



LUND UNIVERSITY
Faculty of Medicine

Adjuvant locoregional radiotherapy for breast cancer Data from SENOMAC

Sara Alkner
Skåne University Hospital, Lund University

- **Why locoregional radiotherapy?**
- **Side effects**
- **Target volumes and dose planning**
- **Deescalation of axillary treatment**
- **SENOMAC**
- **Ongoing and future trials**

2014 – LRRT after MRM and axillary surgery

- 8135 women 1964-86, 22 trials.
- No benefit for recurrences or BCM in N0.
- Benefit for all N+, N1-3 and N4+. Also with systemic therapy

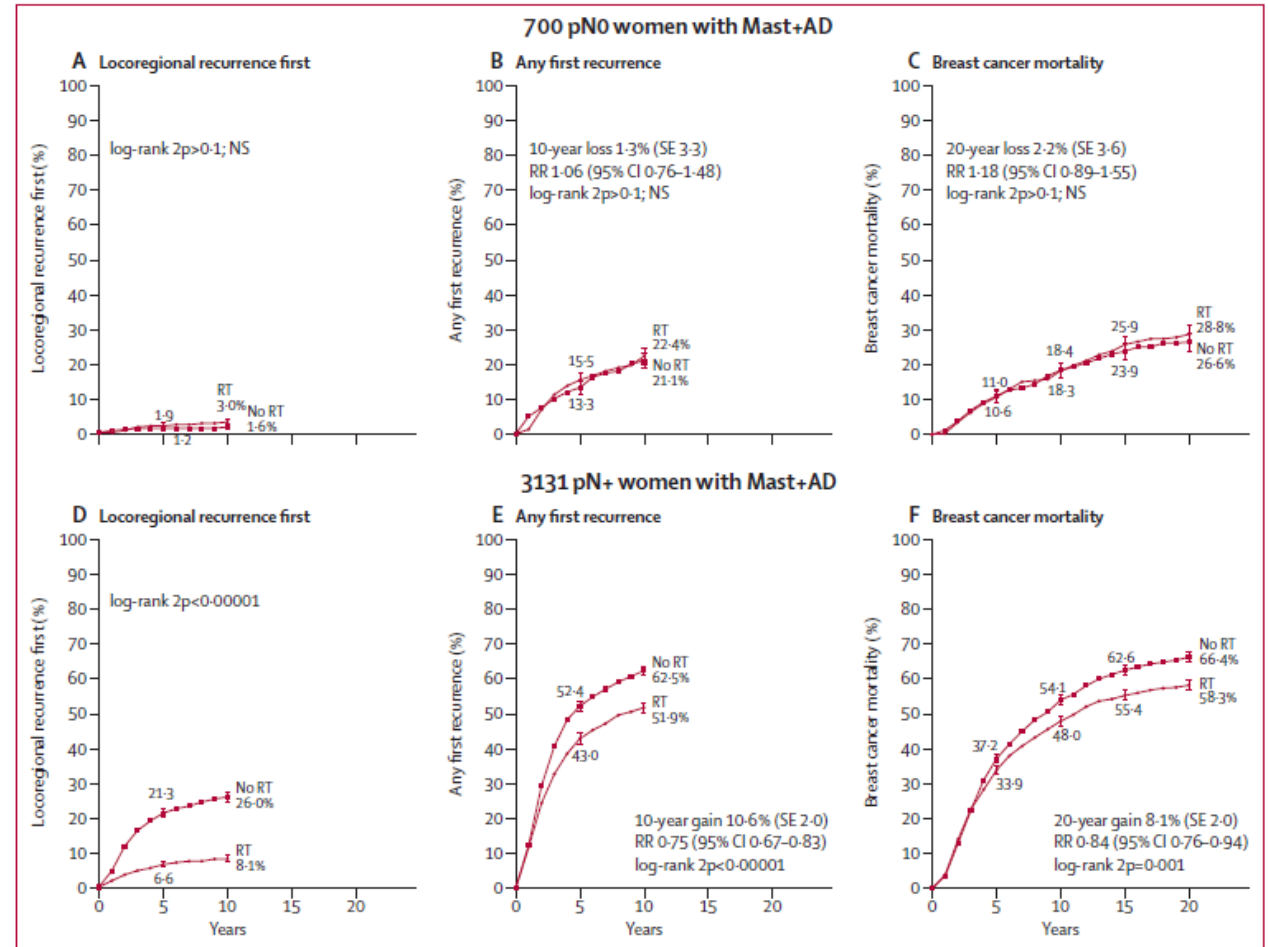
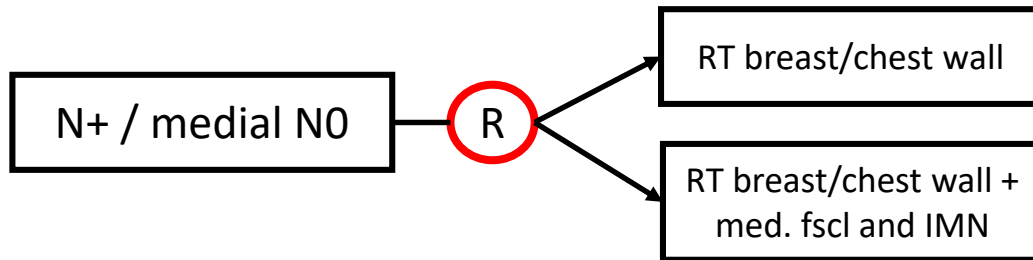


Figure 2: Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 700 women with pathologically node-negative (pN0) disease and in 3131 women with pathologically node-positive (pN+) disease

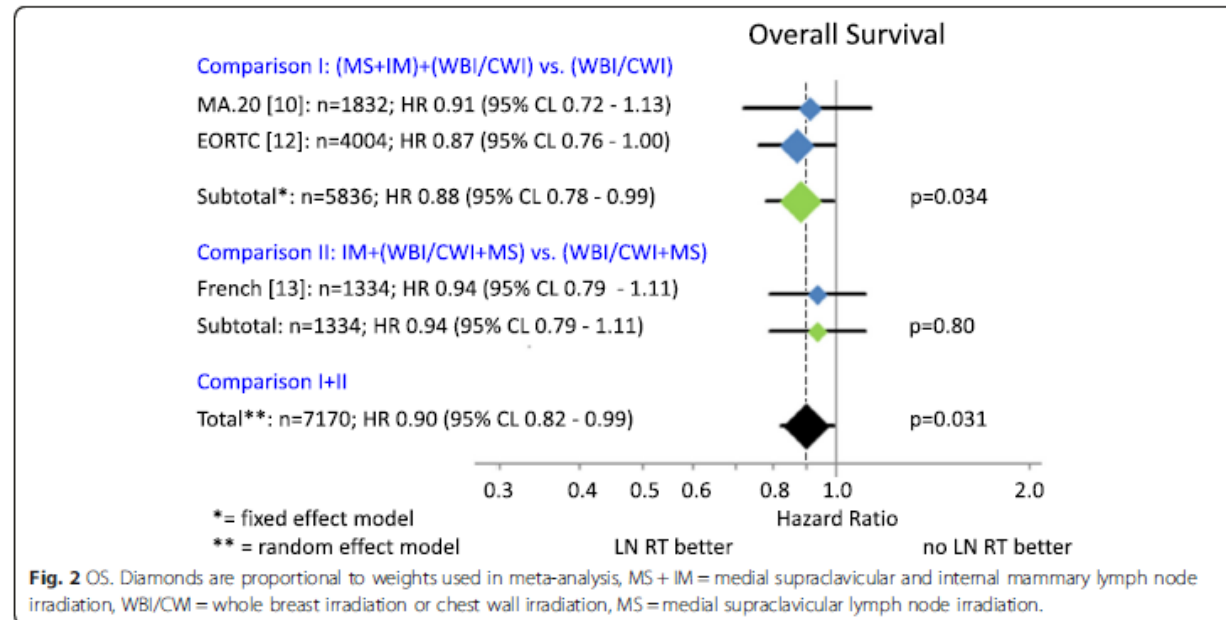
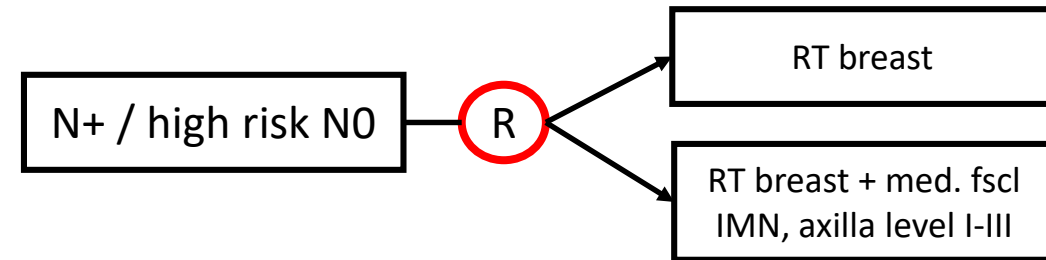
EORTC 22922/10925

- 4000 women, 1996-2004
- 55 % N+, 45 % N0 with medial tumour
- 15 år signific benefit BCM (2,6%), not OS (2,2%)



MA.20

- 1800 pat, 2000-2007
- N+ or high risk N0
- At 10 years lower LRR (3,0%) and better DDFS (3,9 %)
- OS and BCM no significant difference.

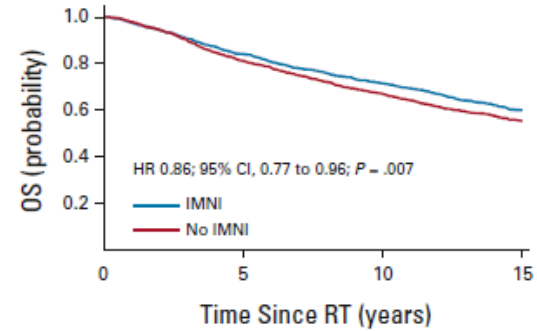


Internal Mammary Node Irradiation in Patients With Node-Positive Early Breast Cancer: Fifteen-Year Results From the Danish Breast Cancer Group Internal Mammary Node Study

Lise B.J. Thorsen, MD, PhD^{1,2}; Jens Overgaard, MD, DMSc¹; Louise W. Matthiessen, MD, PhD³; Martin Berg, MSc⁴; Lars Stenbygaard, MD⁵; Anders N. Pedersen, MD, PhD⁶; Mette H. Nielsen, MD, PhD⁷; Marie Overgaard, MD²; and Birgitte Vrou Offeren, MD, PhD^{1,2} on behalf of the DBCG Radiotherapy Committee

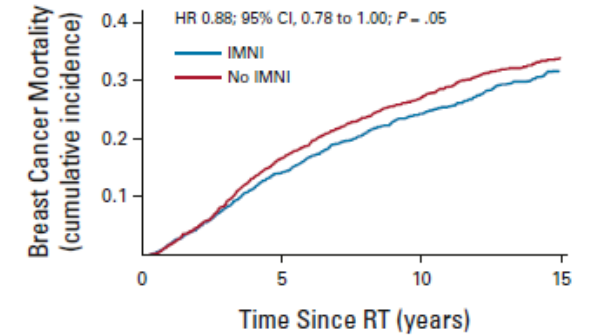
- 3089 pat, unilat N+,
- Rightsided tumours received IMN-RT, not left-sided.
- 14.8 years median follow-up
- OS 60.1% with IMN vs. 55.4% without
- BCM 31.7% with IMN vs. 33.9% without

A



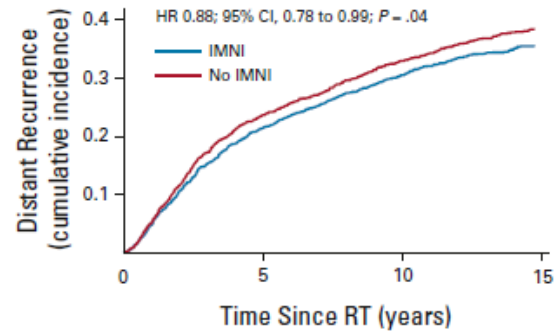
No. at risk:				
IMNI	1,491	1,253	1,063	400
No IMNI	1,598	1,295	1,067	380

B



No. at risk:				
IMNI	1,491	1,253	1,063	400
No IMNI	1,598	1,295	1,067	380

C



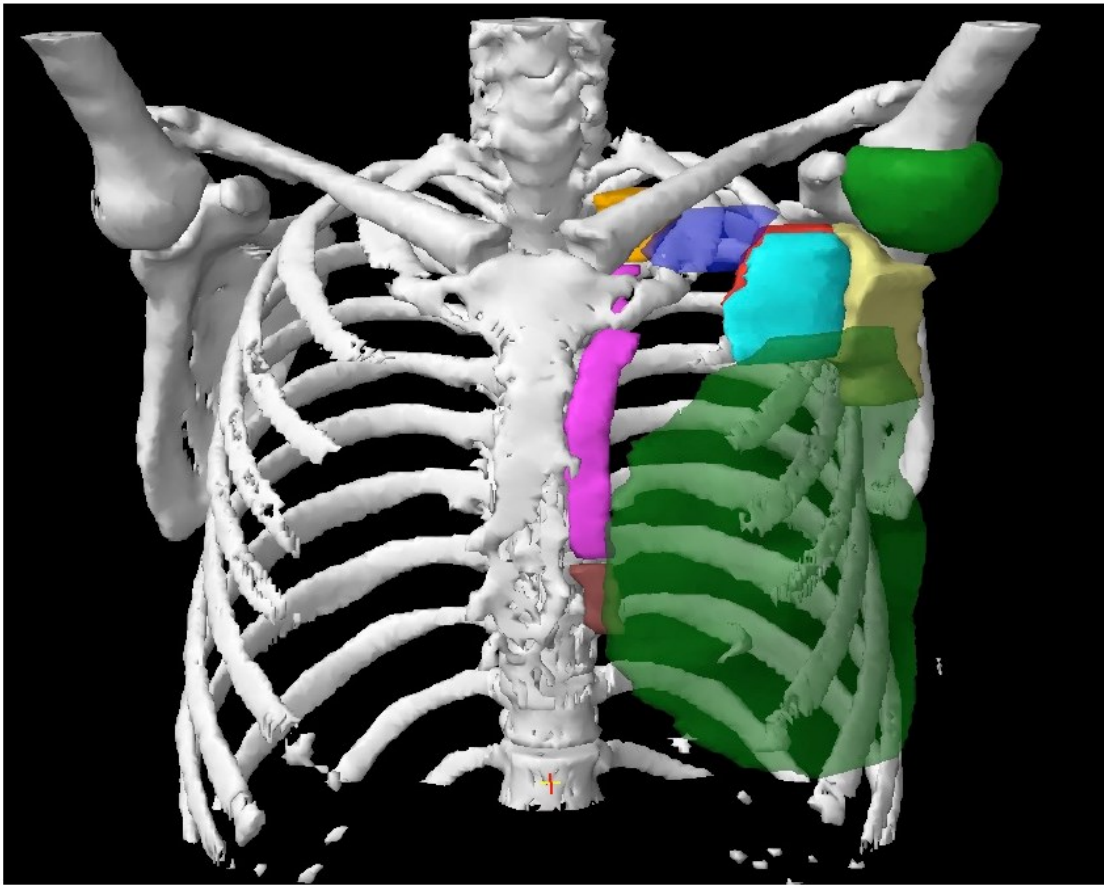
No. at risk:				
IMNI	1,491	1,144	960	269
No IMNI	1,598	1,182	963	247



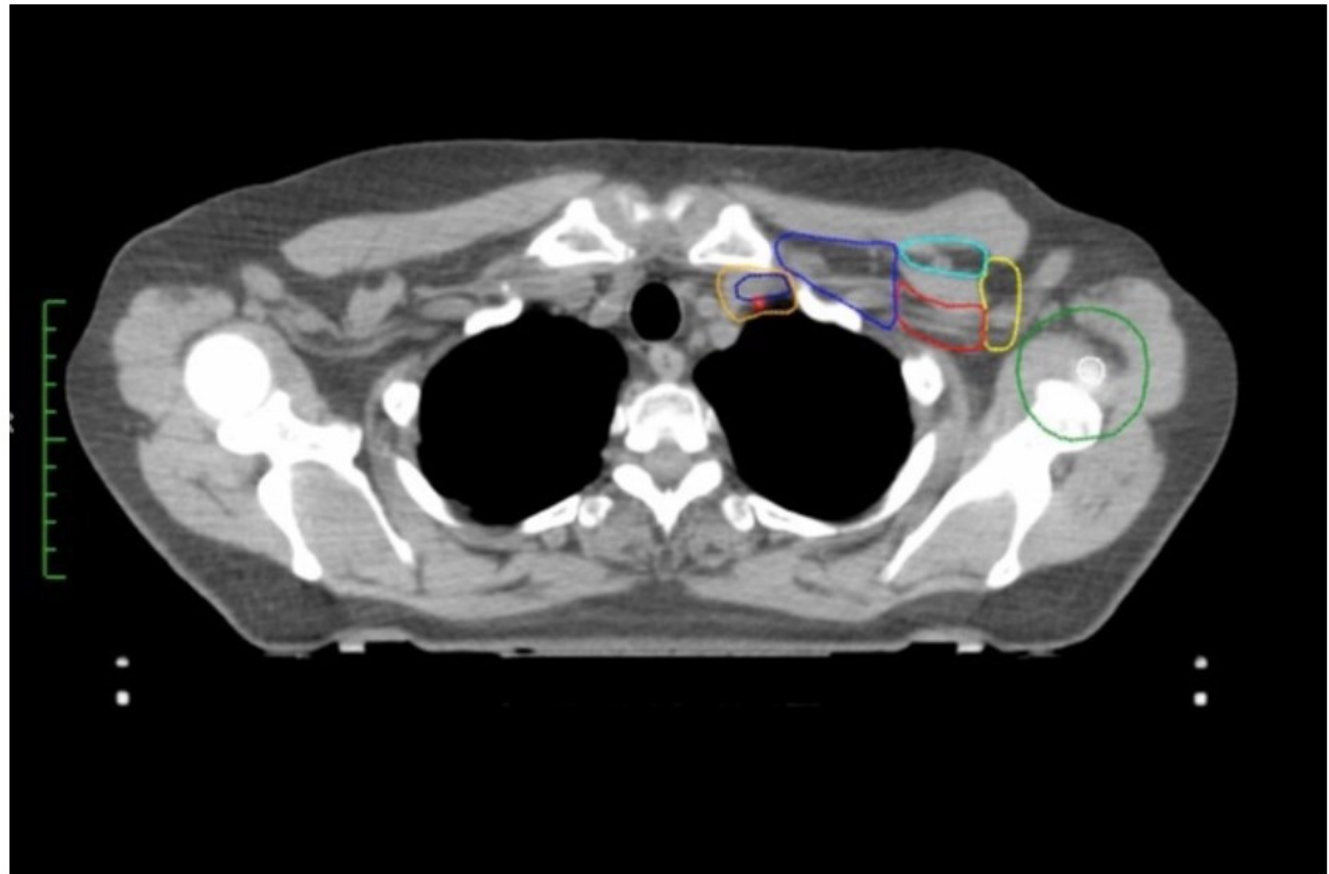
Side effects

- Skin, cosmetic
- Pneumonitis
- Lymphoedema and arm problems
- Complications after reconstructive surgery
- Heart disease
- Secondary malignancies – lung cancer, esophageal cancer, angiosarcoma

Earlier studies showed an increased non breast cancer mortality with radiotherapy!

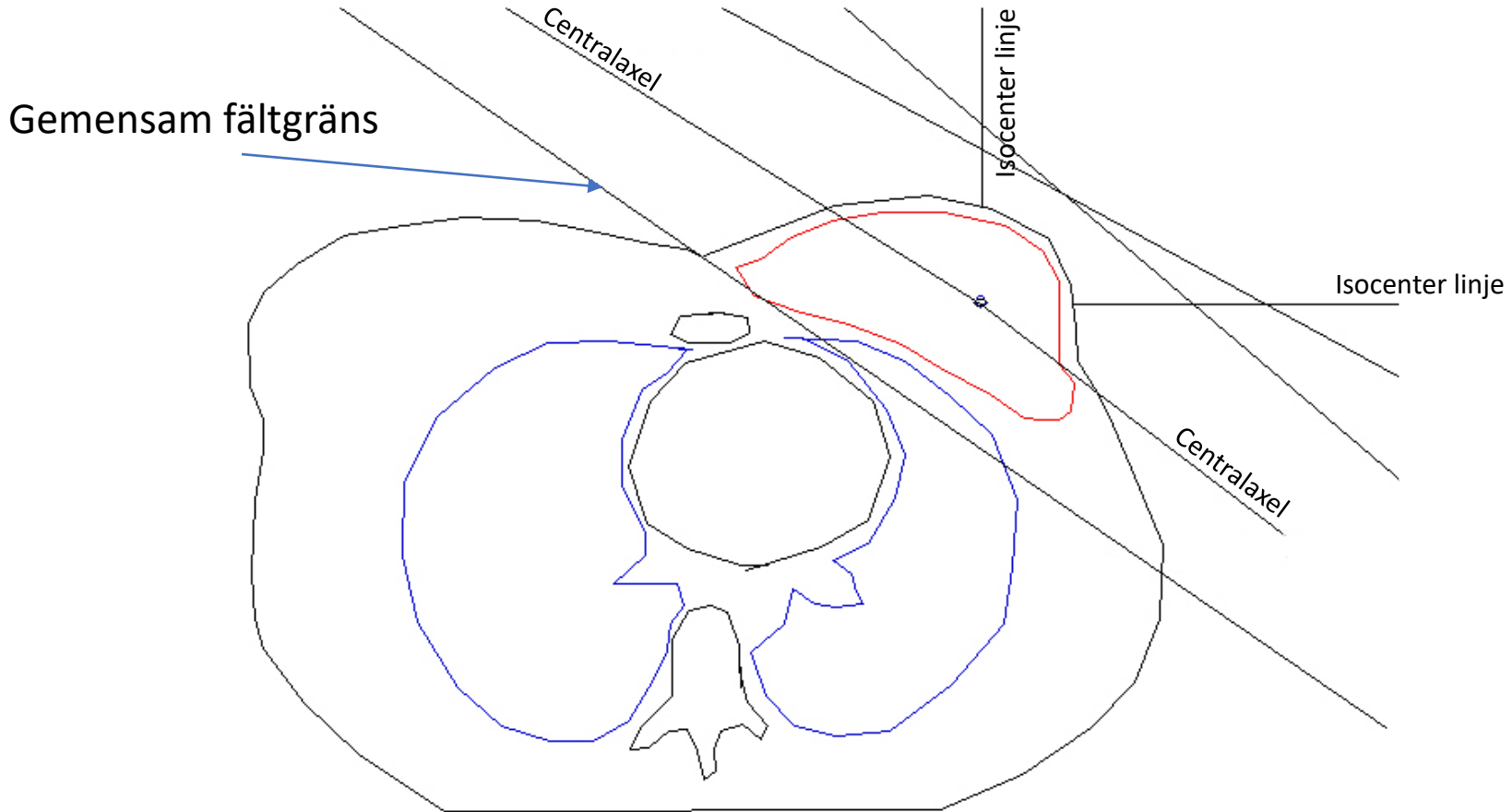


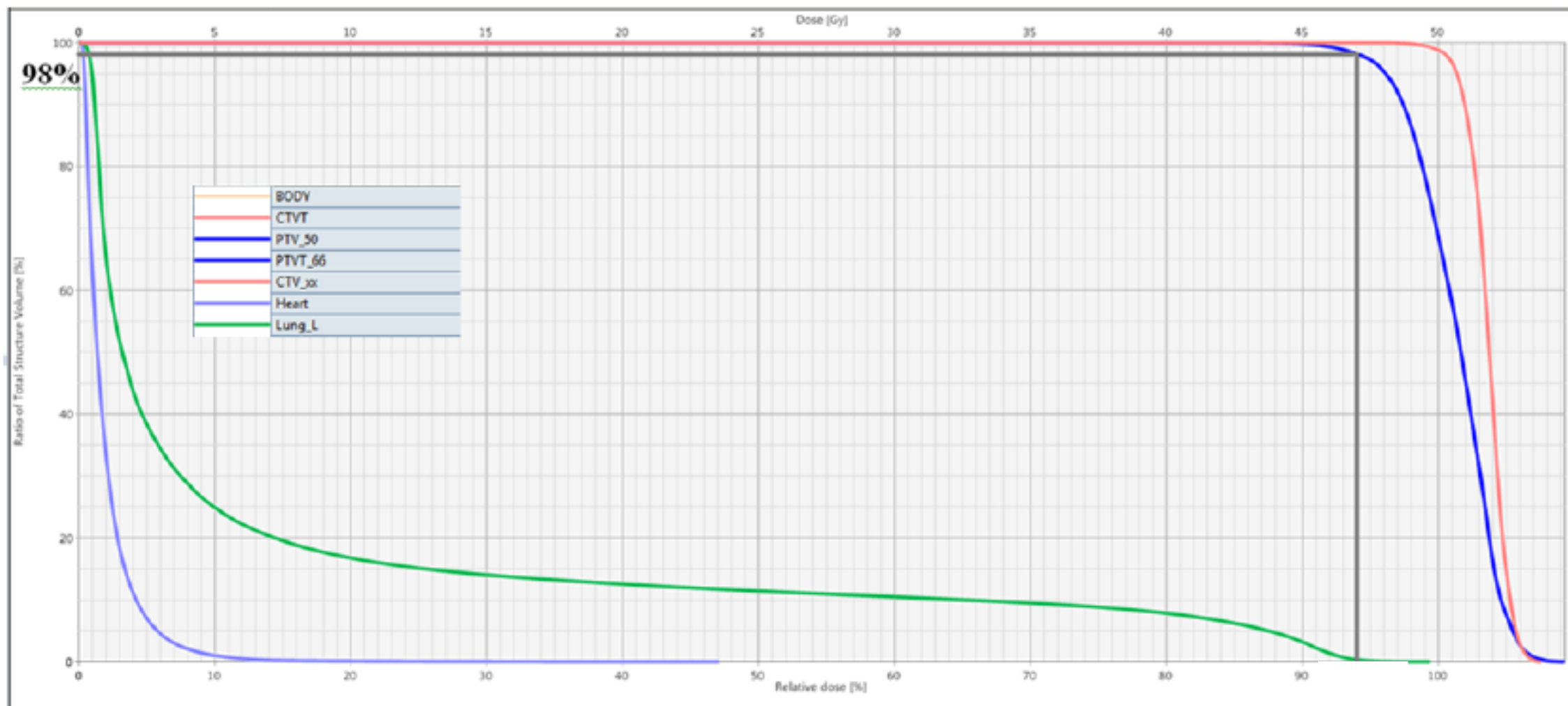
Breast/thoracic wall
Axilla level (I), II, III
FscI IV
Interpectoral
Internal mammary nodes



ESTRO target guidelines
Offersen et al. 2015

Treatment technique – 4 field mam

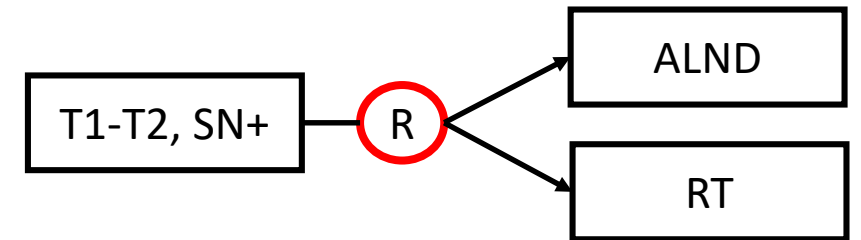




Figur 6 Exempel på dos-volym histogram. Dostäckningen för CTVT och PTV_50 visas. D98% är markerat.

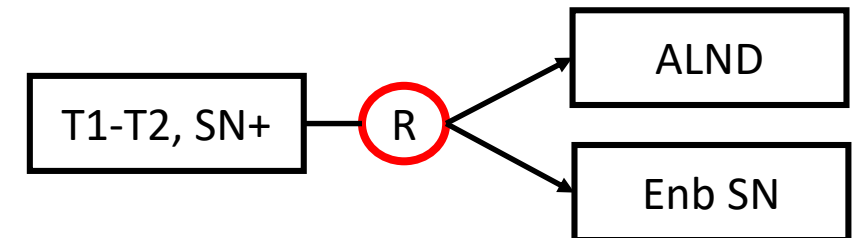
Amaros

- 2001-2010, 1425 pat. T1-2, positive SN
- Rand ALND (744) vs. rt (681)
- 60% macromet, 30% micro, 10% ITC
- Similar 5, 10 year DFS, OS, recurrences
- More lymphedema with surgery

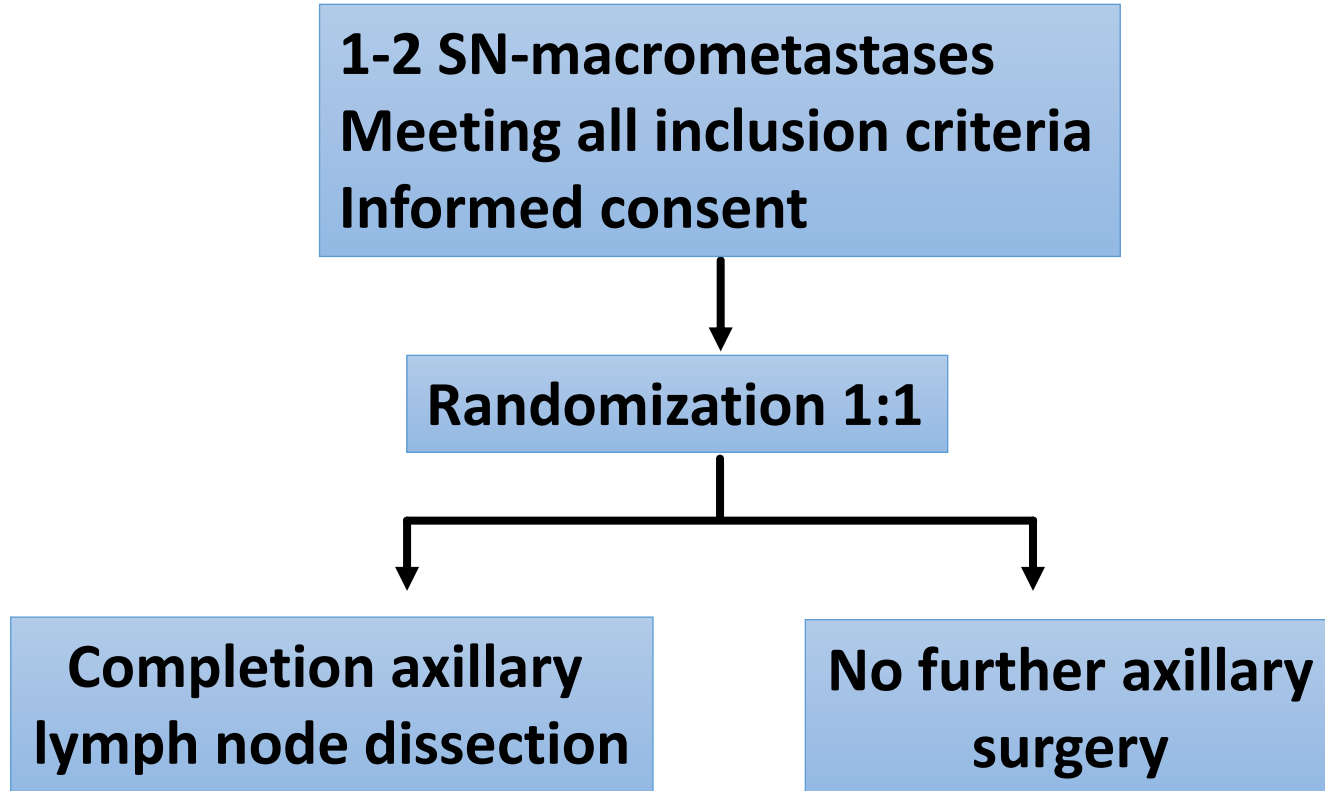


ACOSOG Z0011

- 1999-2004, 891 pat. T1-2, 1-2 SN-met
- Rand ALND (445) vs. enb SN (446)
- Similar 5, 10 year OS, DFS.
- All BCS + rt (high tangential fields)
- 41% micromet (37,5 % vs 44,8 %)



The SENOMAC-trial



Inclusion criteria

T1-3

Clinically N0

Preop ultrasound of the axilla

Breast conserving surgery or
mastectomy

Age \geq 18 years

No neoadjuvant systemic treatment

Exclusion criteria

Regional/distant metastasis outside the
ipsilateral axilla

Prior BC history

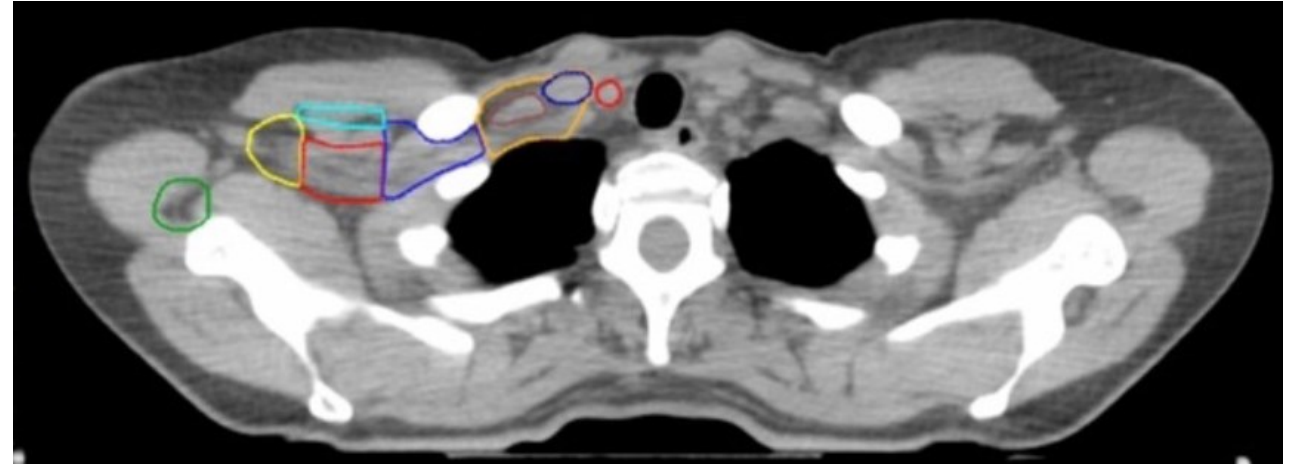
Pregnancy

Medical contraindication for RT or
systemic therapy

Inability to understand study
information

Locoregional radiotherapy

- Locoregional RT according to national guidelines.
- Sweden and Denmark – 94% of enrolled patients.
- Treatment plans before June 2019 reviewed.



ESTRO target guidelines, Offersen et al. 2015

	Level II-IV	IMN	Level I
Sweden	All	1-3 IgII-met and central/medial tumour ≥4 IgII-met	Site dependent
Denmark	All	All	<10 IgII removed

Radiotherapy QA

- Swedish RT plans in 874 out of 907 pts (96%).
 - axillary CTV dichotomized as including level I or not.
- Danish RT plans for 302 out of 332 pts (91%).
- Individual axillary levels according to ESTRO guidelines.
 - 62 randomly selected pts (5% or ≥ 3 pts per Swedish RT-site).
 - 210 Danish pts (39 with level I not in the CTV).

Target volumes

	Sweden	Denmark
Breast/chestwall only	35 (4%)	0
Breast/chestwall and level II-IV	504 (58%)	148 (49%)
Breast/chestwall and level I-IV	334 (38%)	154 (51%)
Level I-IV only	1 (0.1%)	0
IMN included	121 (14%)	302 (100%)

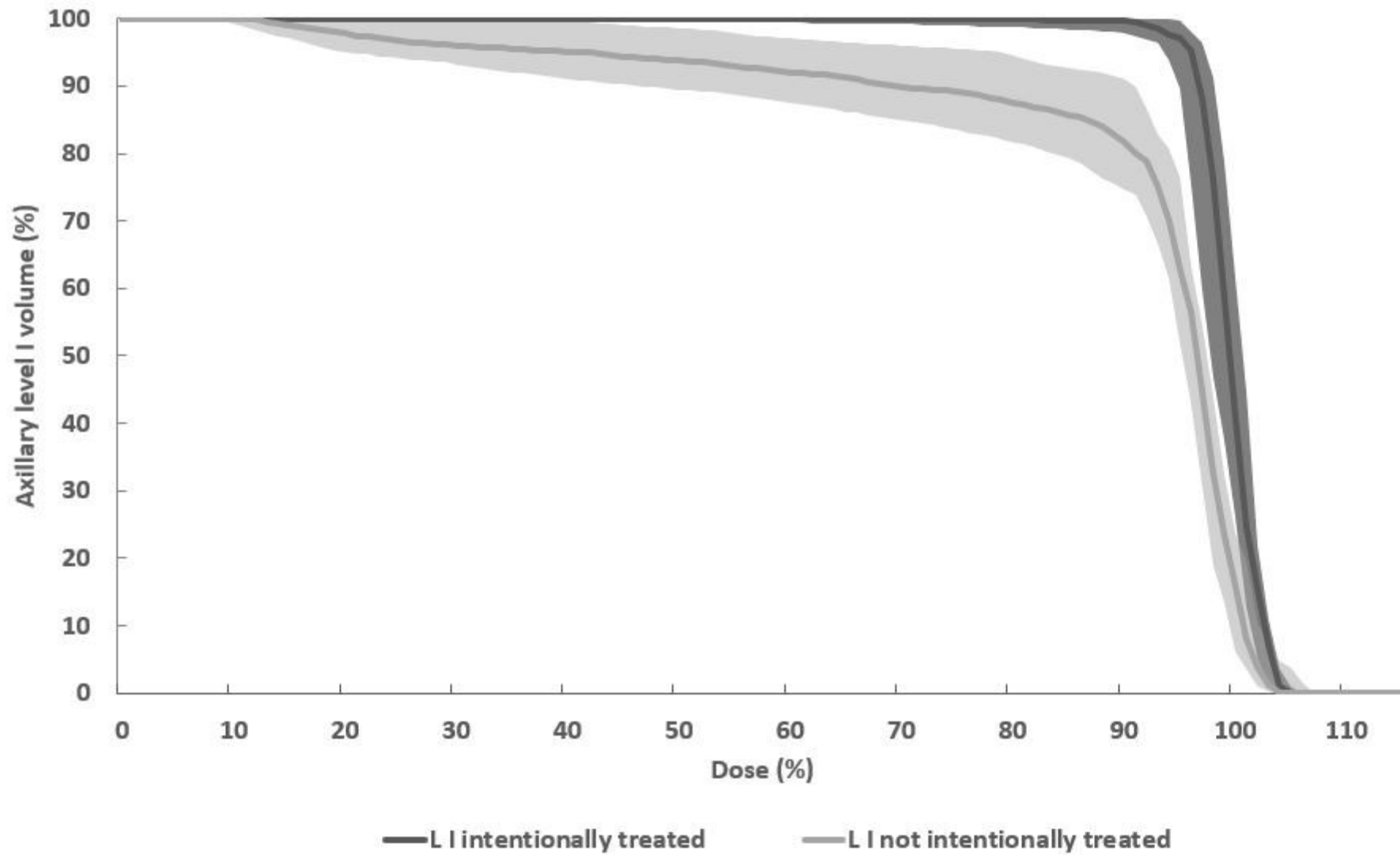
Level I

- Sweden: no difference between randomization groups (37% vs. 40%, $p=0.3$).
- Danmark: included in 14% in ALND-group, 97% in SN-only group.

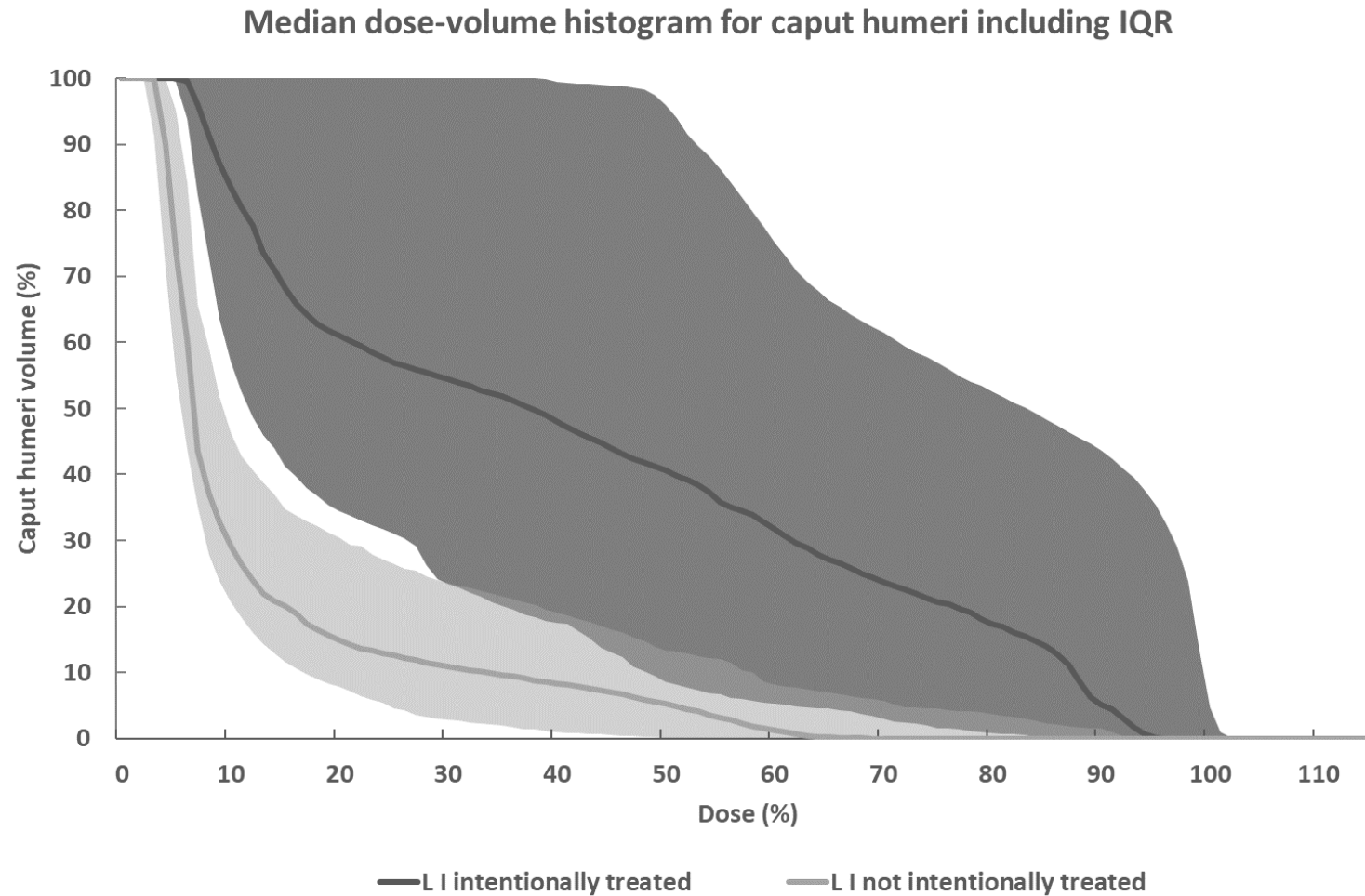
Dose Coverage

Target	Country	V90% (IQR range)	D90% (IQR range)
CTV breast/chest wall + level I-IV	SE	100% (98% - 100%)	97% (95% - 98%)
	DK	100% (98% - 100%)	95% (94% - 95%)
CTV breast/chest wall + level II-IV	SE	82% (75% - 91%)	69% (47% - 91%)
	DK	85% (76% - 89%)	77% (60% - 89%)

Median dose-volume histogram for axillary level I including IQR



Caput humeri



Conclusions from RT-QA in SENOMAC

- Sweden - no difference in target volumes between treatment arms.
- Denmark – level I included if SN-biopsy only, but not if ALND.
- Regardless of inclusion in the original CTV, level I receives a high dose coverage from adjacent fields to the breast/chest wall and level II-IV.

**Differences in regional RT between study arms should
not affect recurrence data in the SENOMAC-trial**

POSNOC

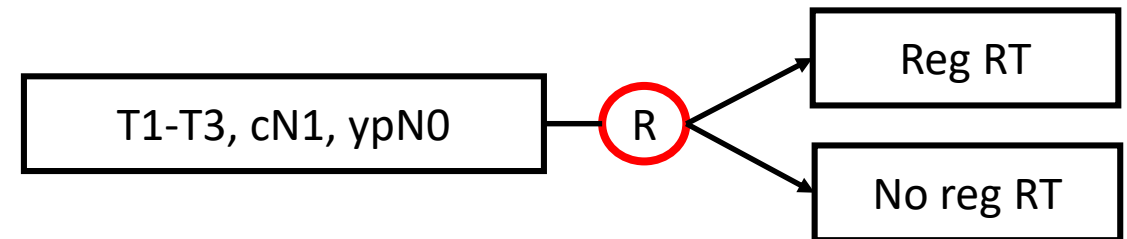
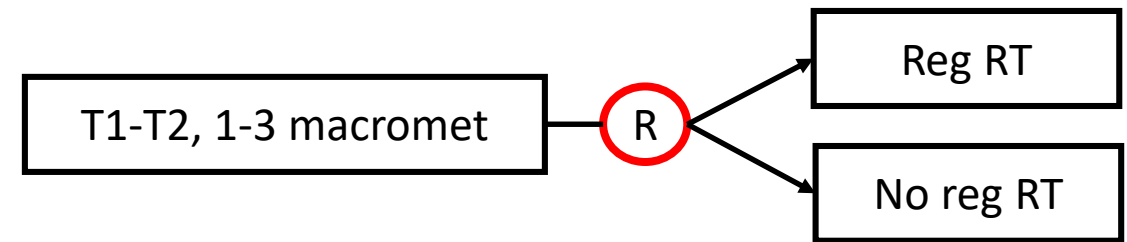
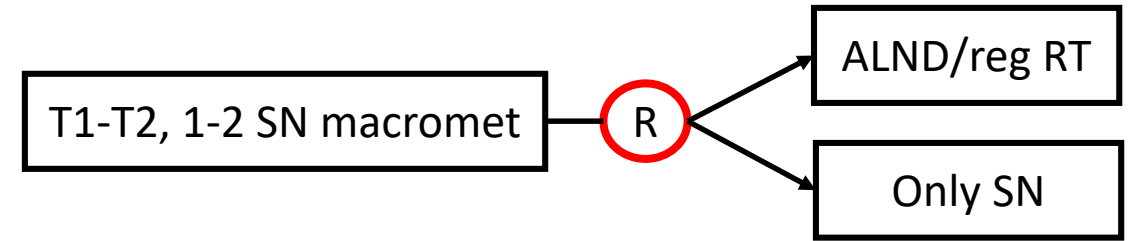
- All histological subtypes, no neoadj chemo.
- BCS+MRM.
- Should get systemisk adj.treatment.
- 1900 pat.

MA.39

- After ALND (1-3 macromet),
- SN+BCS (1-2 macromet), SN+MRM (1 macromet)
- ER+, HER2-, Oncotype dx <18
- No neoadj treatment, endocrine therapy 5 yr
- 2140 patienter

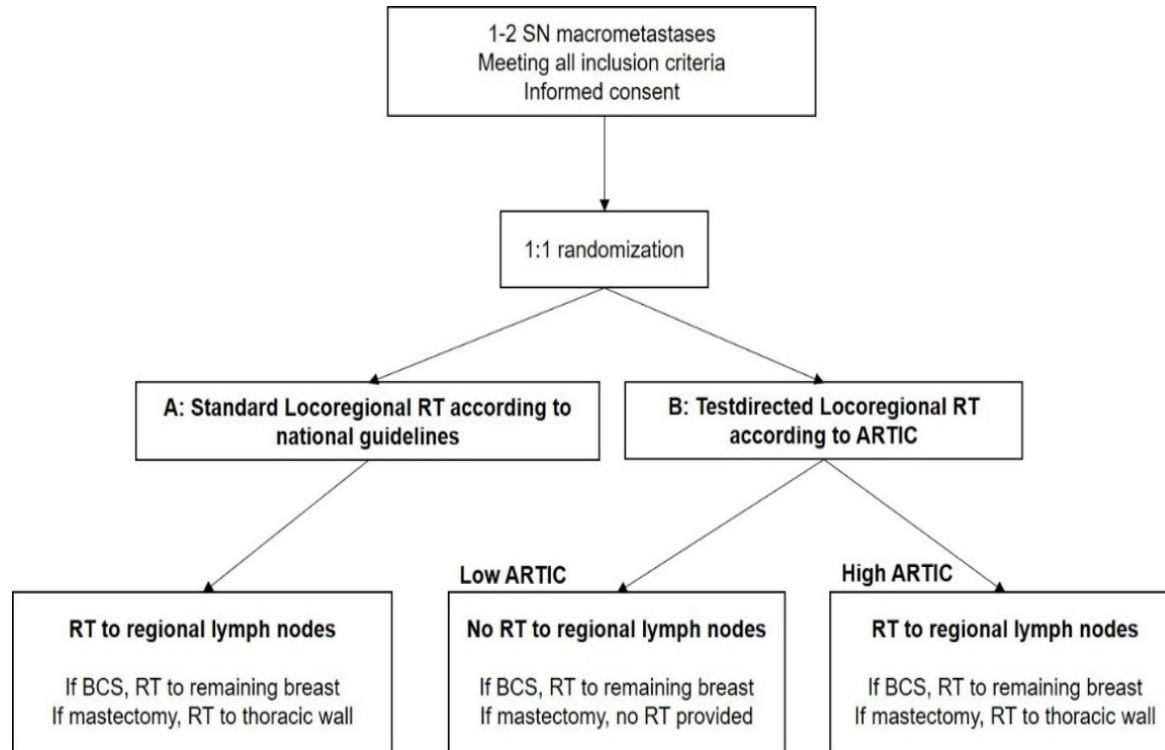
NSABP B51

- N1→N0 after neoadj chemo.
- SN or ALND
- Always WBRT
- Thoracic wall RT after MRM only with reg RT
- 1600 pat



T-REX

Tailored regional radiotherapy using gene expression profiling in clinically node negative breast cancer patients with 1-2 sentinel node macrometastases



1800 patients in Sweden, Norway, Finland
Start Jan 2023

invasive breast cancer T1-T2.
Clinically N0.
Macrometastasis ($\geq 2\text{mm}$) in 1-2
lymph nodes at sentinel node biopsy.
Oral and written consent.
Age ≥ 18 years.

Microscopic extracapsular invasion
and all histological types allowed

Sara Alkner, Jana de Boniface,
Dan Lundstedt, Per Karlsson,
Helena Sackey, Elinore Wieslander,
Pär-Ola Bendahl, Jana Ben Maaouia

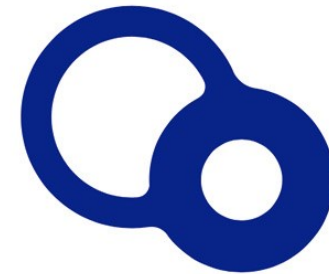
Thanks for the
attention!



Percy Falks Stiftelse

**Fru Berta
Kamprads stiftelse**

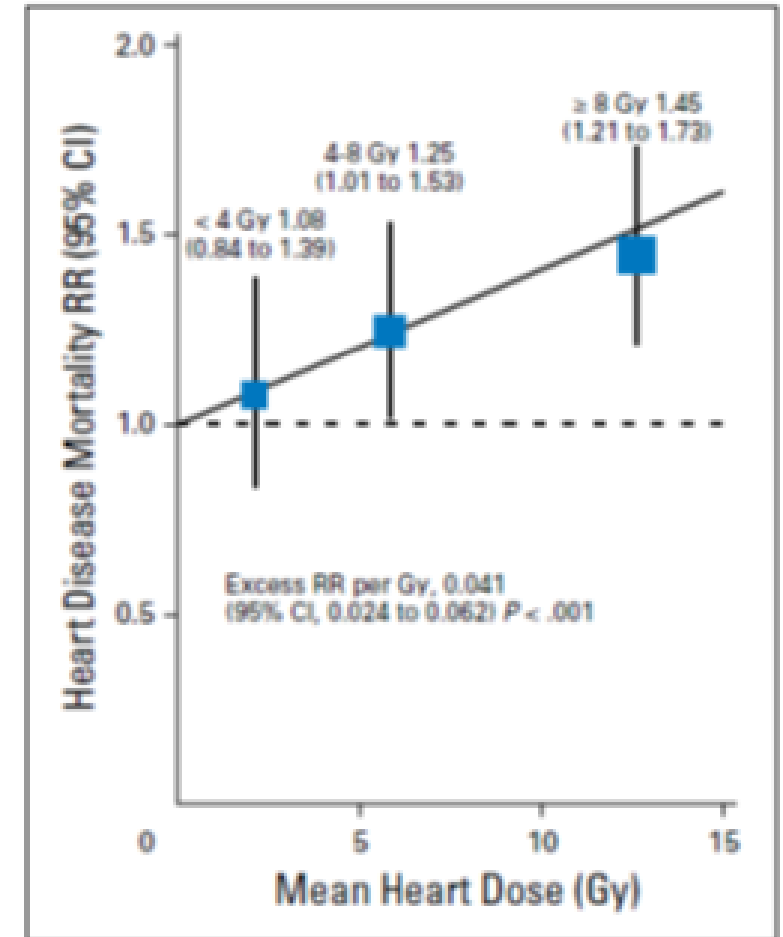
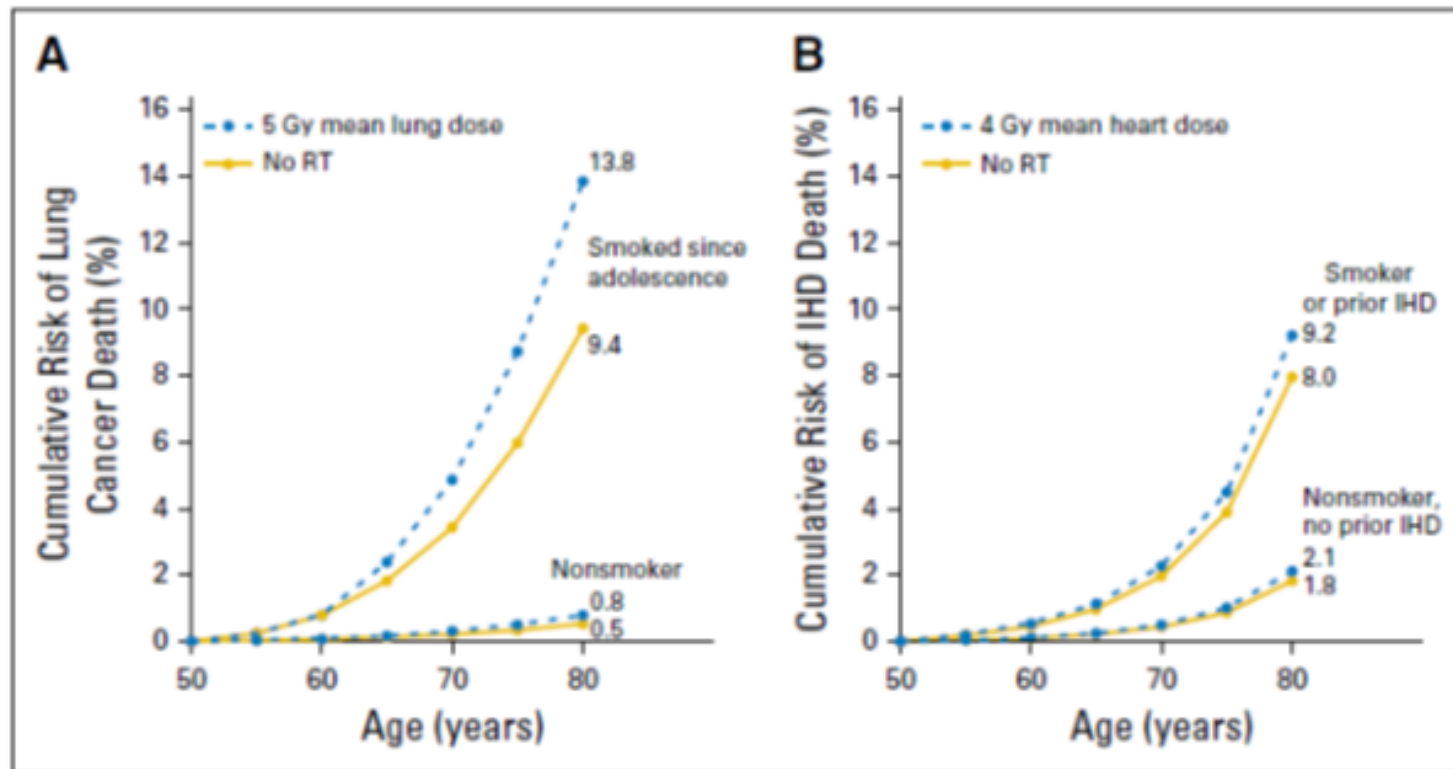
för utforskning och bekämpning av
cancersjukdomar



CANCERFONDEN

Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials

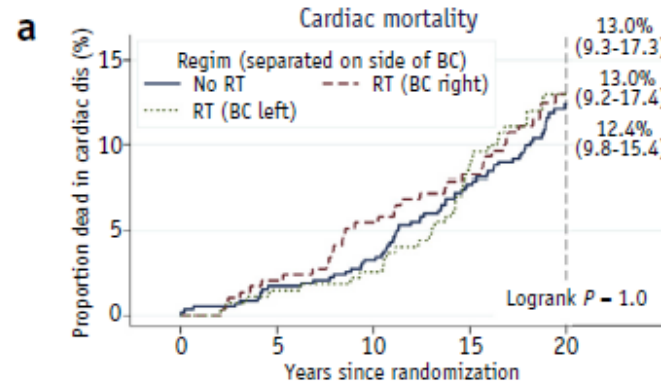
Carolyn Taylor, Candace Correa, Frances K. Duane, Marianne C. Aznar, Stewart J. Anderson, Jonas Bergh, David Dodwell, Marianne Ewertz, Richard Gray, Reshma Jagsi, Lori Pierce, Kathleen I. Pritchard, Sandra Swain, Zhe Wang, Yaochen Wang, Tim Whelan, Richard Peto, and Paul McGale, for the Early Breast Cancer Trialists' Collaborative Group



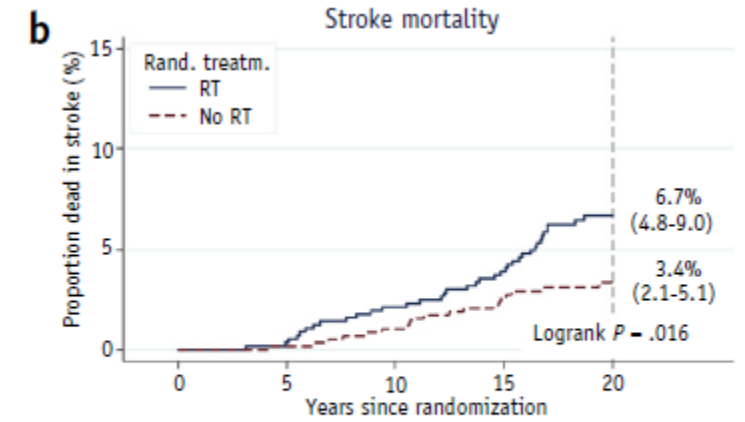
Clinical Investigation

No Increased Cardiac Mortality or Morbidity of Radiation Therapy in Breast Cancer Patients After Breast-Conserving Surgery: 20-Year Follow-up of the Randomized SweBCGRT Trial

Fredrika Killander, PhD,^{*,†} Elinore Wieslander, PhD,[†]
Per Karlsson, Prof,[‡] Erik Holmberg, PhD,^{‡,§} Dan Lundstedt, PhD,[‡]
Lars Holmberg, Prof,^{||,¶} Linda Werner, PhD,^{*} Sasha Koul, PhD,[#]
Mahnaz Haghaneji,[†] Elisabeth Kjellen, Assoc Prof,^{*,†}
Per Nilsson, Assoc Prof,^{†,**} and Per Malmström, Prof^{*,†}



At risk	0	5	10	15	20
No RT	580	539	478	400	197
RT (BC right)	291	274	244	212	101
RT (BC left)	272	254	226	194	90



At risk	0	5	10	15	20
RT	563	528	470	406	191
No RT	580	539	478	400	197

RESEARCH ARTICLE

Open Access



Long-term risk of ischemic heart disease after adjuvant radiotherapy in breast cancer: results from a large population-based cohort

Anna-Karin Wennstig^{1,2*}, Charlotta Wadsten^{1,3}, Hans Garmo^{4,5}, Irma Fredriksson^{6,7}, Carl Blomqvist⁸,
Lars Holmberg^{5,9}, Greger Nilsson^{10,11,12} and Malin Sund¹

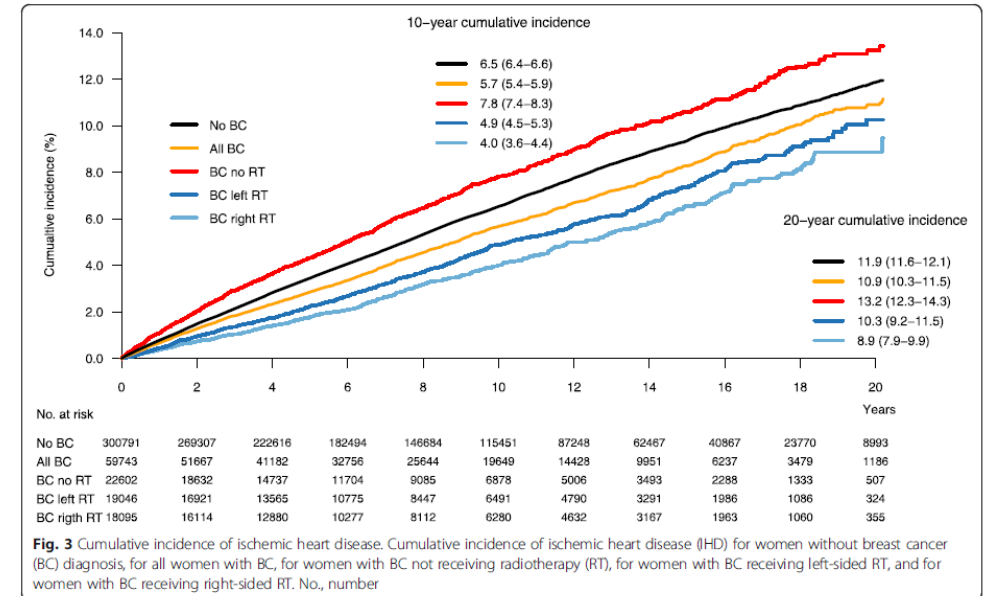


Fig. 3 Cumulative incidence of ischemic heart disease. Cumulative incidence of ischemic heart disease (IHD) for women without breast cancer (BC) diagnosis, for all women with BC, for women with BC not receiving radiotherapy (RT), for women with BC receiving left-sided RT, and for women with BC receiving right-sided RT. No., number

Internationella guidelines

Storbritannien (NICE, NCA)

- Ej både ALND och axillär RT.
- 1-3 Igll - fscl vid dåliga prognostiska faktorer och gott PFS.
- 1-2 SN makromet – ytterligare axill.beh ej nödvändig om WBRT, postmenopausal och lågrisk tumör.

USA (NCCN)

- 1-2 SN makromet – ej ALND om WBRT, T1-2, ej neoadj kemo.
- 1-3 makromet – överväg starkt RT till regionala Igll (fscl, ficl, IMN, ev axill)

Tyskland

- 1-2 SN makromet – WBRT, T1-2, ej neoadj kemo. RT enbart mot axill level 1-2. Evidensgrad - Limited benefit to the patients and can be performed.
- Fscl/ficl – vid 1-3 makromet enbart om andra negativa prognostiska faktorer.

Storbritannien

NICE - 2018

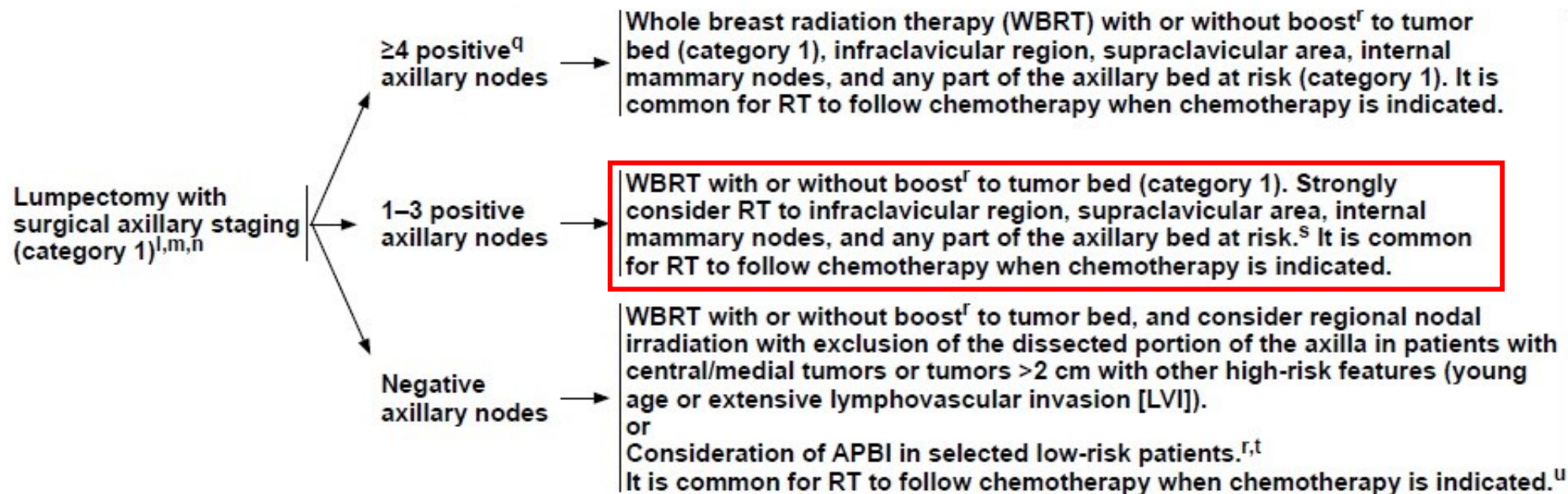
- 1.10.17 Do not offer adjuvant radiotherapy to the axilla after axillary clearance for invasive breast cancer. [2009, amended 2018]
- 1.10.18 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 4 or more involved axillary lymph nodes. [2009]
- 1.10.19 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 1 to 3 positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status. [2009]

NCA - maj 2020

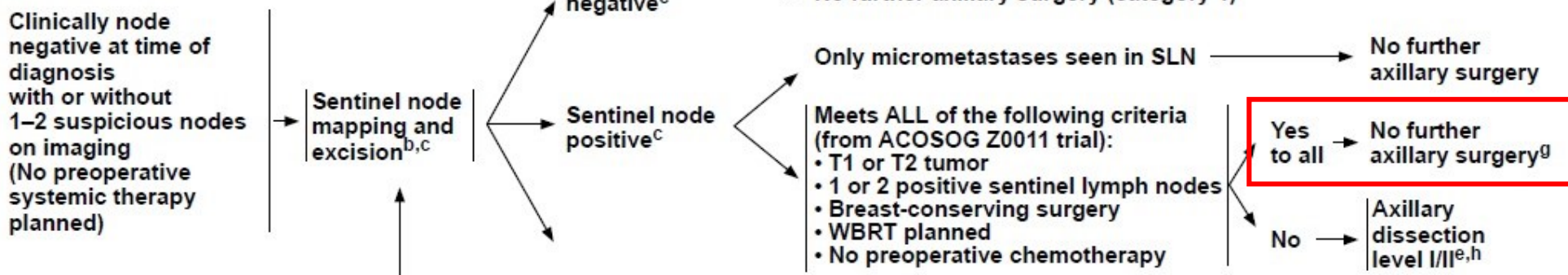
- **1–2 sentinel nodes with macrometastases** – further axillary treatment is no longer mandatory in breast conservation with whole-breast radiotherapy in patients who are postmenopausal and have T1, Grade 1 or 2, oestrogen receptor positive (ER+) and human epidermal growth factor receptor negative (HER2-) tumours. *These patients could also be entered into the POSNOC or equivalent clinical trial.*

Standard treatment, outside a clinical trial is to offer further axillary treatment, In these good prognosis patients radiotherapy may be limited to level 1 and 2 nodes (as defined by the ESTRO Nodal Atlas).

LOCOREGIONAL TREATMENT OF T1-3,N0-1,M0 DISEASE^a



SURGICAL AXILLARY STAGING



- ++ This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.
 - +** This investigation or therapeutic intervention is of limited benefit for patients and can be performed.
 - +/- This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.
 - This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.
- This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

Tyskland 2020



Radiotherapy of axillary lymph nodes in patients with positive sentinel-lymph nodes**, who did not undergo axillary dissection

	Oxford		
	LoE	GR	AGO
BCS and ACOSOG Z0011-criteria⁺ met			
▪ Radiotherapy of the breast including LN level 1 + 2 to 5 mm below the axillary vein (PTV)	2b	B	+*
BCS and ACOSOG Z0011-criteria⁺ not met			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	++*
ME and chest wall RT indicated and ACOSOG Z011-criteria⁺ not met or ME and chest wall RT not planned			
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS) <u>>=3 pos. SLN</u>	1b	B	++
▪ Radiotherapy of the axillary lymph nodes (analog AMAROS)	1b	B	+

* = Study participation recommended
 ** = Macrometastases

⁺ = <T3, no palpable LN, R0, 1-2 positive SN, no extracapsular extension, no NACT

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG)

	Oxford		
	LoE	GR	AGO
<u>RT to supra-/infraclavicular lymphatic regions</u>			
▪ ≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in supra-/infraclavicular LN	1b	A	++
▪ 1–3 positive axillary lymph nodes ¹ in case of - central or medial tumor and G2-3 or ER/PgR-negative - premenopausal patient and G2-3 or ER/PgR-negative	2a	B	+
▪ pN0 with central or medial tumors, if premenopausal and G2-3 and ER/PgR-negative	2a	B	+/-

¹ not applicable for micrometastases