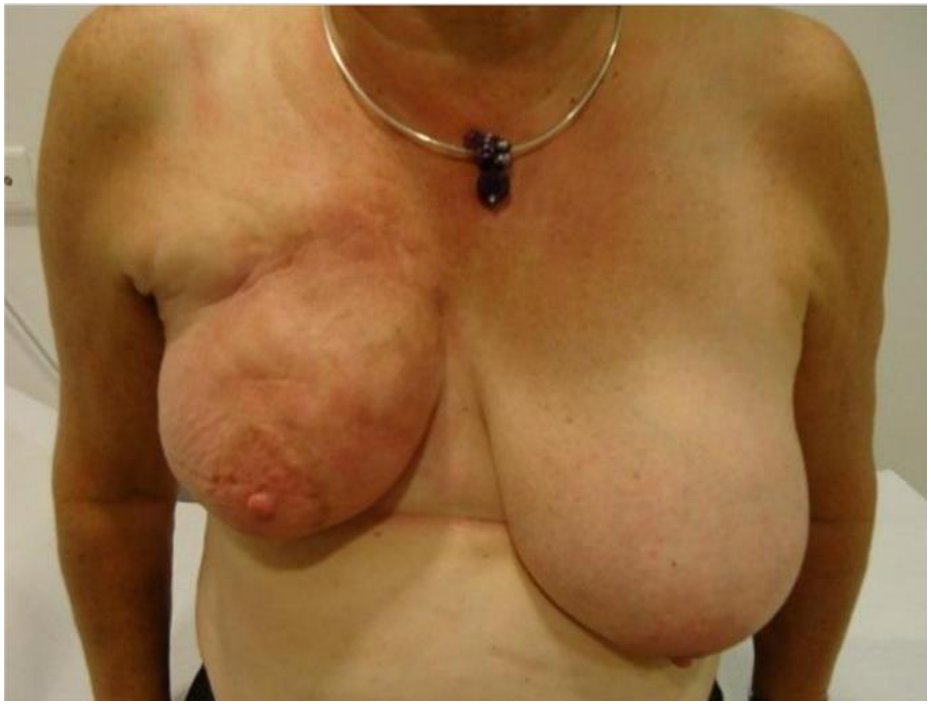
Age 60; BC ➔ TE + SNB + RT

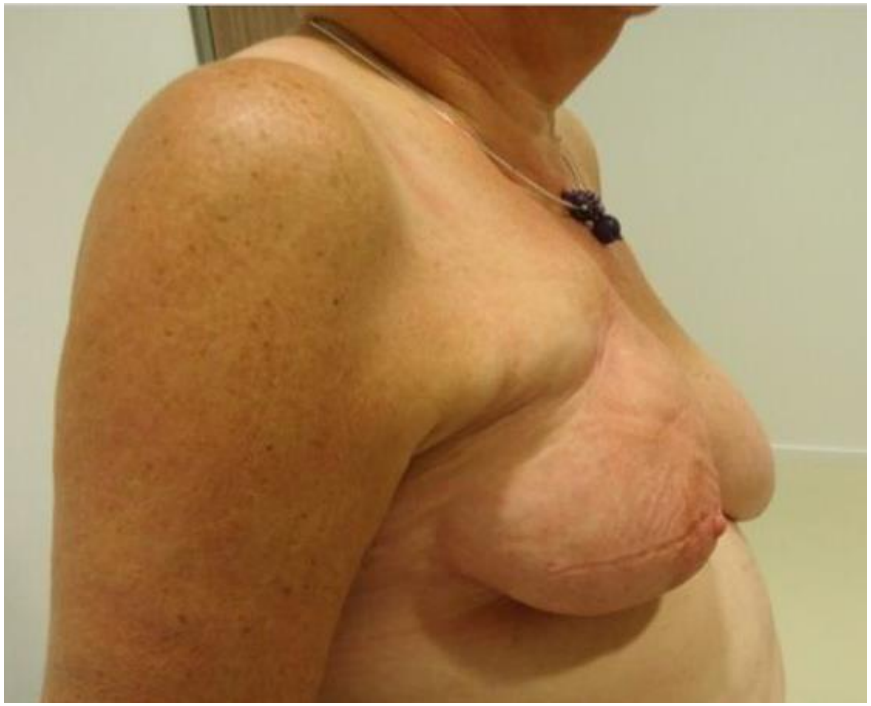
G2 breast toxicity; pictures after 4.5 years

"smoking & DM"

Side-effects: factors: *comorbidity*

Age 64; BC pT1cmG2N0M0 ➔ TE + SNB + RT (SIB)





G3 breast toxicity; pictures after 1.5 years

"muscular reuma"

Side-effects: factors: *comorbidity*

"Radiation-induced morphea of the breast"

Side-effects: factors: *genetic factors*

Variations in risk of normal tissue toxicity after RT (within normal

Use clinical data and molecular pathology to identify genetic risk factors and targets for intervention

More sensitive

More resistant

Andreassen et al, CIRRO project

Radboudumc

Side-effects: factors: *treatment*

Clinical Oncology 24 (2012) 657–672

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Radiation Fibrosis — Current Clinical and Therapeutic Perspectives

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Received 14 July 2011; received in revised form 7 February 2012; accepted 12 April 2012

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Medical Radiology Diagnostic Imaging

Seymour H. Levitt
James A. Purdy
Carlos A. Perez
Philip Poortmans
Editors

Technical Basis of Radiation Therapy
Practical Clinical Applications
Fifth Edition

This well-received book, now in its fifth edition, is unique in providing a detailed description of the technological basis of radiation therapy. Another novel feature is the collaborative writing of the chapters by North American and European authors. This considerably broadens the book's perspective and increases its applicability in daily practice throughout the world. The book is divided into two sections. The first covers basic concepts in treatment planning, including essential physics and biological principles related to time-dosefractionation, and explains the various technological approaches to radiation therapy, such as intensity-modulated radiation therapy, tomotherapy, stereotactic radiotherapy, and high and low dose rate brachytherapy. Issues relating to quality assurance, technology assessment, and cost-benefit analysis are also reviewed. The second part of the book discusses in depth the practical clinical applications of the different radiation therapy techniques in a wide range of cancer sites. All of the chapters have been written by leaders in the field. This book will serve to instruct and acquaint teachers, students, and practitioners in the various fields of oncology with the basic technological factors and approaches in radiation therapy.

ISSN 0942-5373
ISBN 978-3-642-11571-4

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Poortmans *Eds.*

Technical Basis of Radiation Therapy

5th Ed.

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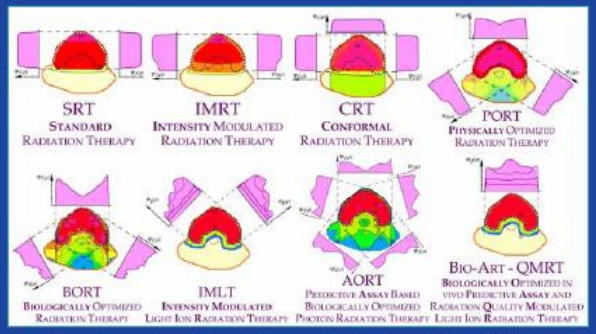
Technical Basis of Radiation Therapy

Practical Clinical Applications

5th Edition



New developments: *to start with*

Primary Tumour Bed (PTB):

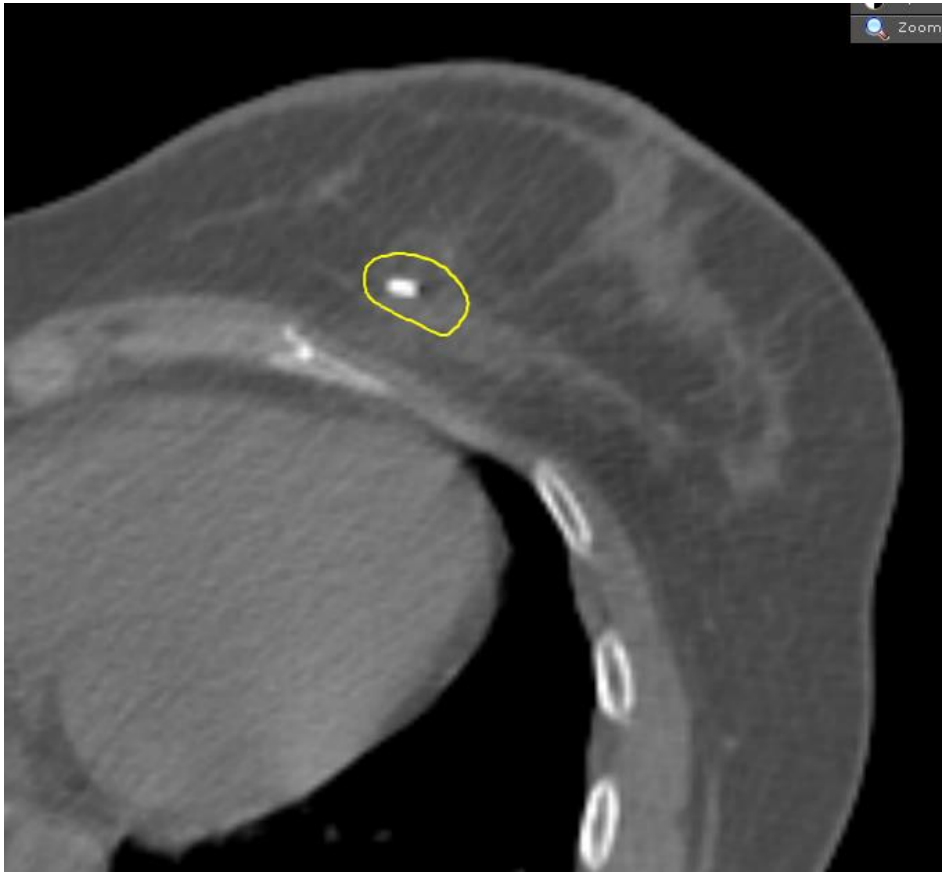
Represents the original tumour

~ GTV

≠ surgical bed

= virtual point

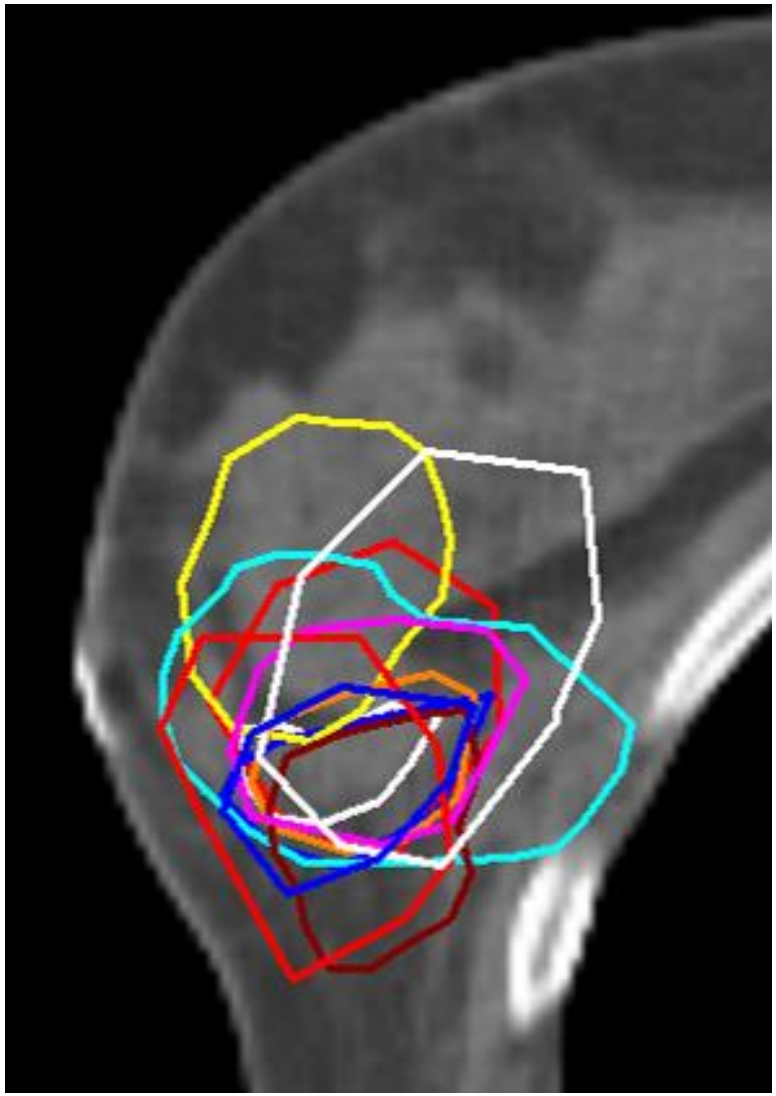
A lot of uncertainties!!!



New developments: *to start with*

Target volume delineation of primary tumour bed:

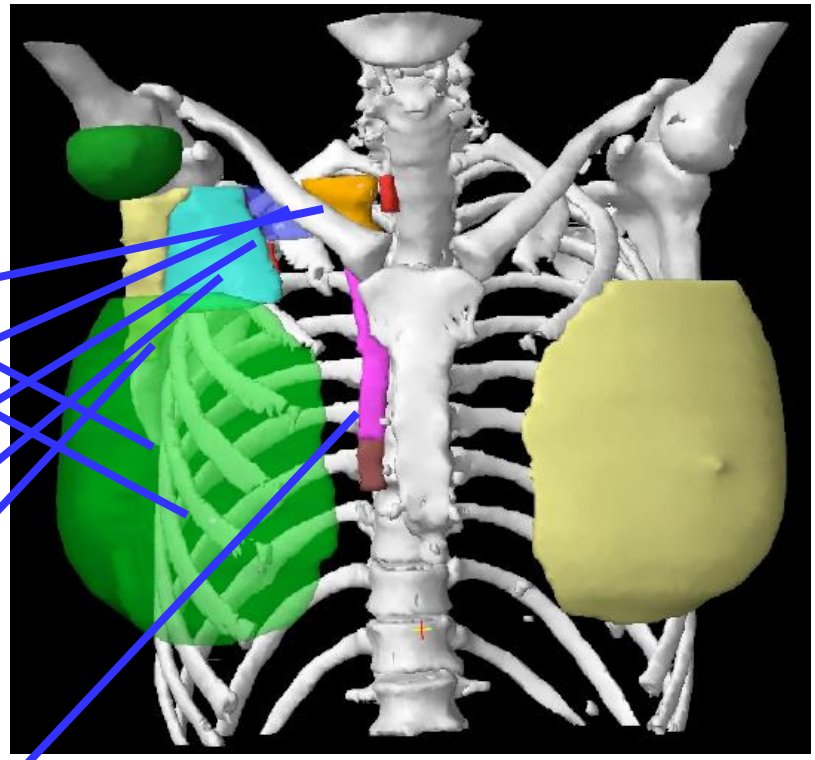
- by dedicated RTO's
- no clips
- no seroma



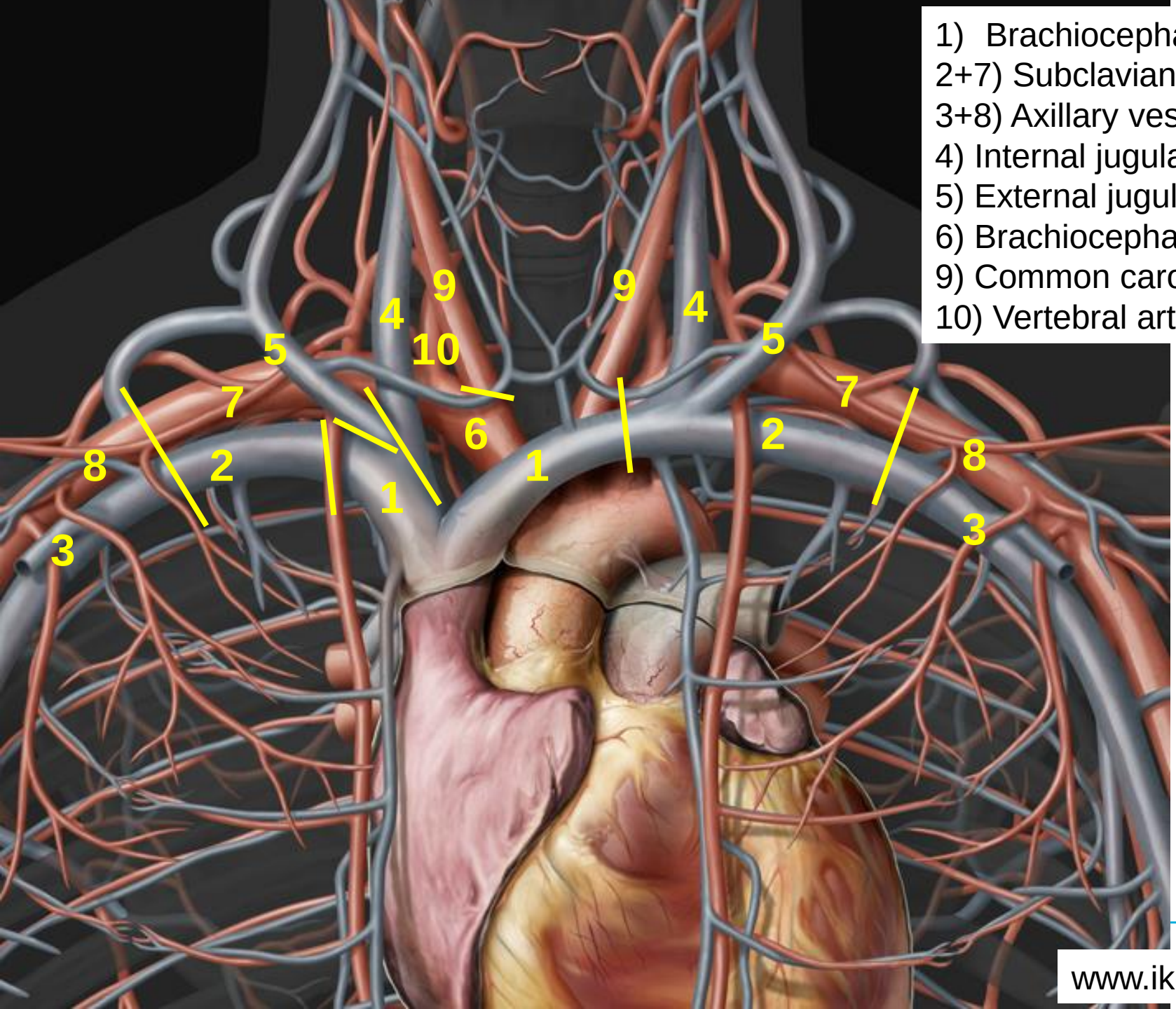
van Mourik AM et al. Radiother Oncol. 2010;94:286-91.

New developments: *to start with*

- Breast
- Thoracic wall
- LN axilla level IV
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary



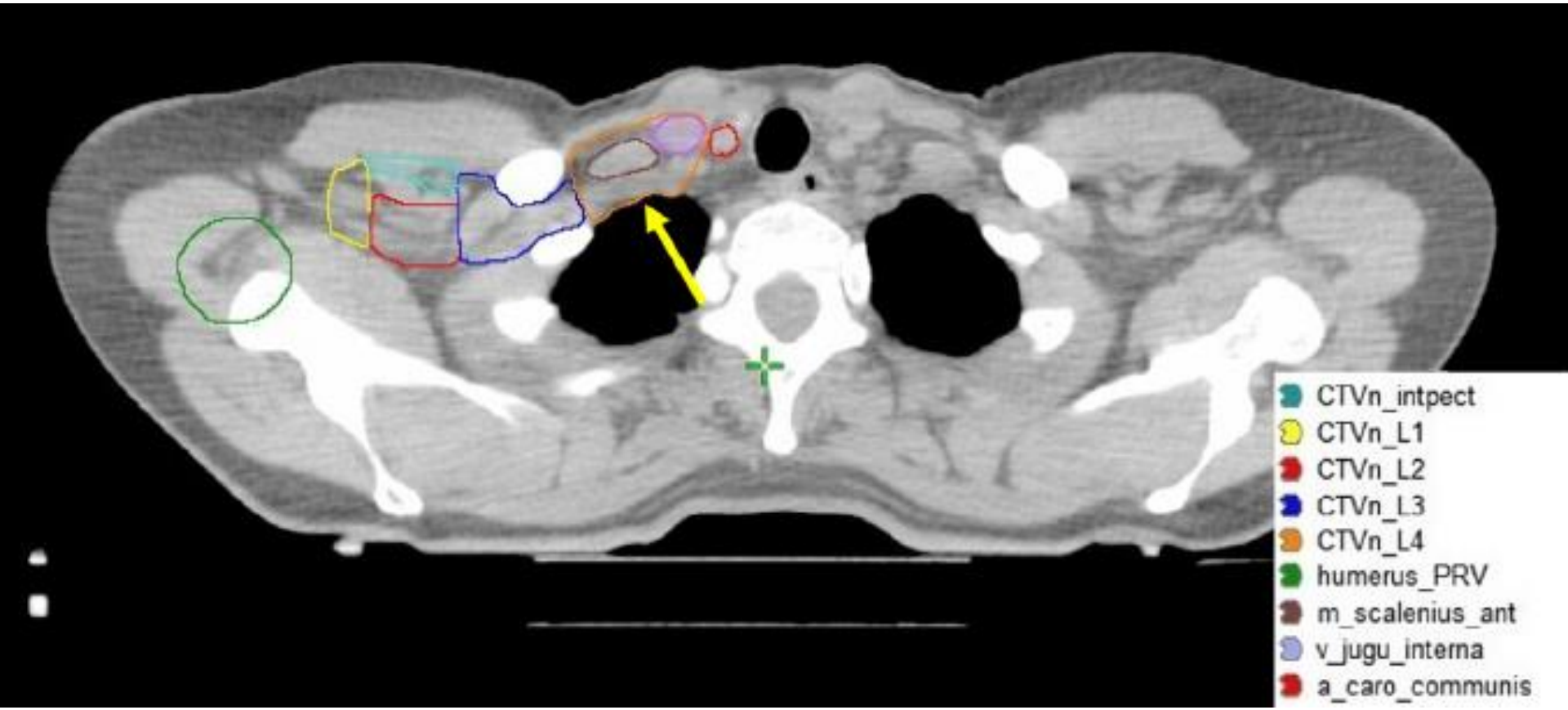
Offersen BV, et al. Radiother Oncol 2015;114:3-10.



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

New developments: *to start with*

Level 1 - level 2 - Rotter - level 3 - level 4



Offersen BV, et al. Radiother Oncol 2015;114:3-10.

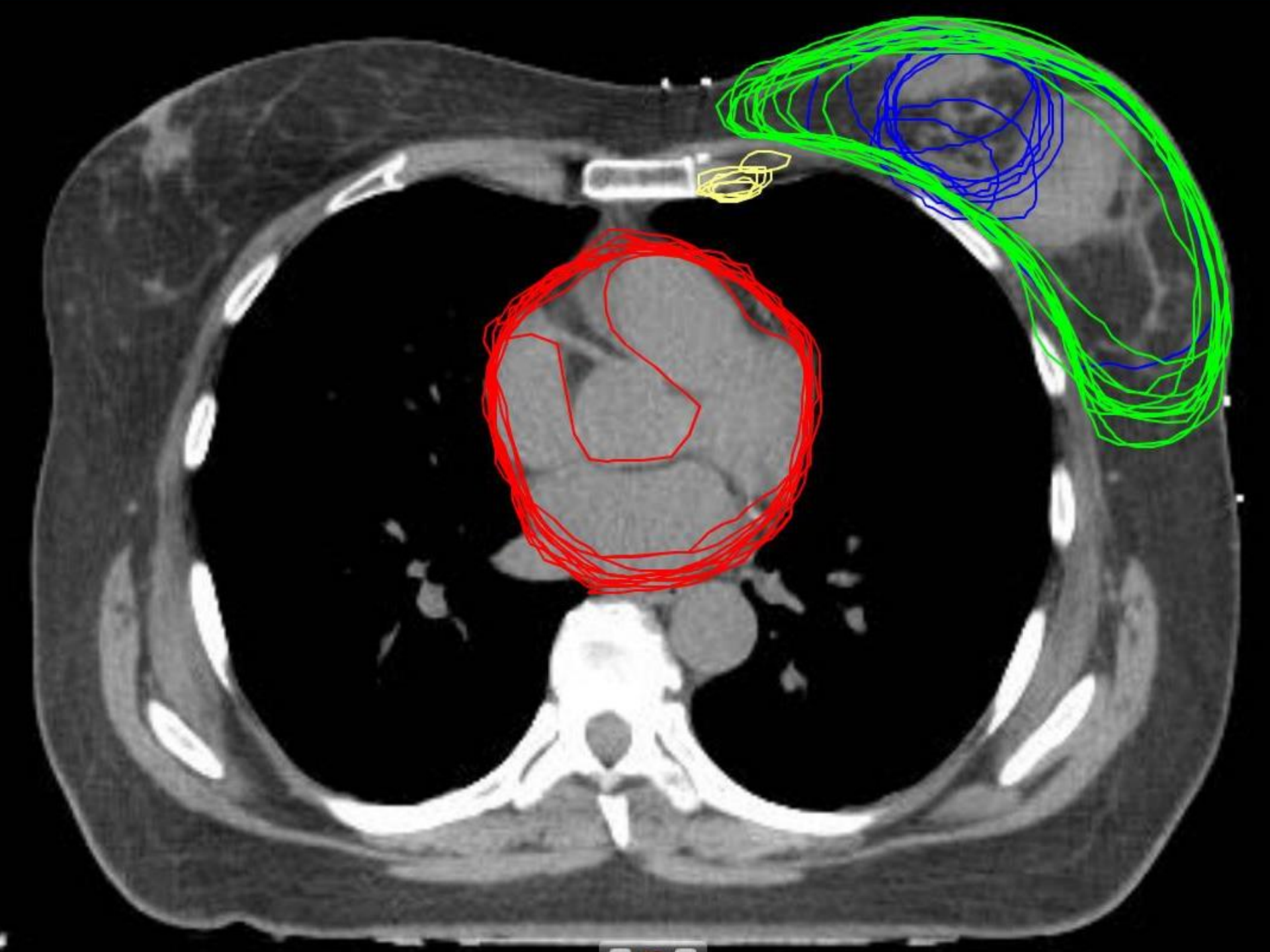
New developments: *to start with*

FALCON

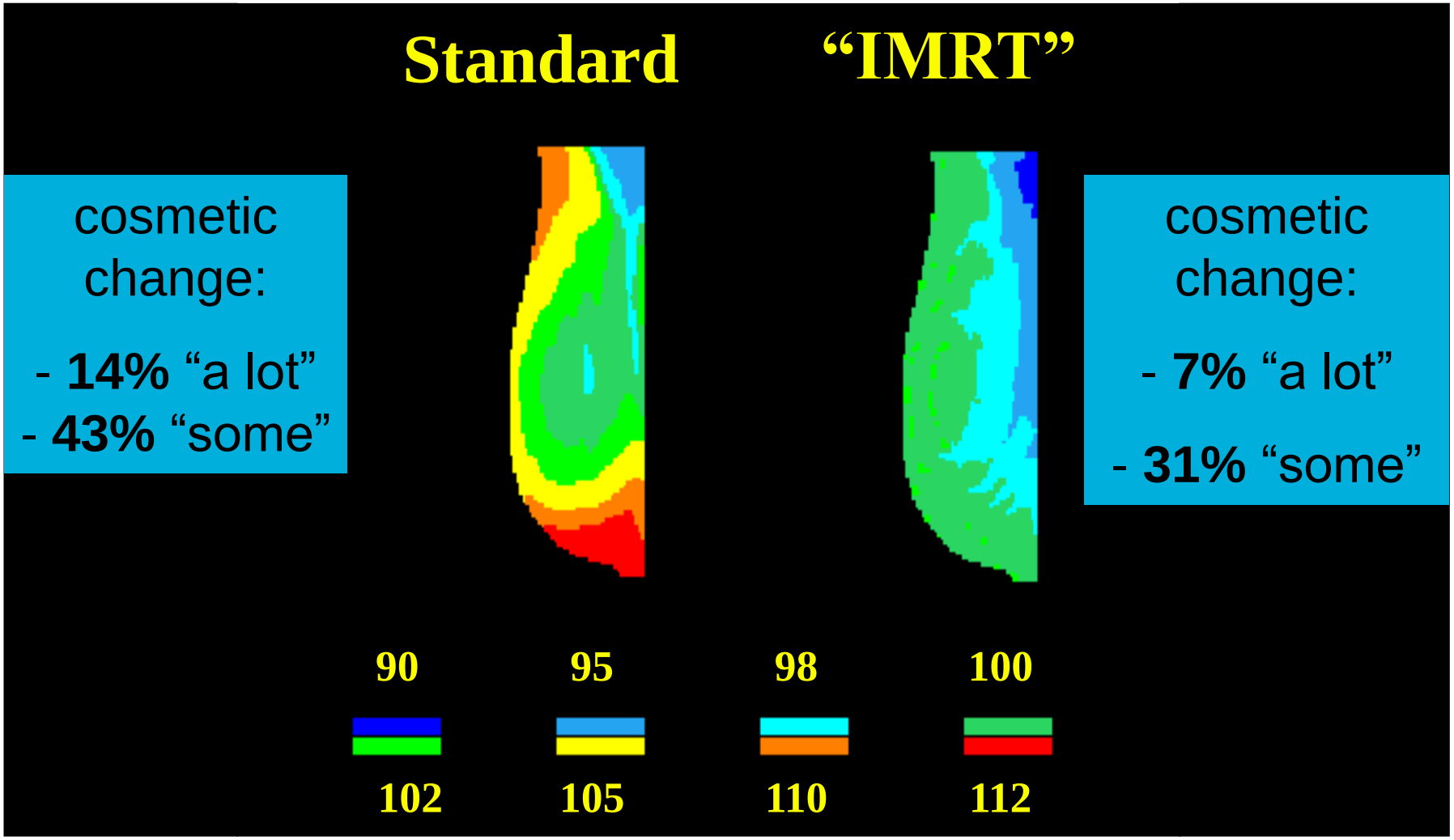
Fellowship in Anatomic deLineation & CONtouring

Aims:

- ✓ Prepare guidelines for volume delineation for all structures relevant in radiation therapy for breast cancer.
- ✓ Work towards an agreement and endorsement by all relevant parties in Europe.
- ✓ Publish & make available in the form of an atlas by electronic means.
- Support translation into a number of major European languages.



New developments: *dose homogeneity*



Donovan, Yarnold et al. Radiother Oncol 2007

New developments: *dose homogeneity*

Volumetric IMRT:

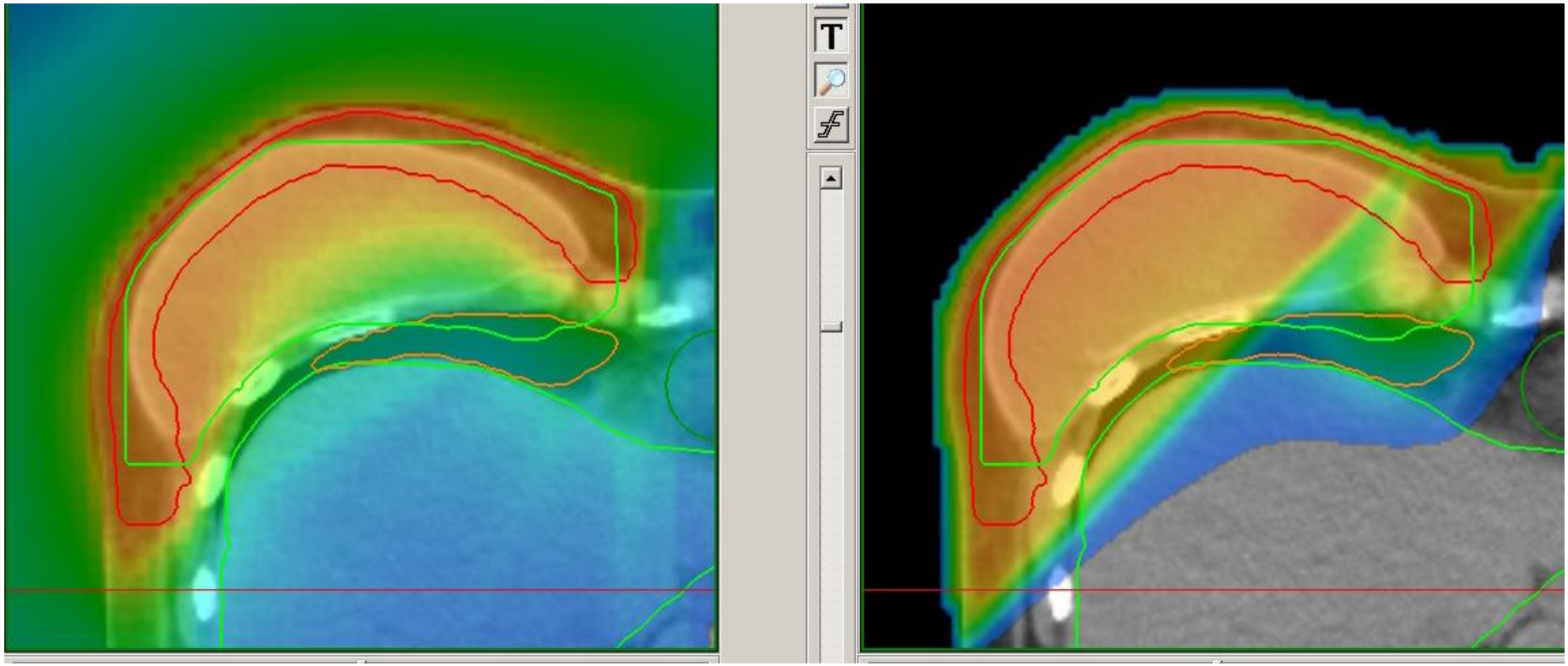
-Better TV coverage

-Improved dose homogeneity

3D-CRT:

-More experience

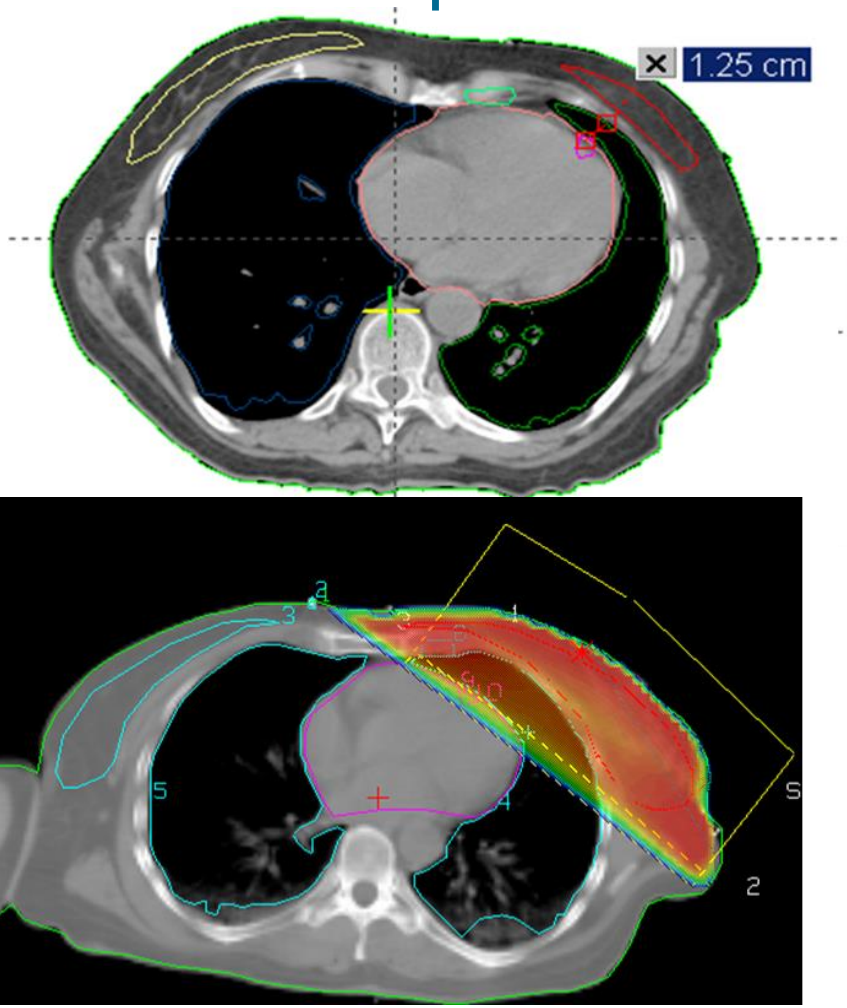
-No “low dose bath”



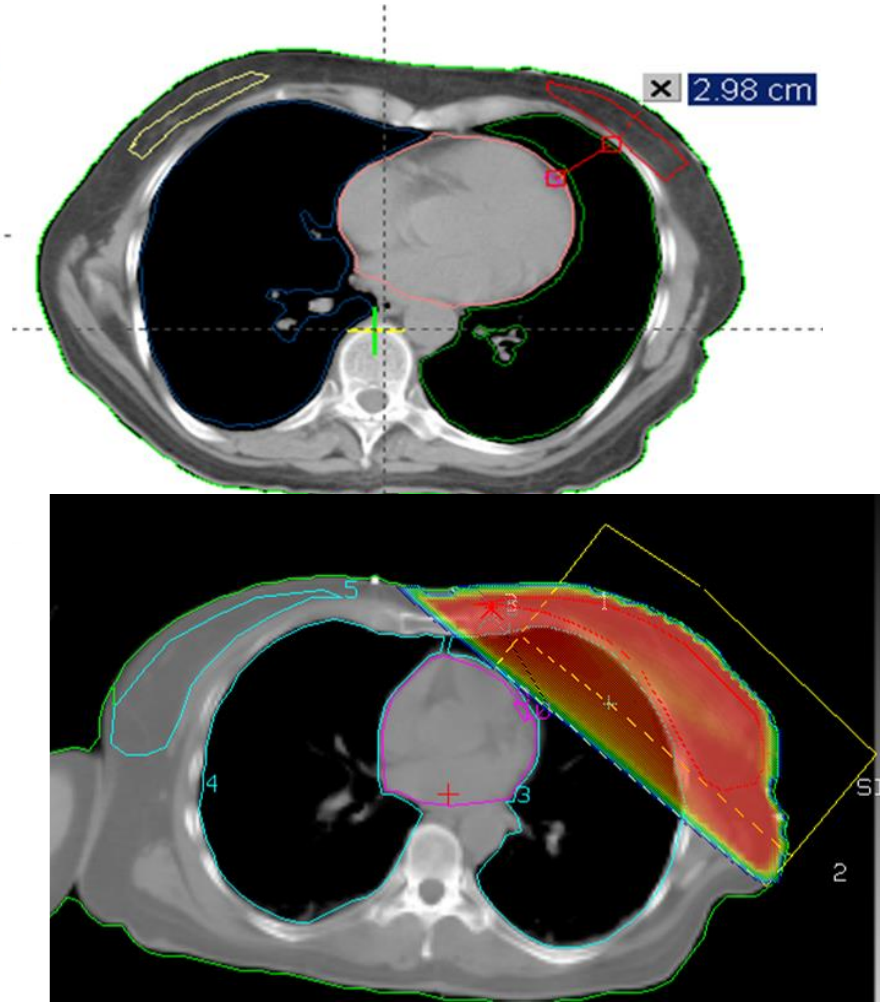
Massabeau C. Med Dosim. 2012

New developments: *lowering the cardiac dose*

Free respiration



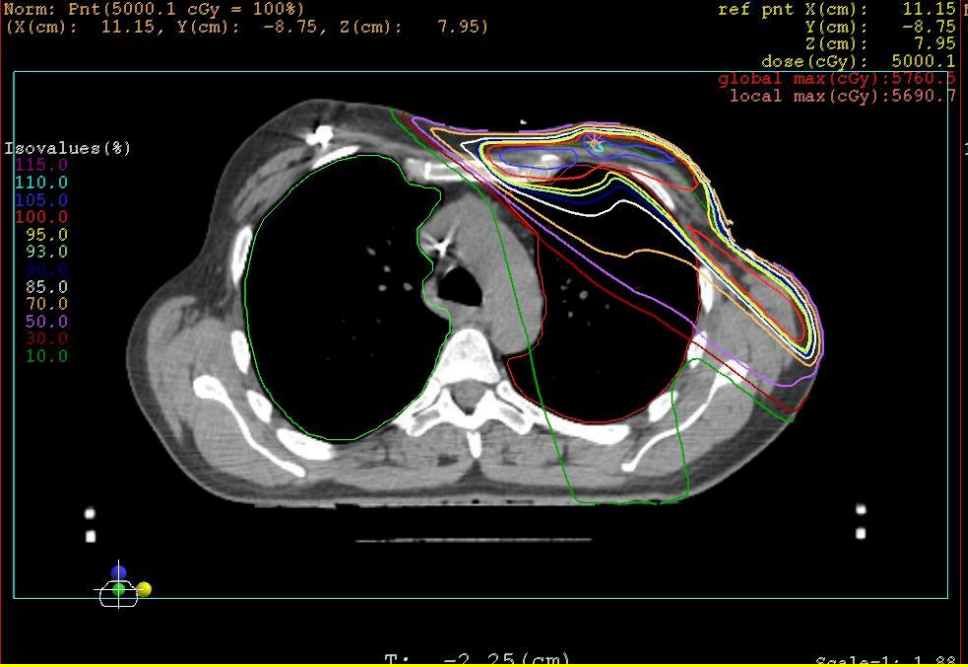
Breath hold

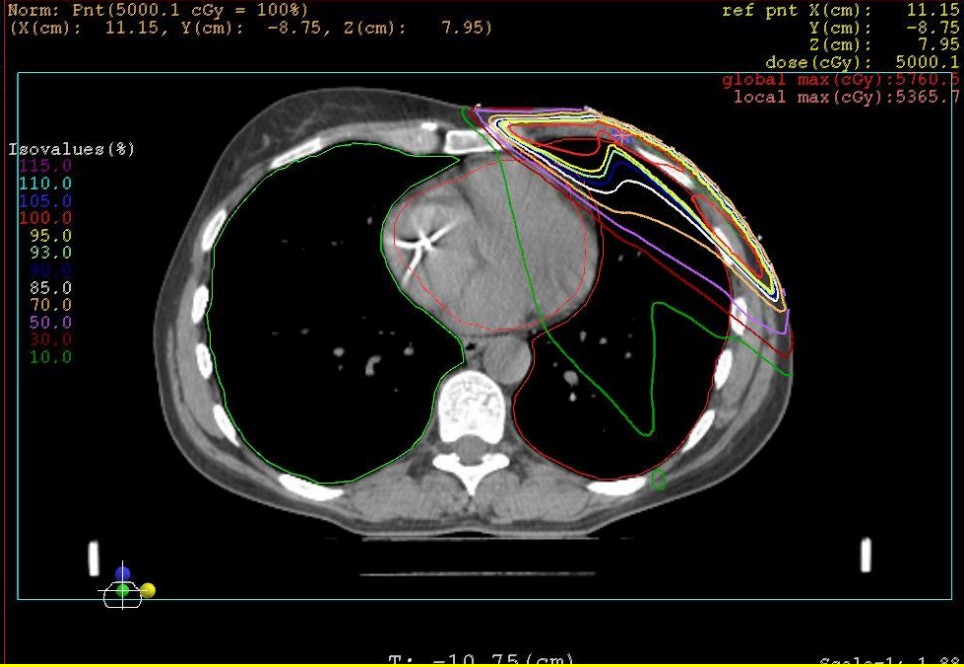


Courtesy of Marianne Aznar, Rigshospitalet, Copenhagen

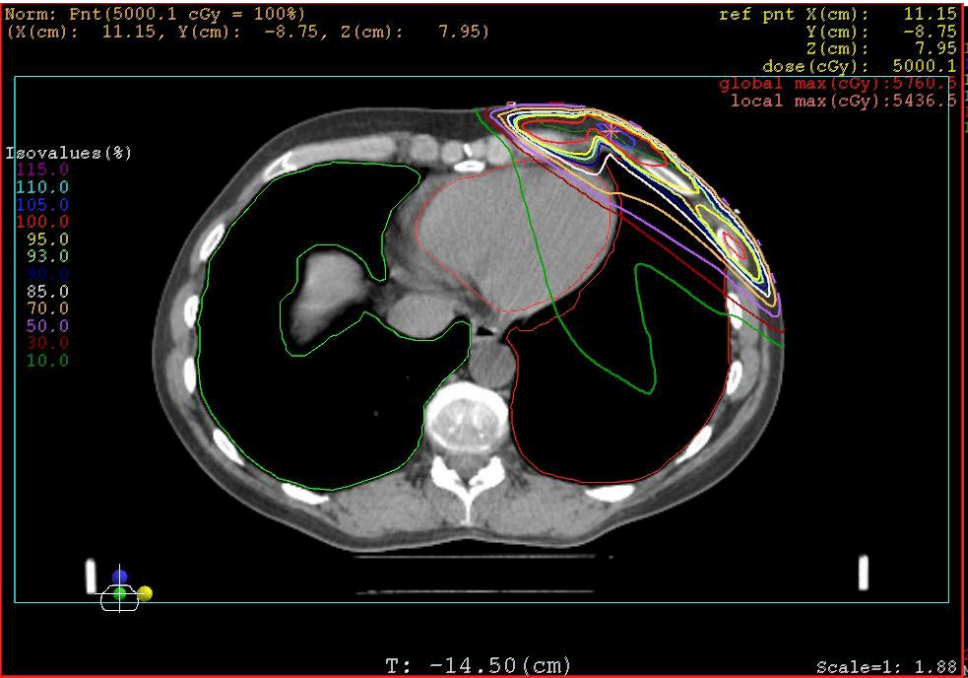
New developments: *combining it all*

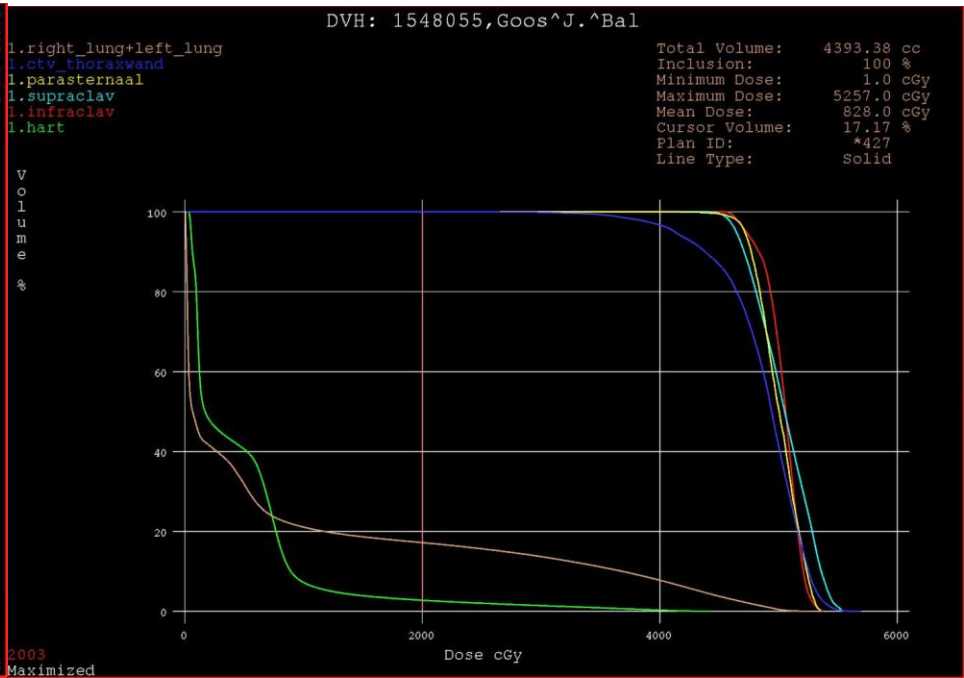
RT of the thoracic wall - with IM-MS: the next steps.

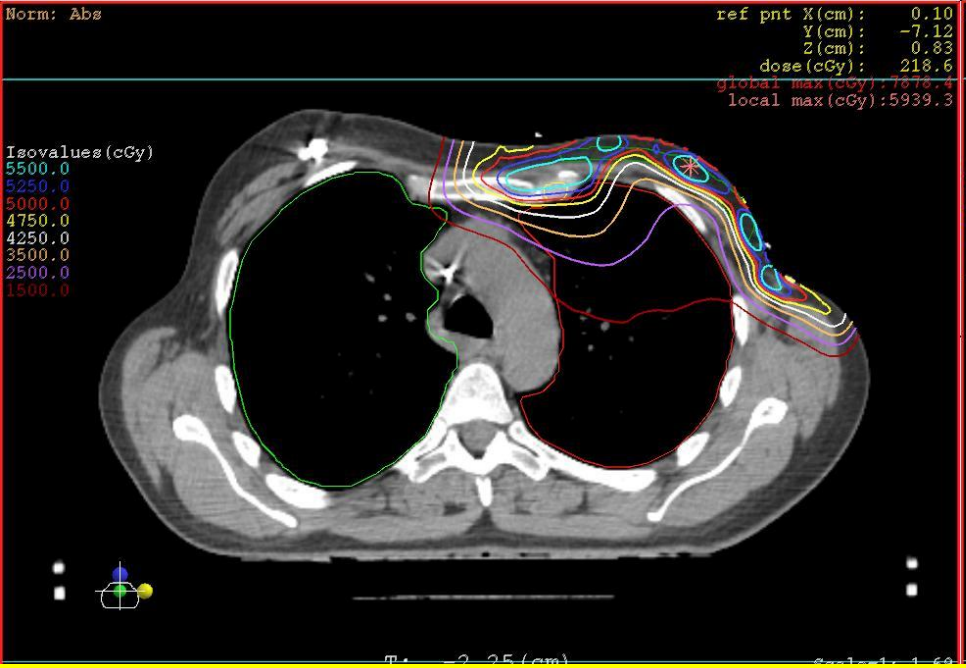


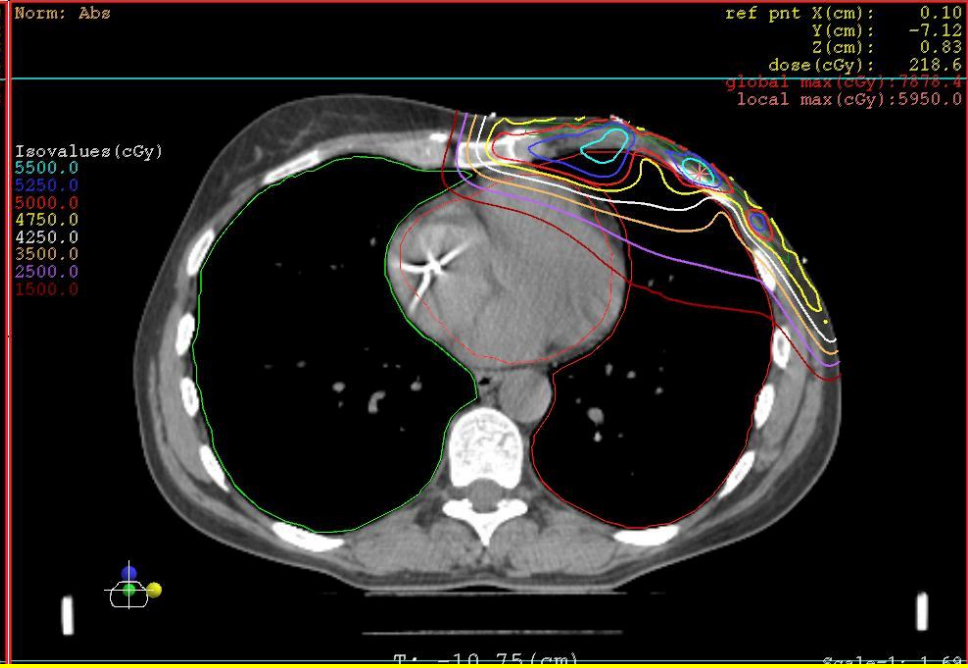


BVI photon technique including the IMC

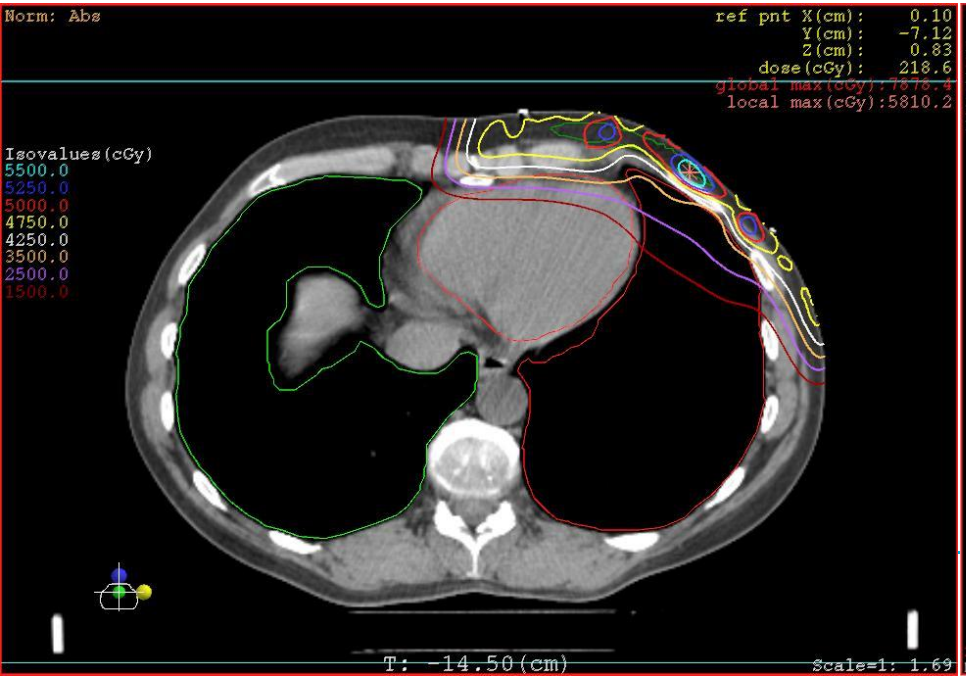


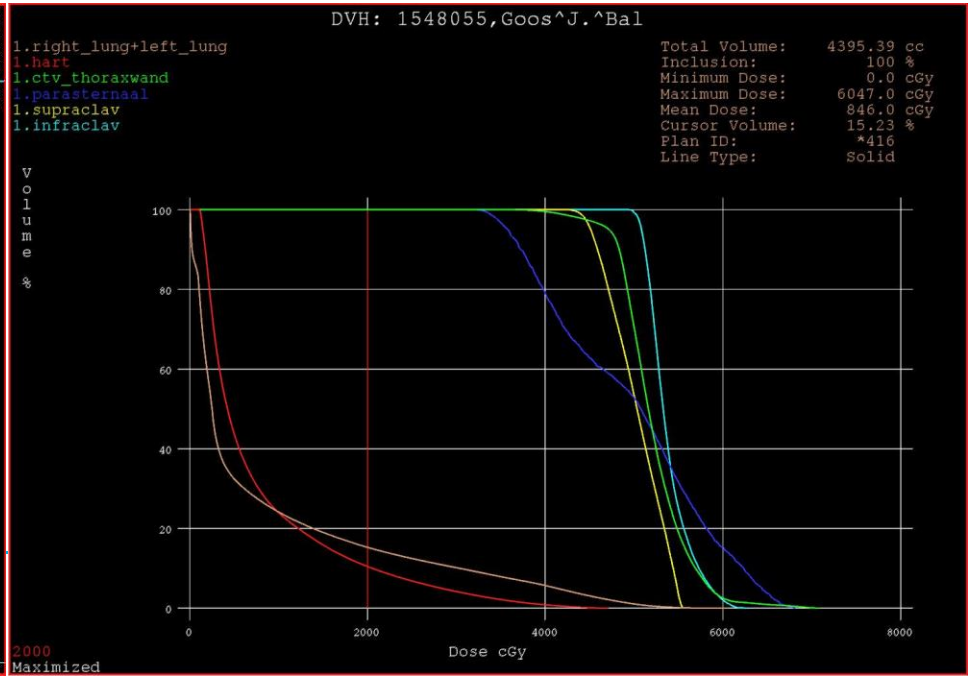




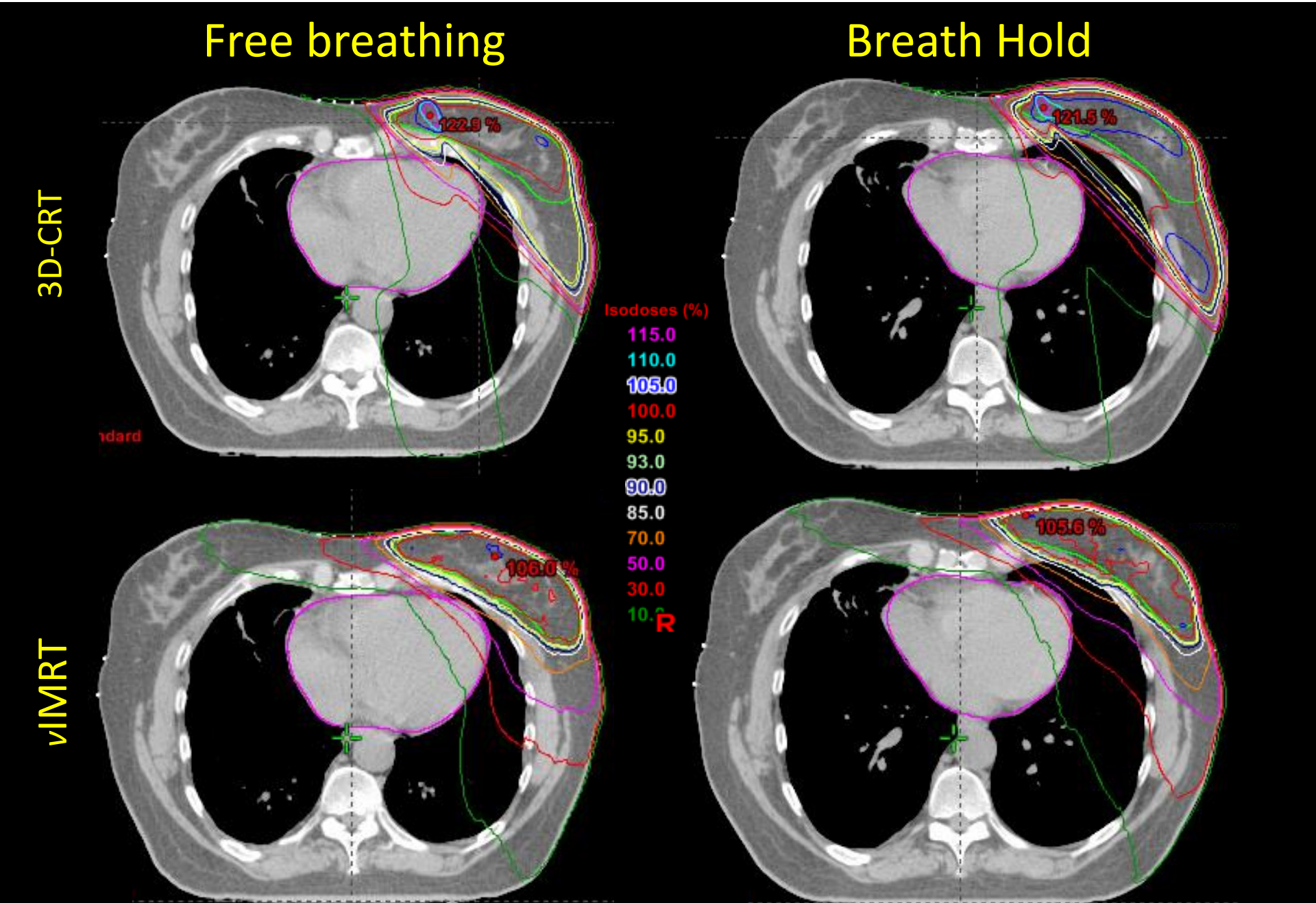


5-field electron technique including the IMC





RT techniques: *vmDIBH + IMRT*



New developments: *combining it all*

RT techniques: *vmDIBH + IMRT*

	Free breathing		Breath hold	
	3D-CRT	vIMRT	3D-CRT	vIMRT
Heart V_{30Gy} (%)	2.7		0.5	
Heart V_{20Gy} (%)	7.7		2.4	
IL Lung V_{20Gy}(%)	16.4		16.5	
IL Lung V_{10Gy}(%)	26.5		23.25	
CL breast D_{mean}(Gy)	0.29		0.62	

Osman SO, et al. Radiother Oncol. 2014;112:17-22.

New developments: *combining it all*

RT techniques: *vmDIBH + IMRT*

	Free breathing		Breath hold	
	3D-CRT	vIMRT	3D-CRT	vIMRT
Heart V_{30Gy} (%)	2.7	0		
Heart V_{20Gy} (%)	7.7	0.6		
IL Lung V_{20Gy}(%)	16.4	5.8		
IL Lung V_{10Gy}(%)	26.5	16.4		
CL breast D_{mean}(Gy)	0.29	3.7		

Osman SO, et al. Radiother Oncol. 2014;112:17-22.

instituut Verbeeten

Radboudumc

New developments: *combining it all*

RT techniques: *vmDIBH + IMRT*

	Free breathing		Breath hold	
	3D-CRT	vIMRT	3D-CRT	vIMRT
Heart V_{30Gy} (%)	2.7	0	0.5	0
Heart V_{20Gy} (%)	7.7	0.6	2.4	0.5
IL Lung V_{20Gy}(%)	16.4	5.8	16.5	5.3
IL Lung V_{10Gy}(%)	26.5	16.4	23.25	15.3
CL breast D_{mean}(Gy)	0.29	3.7	0.62	2.3

Osman SO, et al. Radiother Oncol. 2014;112:17-22.

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Radboudumc

The future, according to some scientists, will be exactly like the past, only far more expensive.

John Sladek, American Science Fiction author, 1937-2000.

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial

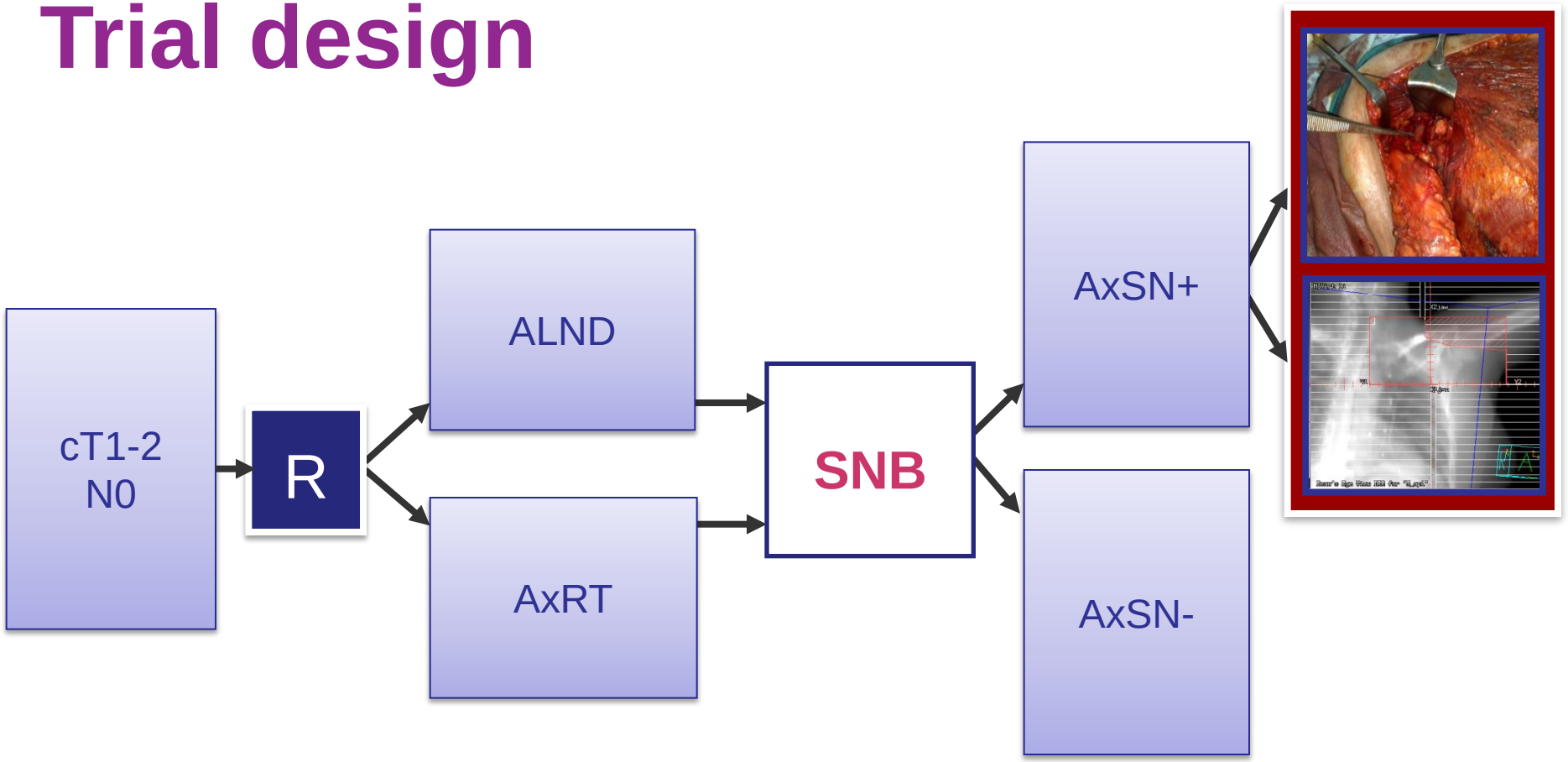
By the EORTC Breast Cancer Group and
Radiation Oncology Group
In collaboration with the Dutch BOOG Group
and ALMANAC Trialists' Group

Emiel J.T. Rutgers
The Netherlands Cancer Institute, Amsterdam

EORTC

Clinical trial information: NCT00014612

Trial design

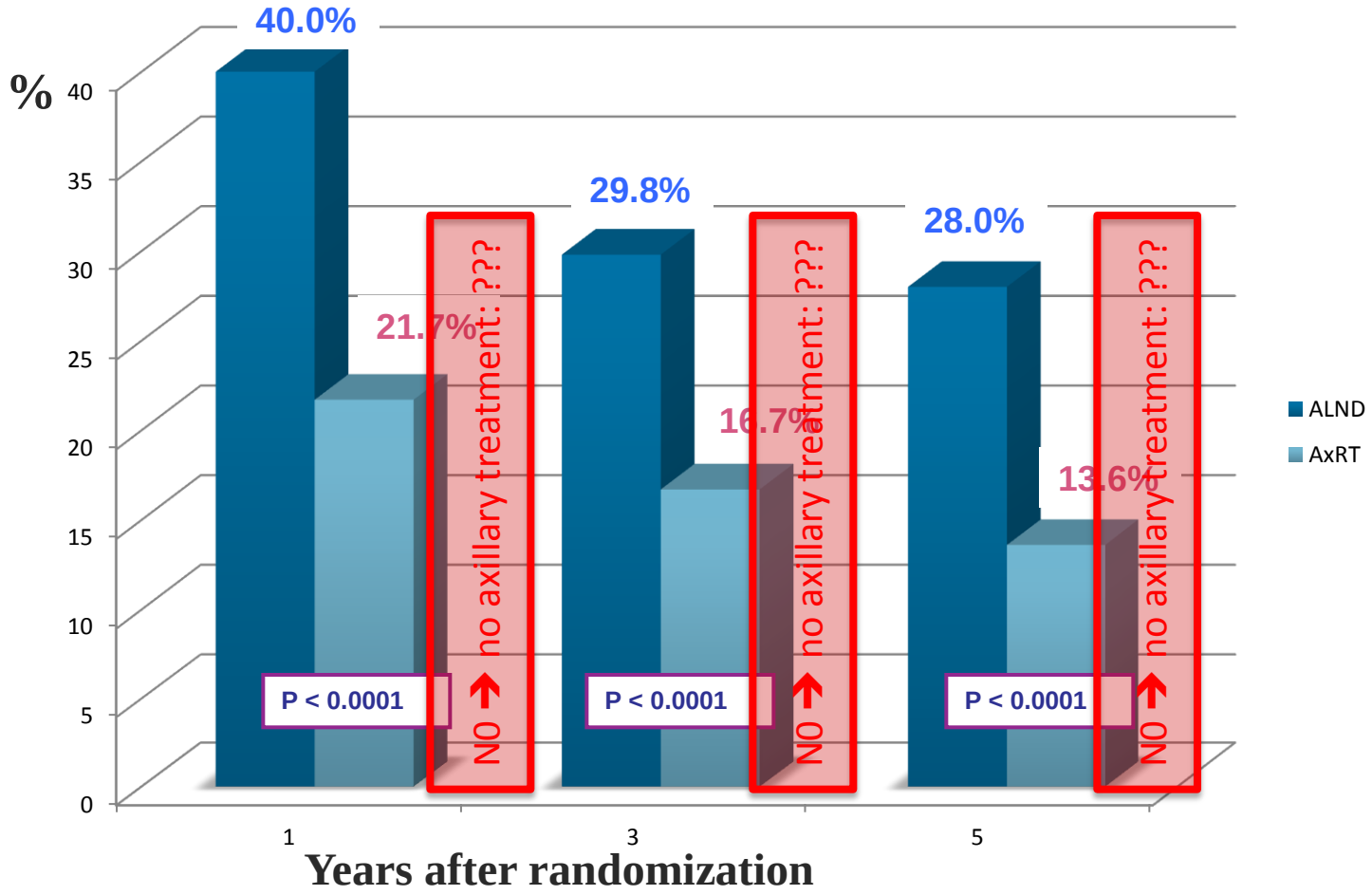


Stratification: institution
Adjuvant systemic therapy by choice

EORTC

Donker M, et al. Lancet Oncol. 2014;15:1303-10.

Lymphedema: clinical observation and/or treatment



EORTC

Donker M, et al. Lancet Oncol. 2014;15:1303-10.

Conclusion

Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients

Significantly less lymphedema after AxRT

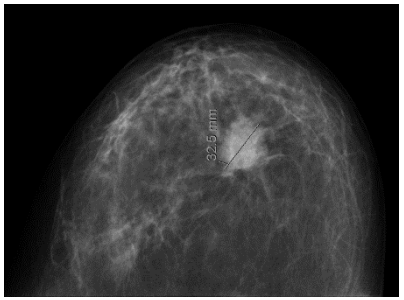
AxRT can be considered standard

Donker M, et al. Lancet Oncol. 2014;15:1303-10.

Principles of breast radiation therapy

- Introduction
- Tasks of the radiation oncologist
- Indications
- Side-effects
- New developments
- The future

The future: *target volumes*

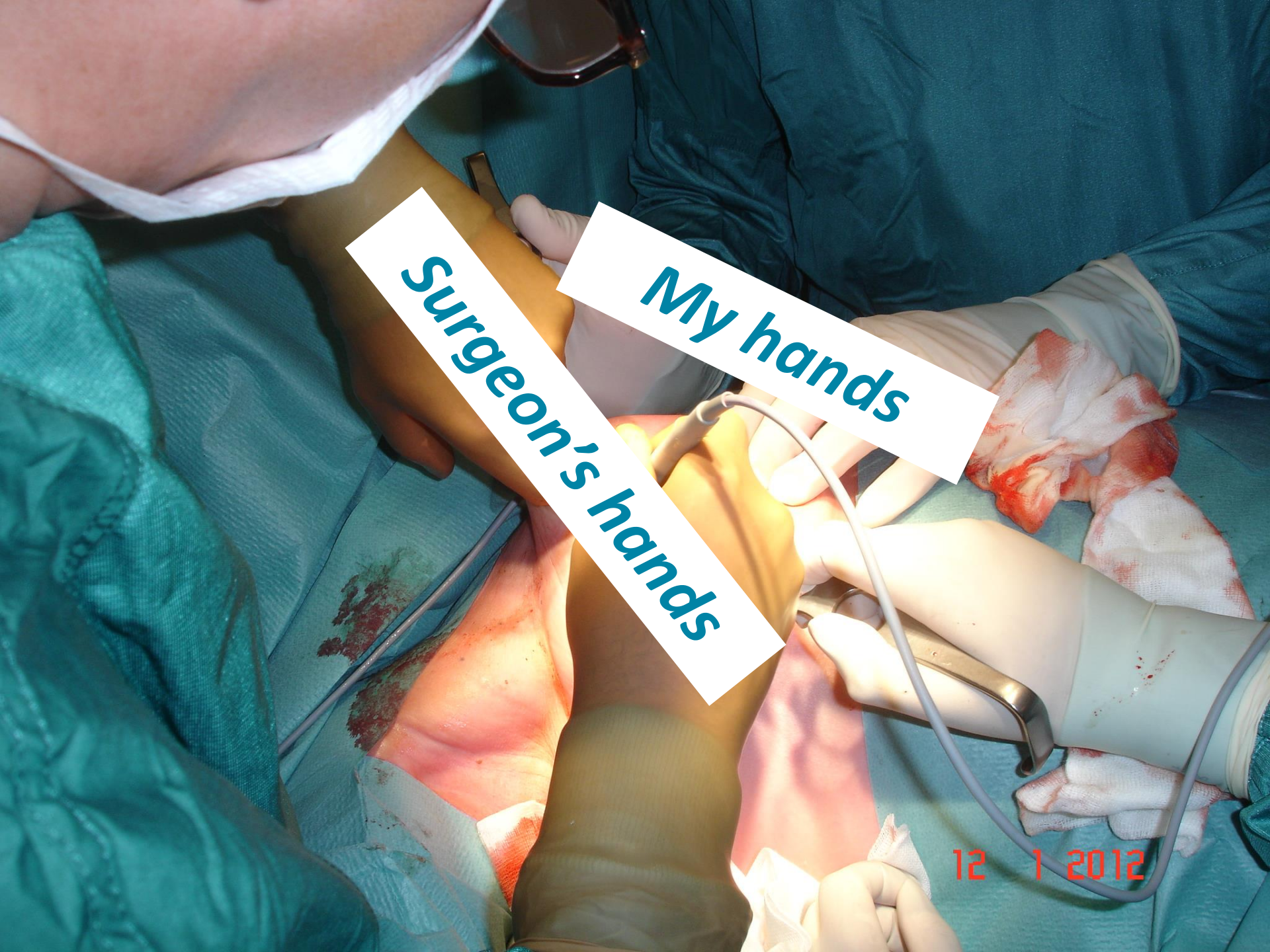


Future work

- Involvement of surgeons:
  - Optimal positioning of clips
  - Information on the position of tumor ↔ scar
    - Involvement of pathologist:
      - 3D information on resection margins
        - Involvement of radiologists:
          - Use of MRI (usually not available in RT position)
            - Involvement of radiation oncologist:
              - Pre-operative localization of tumour:
                - physical examination
                - pre-operative planning-CT scan

Boersma L, Poortmans P et al. R&O 2012

Radboudumc


My hands
Surgeon's hands
12 1 2012

The « omics" are here?

21th century

L. van 't Veer et al Nature 415, p530-536, 2002 *M. vd Vijver et al, NEJM 347; 1999-2009, 2002*

The future: *preventing radioresistance & complications*

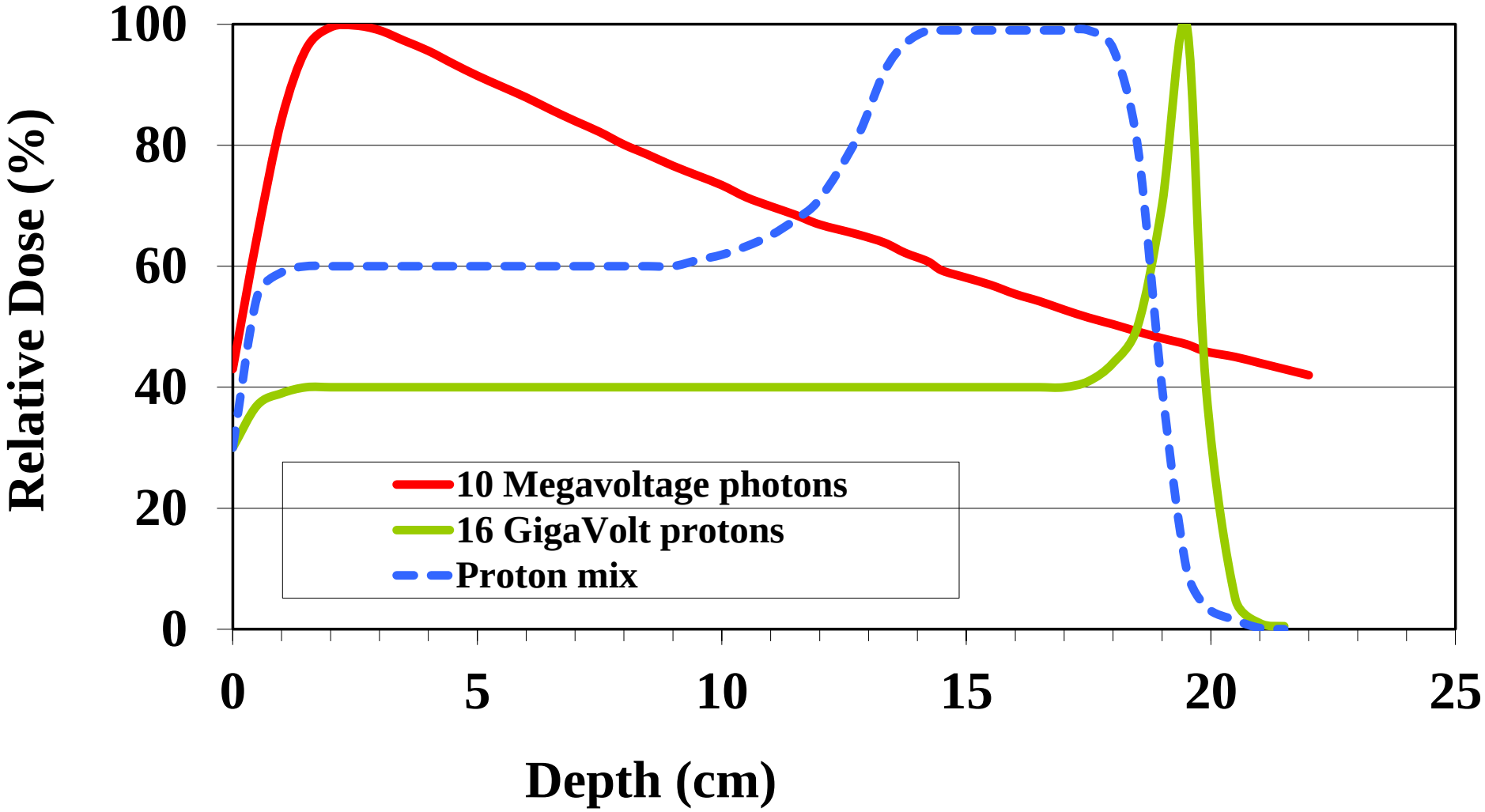
Combining radiation therapy with:

- Chemotherapy
- Hyperbaric oxygen
- Hyperthermia
- Targeted therapy
- Immunotherapy

The future: *particle therapy*

The future: *particle therapy*

Proportional Depth Dose (PDD)



The future: *conclusions*

- Effective in curative setting
- Effective in palliative setting
- The cheapest oncological treatment
- Favourable cost-benefit ratio
- Local treatment – interaction with systemic treatments
- Increasing demand

Side-effects

- Arm edema → no surgery + RT
- Impairment of shoulder movement → no surgery + RT
- Brachial plexus damage → limit dose (RBE)
- Telangiectasia → avoid skin folds
- Change in breast appearance → homogenisation
- Subcutaneous fibrosis → homogenisation
- Pneumonitis and lung fibrosis → limit lung dose
- Ischemic heart disease → limit heart dose
- Secondary malignancy → avoid other RF

Acknowledgements:

The organising team of this great course

My colleagues:

➔ RO's & all others!!!!!!

Colleagues and staff of EORTC and ESTRO

Colleagues and staff of BOOG, IKNL, EBCTCG, ...

Numerous patients

And so many others!


Radboudumc
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