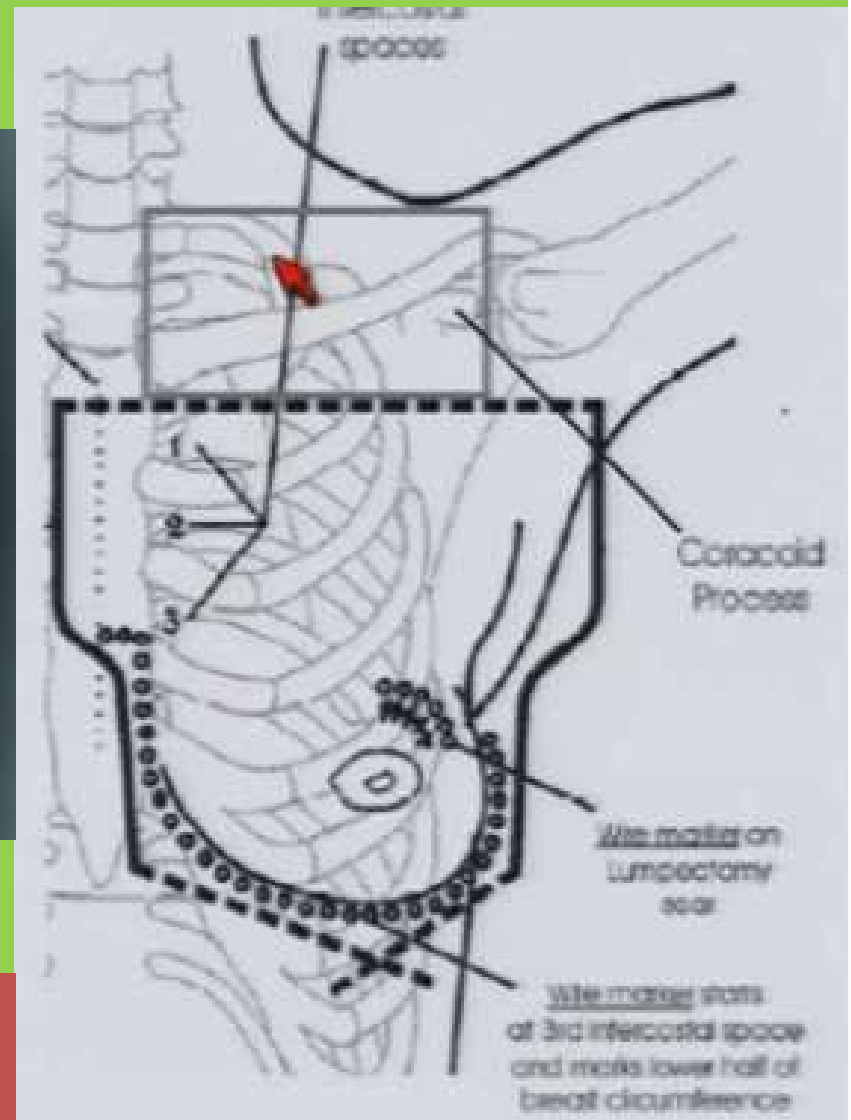


# Radiotherapy of Breast Cancer

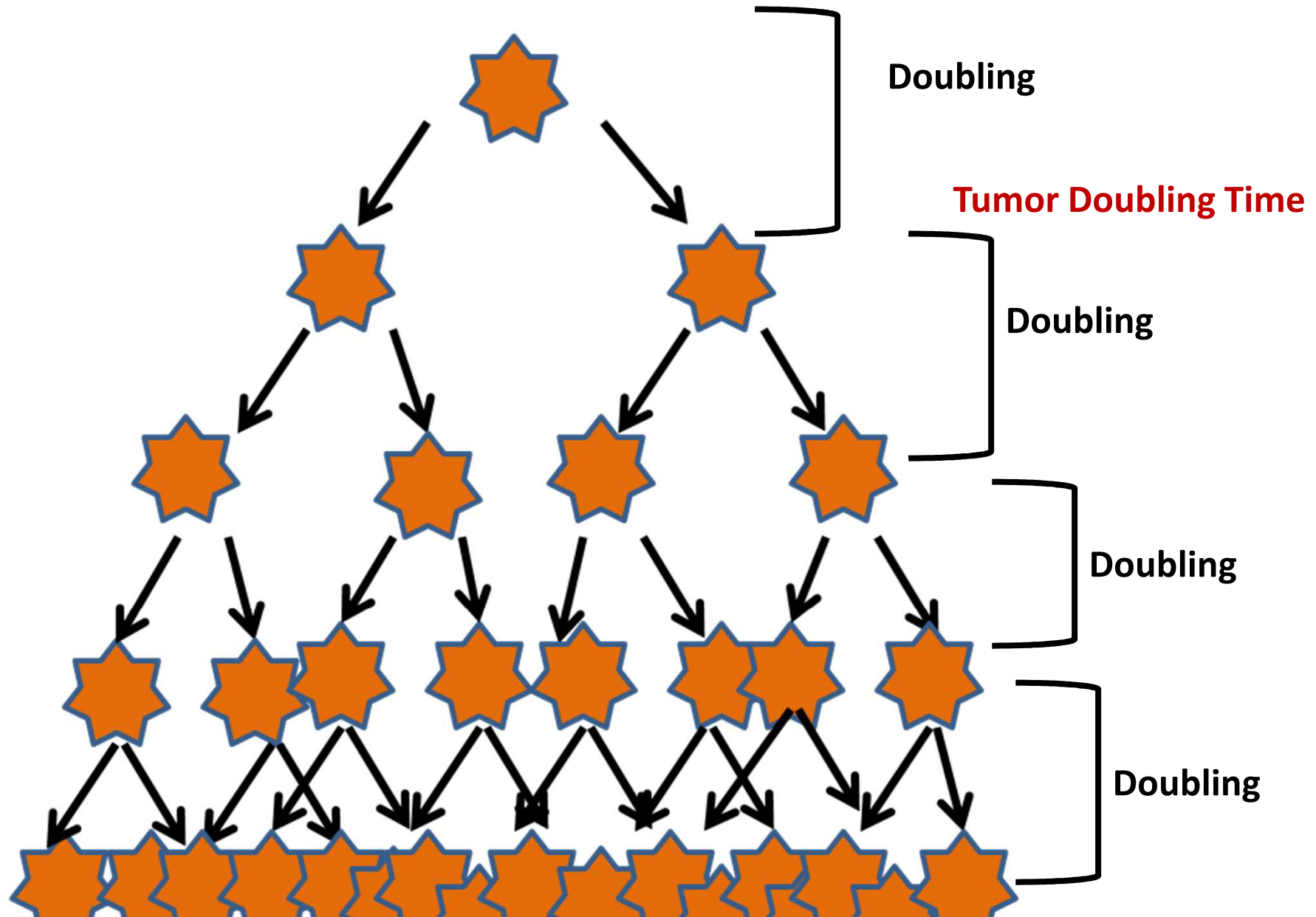
## Overview and Take Home Messages



Dr Manoj Gupta,  
Prof & Head  
AIIMS, Rishikesh.

ICRO Puducherry  
5<sup>th</sup> August, 2017

# Tumor Biology



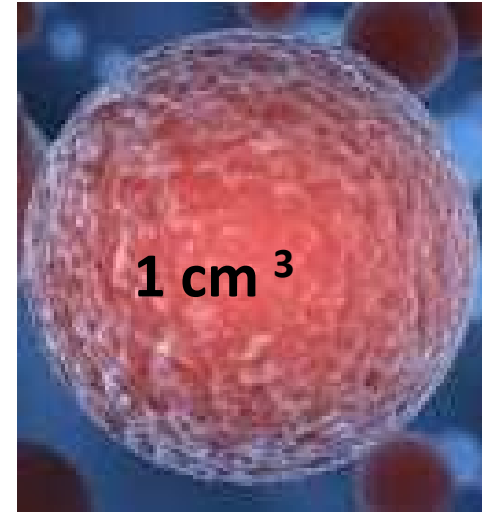


**30 Doublings**

Median Tumor Doubling Time 100 days



$$30 \times 100 = 3000 \text{ days} = 8 \text{ years}$$



1. Primary Gross
2. Microscopic Distant Metastasis

**Source of Distant Metastasis**

**Persistent Primary Disease**

**Surgery and RT**



**Microscopic Met**

**Systemic Therapy**

# Recurrence Risk

- **Positive Axillary Nodes**

- ↑ with more LN involvement
- 1-3 LN+: 5-15% at 10yrs
- $\geq 4$  LN+: 15-50%
- Ratio of LN+ ( $>20\%$ ) = LRR  $>20\%$

- **Tumour Size**

Increases with Size

# Recurrence Risk

- **High Risk Features**

- **Grade III Tumors**

- **LVS1**

- **TNBC**

- **ER/PR Negative Tumours**

# Where are the recurrences?

- >50% chest wall (mastectomy scar/skin)
- 20-40% supraclav or infraclavicular
- <5% post ALND (I/II)
- Internal mammary LN
  - 1/3 path involvement in high risk
  - Few clinical recurrences

# Indication of PMRT

- **Definitive**

- Tm size >5cm
- 4 or >4 axillary nodes metastasis
- Positive Surgical Margins
- Pectoralis muscle involvement

- **Debatable**

- 1 to 3 axillary nodes metastasis
- 2 to 5 cm primary tumor



**Early Breast Cancer**



# **Evidences**

- **Controlled Randomized Trials.**
- **Meta analysis**

**82 b Premenopausal Women  
T1 & T2 (85%)  
1-3 +ve Node (62%)**

The New England  
Journal of Medicine

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VOLUME 337

OCTOBER 2, 1997

NUMBER 14



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POSTOPERATIVE RADIOTHERAPY IN HIGH-RISK PREMENOPAUSAL WOMEN  
WITH BREAST CANCER WHO RECEIVE ADJUVANT CHEMOTHERAPY

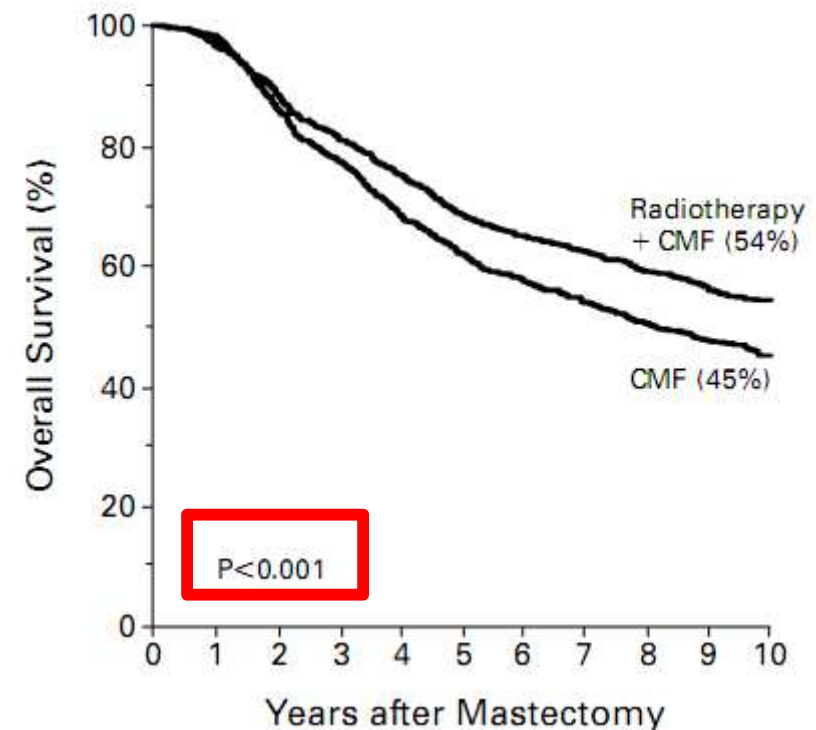
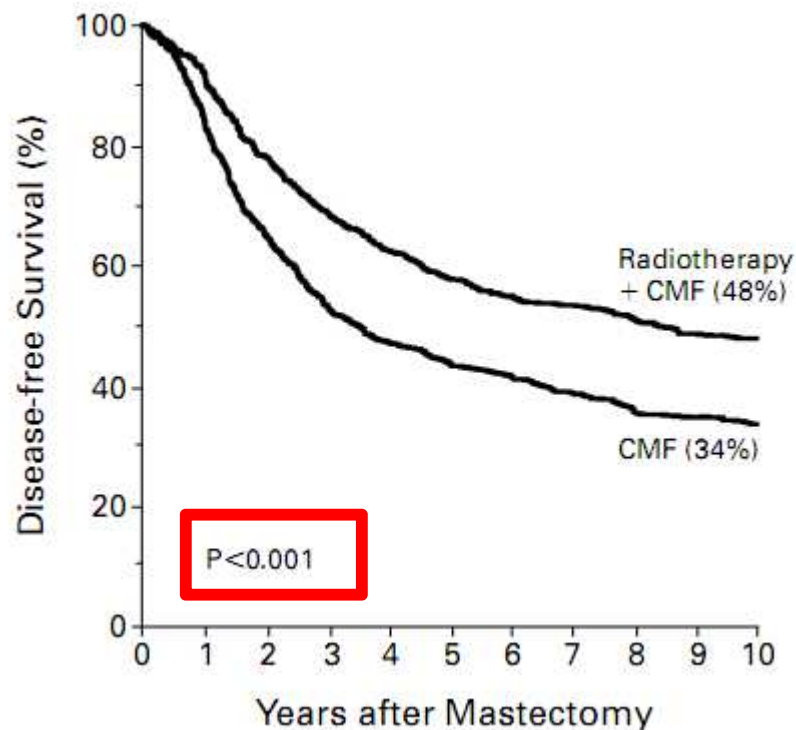
MARIE OVERGAARD, M.D., PER S. HANSEN, M.D., JENS OVERGAARD, M.D., CARSTEN ROSE, M.D.,  
MICHAEL ANDERSSON, M.D., FLEMMING BACH, M.D., MOGENS KJAER, M.D., CARL C. GADEBERG, M.D.,  
HENNING T. MOURIDSEN, M.D., MAJ-BRITT JENSEN, M.Sc., AND KARIN ZEDELER, M.Sc.,  
FOR THE DANISH BREAST CANCER COOPERATIVE GROUP 82b TRIAL

# Danish 82b Trial

N=1708

CMF + PMRT

CMF



**Disease Free Survival**

**Overall Survival**

**Median Follow Up 10Years**

# 82 b Postmenopausal Women

## T1 & T2 (87%)

### 1-3 +ve Node (58%)

ARTICLES

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#### Articles

## **Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial**

*Marie Overgaard, Maj-Britt Jensen, Jens Overgaard, Per S Hansen, Carsten Rose, Michael Andersson, Claus Kamby, Mogens Kjær, Carl C Gadeberg, Birgitte Bruun Rasmussen, Mogens Blichert-Toft, Henning T Mouridsen*

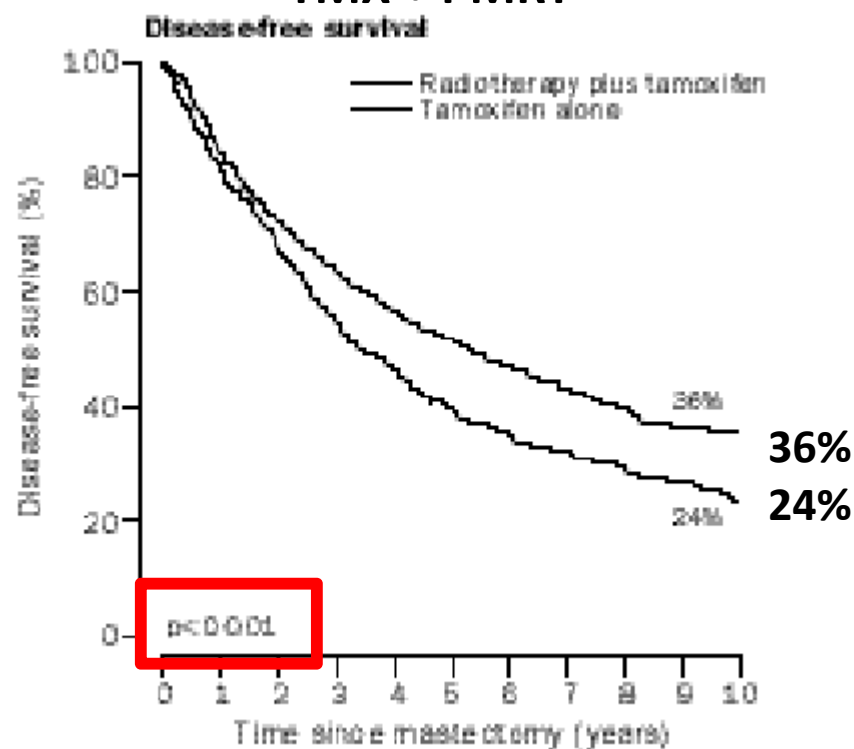
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# Danish 82c Trial

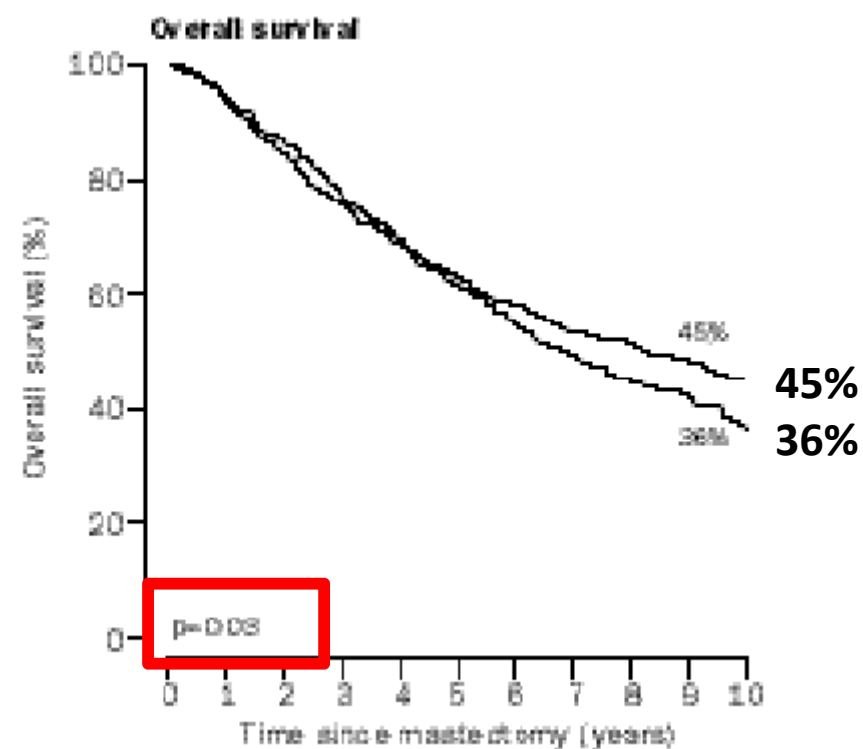
N=1375

TMX + PMRT

TMX



**Disease Free Survival**



**Overall Survival**

**Median Follow Up 10 Years**

# Limitation of these Results

## ECOG: 10 Year Cumulative Incidence of Loco-Regional Failure without XRT

Tumor Size, No. of Nodes	No. of Patients	Isolated LRF	
		%	SE
T1, 1-3	407	9.1	1.5
T2, 1-3	576	7.0	1.1
T3, 1-3	35	22.9	7.2

Danish trial 82b<sup>6</sup>

30

Danish trial 82c<sup>7</sup>

31

Recht et al, JCO, 1999

# Limitation of these Results

## NSABP

	1-3 LN+		
	$\leq 2$	2.1-5	$> 5$
No. of patients	1,045	1,489	229
Isolated LF, %	4.3	7.2	5.2
Isolated RF, %	2.4	3.5	2.3
Isolated LRF, %	6.0	9.7	7.5
LRF with or without DF, %	10.6	15.3	11.4
DF, %	24.6	35.7	40.5

NOTE. Subcolumn headings indicate tumor size (in centimeters).

Abbreviations: LN+, positive lymph nodes; LF, local failure; RF, regional failure; DF, distant failure.

# **Limitation of these Results**

- **Surgery was not adequate specially the axillary dissection as compare to other trials.**
- **Median no of lymph nodes removed**
  - **Danish Trials                      7**



# **Danish Trial 82b & 82c**

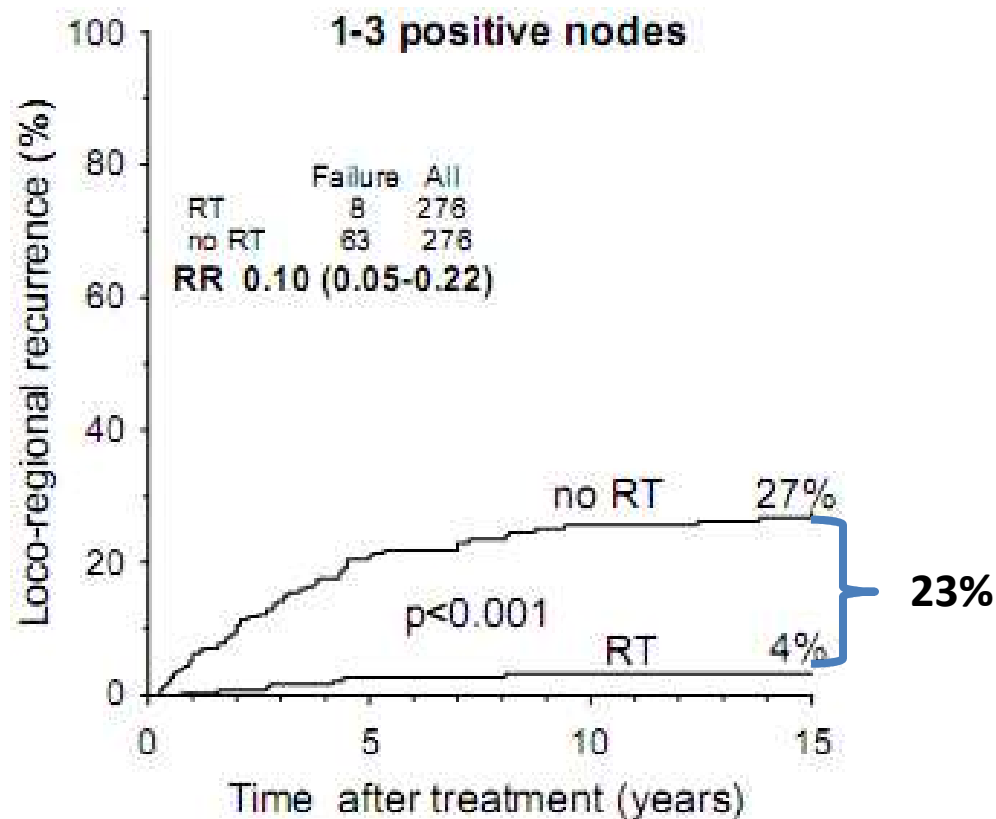
## **Sub-group Analysis**

- **Only select patients with no of nodes removed 8 or more.**
- **Further grouped based on 1-3 nodes or  $\geq 4$  nodes**
- **N=1152**

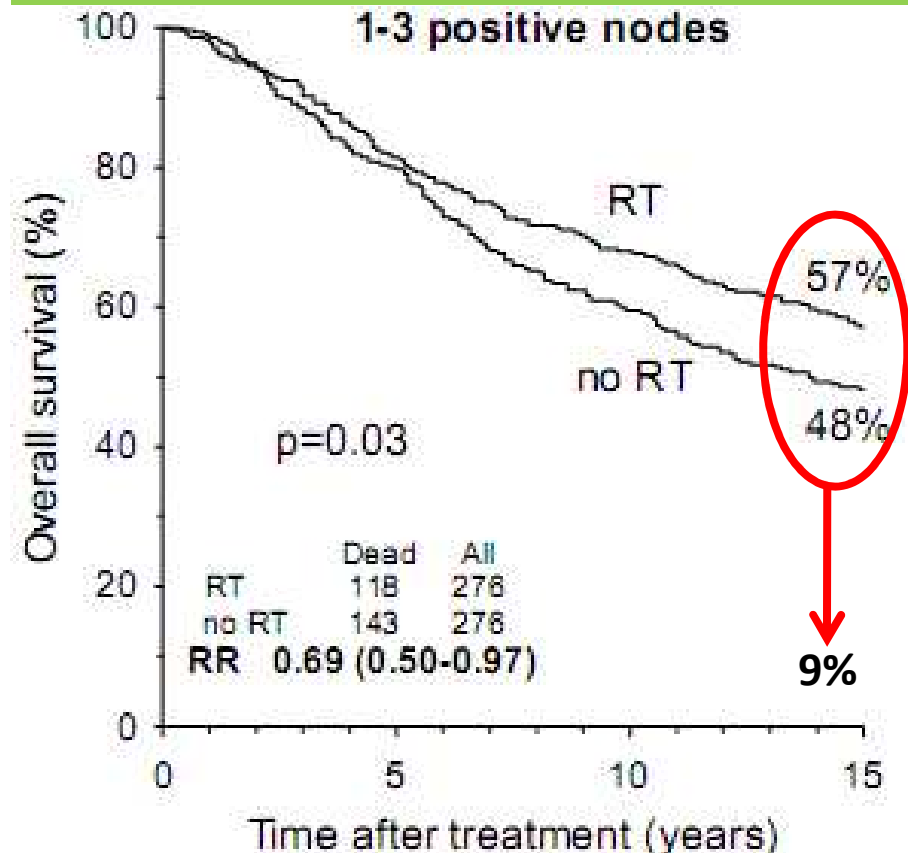
# Danish Trial 82b & 82c

## Sub-group Analysis

### Loco regional Recurrence



### Median Follow Up 15 Years

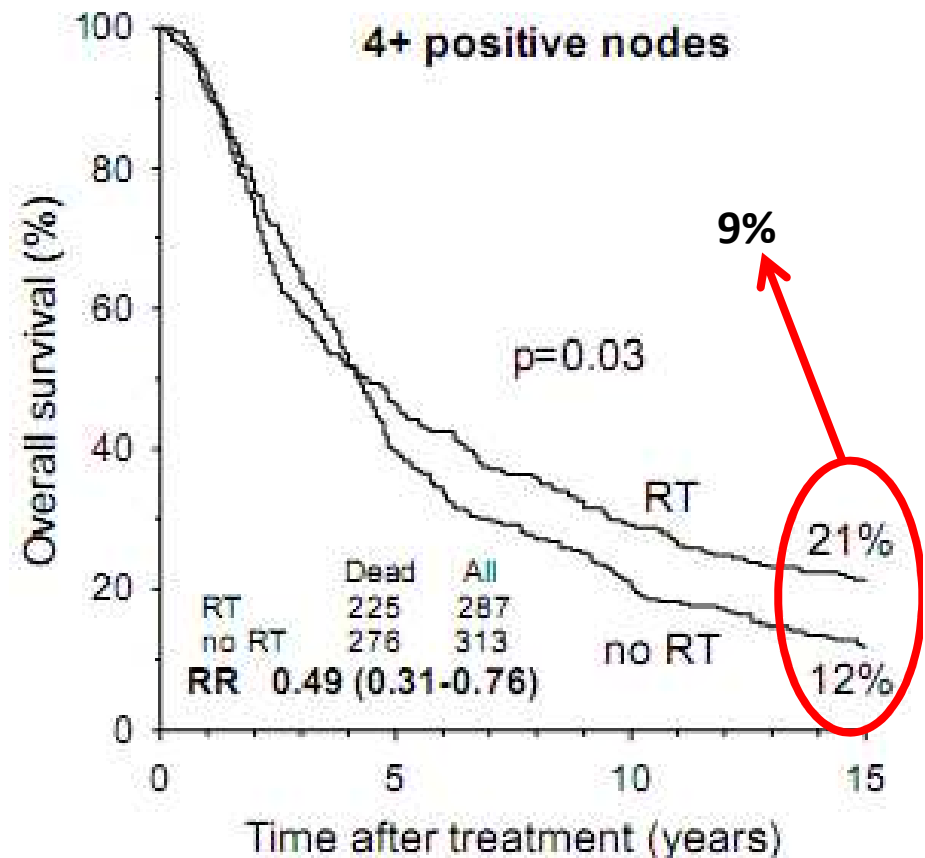
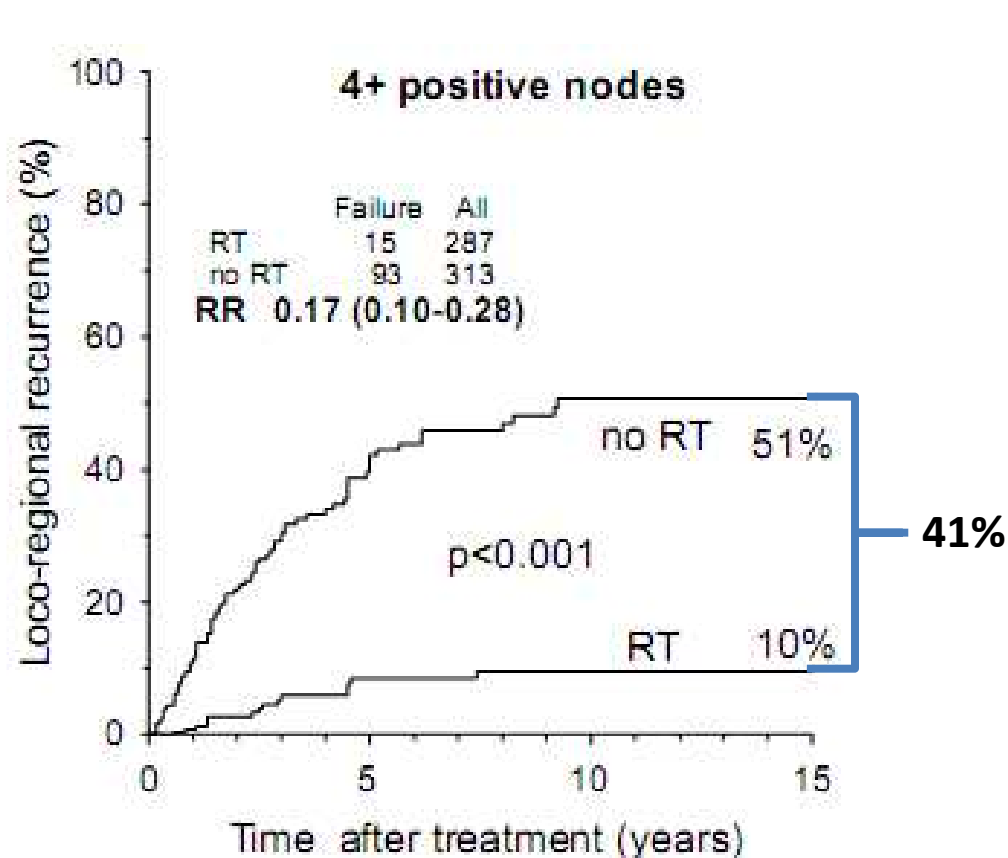


# Danish Trial 82b & 82c

## Sub-group Analysis

Loco regional Recurrence

Median Follow Up 15 Years

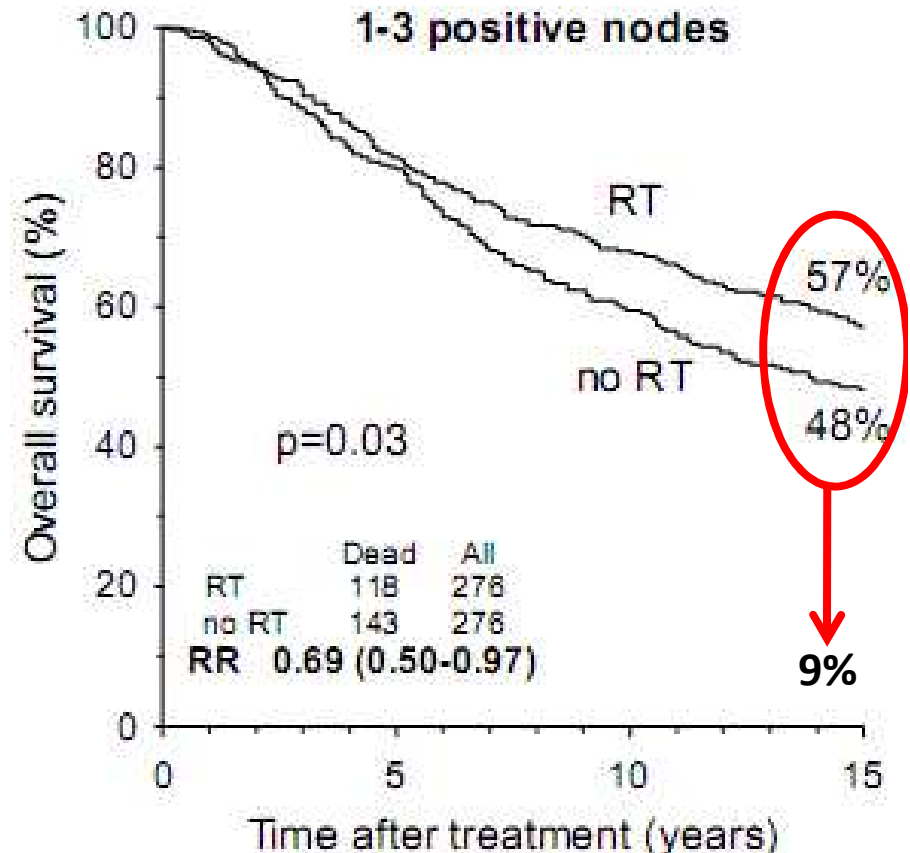
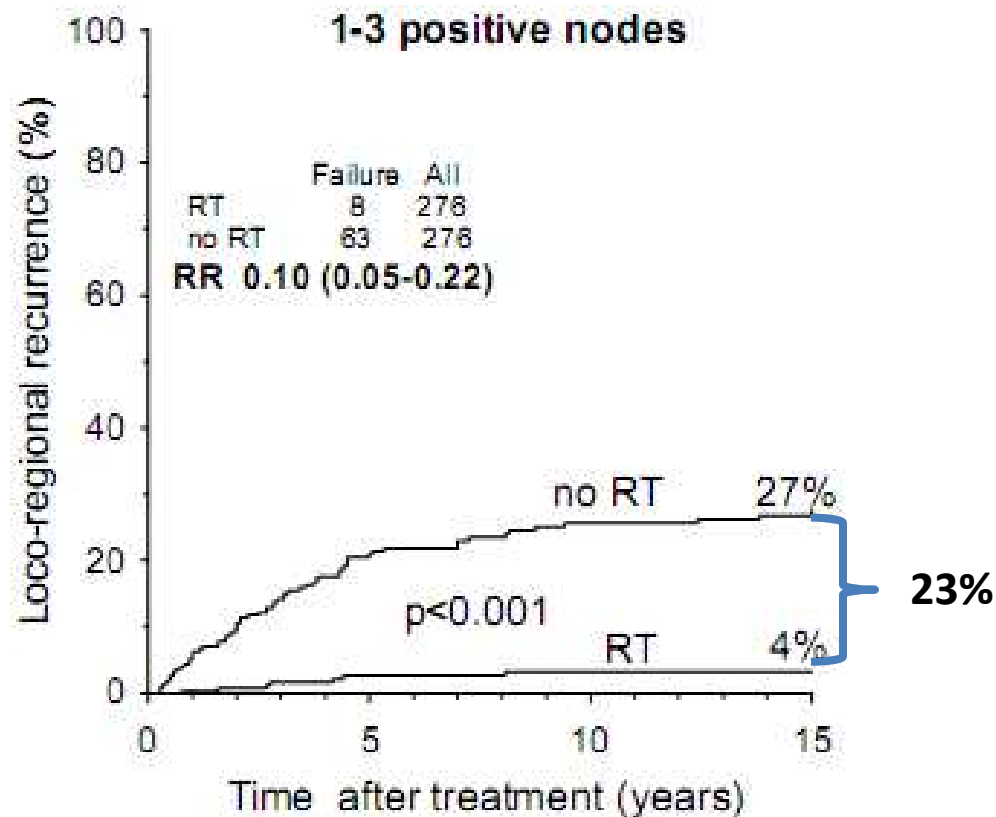


# Danish Trial 82b & 82c

## Sub-group Analysis

Loco regional Recurrence

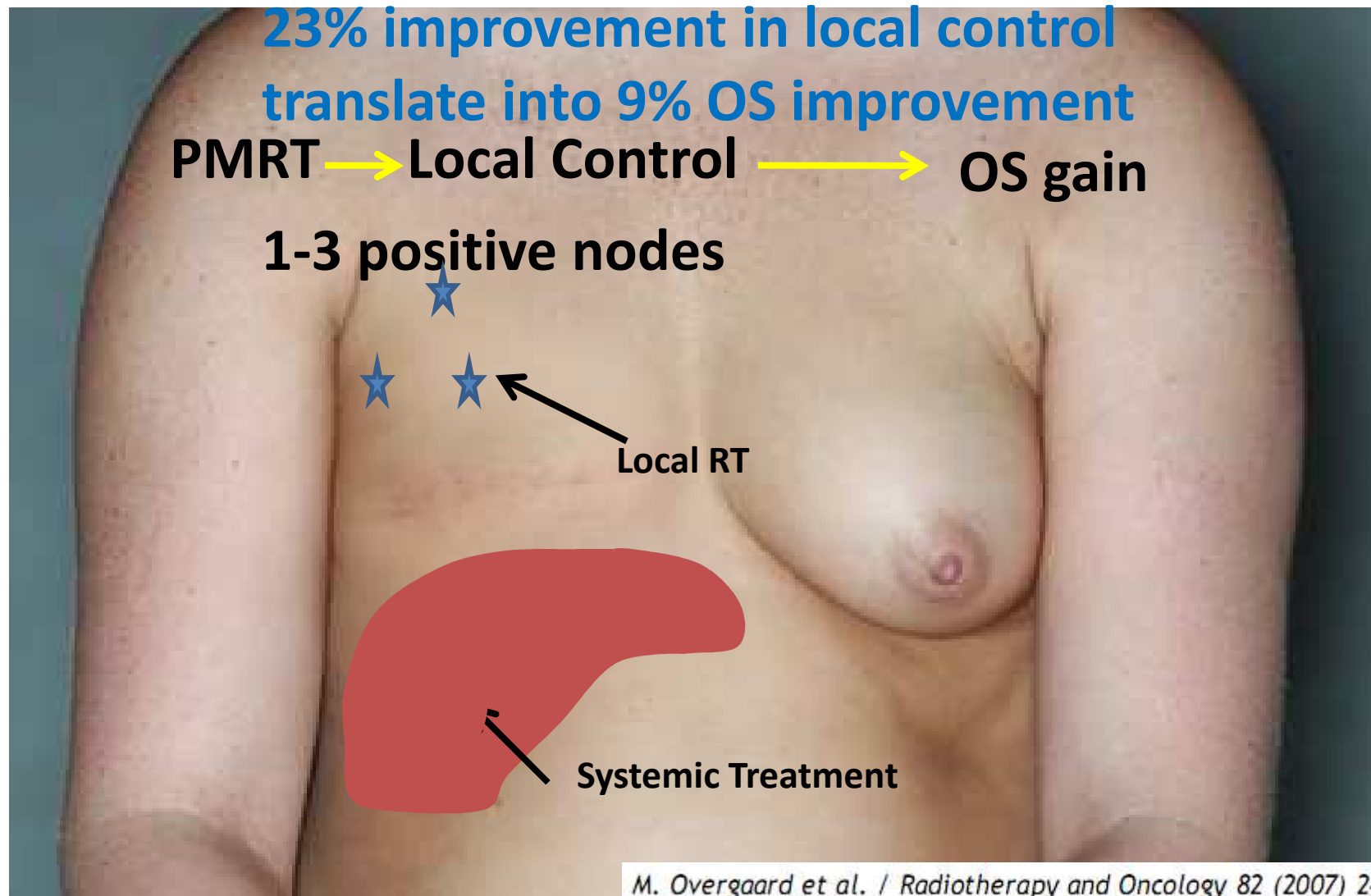
Median Follow Up 15 Years



# Danish Trial 82b & 82c

## Sub-group Analysis (Hypothesis)

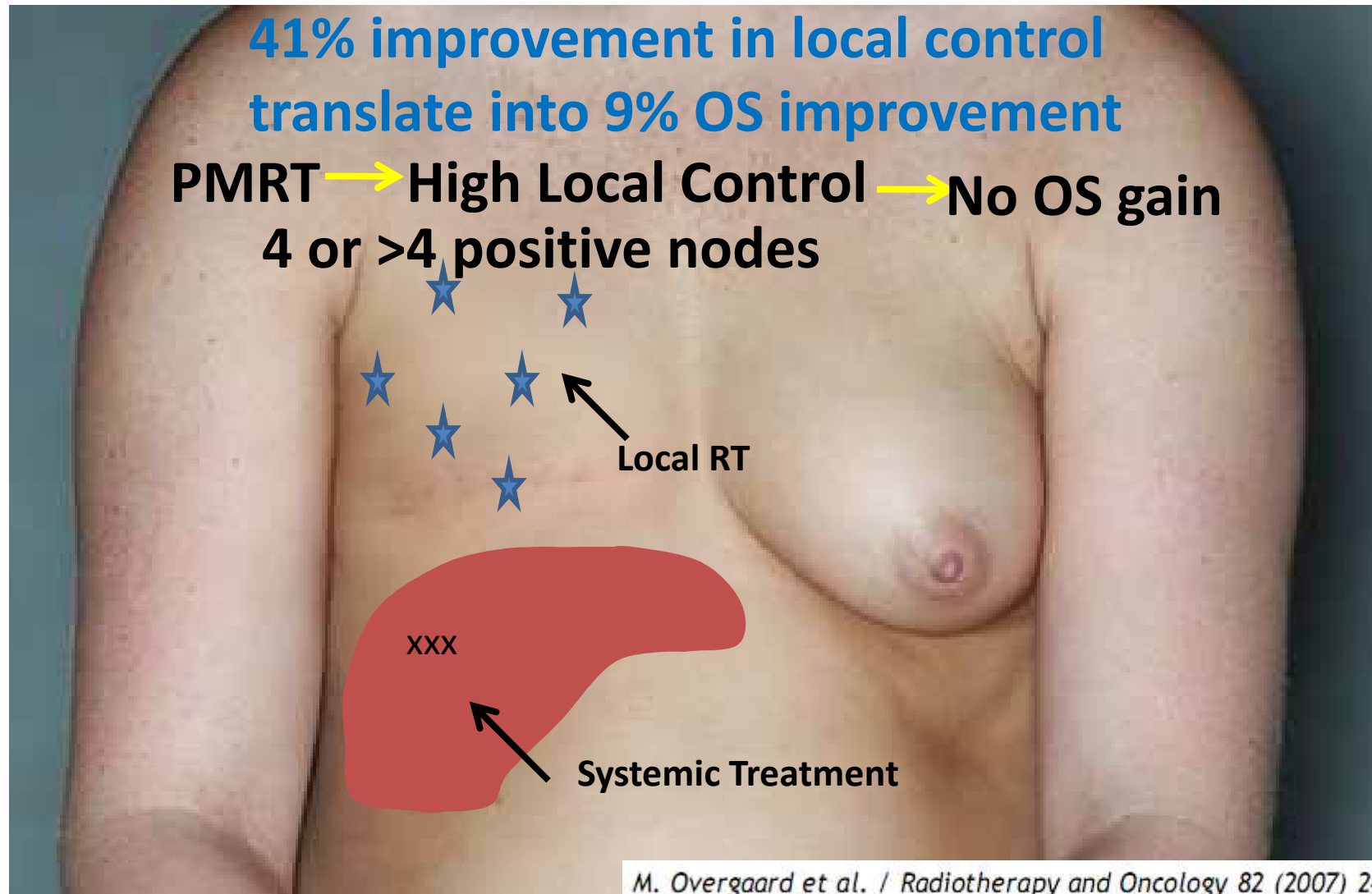
**Larger Proportion of patients will have survival benefit**



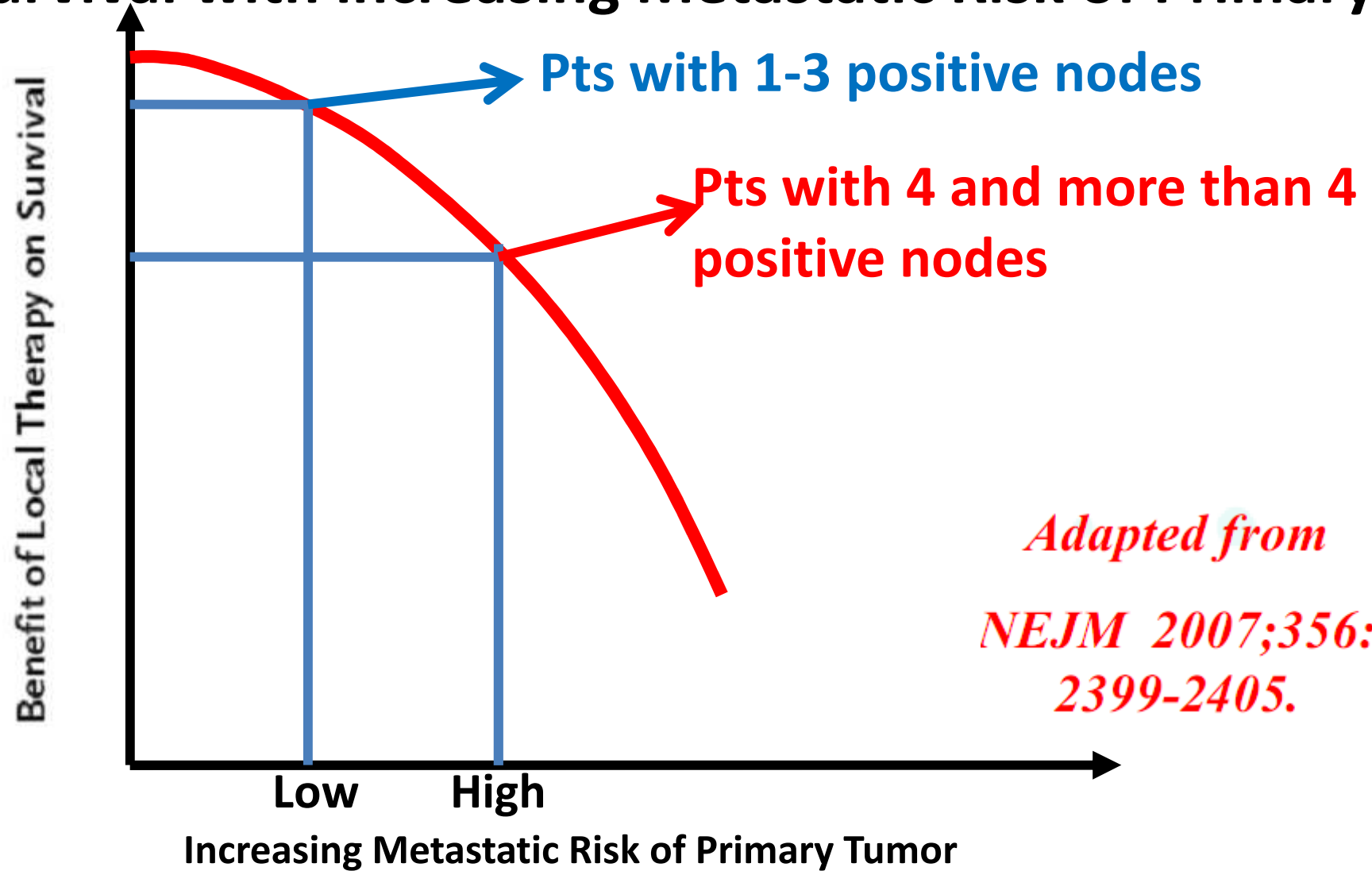
# Danish Trial 82b & 82c

## Sub-group Analysis

Limited Proportion of patients will have survival benefit



# Hypothetical benefit of Local Tumor Control on Survival with increasing Metastatic Risk of Primary.





Contents lists available at ScienceDirect

## Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)



Postmastectomy irradiation

### High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: A subgroup analysis of DBCG 82 b&c ☆

Marianne Kyndi<sup>a,b,\*</sup>, Marie Overgaard<sup>c</sup>, Hanne M. Nielsen<sup>a</sup>, Flemming B. Sørensen<sup>b</sup>, Helle Knudsen<sup>d</sup>, Jens Overgaard<sup>a</sup>

<sup>a</sup> Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

<sup>b</sup> Department of Pathology, Aarhus University Hospital, Denmark

<sup>c</sup> Department of Oncology, Aarhus University Hospital, Denmark

<sup>d</sup> Department of Pathology, Herlev Hospital, Denmark



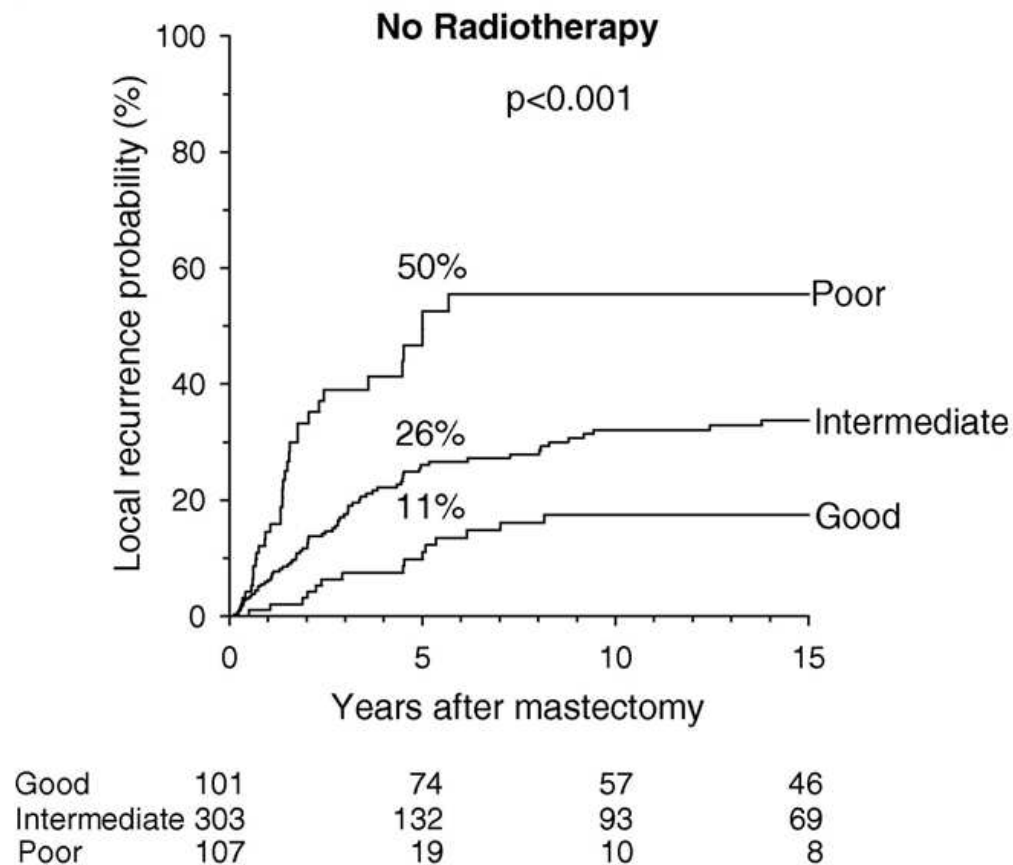
## **Danish Trial 82b & 82c** Sub-group Analysis

- Among patients in 82b and 82c randomized to no radiation, 3 risk groups were identified
- Good: 4 of 5 favorable features
  - $\leq 3$  nodes
  - Size  $< 2$  cm
  - Grade 1
  - ER or PR positive, her2 negative
- Poor: 2 of 3 *Intermediate risk = all others*
  - Grade 3,  $> 3$  nodes, size  $> 5$  cm

# Danish Trial 82b & 82c

## Sub-group Analysis

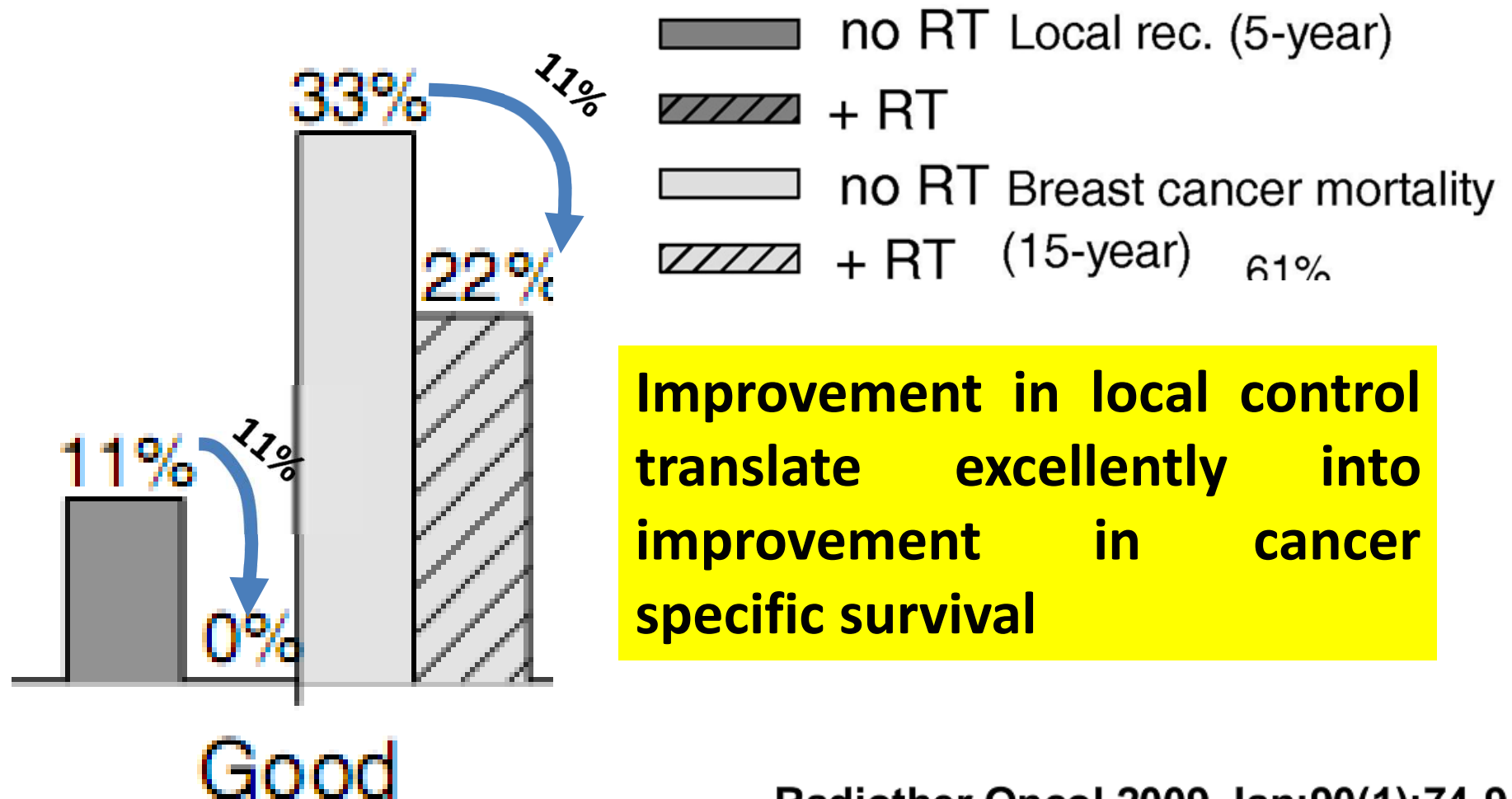
### LRR by Risk Group



# Danish Trial 82b & 82c

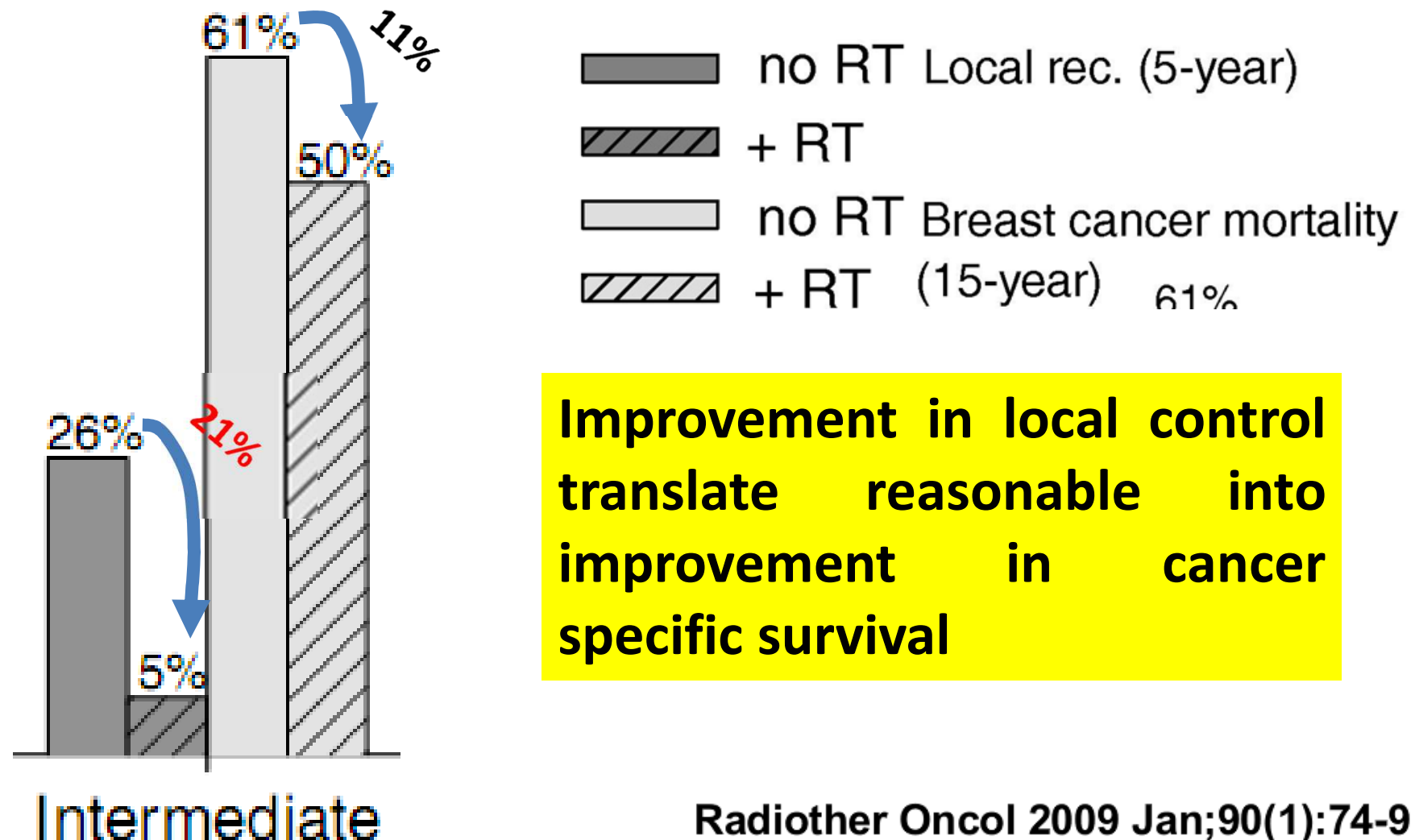
## Sub-group Analysis

5 year LRR & 15 year Breast Cancer Mortality by Risk Group



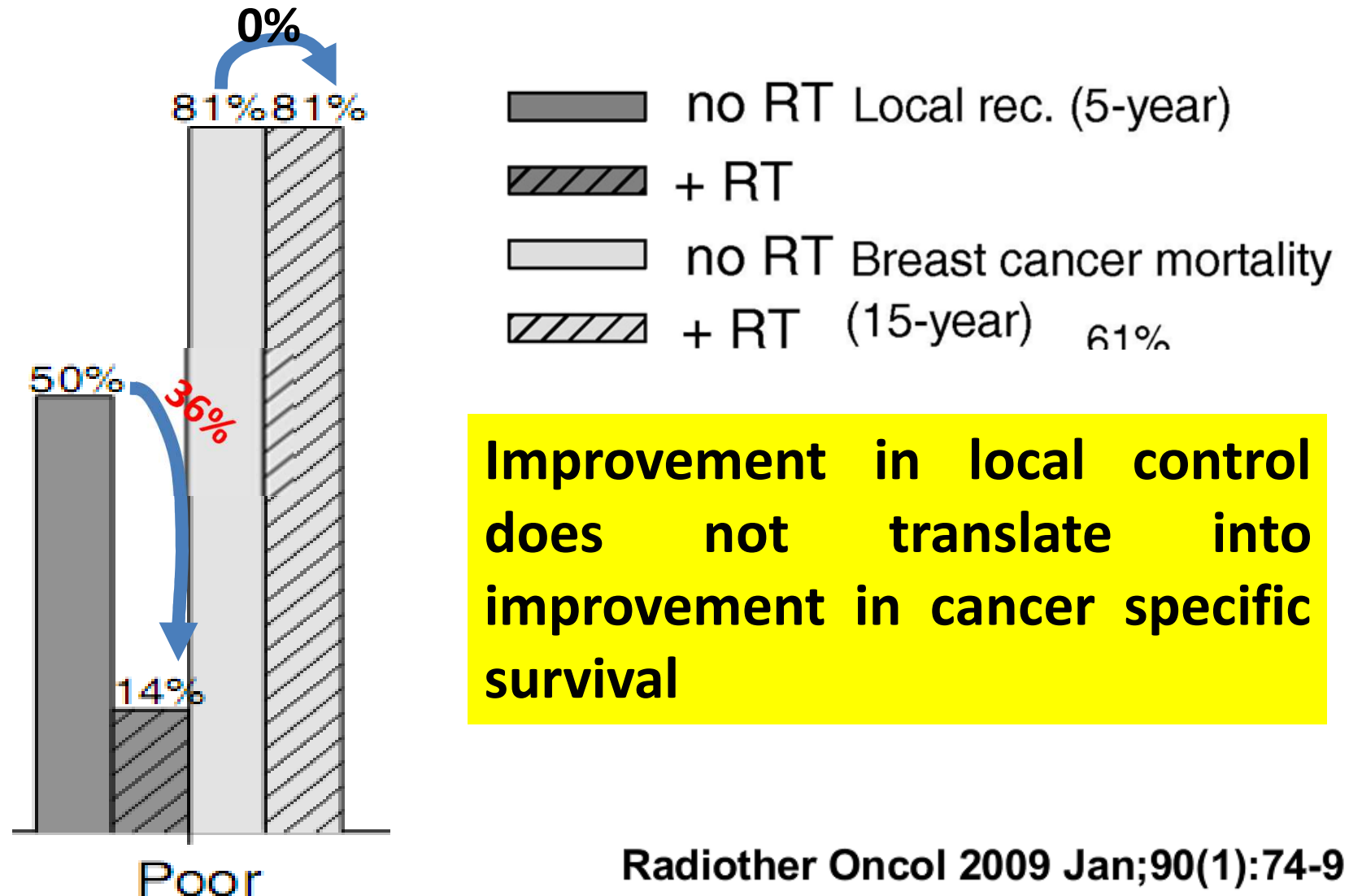
# Danish Trial 82b & 82c Sub-group Analysis

## 5 year LRR & 15 year Breast Cancer Mortality by Risk Group

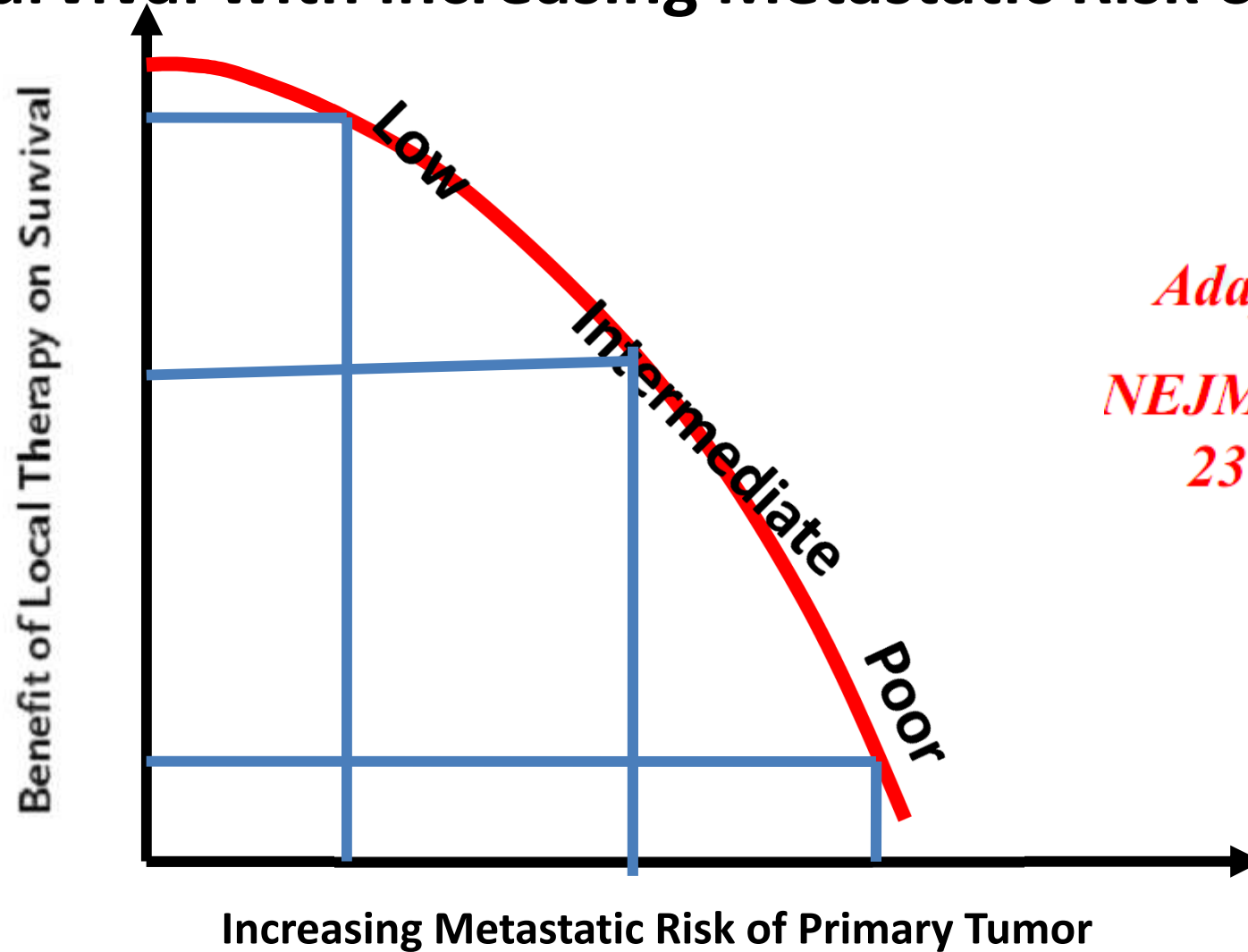


# Danish Trial 82b & 82c Sub-group Analysis

## 5 year LRR & 15 year Breast Cancer Mortality by Risk Group



# Hypothetical benefit of Local Tumor Control on Survival with increasing Metastatic Risk of Primary.



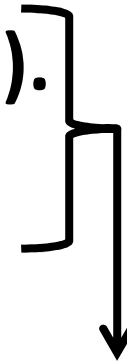
*Adapted from  
NEJM 2007;356:  
2399-2405.*

# Take Home

**All reports related with Danish trial 82b & c  
make strong case of PMRT in patients with 1-3  
positive axillary nodes**

# Criticisms

- Local recurrence was still high in sub group analysis of patients with  $> 8$  nodes removed (27%) surgery alone arm
- Sub optimal Chemotherapy used (CMF).
- Tamoxifan was given for 1 years only.



Less Effective Systemic Therapy



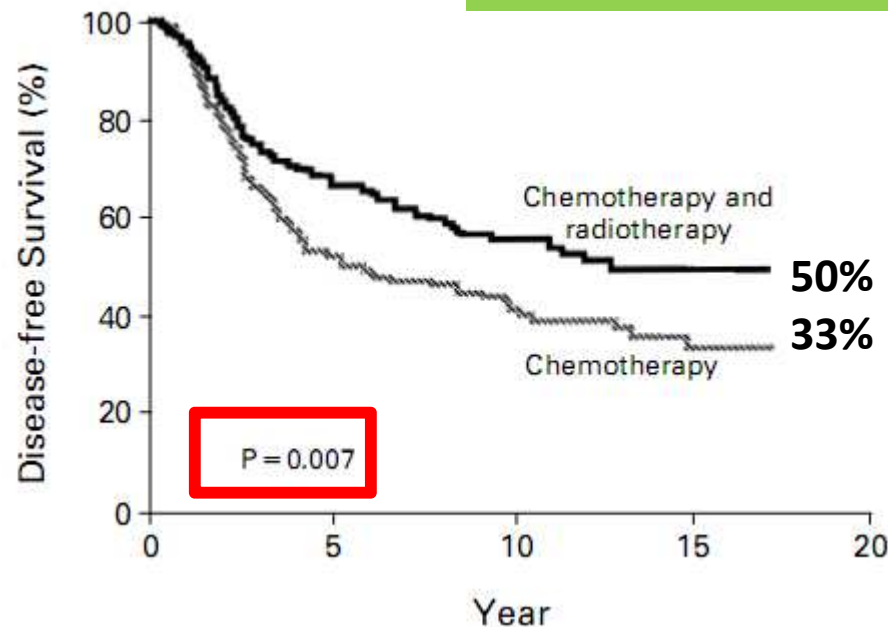
# British Columbia Trial

Pre menopausal Early Breast Cancer Majority T1 & T2 with pN+ve  
N=318 (60% 1-3 nodes +)

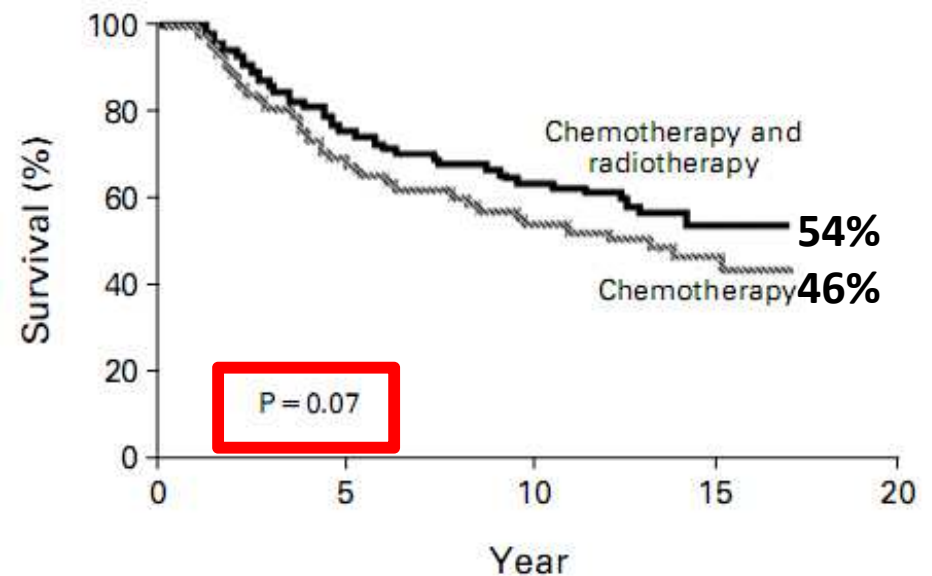
CMF + PMRT

CMF

Median Follow Up 15 Years



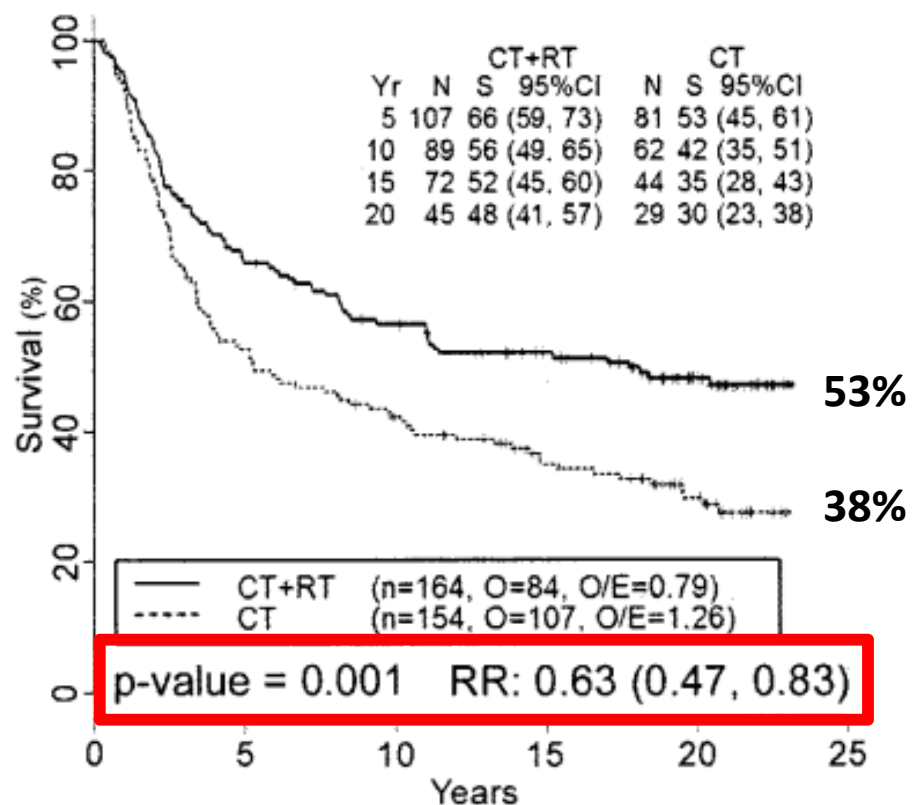
**Disease Free Survival**



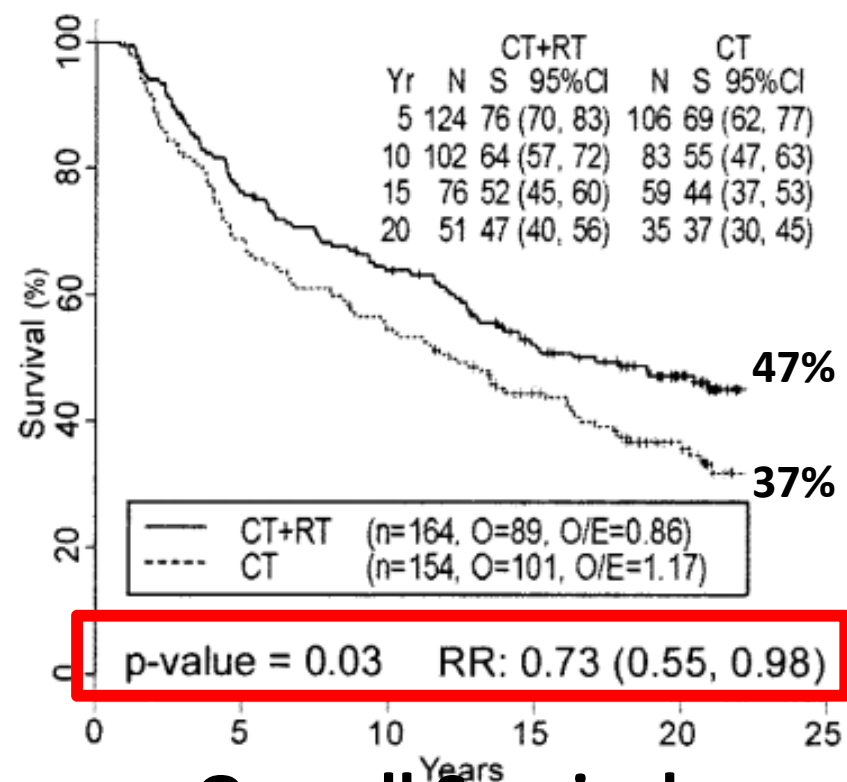
**Overall Survival**

# Updated Result of British Columbia

Median Follow Up 20 Years



**Breast ca Specific Survival**



**Overall Survival**

# Evidences

- **Controlled Randomized Trials.**
- **Meta analysis**

# Oxford 2005 Meta-analysis

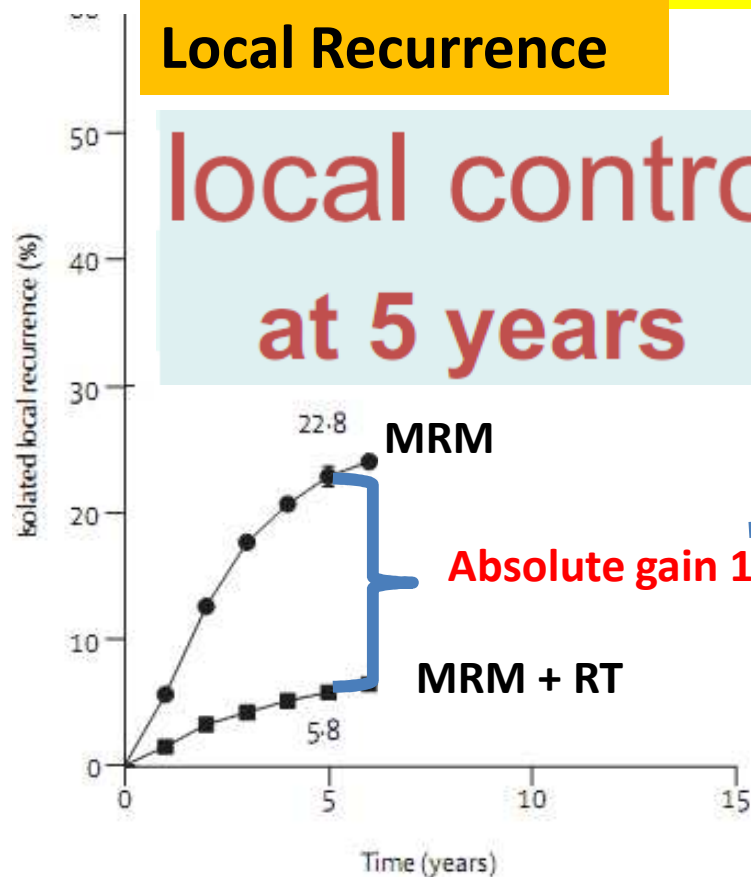
LN + patients → +/- Postmastectomy Radiation

Total No of Patients

8500

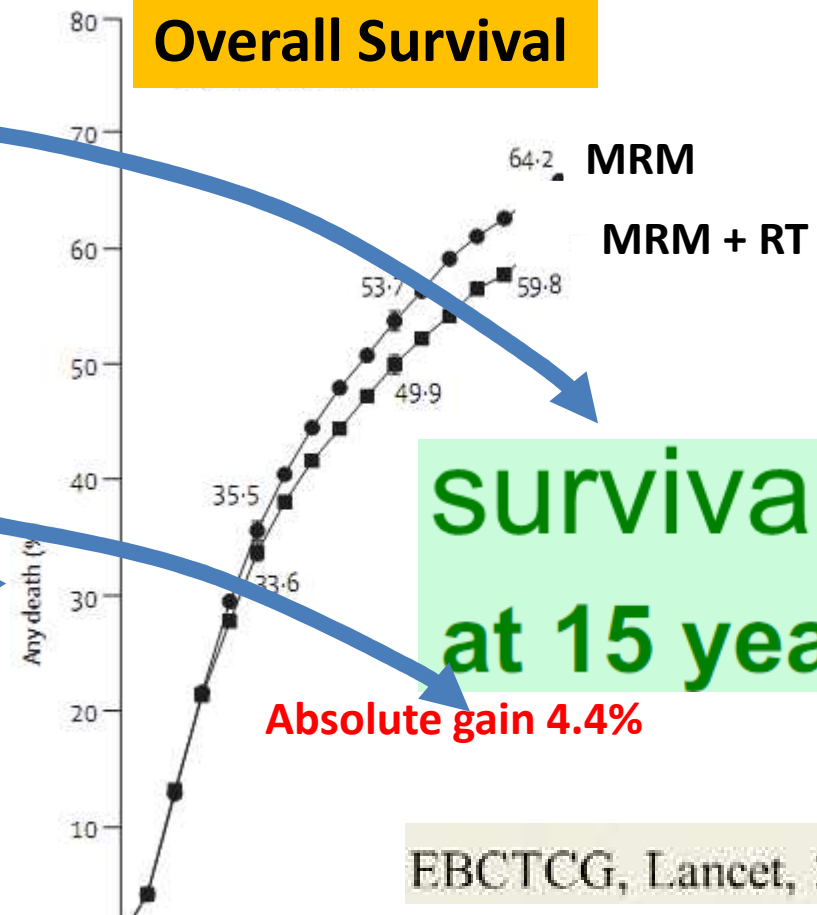
Local Recurrence

local control  
at 5 years



Absolute gain 17%

Overall Survival



survival  
at 15 years

Absolute gain 4.4%

EBCTCG, Lancet, 2005

Every 4 LR avoided, 1 death is avoided over the following 15 years.

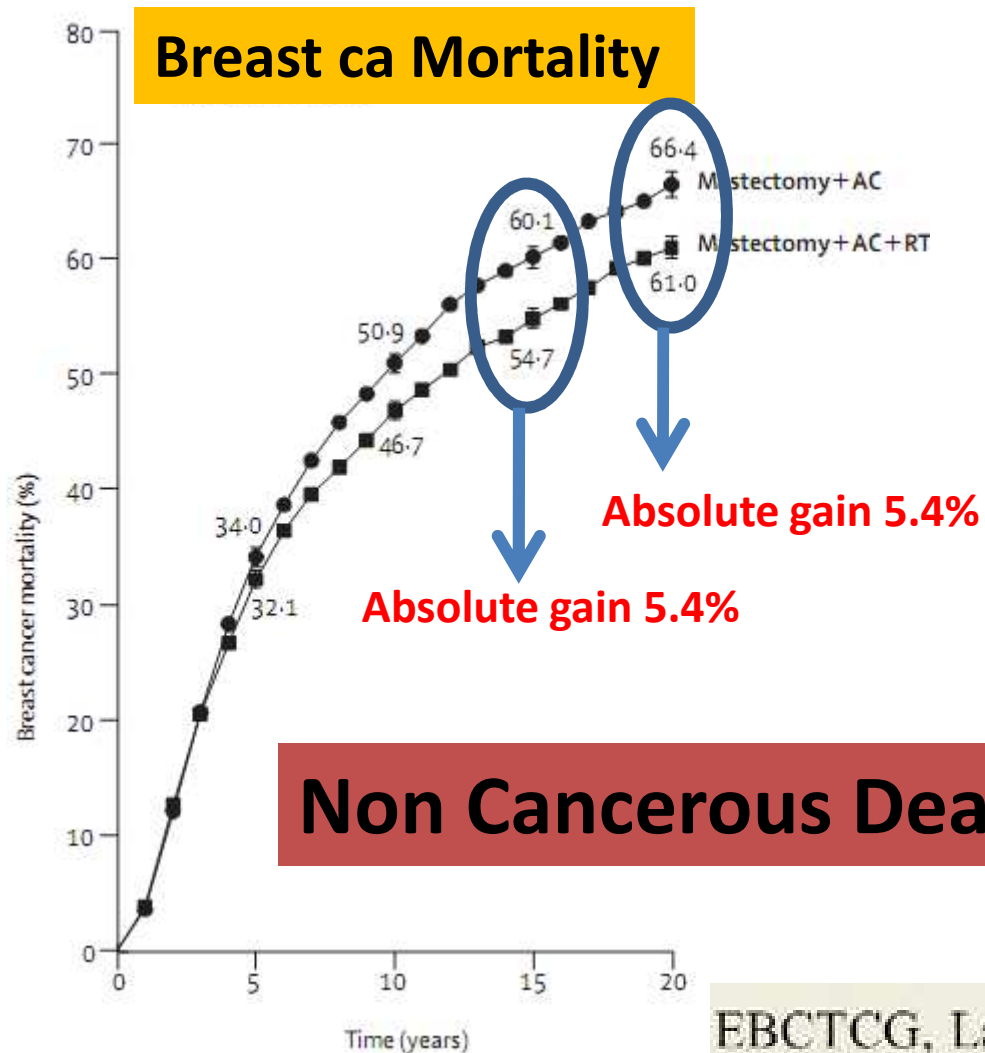
# Oxford 2005 Meta-analysis

LN + patients → +/- Postmastectomy Radiation

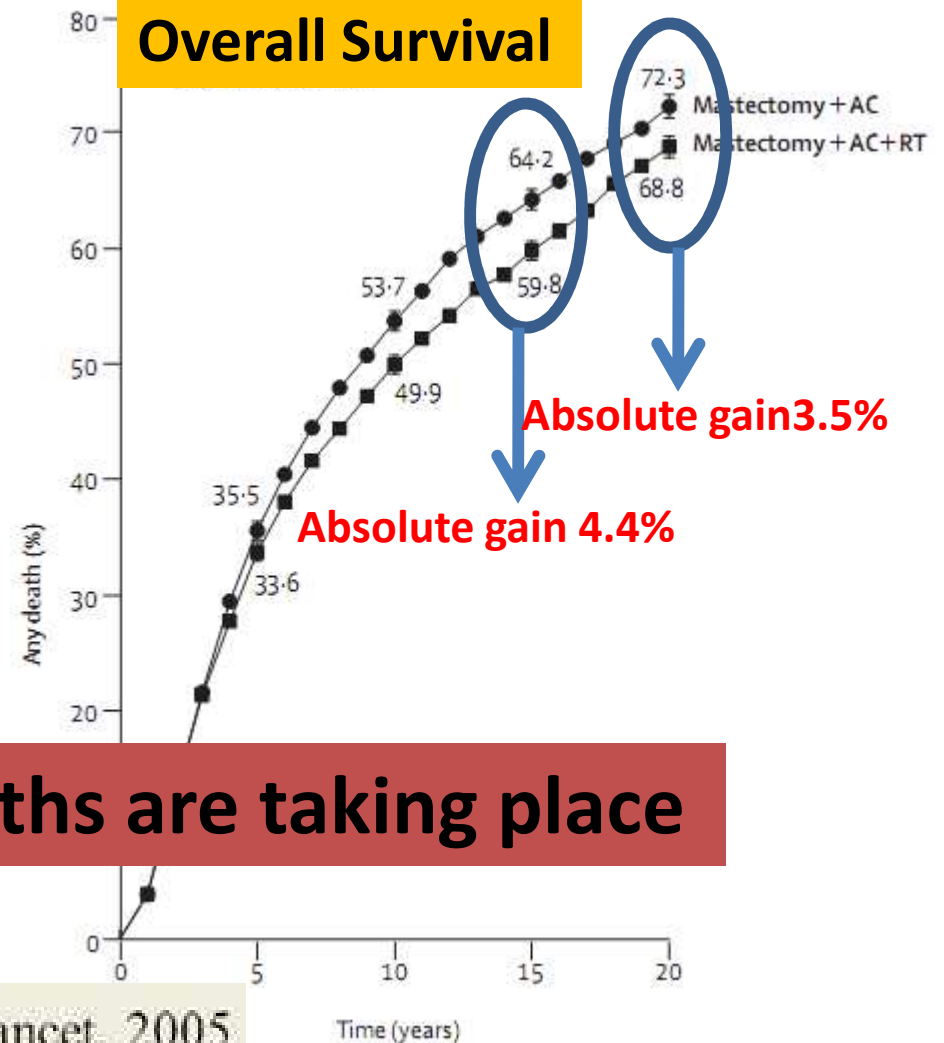
Total No of Patients

8500

## Breast ca Mortality



## Overall Survival



Non Cancerous Deaths are taking place

EBCTCG, Lancet, 2005

---

# 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)\*



[www.thelancet.com](http://www.thelancet.com) Published online March 19, 2014 [http://dx.doi.org/10.1016/S0140-6736\(14\)60488-8](http://dx.doi.org/10.1016/S0140-6736(14)60488-8)



# Negative Axilla

**Dissection  
(700)**

**No effect of RT**

**Sampling  
(870)**

**RT reduces overall and LR recurrences  
No effect on Survival**

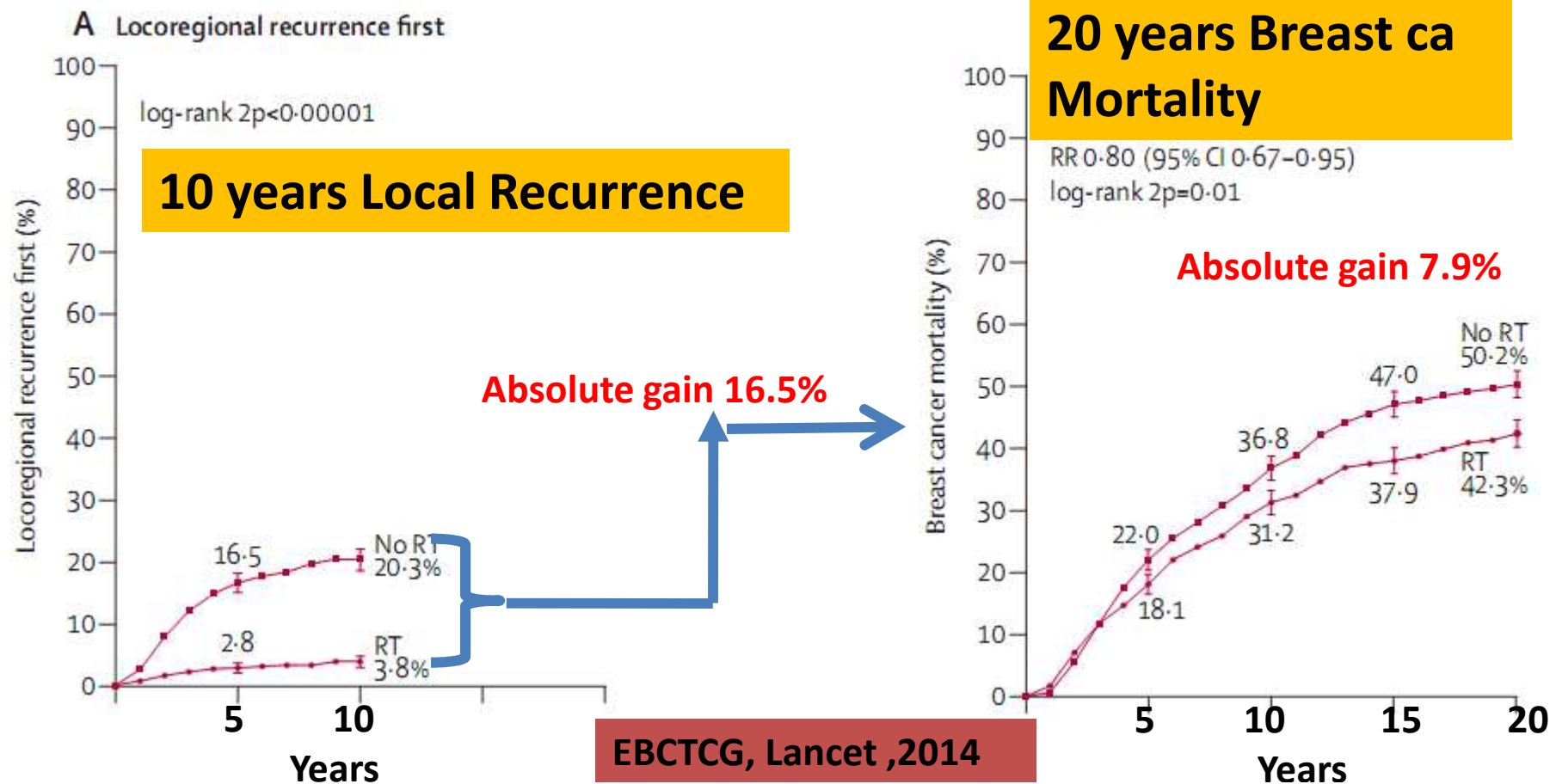
**Take Home    In inadequately dissected Axilla, RT  
may be considered in patients with negative axilla**

# Patients with 1-3 Positive Nodes

Total No of Patients

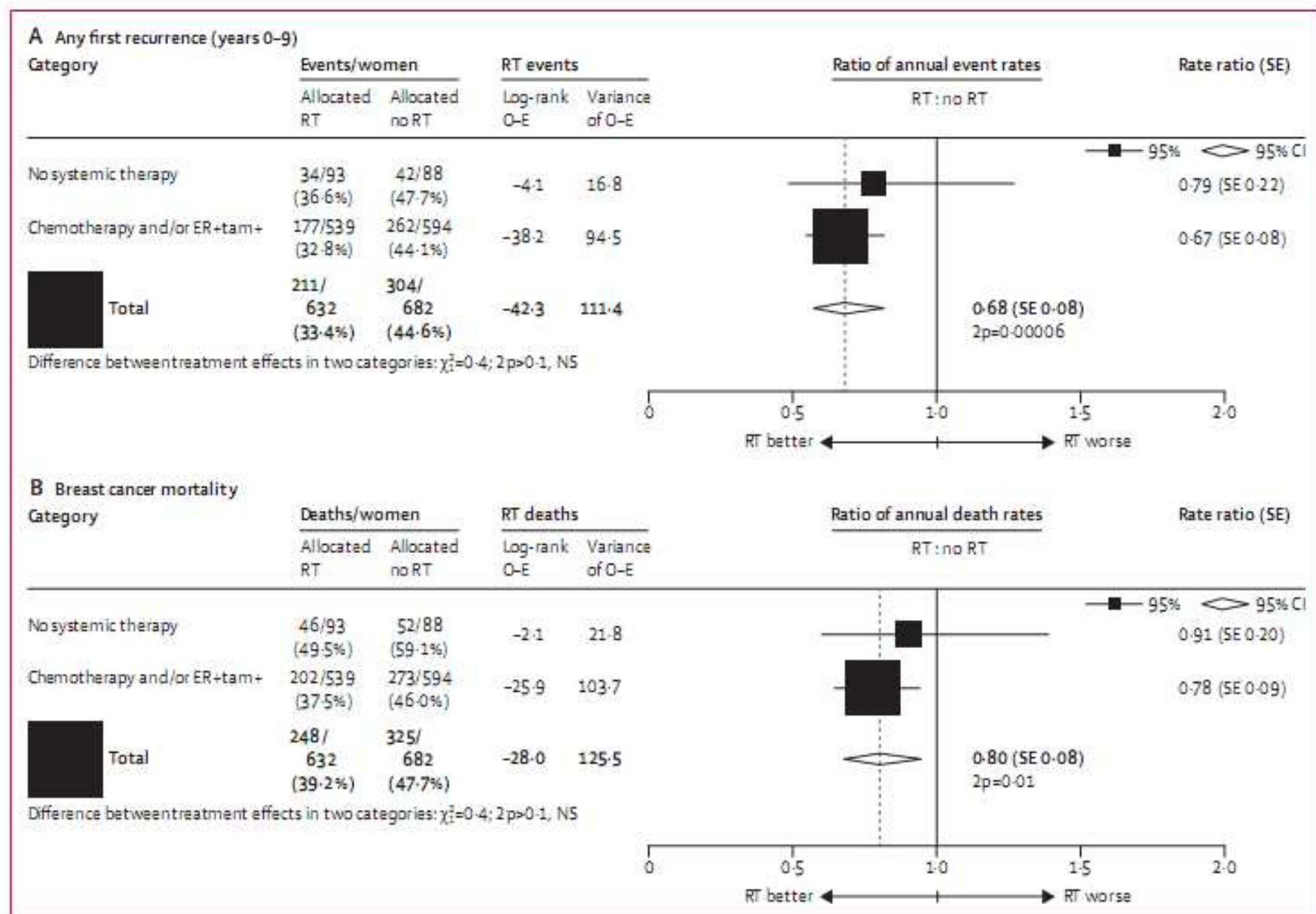
1314

Every 2 LR avoided, 1 death is avoided over the following 20 years.





# Effect of PMRT Based on Systemic Therapy

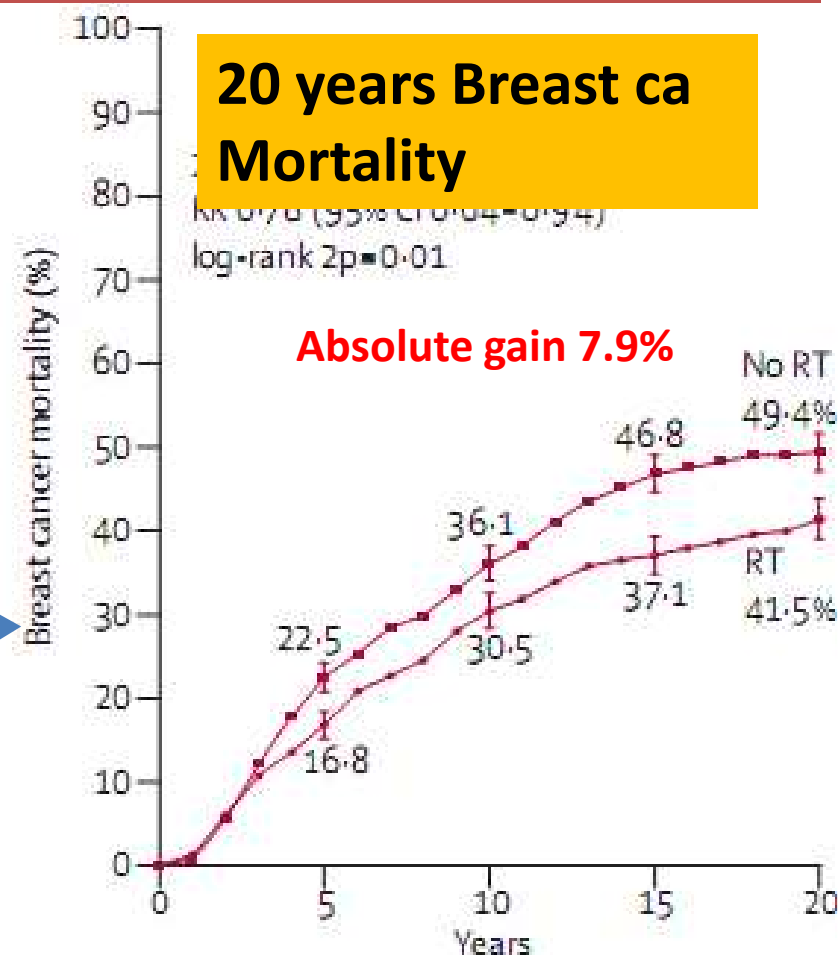
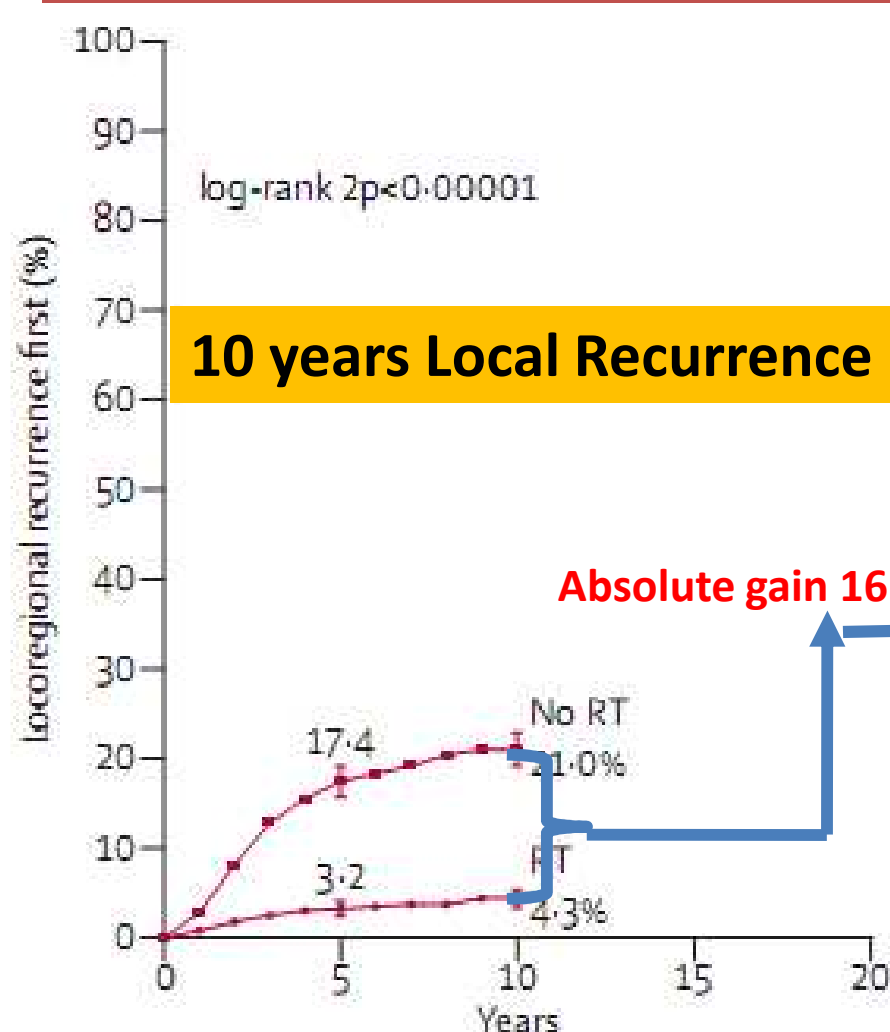


# Oxford 2014 Meta-analysis

*PMRT in 1-3 Positive Nodes Who received Systemic Treatment*

**Total No of Patients 1133**

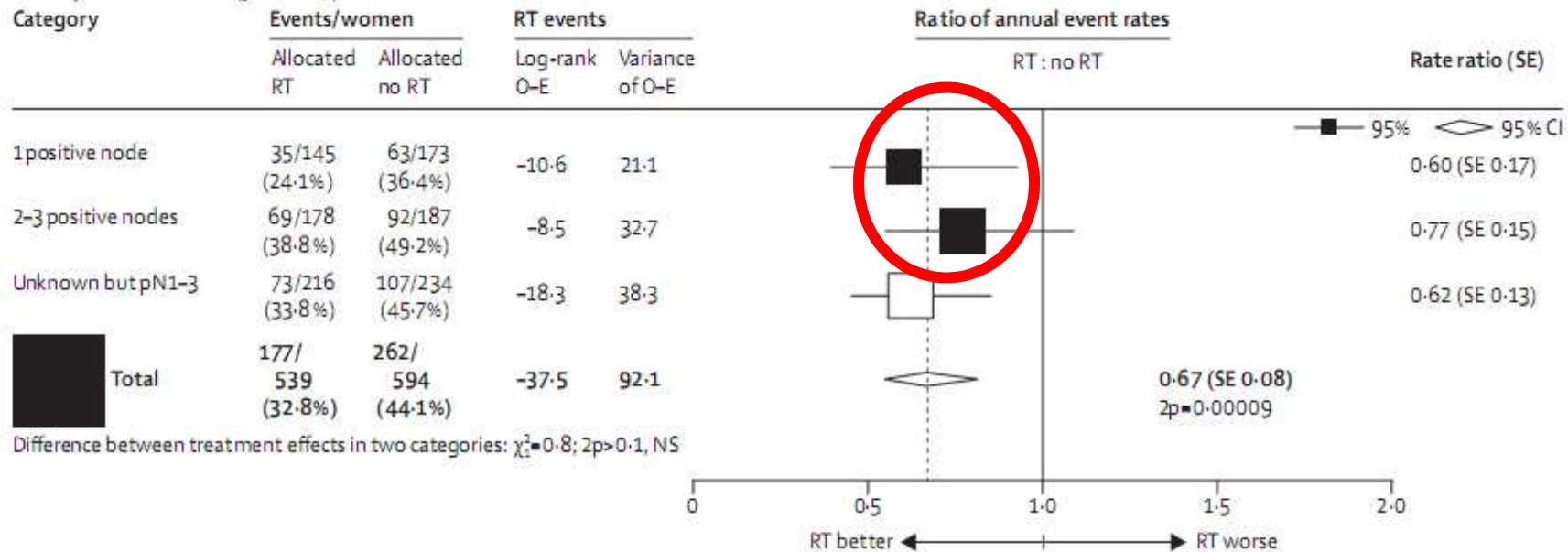
**Every 2 LR avoided, 1 death is avoided over the following 20 years.**



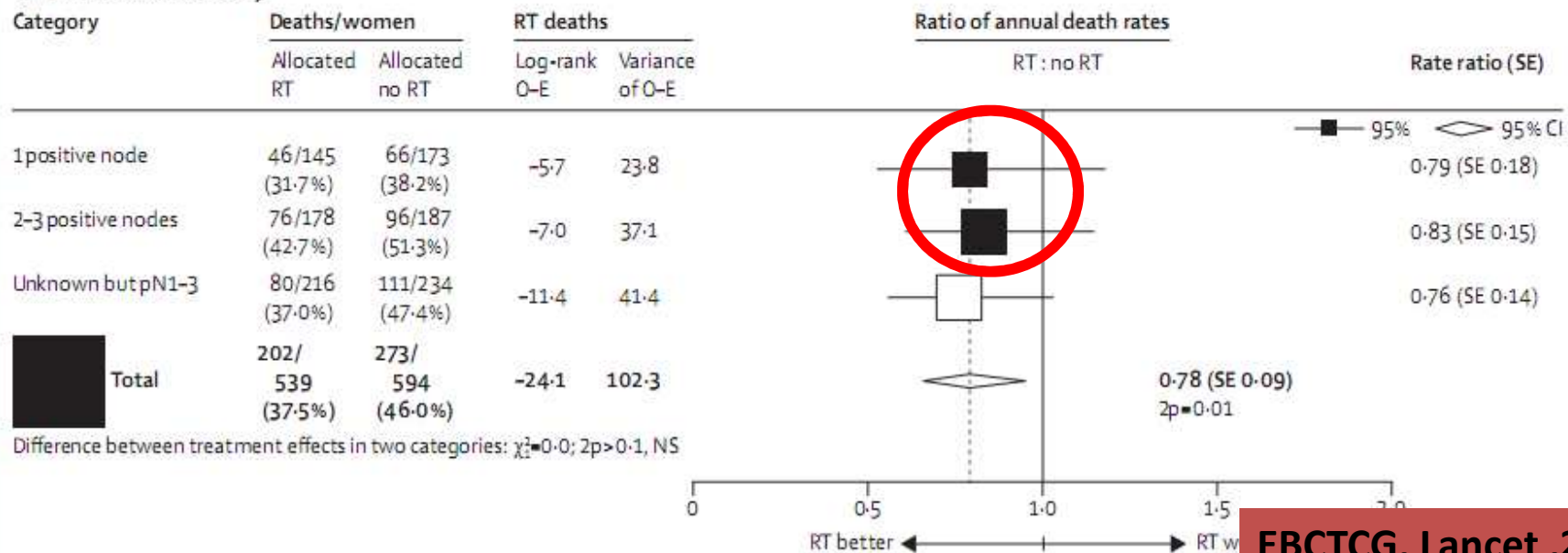
**EBCTCG, Lancet, 2014**

# Effect of PMRT Based on No of Nodes

## A Any first recurrence (years 0-9)



## B Breast cancer mortality



# Limitation of Oxford Meta-analysis

- All trials since 1960 onwards.
- Radiotherapy technique was old.
- Usually radiation was given to all regional lymphatic (Axilla, S/C and IM)



**More Long term side effects**

**With Modern radiotherapy the impact in improving the outcome may be much higher**

# Limitation of Oxford Meta-analysis

- **With Modern Systemic Chemotherapy**
- **Much improved Surgical Technique**



**5 years Local Recurrence may be much less than in these trial**

**The impact of Radiotherapy in improving the outcome likely to be smaller**

# **Oxford Meta-analysis**

- **This also support the use of PMRT in patients with early breast ca with 1-3 positive nodes**

## Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

Abram Recht, Beth Israel Deaconess Medical Center, Boston, MA; Elizabeth A. Comen, Alice Y. Ho, Clifford A. Hudis, Monica Morrow, Memorial Sloan Kettering Cancer Center, New York; Jeffrey J. Kirshner, Hematology Oncology Associates of Central New York, East

*Abram Recht, Elizabeth A. Comen, Richard E. Fine, Gini F. Fleming, Patricia H. Hardenbergh, Alice Y. Ho, Clifford A. Hudis, E. Shelley Hwang, Jeffrey J. Kirshner, Monica Morrow, Kilian E. Salerno, George W. Sledge Jr, Lawrence J. Solin, Patricia A. Spears, Timothy J. Whelan, Mark R. Somerfield, and Stephen B. Edge*

### **Clinical Question 1**

Is PMRT indicated in patients with T1-2 tumors with one to three positive axillary lymph nodes who undergo ALND?

### **Recommendations**

*Recommendation 1a.* The panel unanimously agreed that the available evidence shows that PMRT reduces the risks of locoregional failure (LRF), any recurrence, and breast cancer mortality for patients with T1-2 breast cancer and one to three positive lymph nodes. 1

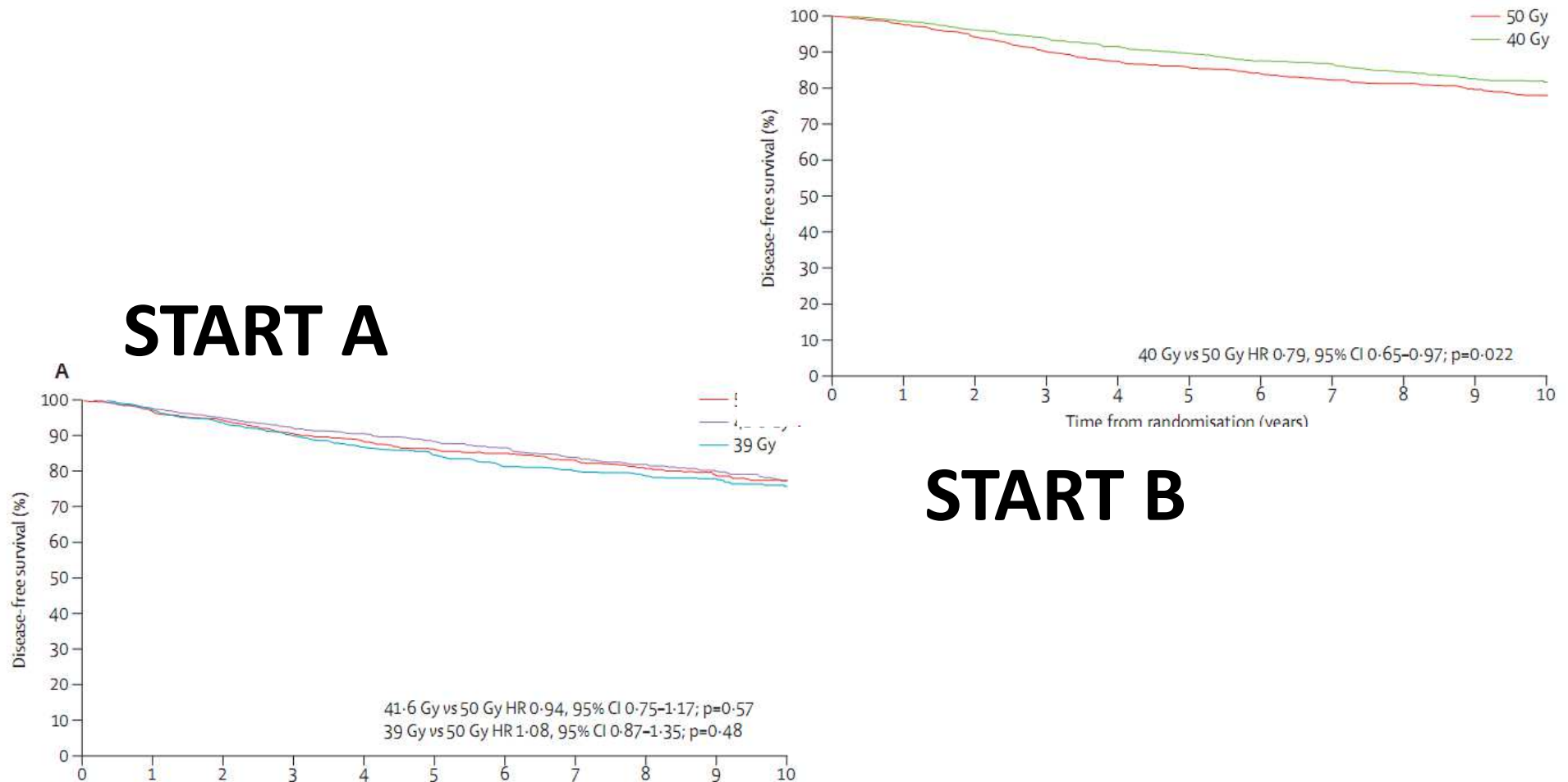


**START TRIALS**



# Q1. Hypo fraction is Effective?

**A 1. YES as effective as conventional**



# START A

Age (years)				
20-29	5 (0.7)	4 (0.5)	3 (0.4)	12 (0.5)
30-39	38 (5.1)	40 (5.3)	38 (5.2)	116 (5.2)
40-49	116 (15.5)	136 (18.1)	129 (17.5)	381 (17.0)
50-59	280 (37.4)	283 (37.7)	286 (38.8)	849 (38.0)
60-69	215 (28.7)	192 (25.6)	194 (26.3)	601 (26.9)
70-79	87 (11.6)	85 (11.3)	78 (10.6)	250 (11.2)
80+	8 (1.1)	10 (1.3)	9 (1.2)	27 (1.2)
Pathological node status				
Positive	222 (29.6)	197 (26.3)	224 (30.4)	643 (28.8)
Negative	514 (68.6)	536 (71.5)	497 (67.4)	1547 (69.2)
Not known (no axillary surgery)	12 (1.6)	27 (3.3)	25 (3.2)	11 (2.3)
Not known (missing data)	1 (0.1)	0 (0.0)	1 (0.2)	2 (0.1)
Tumour size (cm)				
<1	24 (3.2)	26 (3.5)	24 (3.3)	74 (3.3)
1-	362 (48.3)	347 (46.3)	355 (48.2)	1064 (47.6)
2-	202 (27.0)	203 (27.1)	198 (26.9)	603 (27.0)
3-	156 (20.8)	169 (22.5)	157 (21.3)	482 (21.6)
Not known	5 (0.7)	5 (0.7)	3 (0.3)	13 (0.6)
Tumour grade				
1	157 (21.0)	150 (20.0)	149 (20.2)	456 (20.4)
2	369 (49.3)	379 (50.5)	368 (49.9)	1116 (49.9)
3	212 (28.3)	207 (27.8)	210 (28.5)	629 (28.1)
Not known (not applicable)*	11 (1.5)	10 (1.3)	6 (0.8)	27 (1.2)
Not known	0 (0.0)	4 (0.6)	4 (0.5)	8 (0.4)
Adjuvant therapy				
None	52 (6.9)	53 (7.1)	67 (9.1)	172 (7.7)
Tamoxifen/no chemotherapy	416 (55.5)	418 (55.7)	376 (51.0)	1210 (54.1)
Chemotherapy/no tamoxifen	86 (11.5)	77 (10.3)	82 (11.1)	245 (11.0)
Tamoxifen+chemotherapy	173 (23.1)	187 (25.0)	188 (25.5)	548 (24.5)
Other endocrine therapy†	17 (2.3)	13 (1.7)	17 (2.3)	47 (2.1)
Not known	5 (0.7)	2 (0.2)	7 (0.9)	14 (0.6)

**77% > 50 yrs**

**70% N0**

**78% T1**

**70% Low Grade**

**64% No CCT**

# START B

Age (years)			
20-29	7 (0.6)	0 (0.0)	7 (0.3)
30-39	62 (5.6)	39 (3.5)	101 (4.6)
40-49	179 (16.2)	170 (15.3)	349 (15.8)
50-59	427 (38.6)	447 (40.3)	874 (39.5)
60-69	304 (27.5)	327 (29.5)	631 (28.5)
70-79	117 (10.6)	119 (10.7)	236 (10.7)
80-	9 (0.8)	8 (0.7)	17 (0.8)

**79% > 50**

Pathological node status			
Positive	238 (21.5)	266 (24.0)	504 (22.8)
Negative	831 (75.2)	804 (72.4)	1635 (73.8)
Not known (no axillary surgery)	36 (3.3)	39 (3.5)	75 (3.4)
Not known (missing data)	0 (0.0)	1 (0.1)	1 (0.04)

**74% N0**

Tumour size (cm)			
<1	151 (13.7)	167 (15.0)	318 (14.4)
1-	552 (50.0)	542 (48.8)	1094 (49.4)
2-	287 (26.0)	288 (25.9)	575 (26.0)
3-	113 (10.2)	107 (9.6)	220 (9.9)
Not known	2 (0.2)	6 (0.5)	8 (0.4)

**90% T1**

Tumour grade			
1	306 (27.7)	311 (28.0)	617 (27.9)
2	518 (46.9)	532 (47.9)	1050 (47.4)
3	261 (23.6)	248 (22.3)	509 (23.0)
Not known (not applicable)*	15 (1.4)	15 (1.3)	30 (1.3)
Not known	5 (0.4)	4 (0.4)	9 (0.4)

**75% Low Grade**

Adjuvant therapy			
None	37 (3.3)	47 (4.2)	84 (3.8)
Tamoxifen/no chemotherapy	782 (70.8)	810 (73.0)	1592 (71.9)
Chemotherapy/no tamoxifen	77 (7.0)	78 (7.0)	155 (7.0)
Tamoxifen+chemotherapy	181 (16.4)	155 (14.0)	336 (15.2)
Other endocrine therapy†	16 (1.4)	11 (1.0)	27 (1.2)
Not known	12 (1.1)	9 (0.8)	21 (0.9)

**75% No CCT**

# Evidences generated are for

- Age > 50 years
- T1
- N0
- Low or Intermediate Grade
- Good prognostic factors where Chemotherapy is not indicated
- **ASTRO Guidelines**

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1–2 N0 and patient has been treated with breast- conserving surgery.
3. Patient has not been treated with systemic chemotherapy.

# Q2. Role of Tumor bed boost?

## Issues:

1. May reduce the local recurrence as established in CF WBI.
2. May increase local toxicity thus cosmesis may be poor.

	START A (10)	START B (16)
Energy	6 MV*	6 MV*
Wedges	Yes	Yes
Inhomogeneity cCorrections	Variable	Variable
Planning	2D or 3D	2D or 3D
Central Axis Dose Homogeneity	-5% to +5%	-5% to +5%
Separation		
Percent receiving boost	61%	39%
Boost dose	10 Gy, 5 fr	10 Gy, 5 fr
Boost modality	Electrons	Electrons
Percent receiving regional nodal irradiation	14%	7%
Target for nodal irradiation	SCV $\pm$ Ax	SCV $\pm$ Ax
Use of PAS	-	-
Dose to regional nodes	Same as breast	Same as breast

**Boost may be used with Hypo fraction RT**



# Q3. Regional Nodal Irradiation?

## Issues:

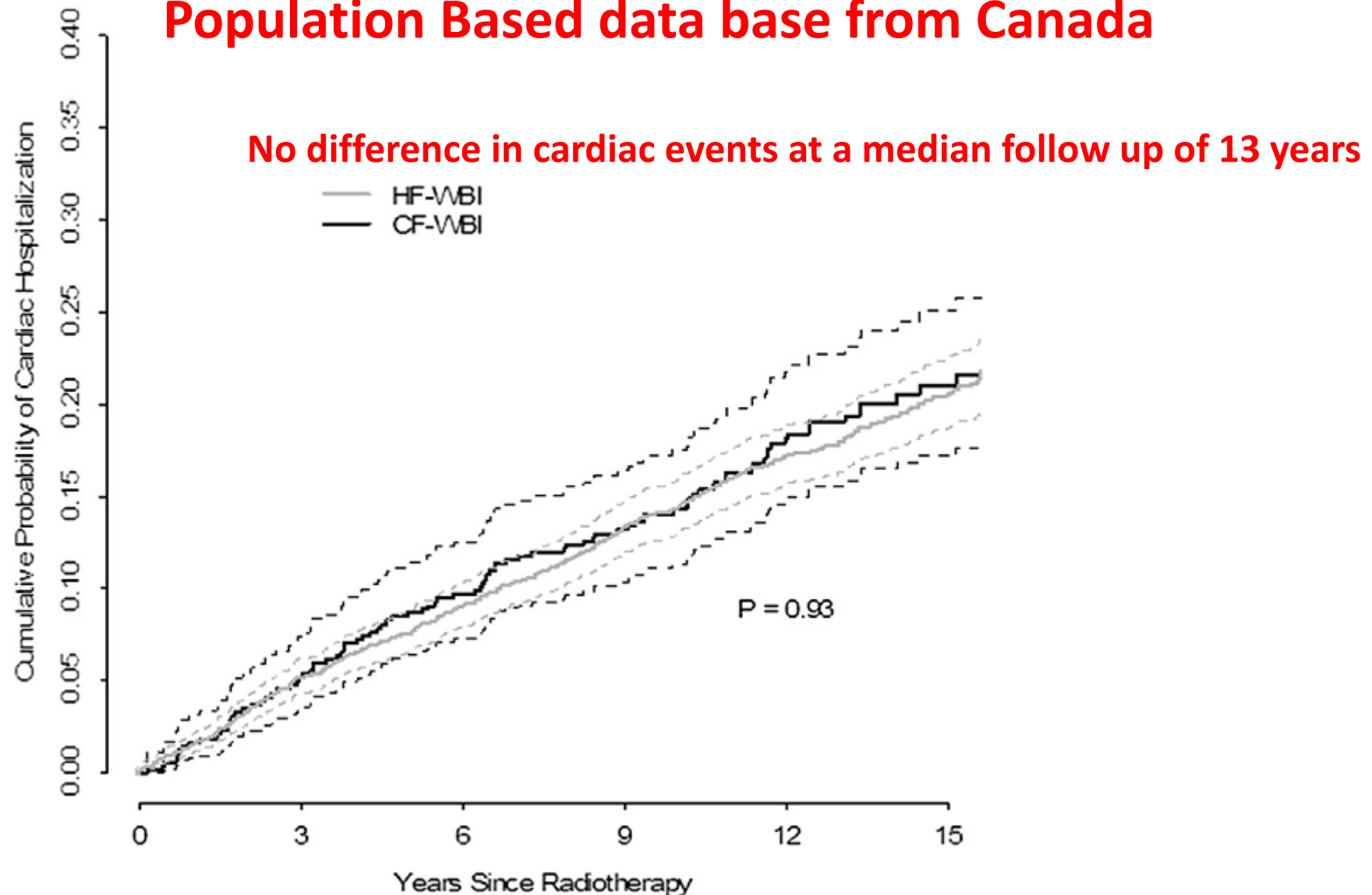
1. May increase the axillary toxicity like arm edema, brachial plexus injury etc.

	START A (10)	START B (16)
Energy	6 MV*	6 MV*
Wedges	Yes	Yes
Inhomogeneity cCorrections	Variable	Variable
Planning	2D or 3D	2D or 3D
Central Axis Dose Homogeneity	−5% to +5%	−5% to +5%
Separation	—	—
Percent receiving boost	61%	39%
Boost dose	10 Gy, 5 fr	10 Gy, 5 fr
Boost modality	Electrons	Electrons
Percent receiving regional nodal irradiation	14%	7%
Target for nodal irradiation	SCV ± Ax	SCV ± Ax
Use of PAS	—	—
Dose to regional nodes	Same as breast	Same as breast

**Data scanty to draw firm conclusion but present evidence do not show increased toxicity.**

# Q4. Status of HF-WBI in Left sided breast?

Population Based data base from Canada



# Take Home from START

- **Hypo fraction is equally effective in very early CA breast treated with BCS.**
- **Patients with poor prognostic features require conventional fraction RT.**
- **Boost may be given with HF-WBI.**
- **When nodal irradiation is required it is better to use conventional fractions.**
- **Safe for left sided breast as well.**



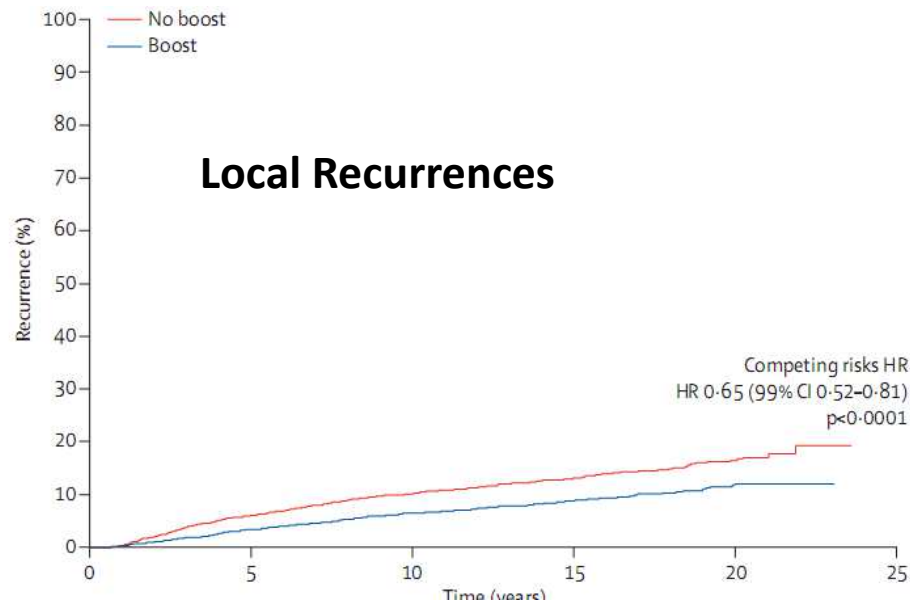
**BOOST VS. NO BOOST**

# **EORTC**

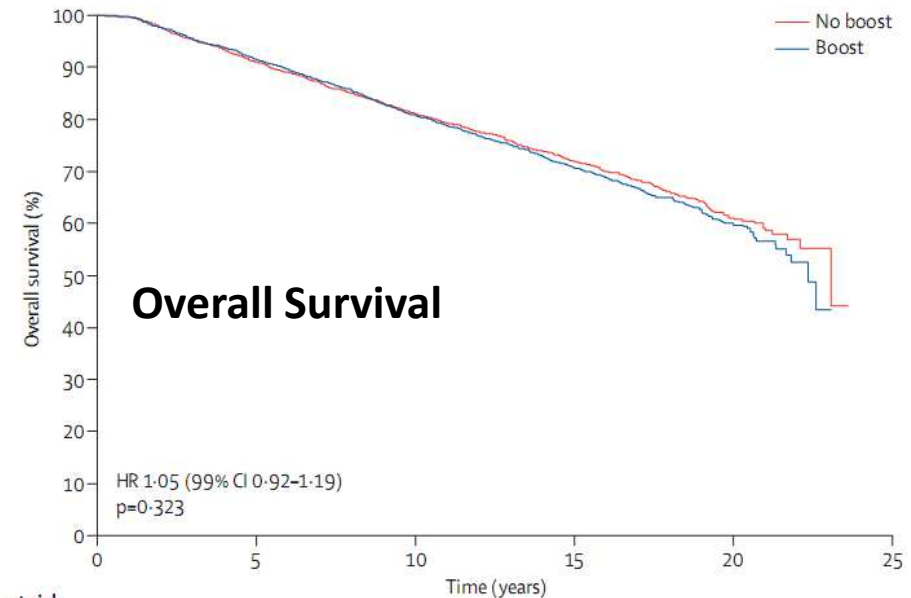
- **No of Patients**            **5318**
- **Follow Up**                **20 years**
- **Overall Survival**        **No difference**

# Ipsilateral Local Recurrence

## Statistical Significance difference



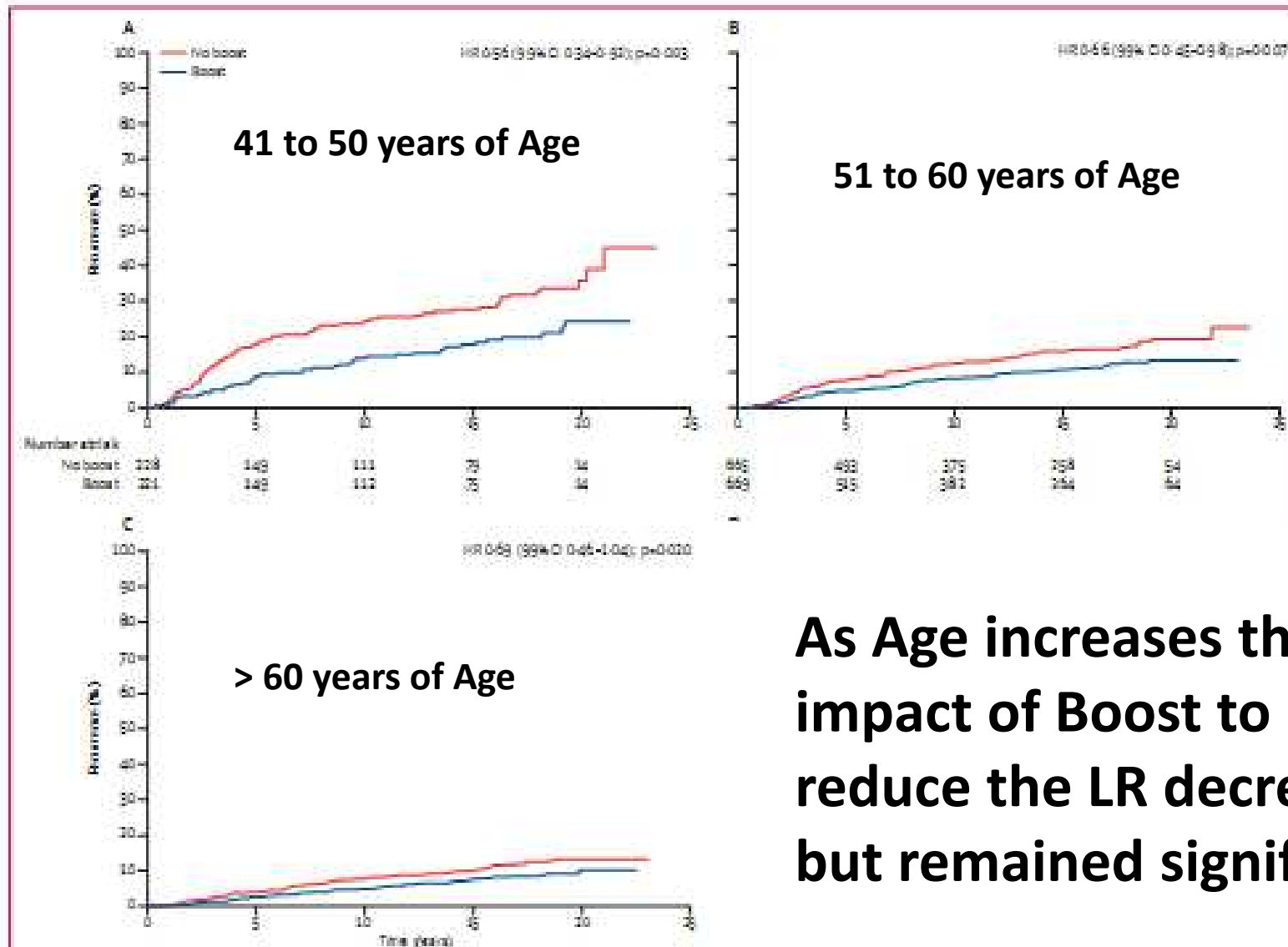
## No difference



	No boost group (n=2657)	Boost group (n=2661)
Number of positive nodes		
Unknown	25 (1%)	20 (1%)
0	2078 (78%)	2090 (79%)
1-3	452 (17%)	449 (17%)
≥4	102 (4%)	102 (4%)

**21% is node positive**

# Ipsilateral Local Recurrence



# **Take Home for Boost**

- **Decreases Local Recurrences.**
- **Reduces mastectomy rate.**
- **Not improved overall survival.**
- **May improve survival in node positive patients.**
- **Impact is more in younger patients.**
- **More than 60 years of age, may be omitted as impact is less and no improvement in OS but more fibrosis.**



Thanks

Greetings From Rishikesh

