



La linfoadenectomia è un intervento imprescindibile per le decisioni terapeutiche

Fondazione I.R.C.C.S Istituto Nazionale Tumori di Milano
Dott.ssa Maria Carmen De Santis
mariacarmen.desantis@istitutotumori.mi.it



OUTLINE

- Regional Nodal Irradiation (RNI) after axillary surgery
- RNI after no axillary surgery

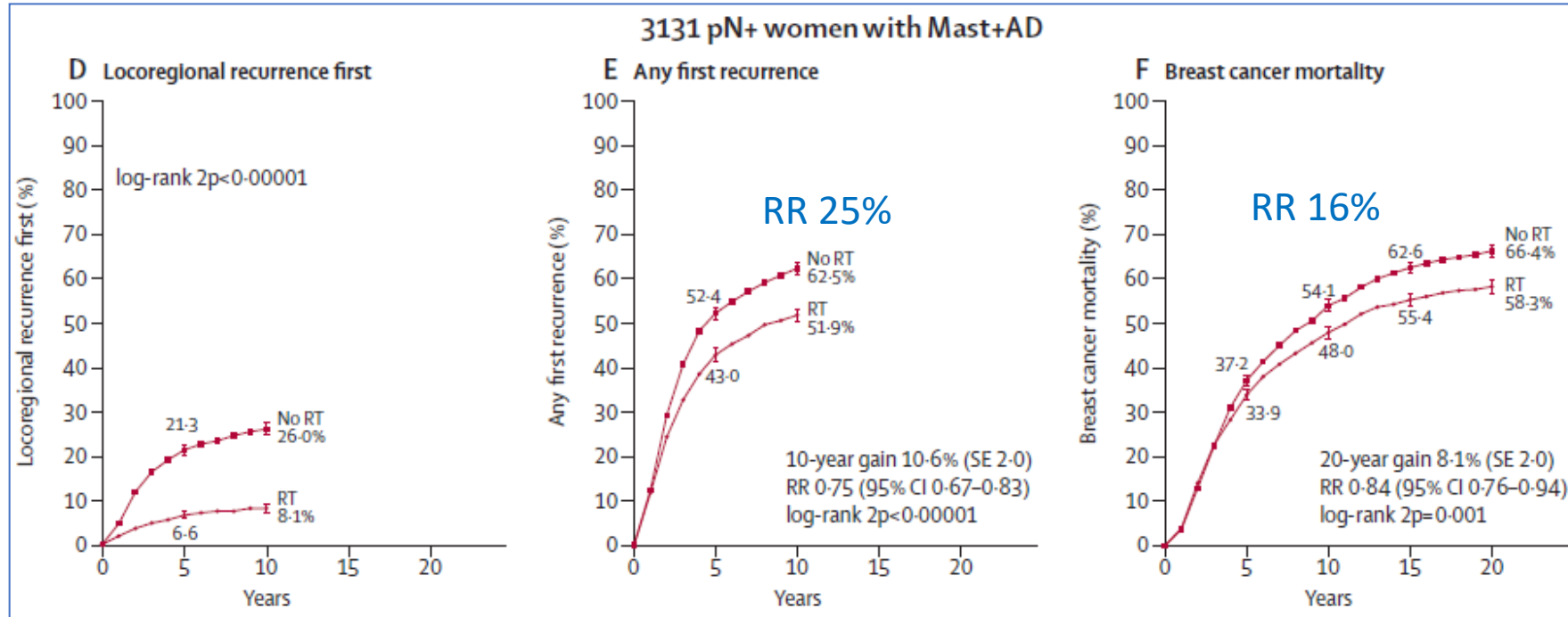


Post mastectomy radiotherapy (PMRT)

PMRT **reduced** in pN+ the

10-year risk of a recurrence of any type by **10,6%** (62.5% vs 51.9%)

20-year risk of death from breast cancer by **8,1%** (66.4% vs 58.3%)

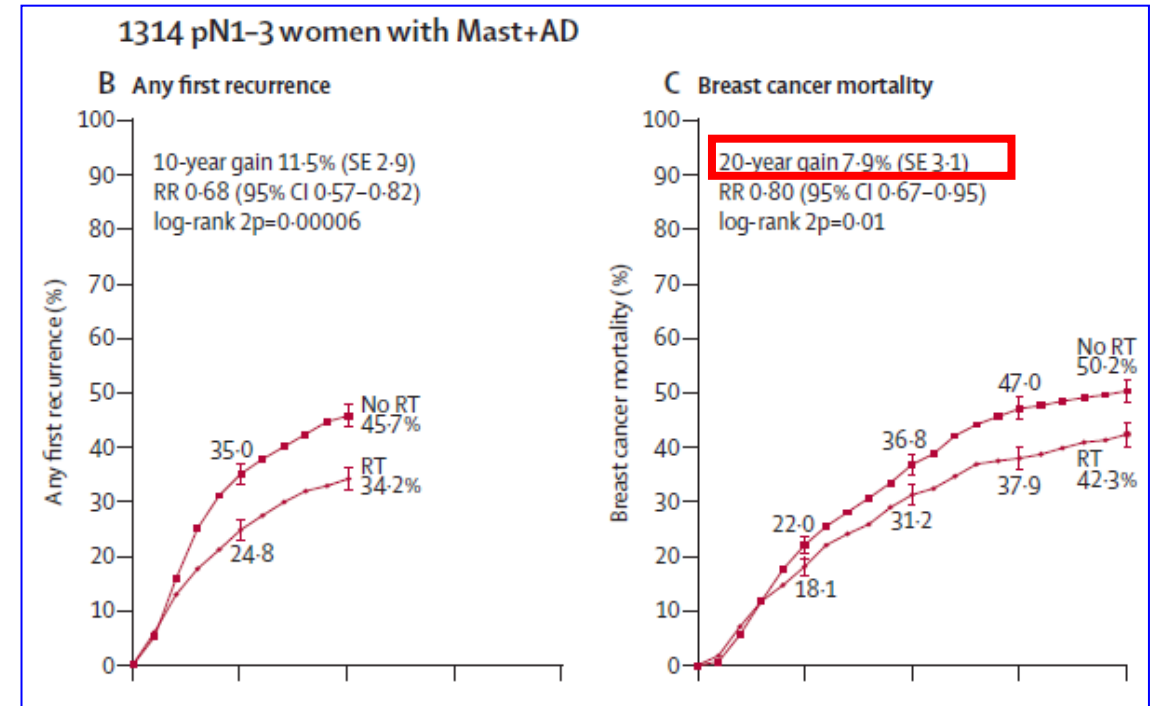
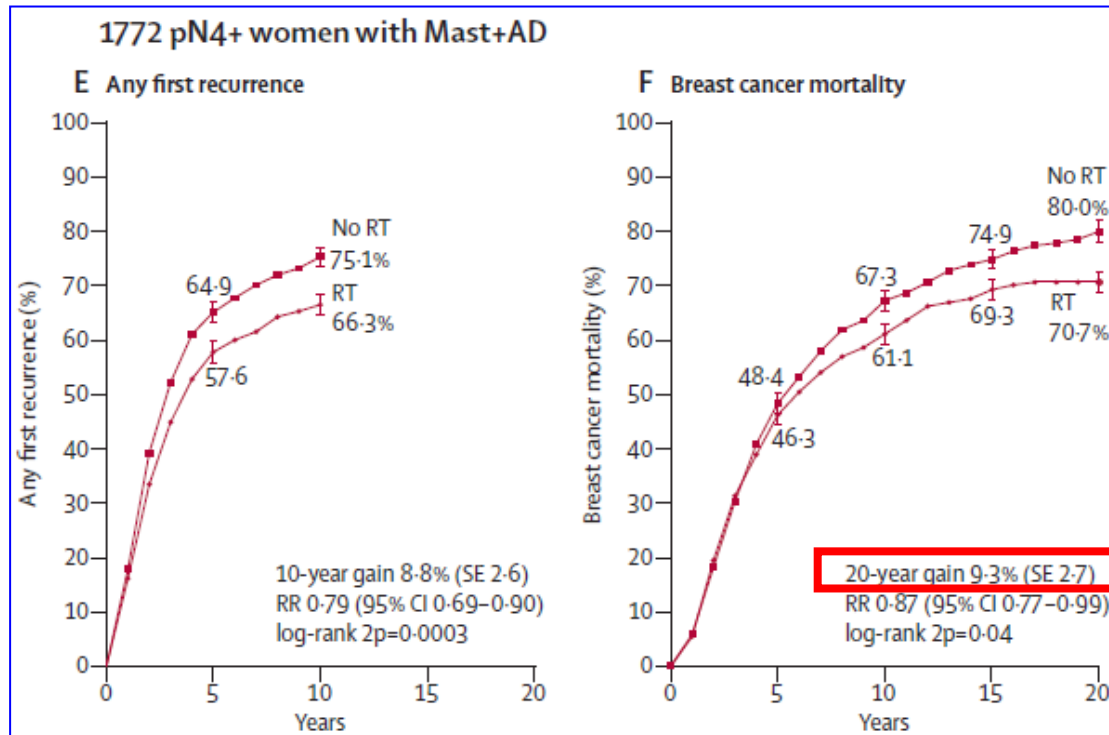


About **one breast cancer death** was **avoided** in the 20 years for every **1,5 recurrences** of any type avoided during the first 10 years after radiotherapy

EBCTCG, *Lancet* 2014; 383: 2127-35

Post mastectomy radiotherapy (PMRT)

Patients with **high risk for LRR:**
 pT3N+, pT4, N+ ≥ 4



Patients with **intermediate risk**
 for LRR: pN+ 1-3

EBCTCG, *Lancet* 2014; 383: 2127-35

Regional Nodal Irradiation

EORTC 22922/10925 trial

4004 pts
Mastectomy or BCS and ALND (+/- SNB)

2002 randomized to RNI

2002 randomized to no RNI

-OS HR: 0.87 (p=0.06)
- DFS HR: 0.89 (p=0.04)
-DMS HR: 0.86 (p=0.02)
-BCCS HR: 0.82 (p=0.02)

MA.20 trial

1832 pts
BCS and ALND (+/- SNB)
N+ or N0 with G3, LVI or ER-

916 randomized to RNI

916 randomized to RNI

-OS HR: 0.91 (p=0.38)
- DFS HR: 0.76 (p=0.01)
-DMFS HR: 0.76 (p=0.03)

Poortmaans P. et al. NEJM 2015
Whelan TJ. et al. NEJM 2015

Regional Nodal Irradiation

SABCS 2019 – EBCTCG meta-analysis

Regional node irradiation: Meta-analysis of 13,500 women in 14 trials

Regional node RT versus not

14 trials, ~13,500 women

Comparison: Node RT versus not	No. trials	No. women
Axilla SCF	2	652
IMC	3	4683
IMC SCF axilla	9	8069
All trials	14	13,404

Data analysis plan: regional node RT

1. All trials together
2. Separate older & newer trials

Target coverage better in newer trials

Heart dose: Older trials >8 Gy

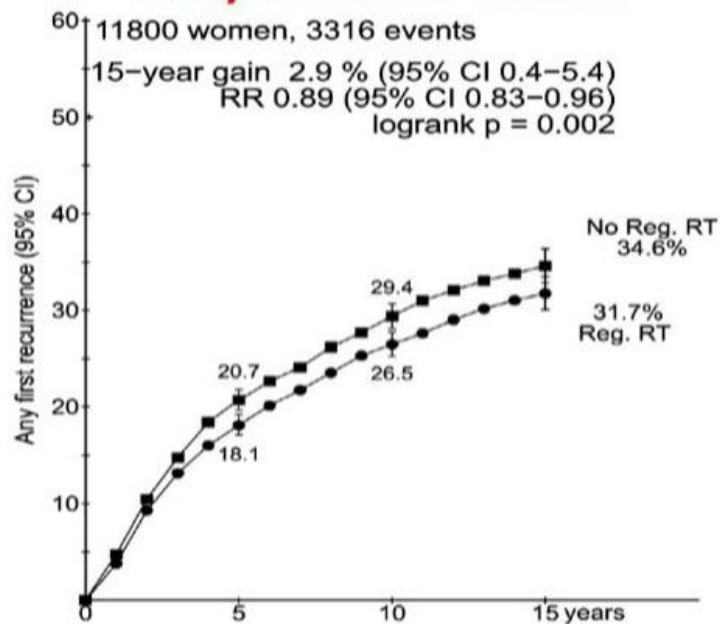
Newer trials <8 Gy

Dodwell, D. et al. General Session Abstracts GS4-02-GS4-02, American Association for Cancer Research, 2019

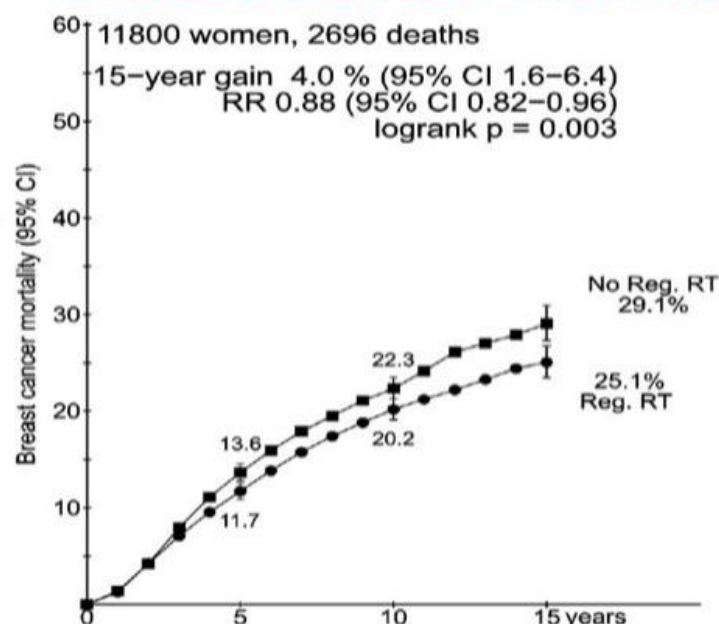
Regional Nodal Irradiation

1. All regional node RT trials

Any recurrence



Breast cancer mortality



15-year Any recurrence

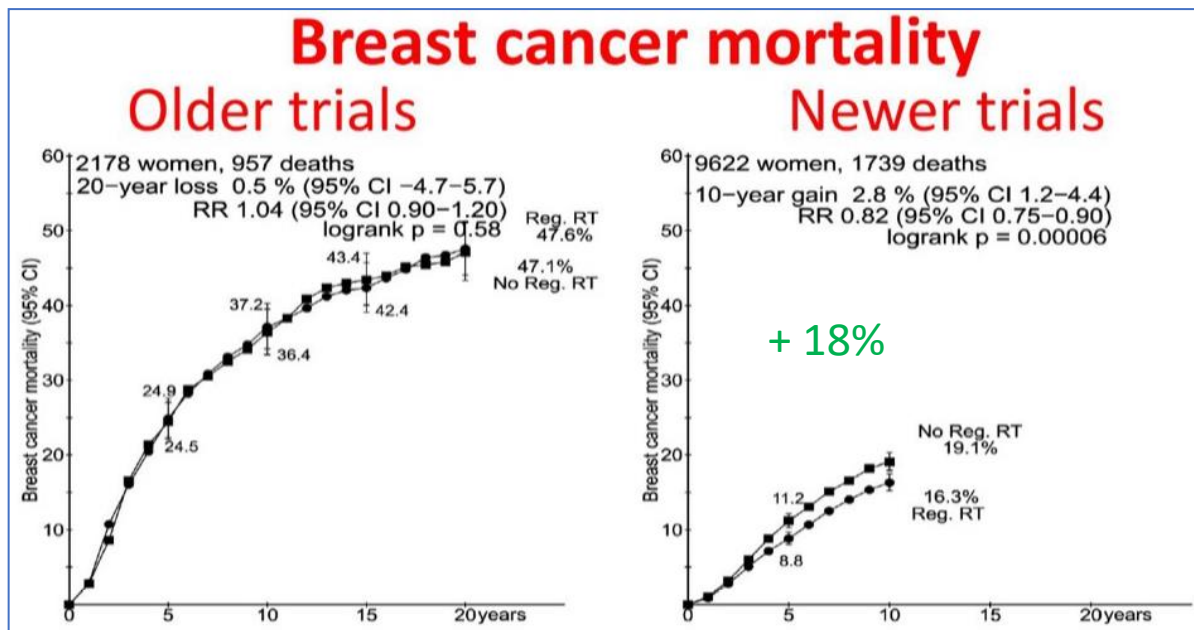
RT vs no RT: 31,7% vs 34,5%
(gain 2.9%)
P = 0.002

15-year Breast cancer mortality

RT vs no RT: 25,1% vs 29,1%
(gain 4%)
P = 0.003

Dodwell, D. et al. General Session Abstracts GS4-02-GS4-02, American Association for Cancer Research, 2019

Regional Nodal Irradiation

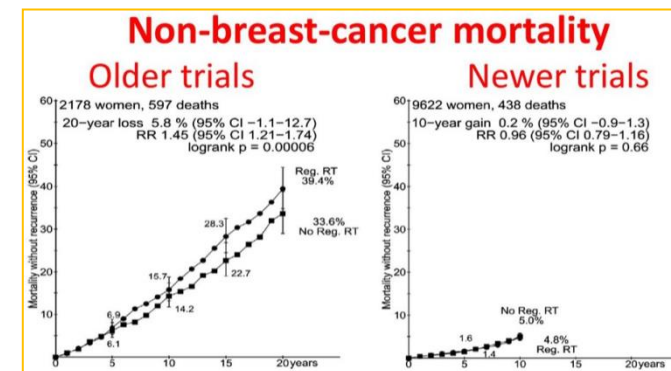


Older trials
 RT vs no RT: 39,4% vs 33,6% (20-year loss 5.8%)
 P = 0.00006

Newer trials
 RT vs no RT: 4,8% vs 5% (10 year-gain 0.2%)
 P = 0.96

Older trials
 RT vs no RT: 47,6% vs 47,1% (20-year loss 0.5%)
 P = 0.58

Newer trials
 RT vs no RT: 16,3% vs 19,1% (10 year-gain 2.8%)
 P = 0.00006

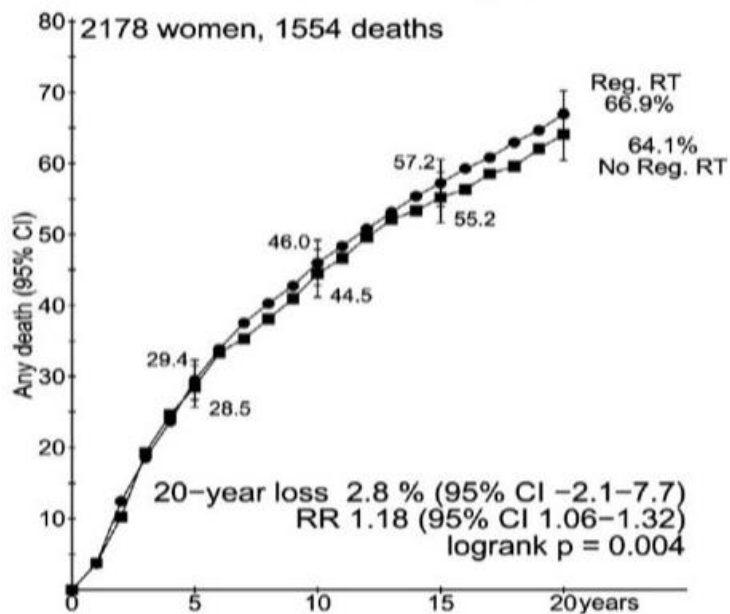


Dodwell, D. et al. General Session Abstracts GS4-02-GS4-02, American Association for Cancer Research, 2019

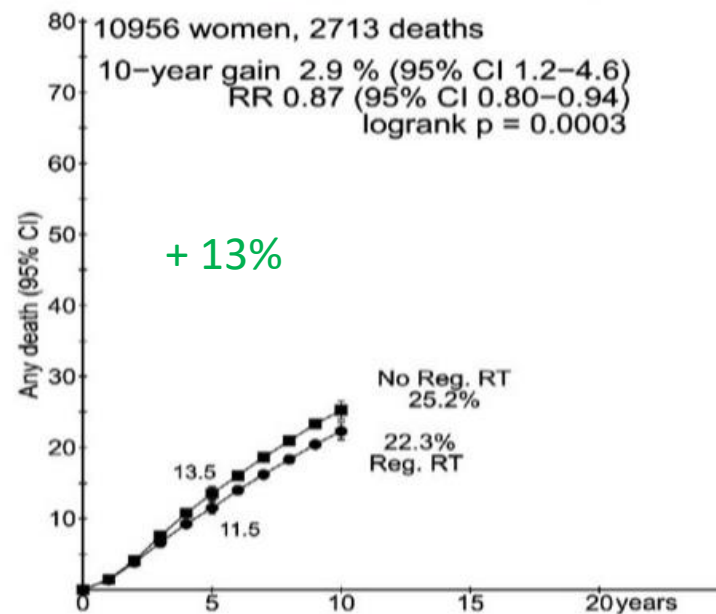
Regional Nodal Irradiation

Overall mortality

Older trials



Newer trials



Older trials

RT vs no RT: 66,9% vs 64,1%
(20-year loss 2.8%)

P = 0.004

Newer trials

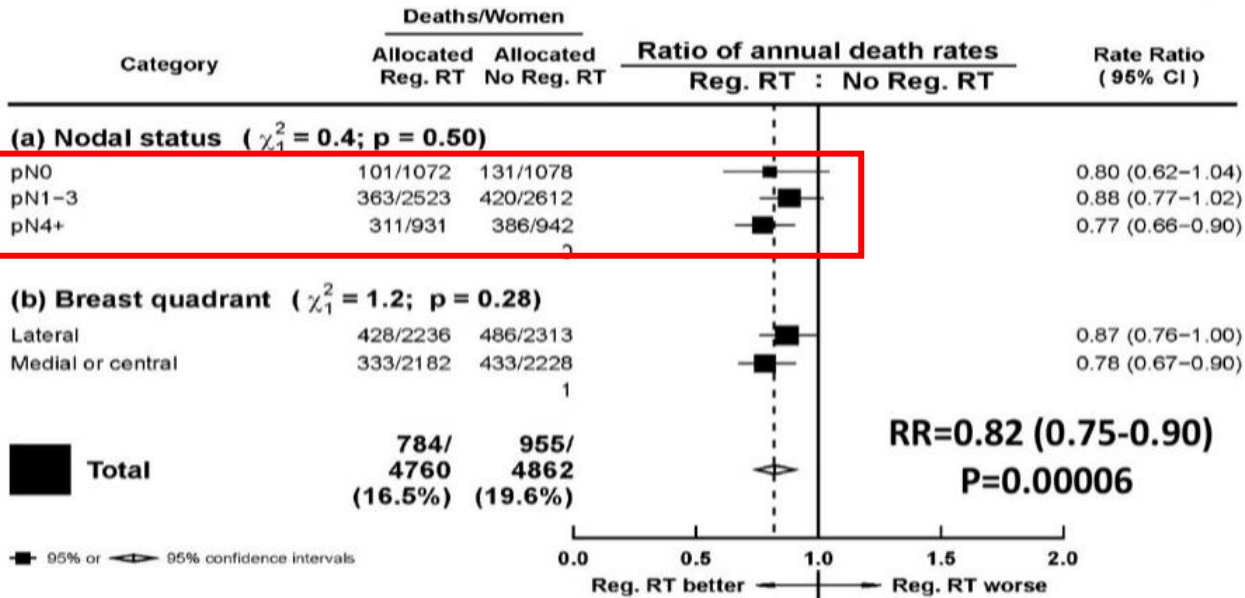
RT vs no RT: 22,3% vs 25,2%
(10 year-gain 2.9%)

P = 0.0003

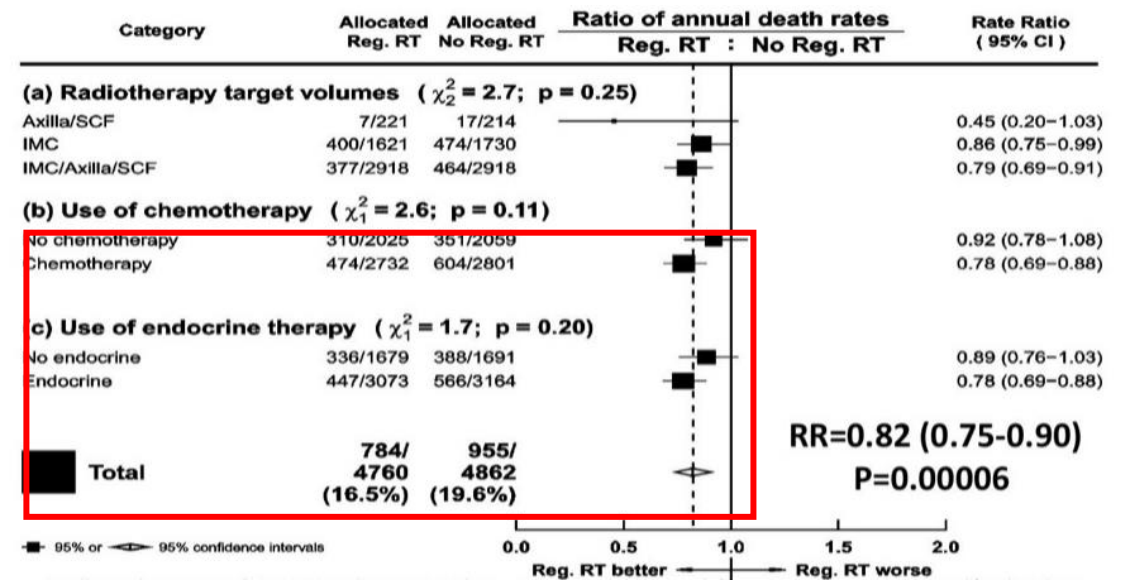
Dodwell, D. et al. General Session Abstracts GS4-02-GS4-02, American Association for Cancer Research, 2019

Regional Nodal Irradiation

Newer trials: Breast cancer mortality



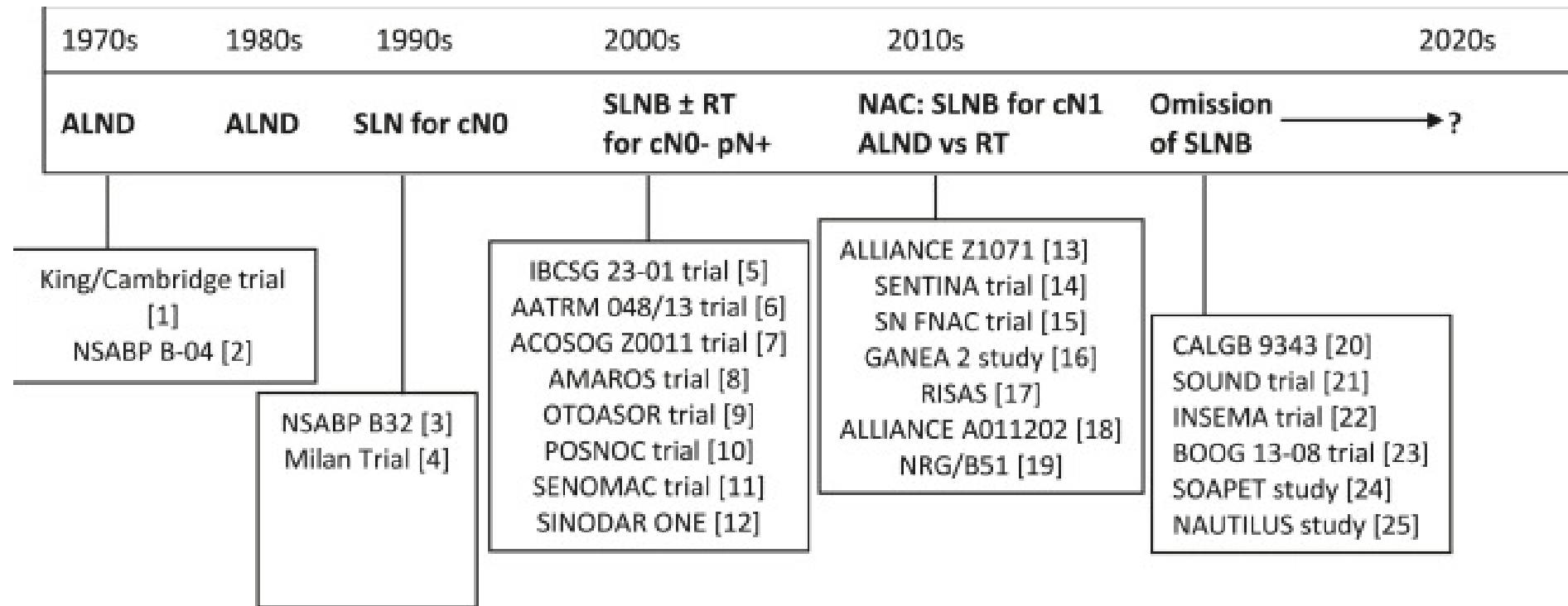
Absolute mortality reduction greatest in patients *underwent systemic therapy*



Absolute mortality reduction greatest in *pN4+*

Dodwell, D. et al. General Session Abstracts GS4-02-GS4-02, American Association for Cancer Research, 2019

Descalation of axillary surgery



ALND=axillary lymph node dissection; NAC, neoadjuvant chemotherapy; RT=radiation therapy;
SLN=sentinel lymph node; SLNB=sentinel lymph node biopsy

Hersch E.H et al. The Breast 2022

RNI after no ALND

Axillary lymph node dissection (ALND)

Omission of ALND in negative sentinel lymph node biopsy

Omission of ALND in positive sentinel lymph node biopsy

Proportion of non-SLN metastases- Axillary Recurrence Rate

Galimberti et al. Lancet Oncol 2018 **13%-2%**

Giuliano et al. JAMA 2017 **27%-N=5**

Bartels et al. JCO 2022 **33%-1.8%**

Savolt et al. EJSO 2017 **38.5%-1.7%**

Tinterri et al. The Breast 2022 **44%-N=1**

RNI after no ALND

IBCSG 23-01

943 SLNB pts

- Tumor T1-T2
- 1 or more micrometastatic SLN with no extracapsular extension

465 assigned to ALND

464 analyzed

469 assigned to no ALND

467 analyzed

5-year DFS: 84.4 vs 87.8 (p=0.16)

HR 0.78 (non inferiority p=0.0042)

10 year DFS: 74.9% vs 76.8% (p=0.24)

HR 0.85 (non inferiority p=0.0024)

Galimberti V. et al. Lancet Oncol 2013

Galimberti V. et al. Lancet Oncol 2018

RNI after no ALND

ACOSOG Z0011

891 pts

- Tumor T1-T2
- 1 or 2 metastatic SLN

445 randomized to ALND

420 analyzed

446 randomized to no ALND

436 analyzed

5-year OS: 91.8% vs 92.5%
10-year OS: 83.6% vs 86.3%

HR 0.87
HR 0.85 (p=0.02 non-inferiority)

5-year DFS: 82.2% vs 83.9%
10-year DFS: 78.2% vs 80.2%

HR 0.88
HR 0.85 (p=0.32)

Giuliano AE. et al. JAMA 2011
Giuliano AE. et al. JAMA 2017

ACOSOG Z0011

Main issues

Study design and endpoints

Primary end point: Overall survival
Non inferiority if the hazard ratio (HR) < 1.3

Survival difference of *up to 30%* more would be accepted

QA

115 sites enrolling pts May 1999 - Dec 2004

1.4 pts per site per year

- volume of breast cancer pts treated at these sites
- allowing a selected group of patients with better prognostic factors to be recruited

Underpowered

*Failure to achieve target accrual
(856/1900 pts)*

Lower statistical power at around 35%

166/856 (19.4%) lost to FUP

DMSC: “These developments may have impaired the ability of trial Z0011 to fulfil its primary objective”

ACOSOG Z0011

Main issues: Patients

Inclusion of ineligible patients

- 287 registered pre-SLND
- Pts ≥ 3 N+ included in the analysis (3.7% of patients in the SLNB arm)
- “Ineligible patients were included in the analyses” 103/856 pts (11.6%) (paper does not provide a description of the reasons why)

Imbalance favoring the SLND group

Characteristic	No. (%)	
	ALND (n = 420)	SLND Alone (n = 436)
Lymph node metastases		
0	4 (1.2)	29 (7.0)
1	199 (58.0)	295 (71.1)
2	68 (19.8)	76 (18.3)
3	25 (7.3)	11 (2.7)
≥ 4	47 (13.7)	4 (1.0)
Missing	77	21
LVI		
Yes	129 (40.6)	113 (35.2)
No	189 (59.4)	208 (64.8)
Missing	102	115

41% of patients with ITCs or micrometastases

137/365 (37.5%) in the ALND arm

164/366 (44.8%) in the SLN alone arm

X² value = 3.99 – p = 0.04

ACOSOG Z0011

Protocol violations

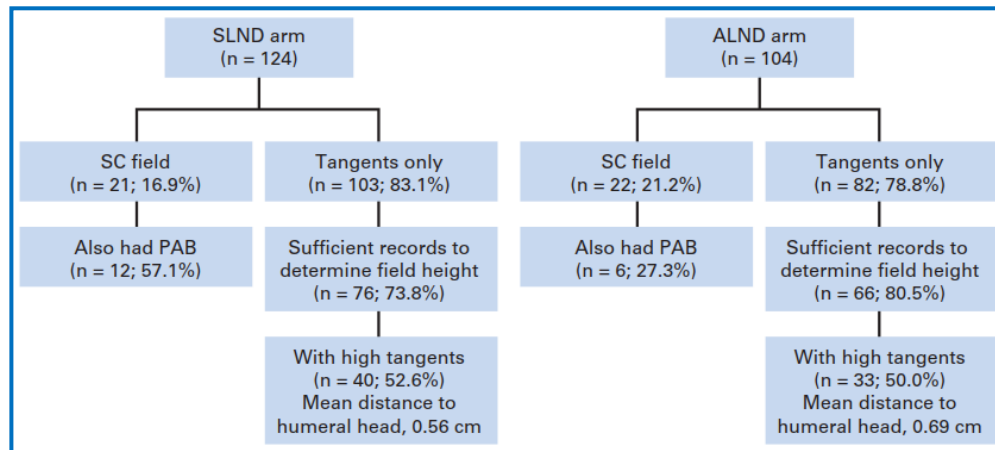
Surgery:

32/420 (7.6%) randomized to ALND had SLN - 11/436 (2.5%) randomized to SLN had ALND

Radiotherapy:

Only 70.7% (605/856) had study case record RT

Detailed RT records only for 228 patients. Only 138 documentation of RT planning



High tangential field

50% ALND arm and 52.6% SLNB arm

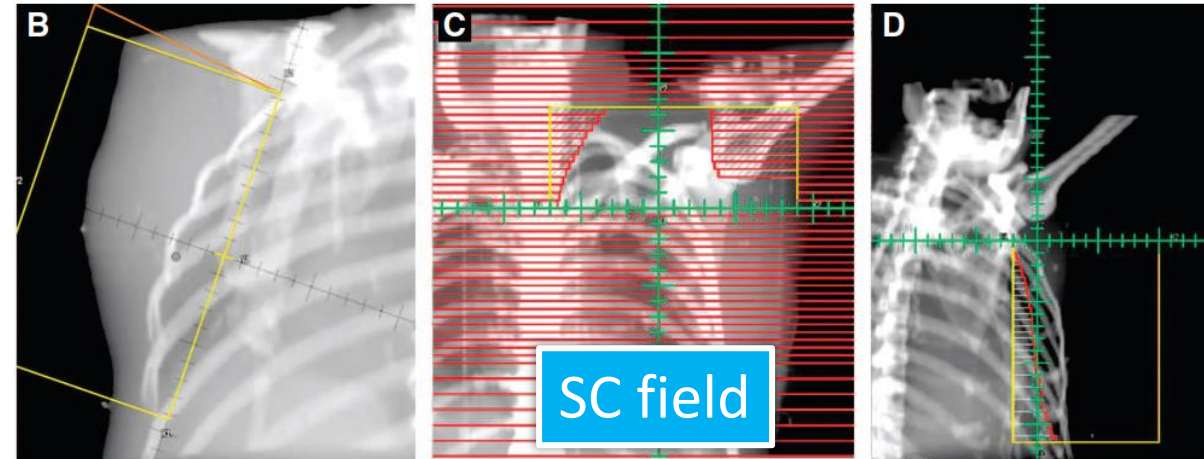
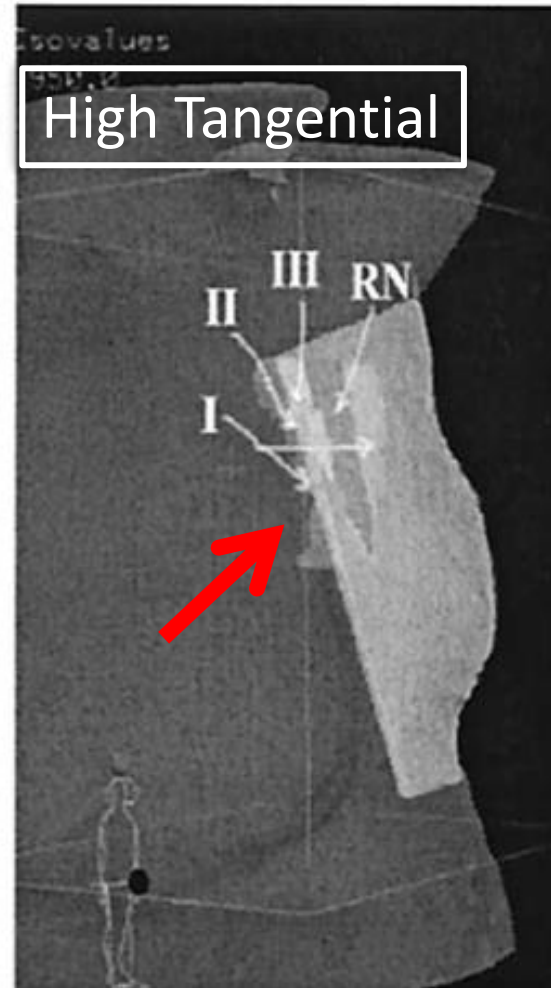
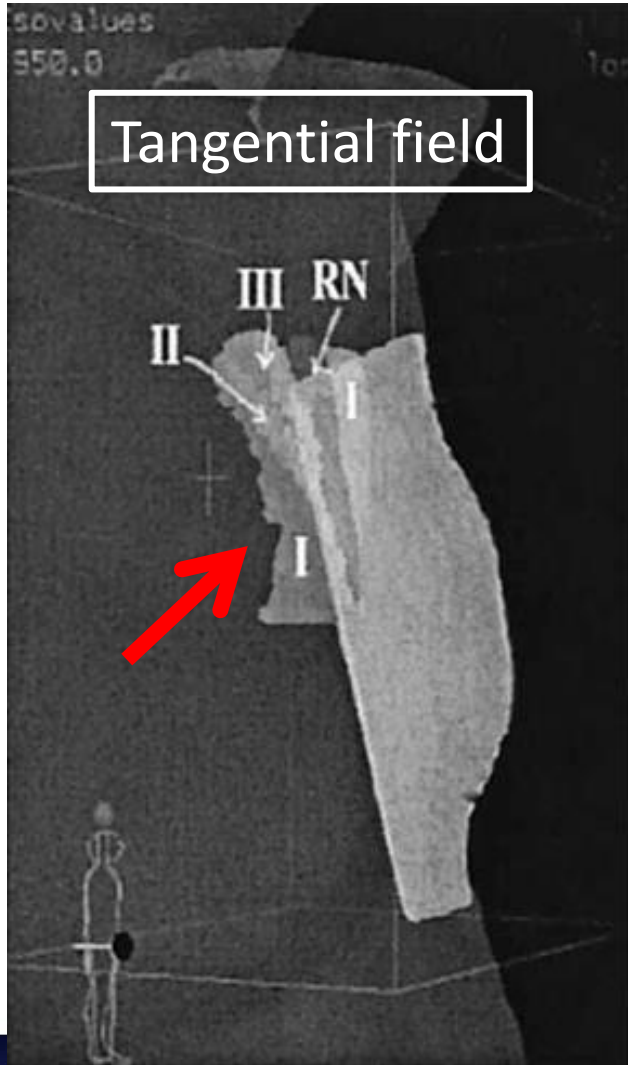
Supraclavicular field

21.2% ALND arm and 16.9% SLNB arm

Pts receiving nodal RT: *greater number of N+* (P < 0.001)

ACOSOG Z0011: The PAST

RT fields



Average dose to Levels I, II, III, and RN :

Tangential fields

66%, 44%, 31%, and 70% of the prescribed dose.

High Tangential fields

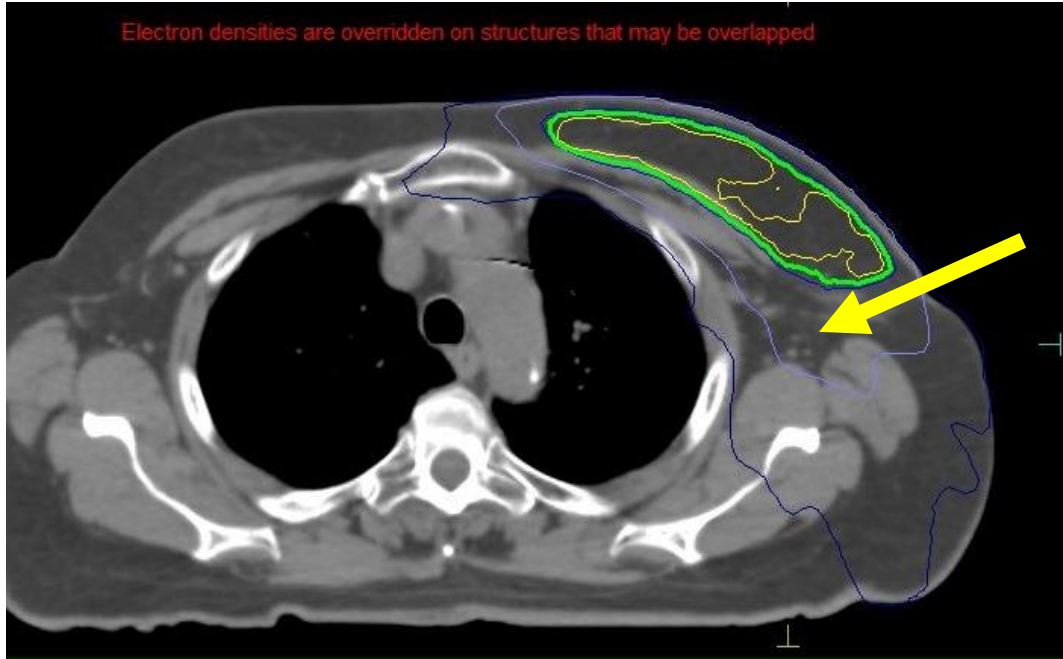
86%, 71%, 73%, and 94% of the prescribed dose

Reznik, et al., *IJROBP* 2005

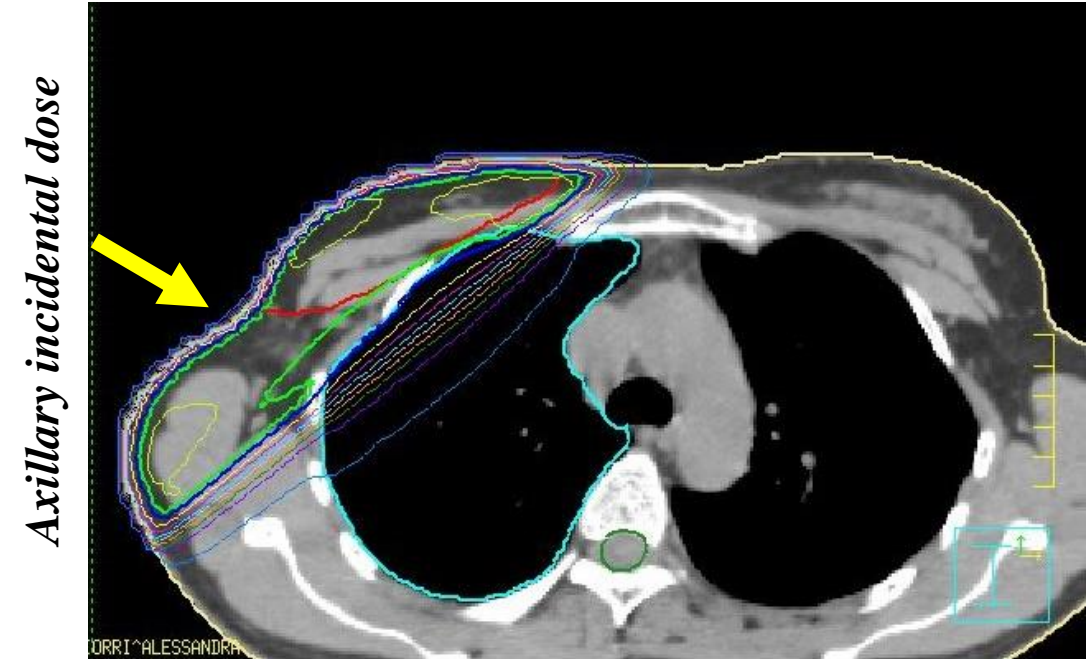
The PRESENT: The Modern Radiotherapy

RT technique

VMAT



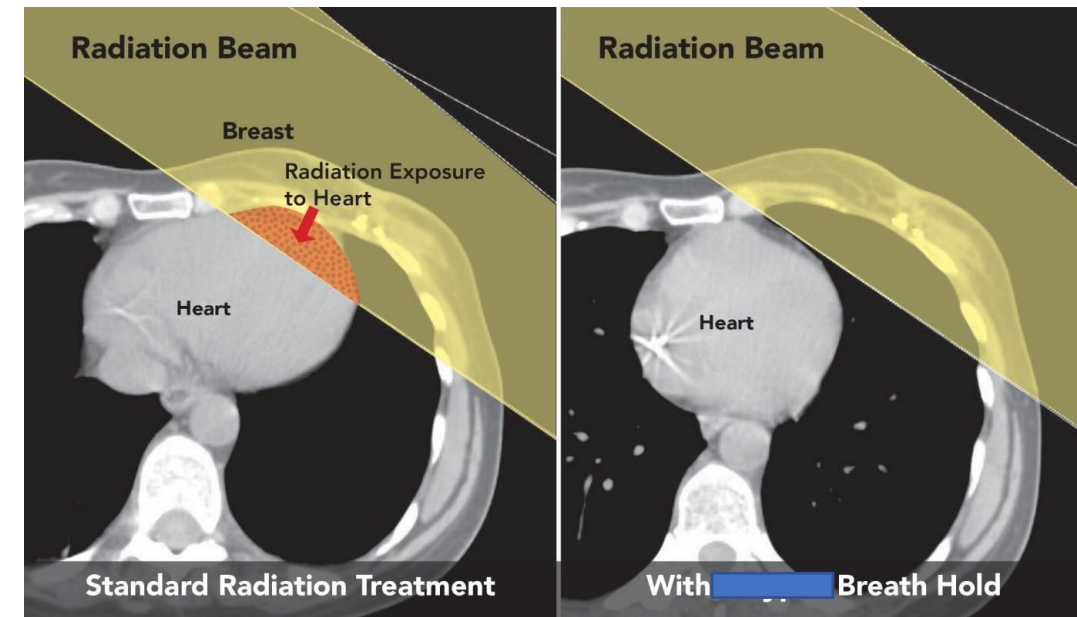
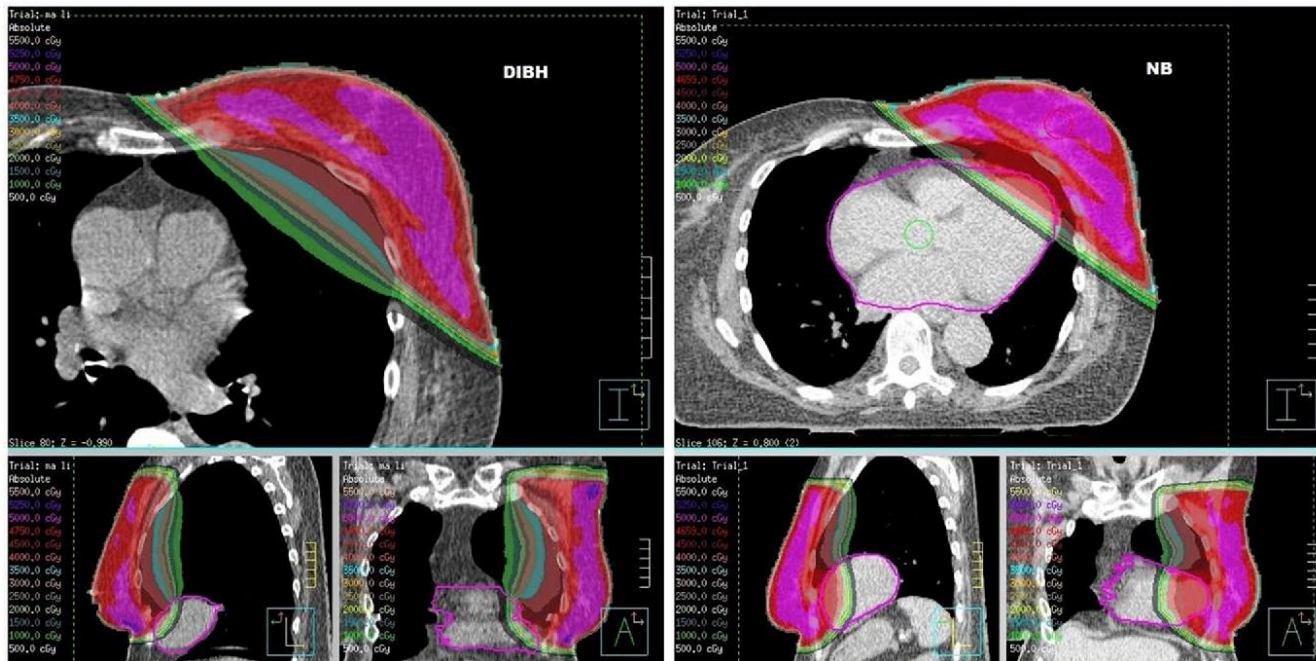
3D-CRT



The PRESENT: The Modern Radiotherapy

RT technique

Deep inspiration breath hold (DIBH)



“... combination of **VMAT and DIBH** ... *reducing heart exposure* for pts treated with locoregional RT of left-sided BC

RNI after no ALND

EORTC 10981-22023 AMAROS

Same axillary control but ALND was associated with a higher lymphedema (24.5 vs 11.9 p<0.001)

4806 pts

- Tumor T1-T2
- No palpable lymphadenopathy

2402 randomized to ALND

744 SLNB + analyzed

2404 randomized to ART

681 SLNB + analyzed

5-year OS: 93.3.% vs 92.5%
10-year OS: 84.6% vs 81.4%

HR 1.17 (p=0.34)

HR 1.17 (p=0.26)

5 year DFS: 86.9.% vs 82.7%
10-year DFS: 75% vs 70.1%

HR 1.18 (p=0.18)

HR 1.19 (p=0.11)

Donker M. et al. Lancet Oncol 2014
Bartels ASL. et al. JCO 2022

RNI after no ALND

- LOBULAR CARCINOMA
- TUMOR BIOLOGY
- MASTECTOMY

Galimberti et al. Lancet Oncol 2018

Giuliano et al. JAMA 2017

Bartels et al. JCO 2022

Savolt et al. EJSO 2017

Tinterri et al. The Breast 2022

RNI after no ALND

Mastectomy

	Number of mastectomies	%
ACOSOG Z0011	0/891	0
IBCSG 23-01	86/934	9.2
AMAROS	248/1425	17.4
OTOASOR	74/474	15.6
SINODAR-ONE	218/879	24.8
Total	626/4603	13.6

Galimberti et al. Lancet Oncol 2018

Giuliano et al. JAMA 2017

Bartels et al. JCO 2022

Savolt et al. EJSO 2017

Tinterri et al. The Breast 2022

RNI after no ALND

LYMPHOADENECTOMY or NOT LYMPHOADENECTOMY?

“ A complete axillary dissection remains standard for women.....in the clinical situations when knowing the extent of axillary involvement would affect systemic or radiation recommendations”

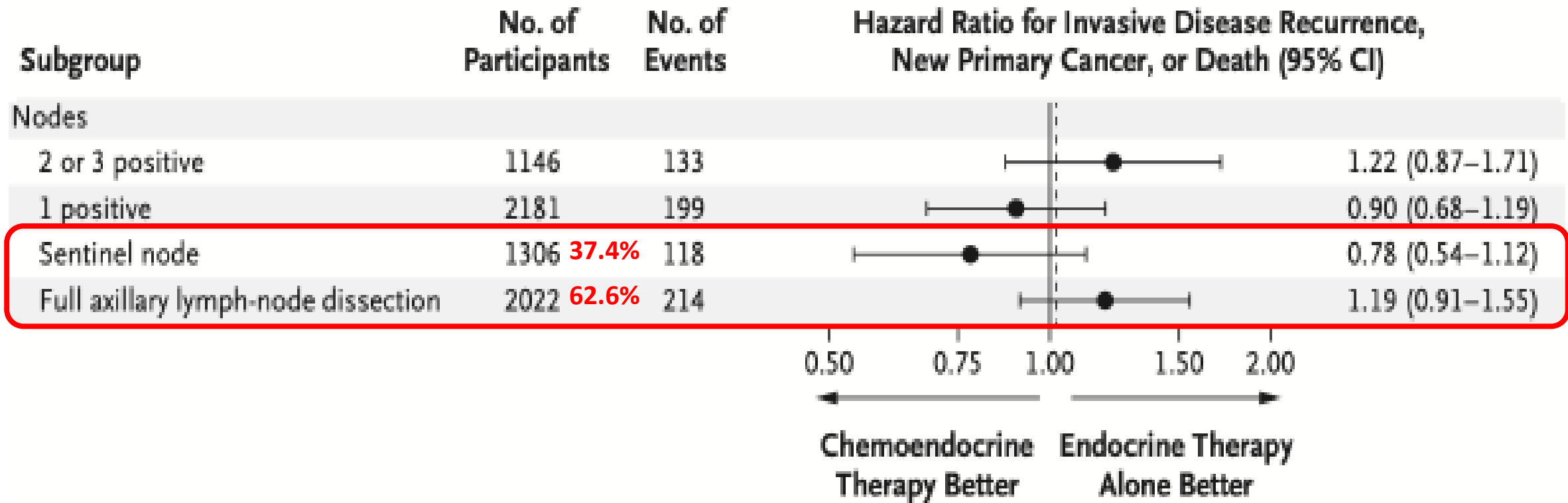
RNI after no ALND

LYMPHOADENECTOMY or NOT LYMPHOADENECTOMY?

- Many radiotherapy guidelines use the number of lymph node metastases as cut-off
 - Intensified radiotherapy and systemic treatment in high risk breast cancer
 - Recent systemic treatment trials require distinction pN1/pN2 ; ALND is necessary to quantify the exact number of positive nodes to appropriately tailor systemic therapy recommendations.
1. RxPonder
 2. MonarchE

RxPONDER Trial (Postmenopausal Cohort)

Outcomes According to Axillary Surgery and Nodal Involvement



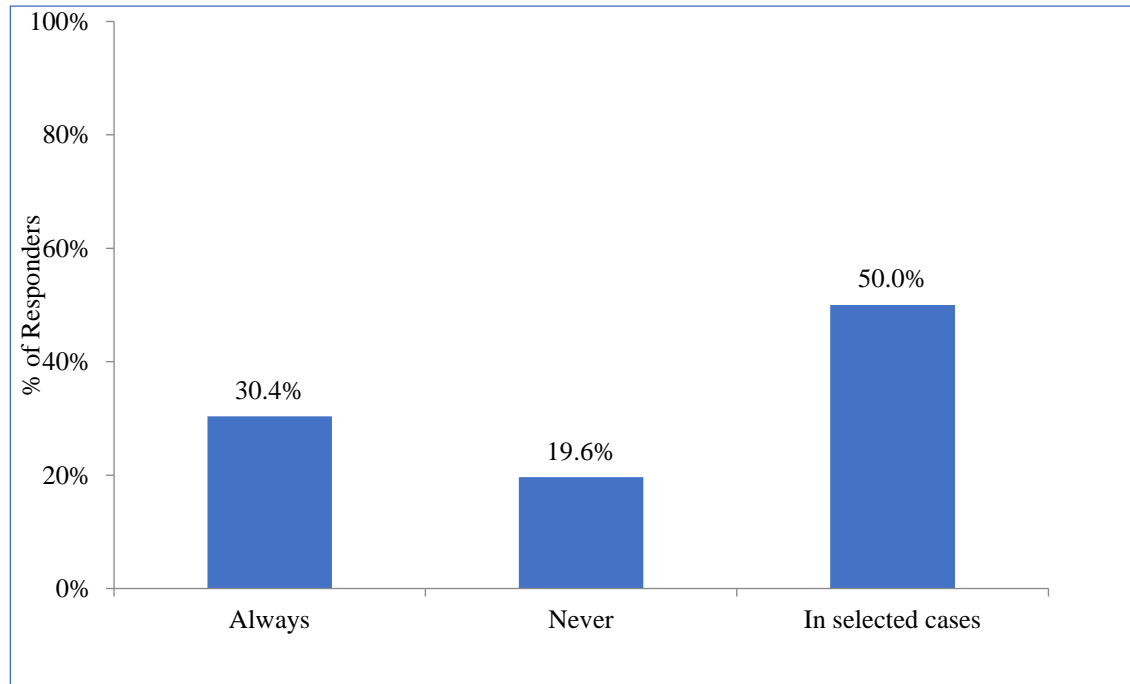
RNI after no ALND

LYMPHOADENECTOMY or NOT LYMPHOADENECTOMY?

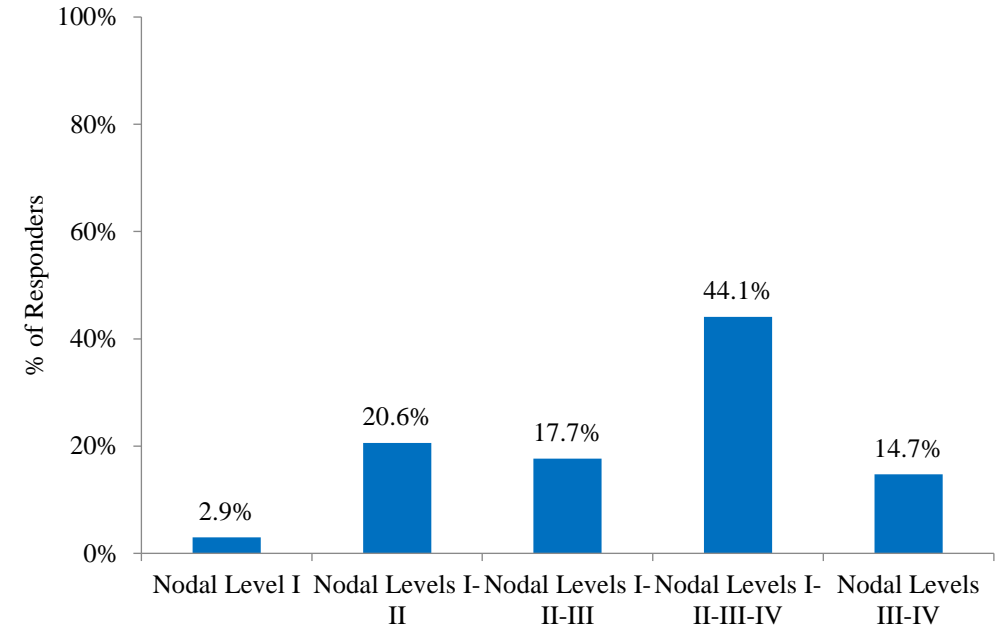
- Axillary Lymph node dissection is no routine staging procedure in the era of biology-driven treatment individualisation????

RNI after no ALND

Regional Nodal Irradiation in patients who did not undergo ALND



Target volume for Regional Nodal Irradiation

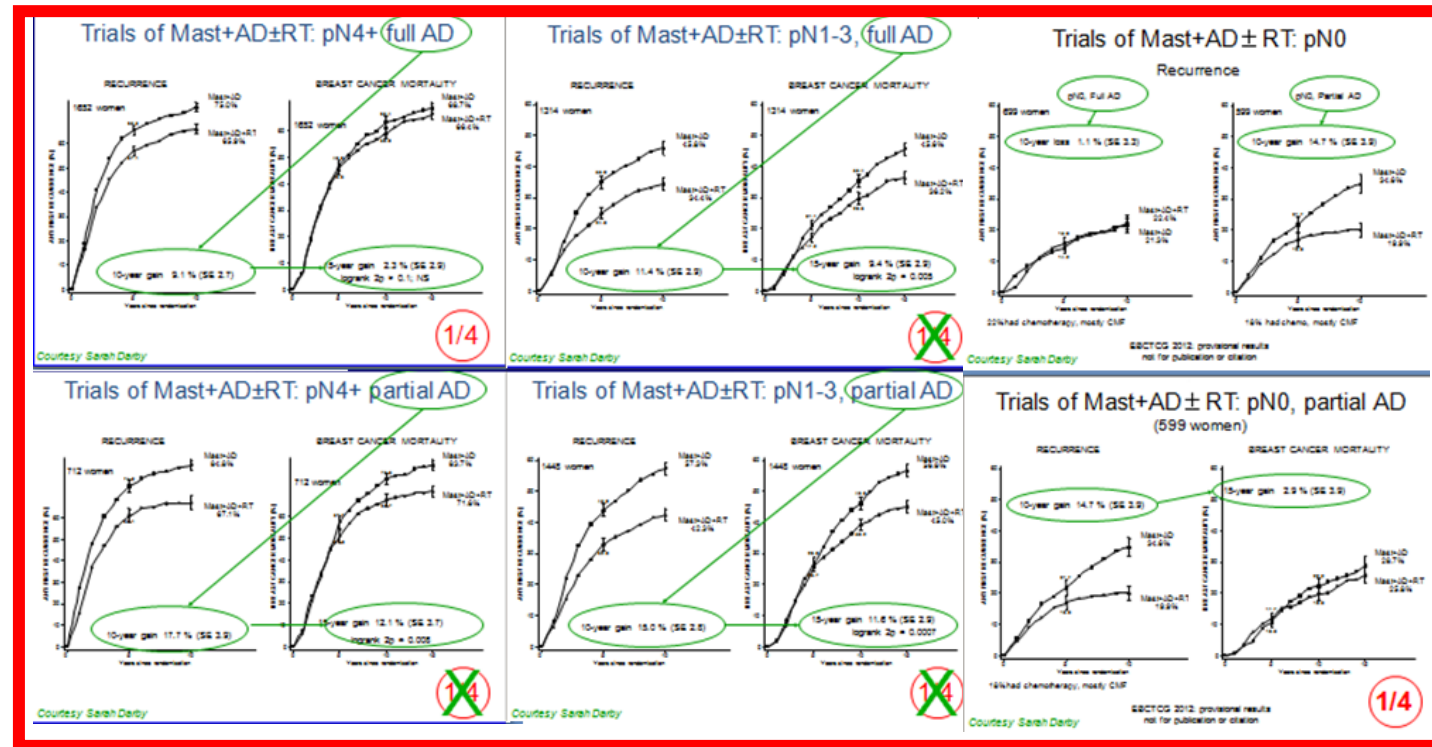


Data submitted

So.....At The END!!!

Trials of Radiotherapy after Mastectomy and Axillary Dissection (Mast+AD±RT)

Full axillary dissection: Individual level info: 10+ nodes removed;
 Trial level info: ≥ Level I & II dissection or median # of node removed ≥10

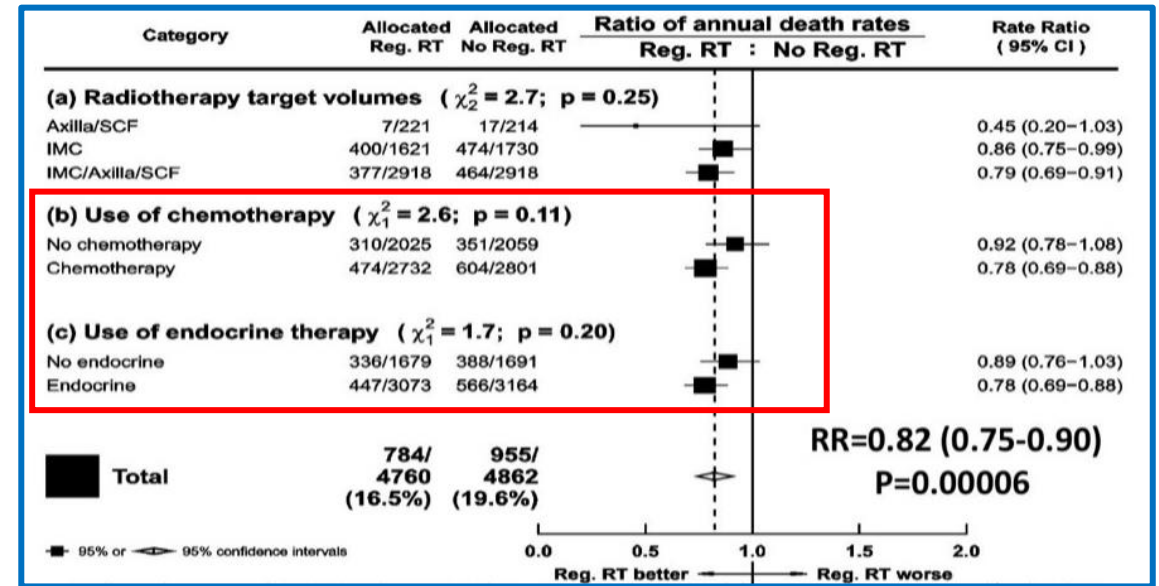
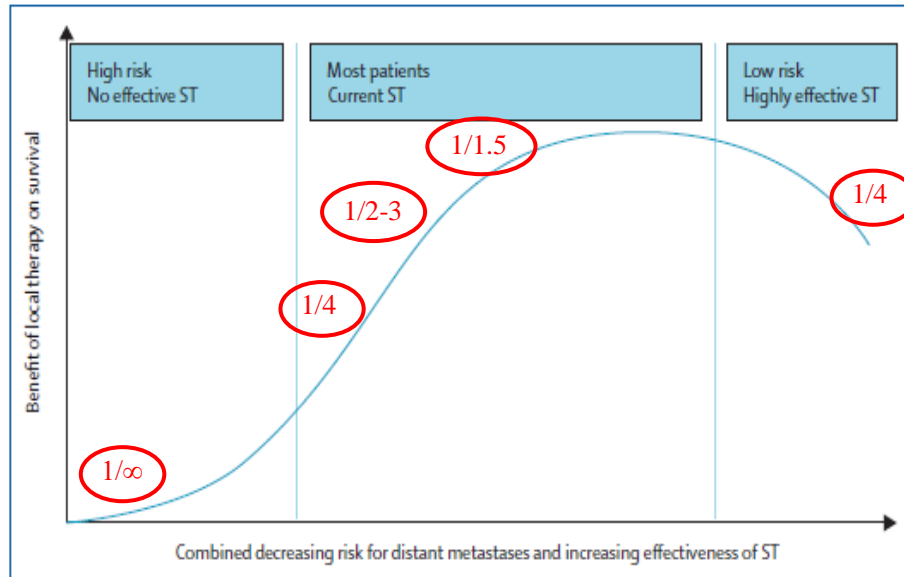


Riduzione mortalità e Recidiva 1/4 → 1/ 2-3 → 1/1,5

Courtesy of P. Poortmans : March 2014

So.....At The END!!!

RT and systemic therapy



Improvement of systemic therapy will decrease the risk of death due to distant metastasis, after which the importance of optimised locoregional control will, relatively, contribute more to survival

GRAZIE PER L'ATTENZIONE

