



# Evidence based medicine for breast radiation therapy and limitations

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6<sup>th</sup> International Congress of Breast Disease centers

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# What is « evidence based medicine » in radiotherapy for breast cancer ?

► Are we all talking about of the same level of evidence ?

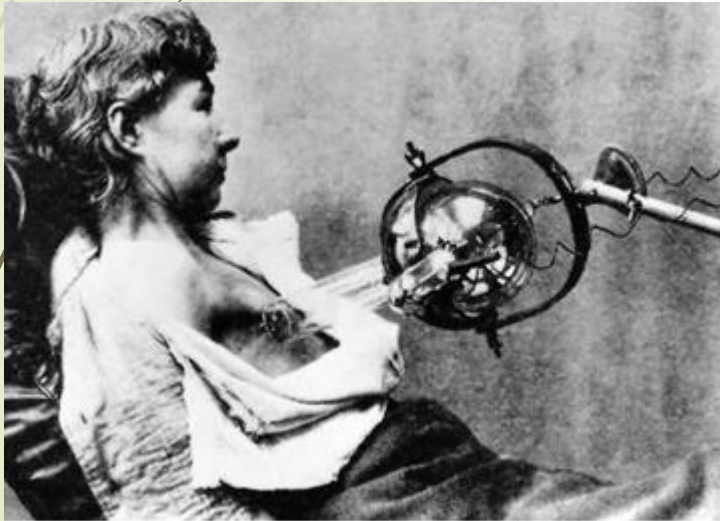
IA	Evidence from meta-analysis of randomized controlled trials
IB	Evidence from at least one randomized controlled trial
IIA	Evidence from at least one controlled study without randomization
IIB	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

# Radiation therapy for Breast cancer

## What have we learned for 120 years ?

### Invasive breast tumors

1895 - 1900



The same active ingredient :

beams of photons X

2015



Electrons  
Protons

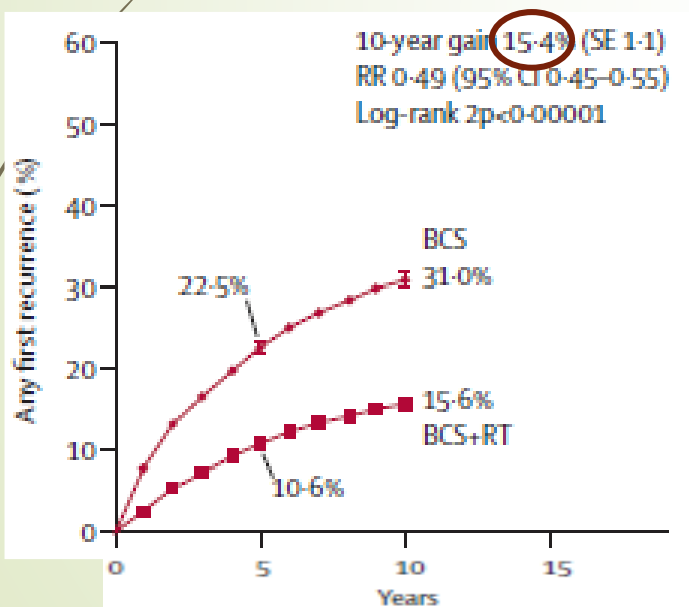
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# What do we really know?

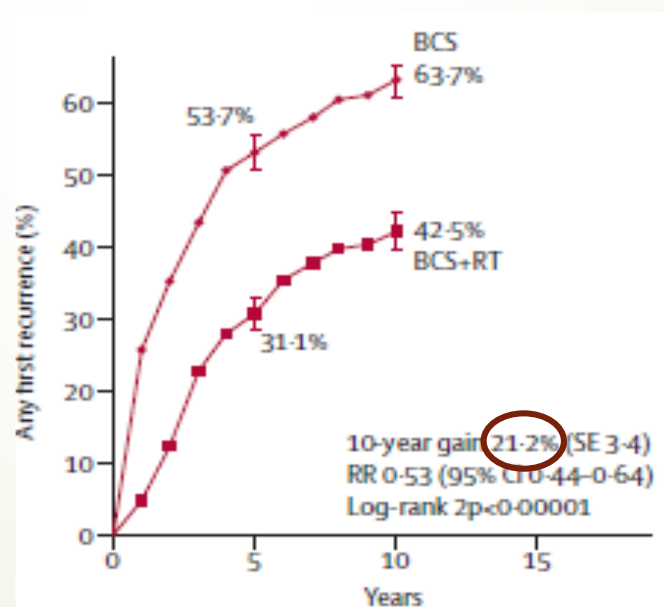
In conservative treatment, post-operative radiotherapy reduces the 10-year risk of any first recurrence

## Meta-analysis of Early Breast Cancer Trialists Collaborative Group (EBCTCG)

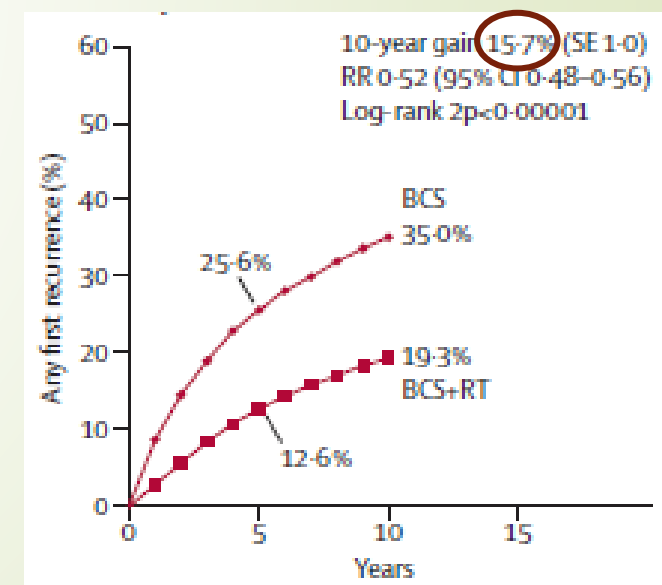
- 10,801 women in 17 trials beginning before 2000 and comparing RT vs no RT
- Median follow-up : 9.5 years



pN0 = 7287 pts (67%)



pN+ = 1050 pts



All = 10 801 pts

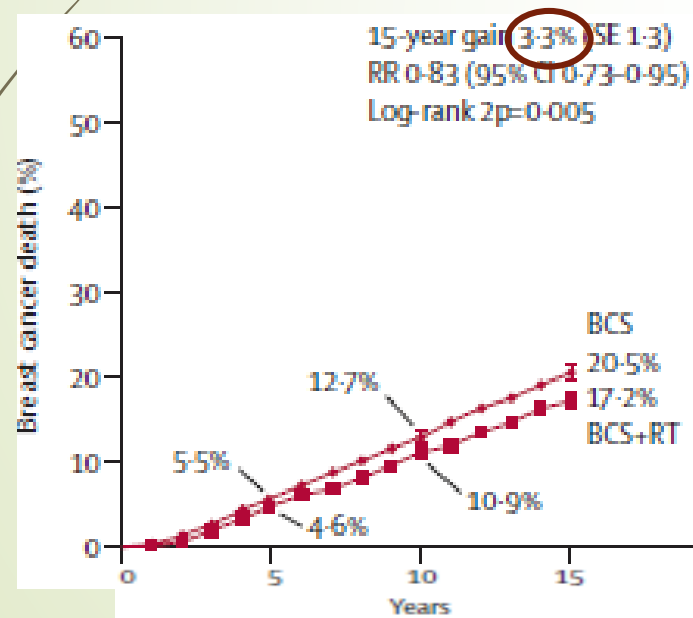
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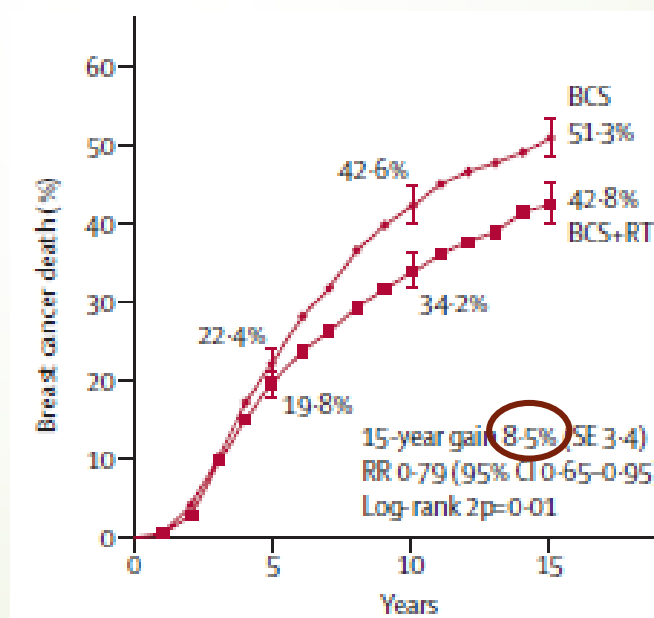
In conservative treatment, post-operative radiotherapy reduces the 15-year risk of breast cancer death

## Meta-analysis of EBCTCG

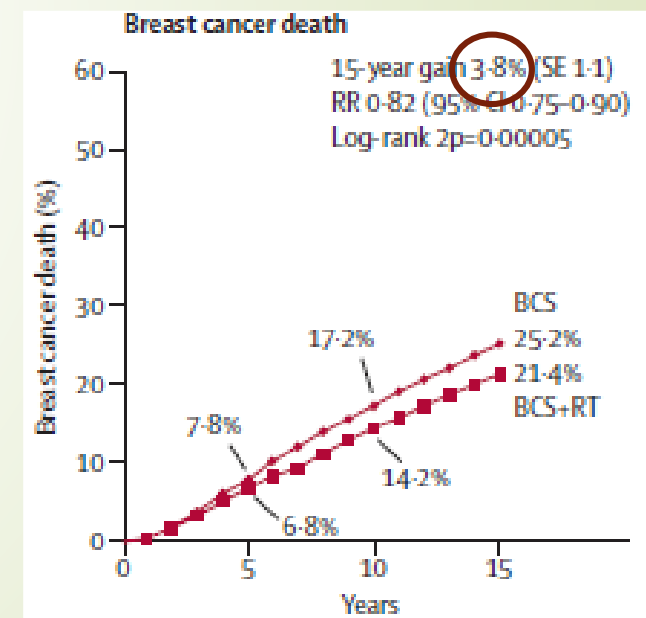
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pN0 = 7287 pts (67%)



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All = 10 801 pts



# What limitations for these results ?

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## The example of radiotherapy

17 trials	Breast irradiation	Boost irradiation	Regional nodal irradiation
76B NSABP B-06 82Y St George's	50 Gy (2 Gy/f) c or m 54 Gy d (2 Gy/f) m	None 10 Gy (2 Gy/f) o or e	None 0-50 Gy (2 Gy/f) m (IMC and SC/AF)†
84P Ontario COG 85B Scottish	40 Gy (2.5 Gy/f) c 50 Gy (2-2.5 Gy/f) m	12.5 Gy (2.5 Gy/f) c 10-30 Gy (2-3 Gy/f) o,e or i	None 50 Gy (2-2.5 Gy/f) m (IMC), 0-45 (2.3 Gy/f) m (SC/AF)†
85D West Midlands	40 Gy (2.7 Gy/f) or 50 Gy (2 Gy/f) d c	15 Gy (3 Gy/f) e/c	40 Gy (2.7 Gy/f) or 50 Gy (2 Gy/f) c (SC/AF)†
86C CRC UK	Various	Various	Various
81L Uppsala-Orebro 87R INT Milan III 90M Tampere 91P SweBCG 91-RT	54 Gy (2 Gy/f) c or m 50 Gy (2 Gy/f) c or m 50 Gy (2 Gy/f) m 48-54 Gy (1.9-2.2 Gy/f) m	None 10 Gy (2 Gy/f) o or e None None	None None None None
89L NSABP B-21	50 Gy (2 Gy/f) c or m	10 Gy (2 Gy/f) o¶	None
91J GBSG V Germany 92A PMH Toronto	50 Gy (2 Gy/f) m 40 Gy (2.5 Gy/f) or 50 Gy (2 Gy/f) c or m	10-12 Gy (2.0 Gy/f) e 12.5 Gy (2.5 Gy/f) o or e¶	None None
92P BASO II 94C CALGB 9343††	45-50Gy (2-2.3 Gy/f) m 45 Gy (1.8 Gy/f) c or m	10-15 Gy (2-3 Gy/f) e 14 Gy (2 Gy/f) e	None None
96Y ABCSG 8a††	50 Gy (2 Gy/f) c or m	10 Gy (0-2 Gy/f) e or I ¶	None
99W PRIME 1††	45-50Gy (2-2.3 Gy/f) m	0-15 Gy (0-2 Gy/f) e	None

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# What do we really know?

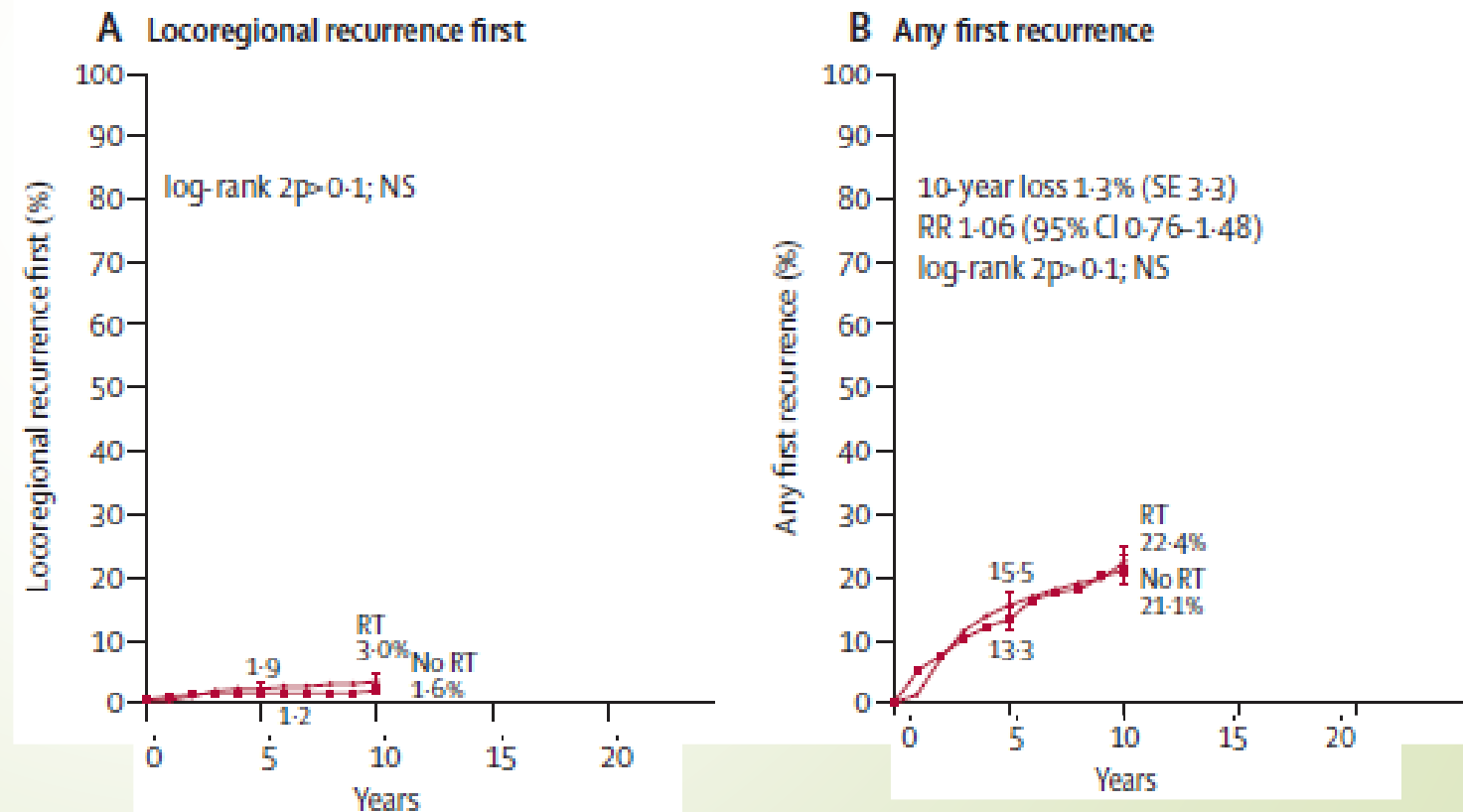
After mastectomy, post-operative radiotherapy has no significant effect on the 10-year recurrence for pN0 patients on axillary dissection.

Chest wall and nodes

pN0 = 700 pts (8,6 %, axillary dissection)

## Meta-analysis of EBCTCG

- 8 135 women in 22 trials
- beginning before 2000
- comparing RT vs no RT
- pN status unknown in 720 patients
- 3 887 axillary dissections
- 4 065 samplings
- 183 extent unknown
- Median follow-up : 9.4 years



# What do we really know?

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After mastectomy, post-operative radiotherapy has no significant effect on the 20-year cancer breast mortality for pN0 patients on axillary dissection.

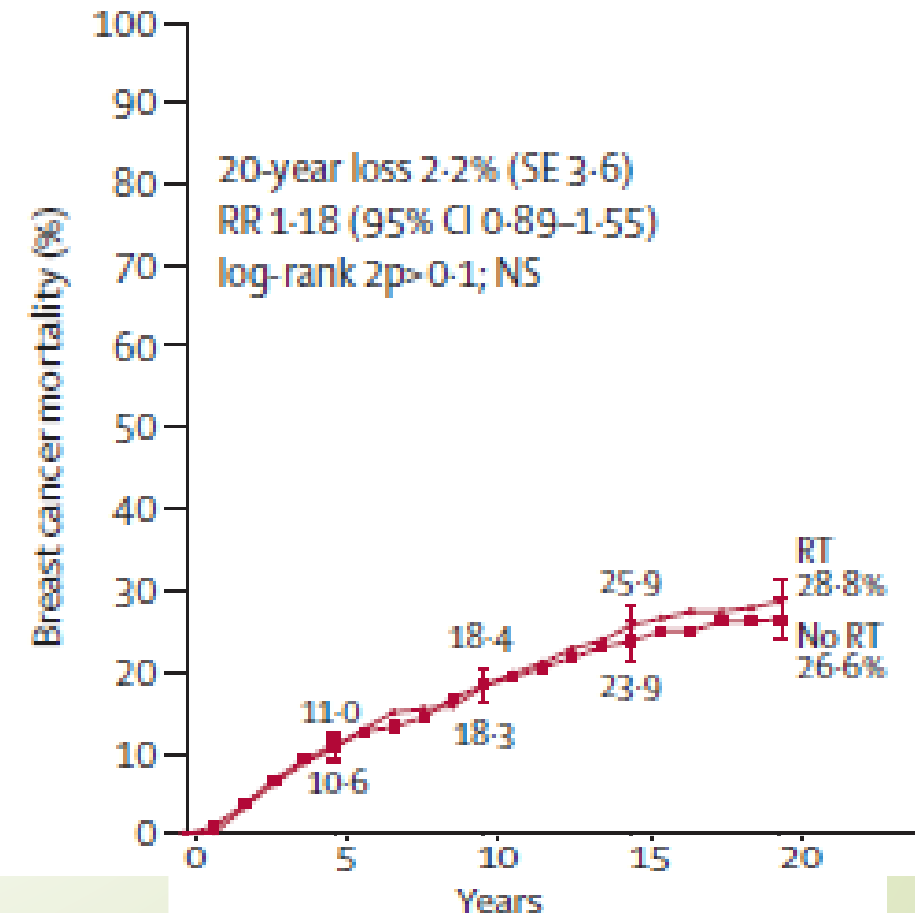
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## Chest wall and nodes

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### C Breast cancer mortality





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# What do we really know?

After mastectomy, post-operative radiotherapy reduces the 10-year risk of any first recurrence for pN+ patients

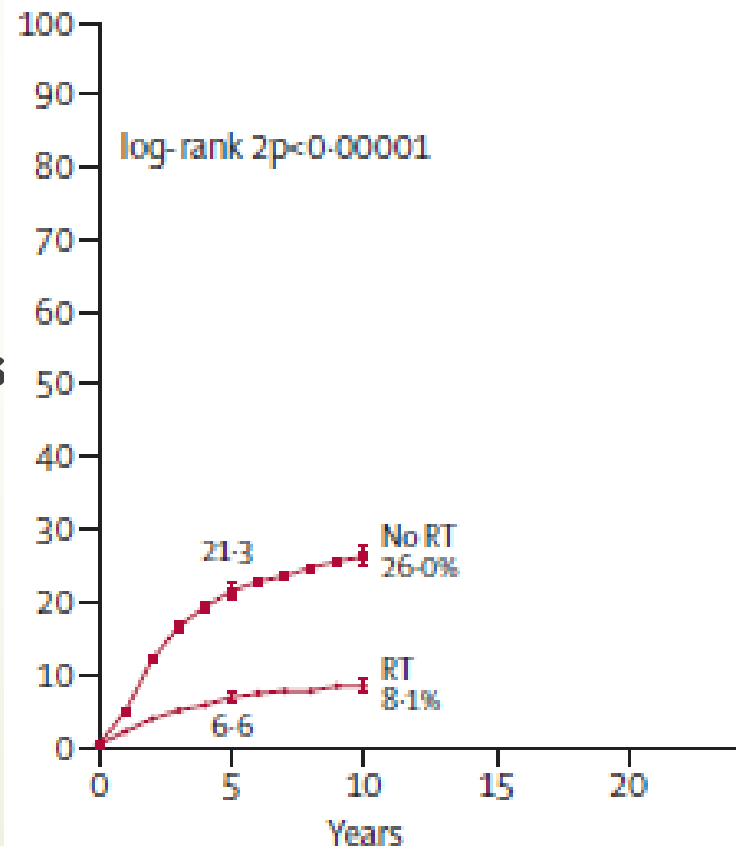
Chest wall and nodes

pN+ = 3 131 pts (38.4%, axillary dissection)

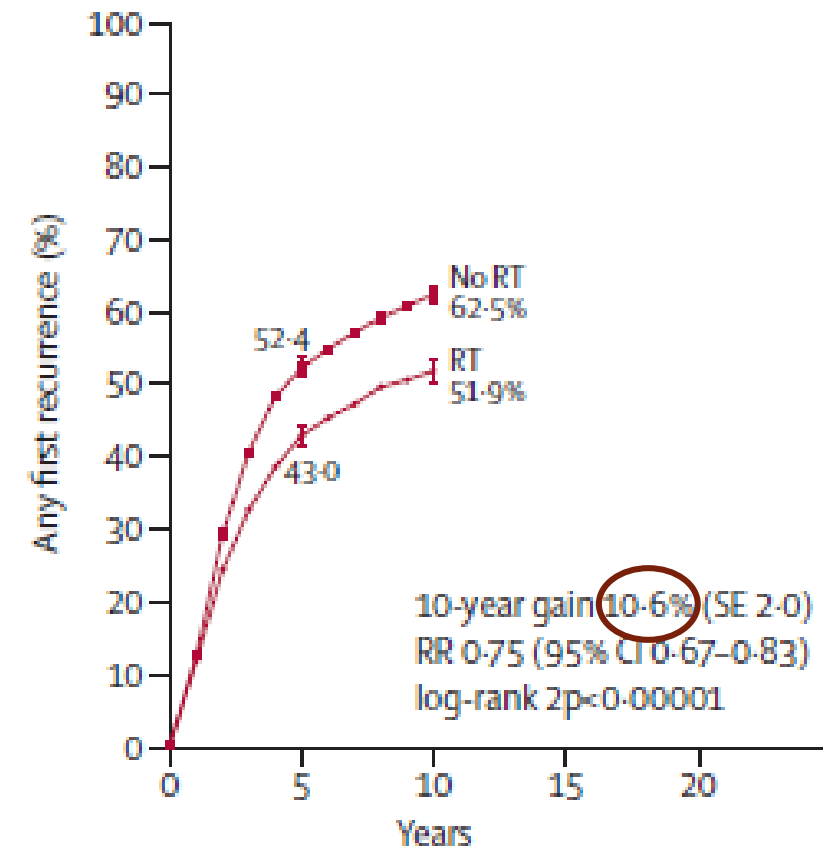
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D Locoregional recurrence first



E Any first recurrence



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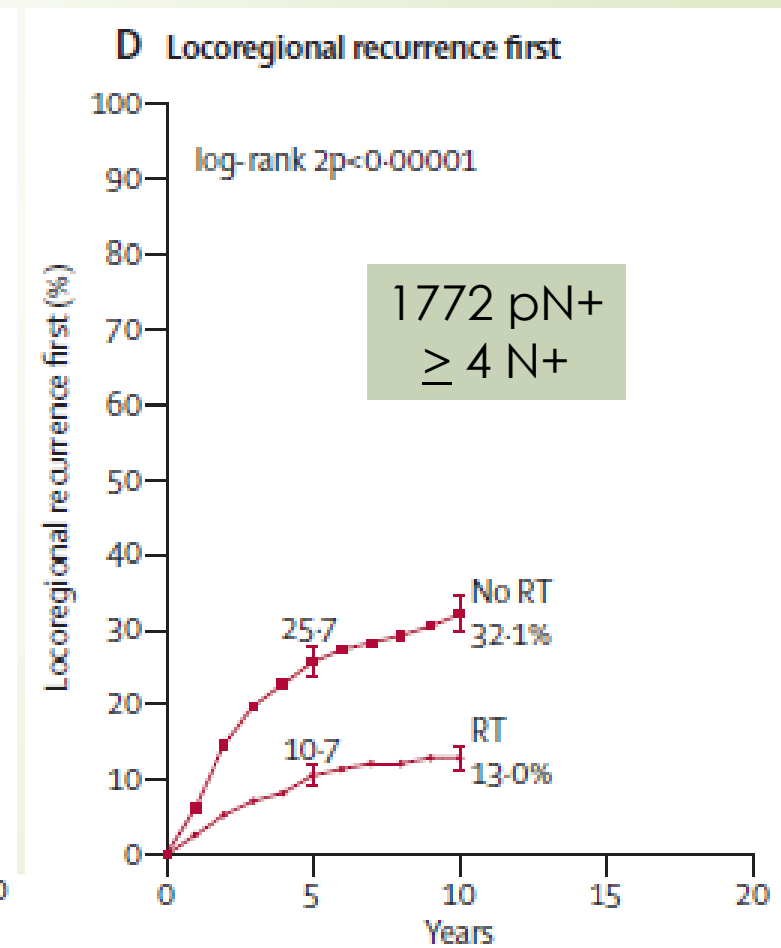
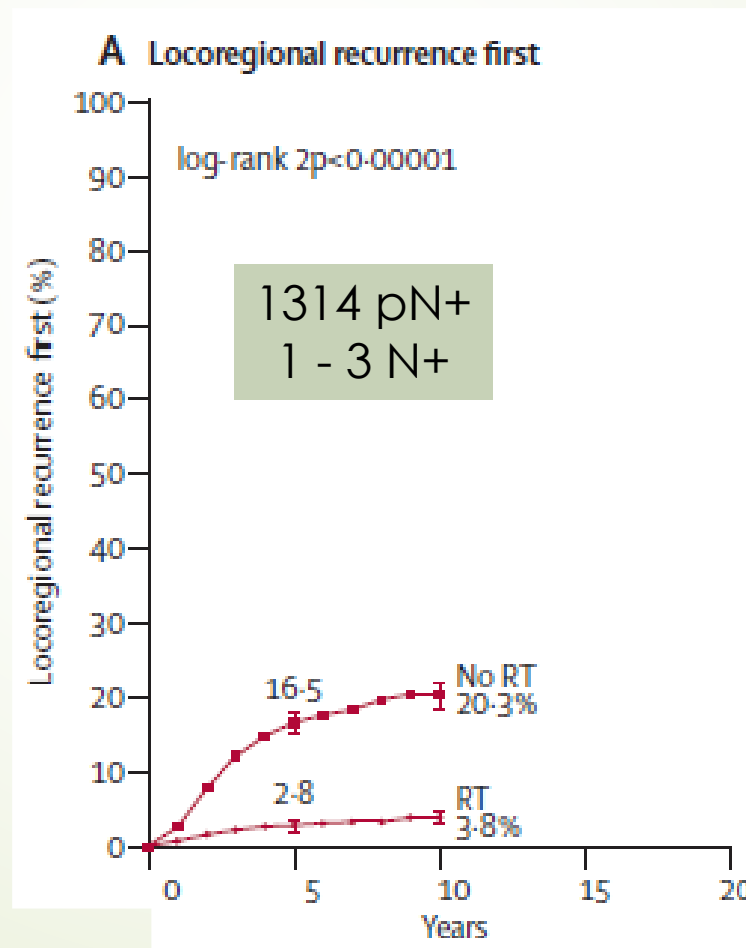
# What do we really know?

After mastectomy in pN+ patient, there is a benefit of post-operative radiotherapy on loco-regional recurrence rate whatever is the number of positive nodes

## Chest wall and nodes

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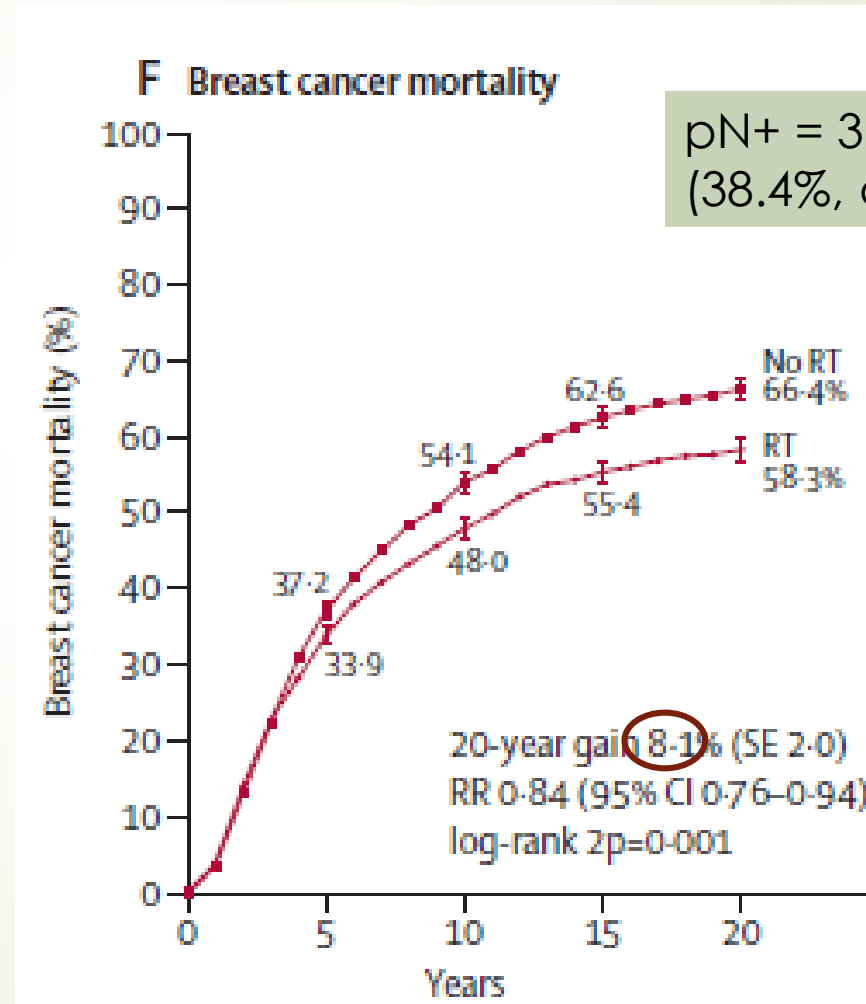
# What do we really know?

After mastectomy, post-operative radiotherapy reduces the 20-year risk of cancer breast mortality for pN+ patients

Chest wall and nodes

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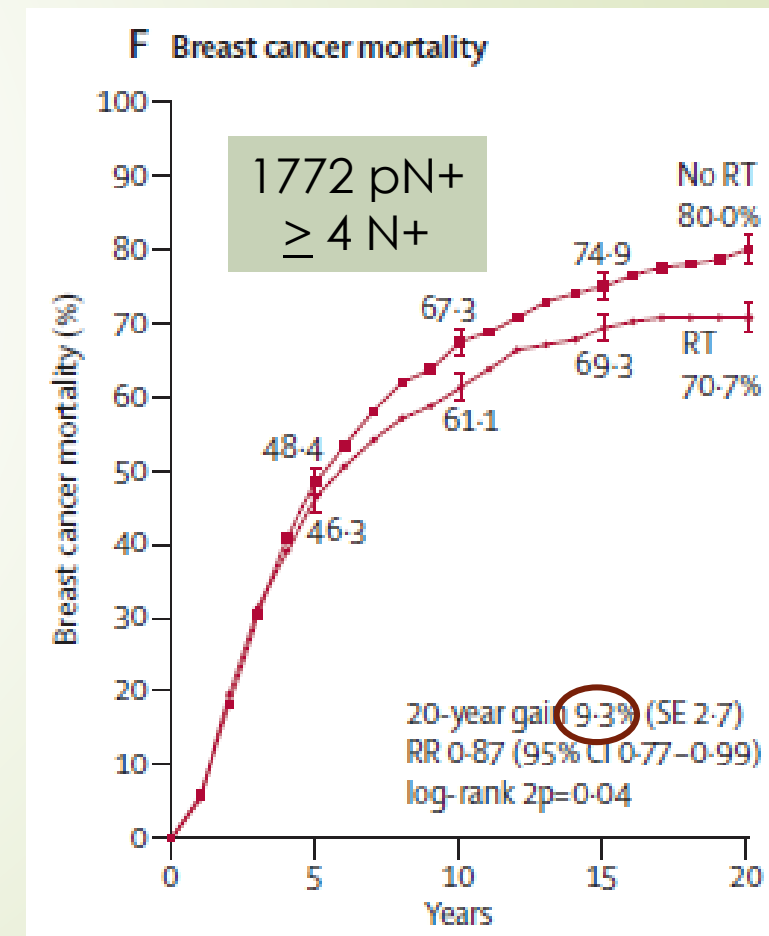
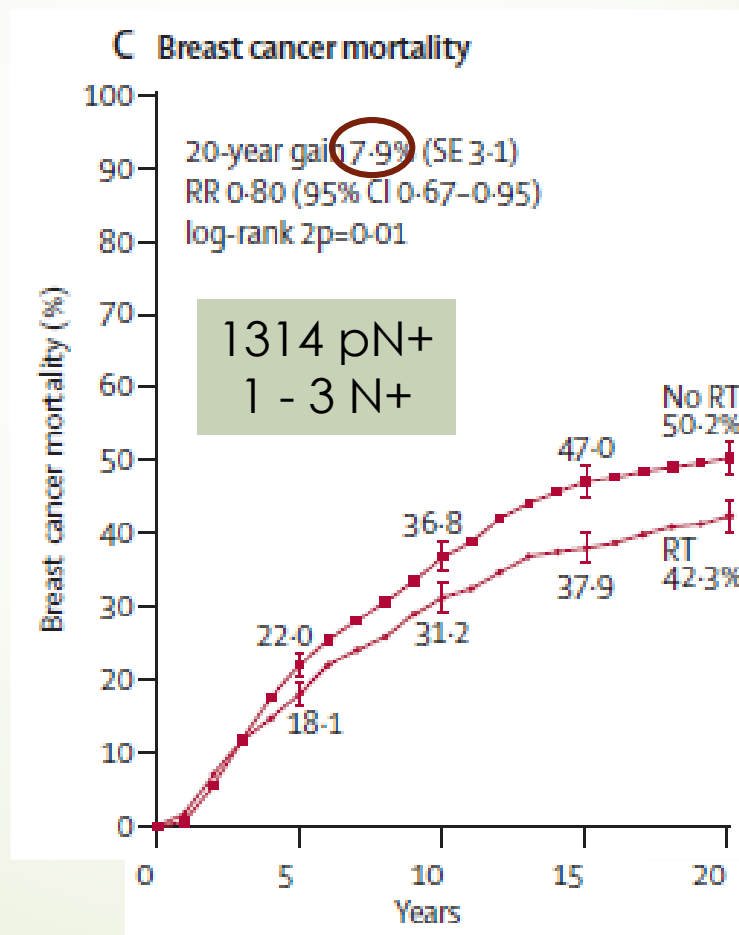
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After mastectomy in pN+ patient, there is a benefit of post-operative radiotherapy on breast-cancer mortality whatever is the number of positive nodes

## Chest wall and nodes

### Meta-analysis of EBCTCG

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# What do we really know?

After mastectomy in pN+ patients, the chest wall has to be irradiated to limit loco-regional recurrence

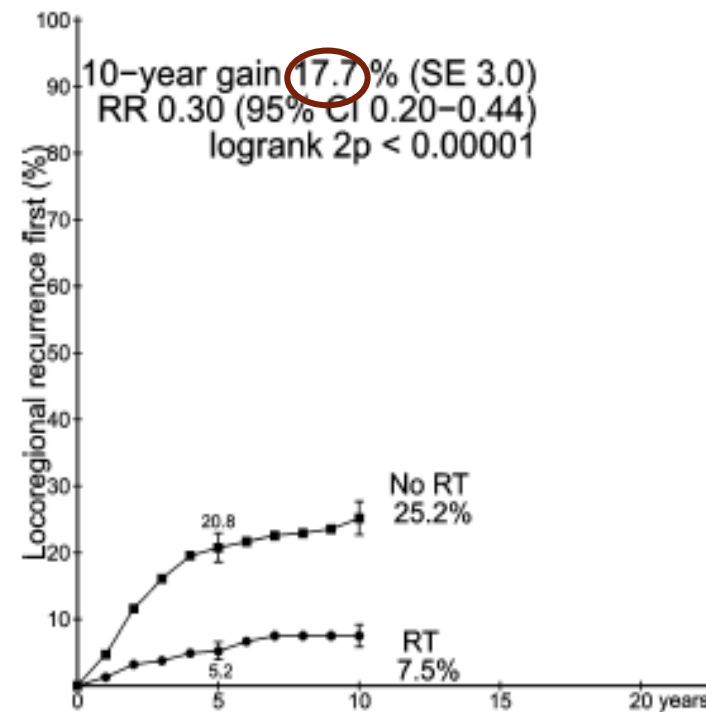
Regional nodes only : 8 trials

1029 pN+

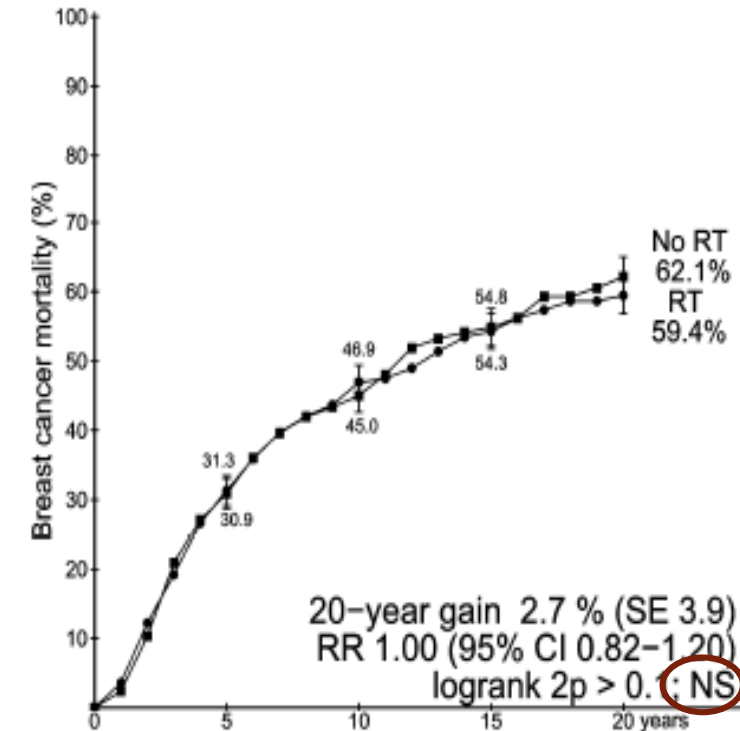
## Meta-analysis of EBCTCG

- 2304 women in 8 trials
- beginning before 2000
- comparing RT vs non RT
- pN status known in 1494 pts
- Median follow-up : 7.2 years

Locoregional recurrence first



Breast cancer mortality





# What limitations for these results ?

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The example of radiotherapy

22 trials

	Chest wall	Supraclavicular Axillary fossa	IMC	Boost on scar
Dose range (Gy)	25 - 60	18 - 60	0 - 60	2 trials

- ✓ **Fractionation range : 1.3 Gy – 4.5 Gy**
- ✓ **Variation of dose per fraction between chest wall and nodes : 4 trials**
- ✓ **Mix of various techniques :** Orthovoltage, Cobalt, Megavoltage, Electrons

# Other limitations for both meta-analysis?

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Because of an essential long follow-up

Meta-analysis couldn't take into account

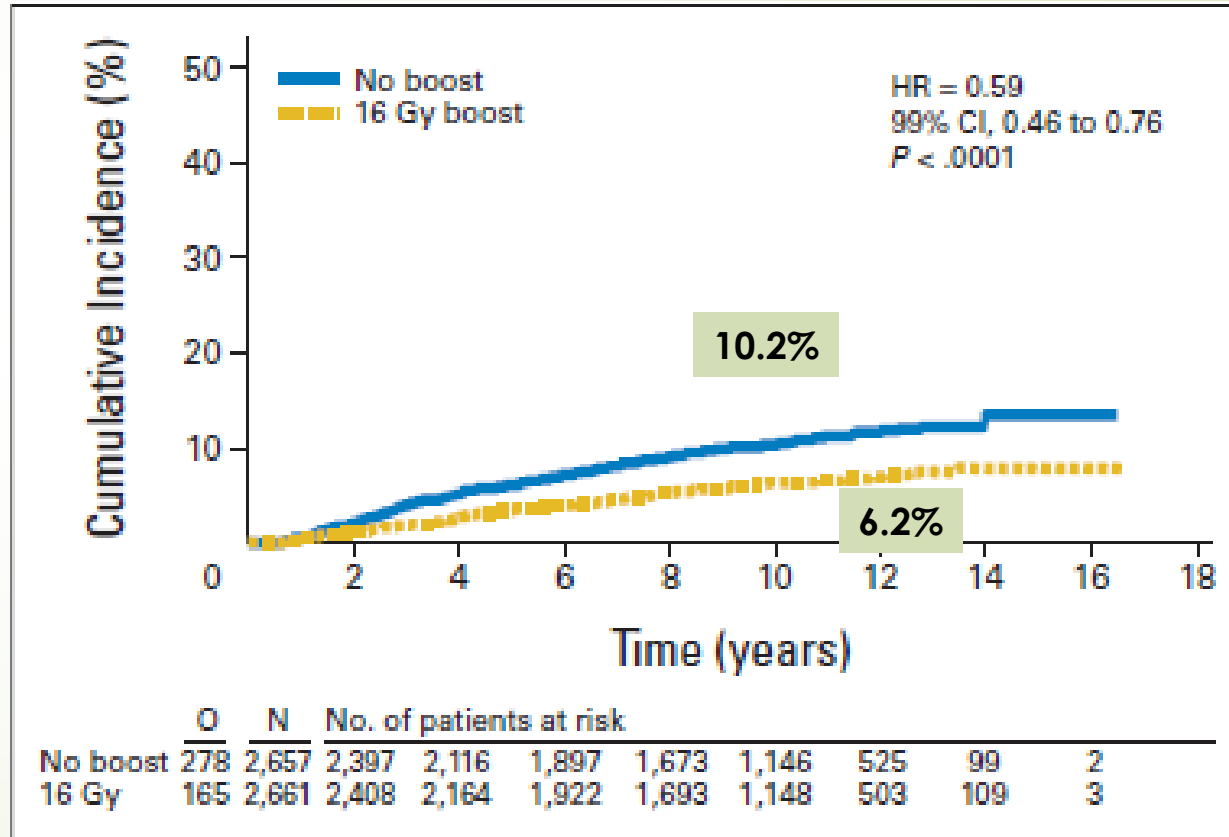
- Tumor size / pT
- Sentinel procedure in nodal assessment
- Type of surgery and margins status
- Advances in anatomopathology : grading, isolated tumor cells ...
- Advances in systemic treatment : taxanes, aromatase inhibitors, trastuzumab ...
- **After mastectomy, isn't there some benefit in pN0 patients ?**
  - T3-T4
  - young age, multifocal tumors, grade III, vascular invasion, triple negative and HER 2 positive tumors

# Boost or not boost in conservative treatment ?

Boost improved local control at ten years.

## Phase III of EORTC 22 881-10 882

- 5,318 women
- 31 centers, 9 countries
- From 1989 to 1996
- Comparing boost (16 Gy = 2,661 pts) vs no boost (2,657 pts)
- Microscopically complete resection + axillary dissection
- Whole breast irradiation 50 Gy (5x2Gy)
- Boost = tangential fields, electrons or low dose rate brachytherapy
- Median follow-up : 10.8 years

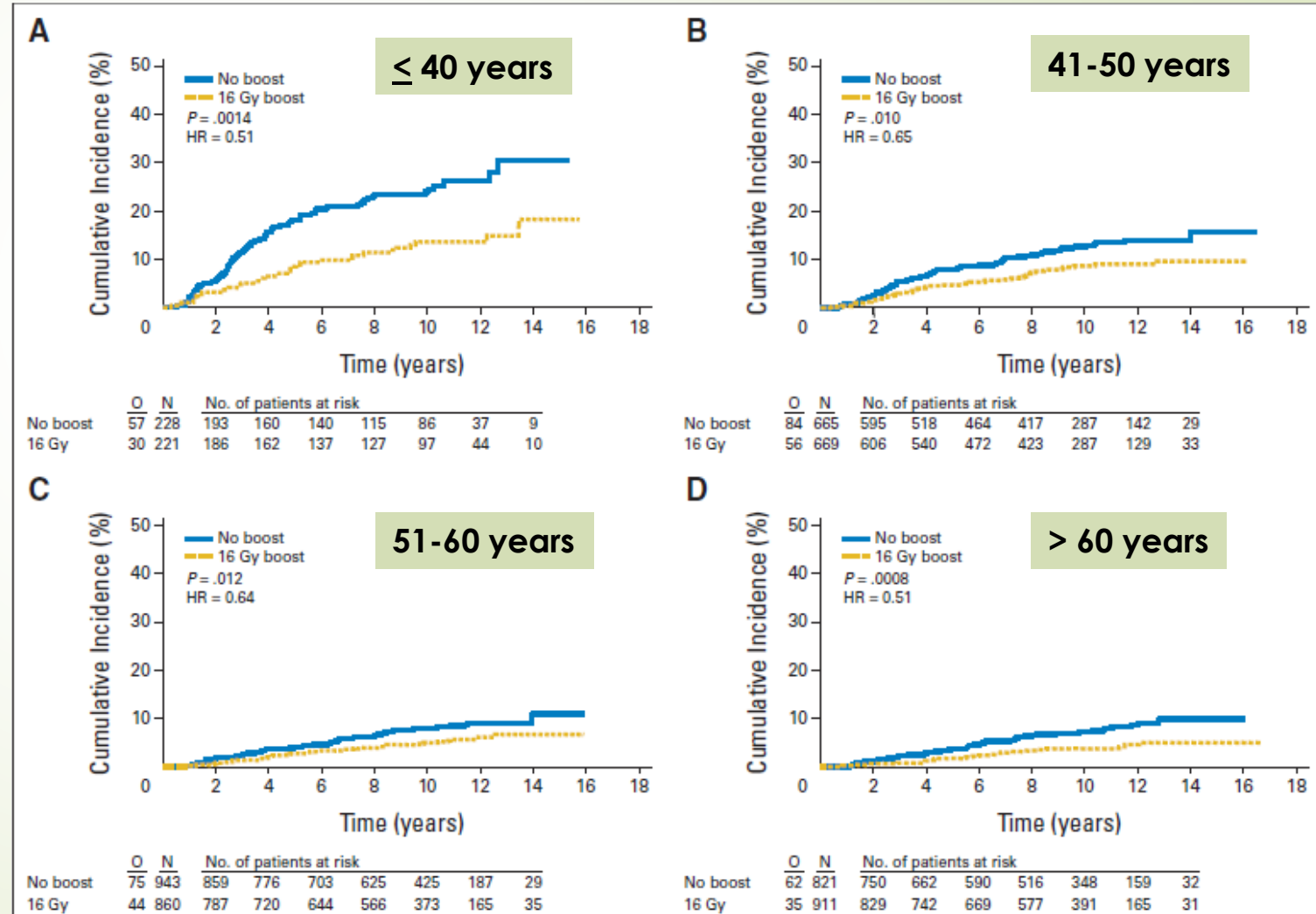


# Boost or not boost in conservative treatment ?

Boost improved local control at ten years in all age groups.

## Phase III of EORTC 22 881-10 882

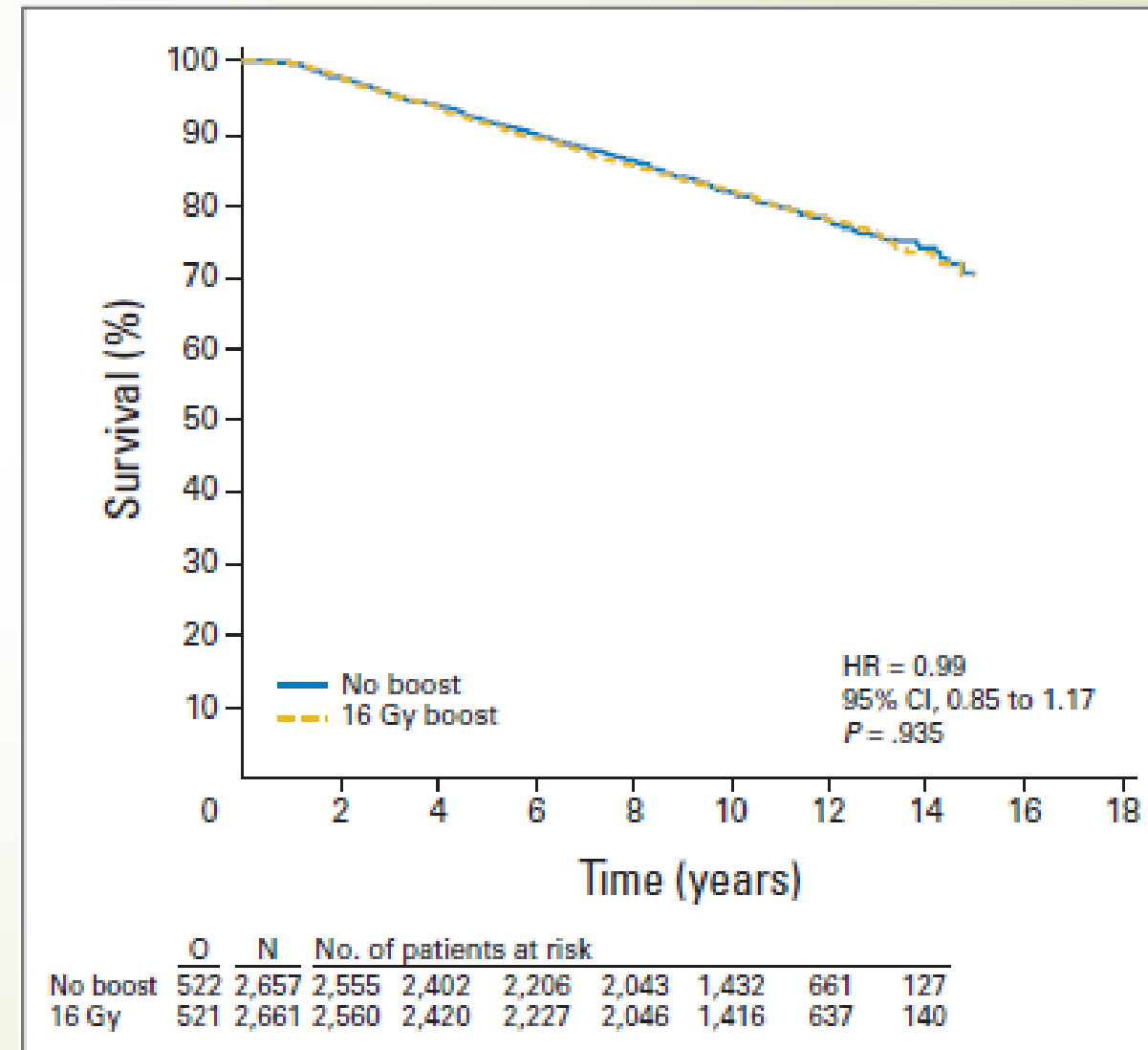
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# Boost or not boost in conservative treatment ?

Boost does not improved disease-free survival at ten years.

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# IMN or no IMN irradiation?

## Is the question always discussed?

### ► Is the issue worth debating ?

Local recurrences after mastectomy and systemic treatment without RT (%)

	N pts	Total	Chest wall	Clavicular	Axillary	IMN
NSABP 2004	5758	19,8	56,9	22,6	11,7	<1
IBCSG 2003	5352	21	53	26	13	1
MD Anderson Cancer Center 2005	1031	19	67*	43	11	0

### ► Numerous retrospective studies with conflicting results

### ► Pulmonary and cardiac toxicity

### ► IMN involvement on surgical dissection

Tumor location	Axillary status	
	pN+	pN0
Internal	32–65%	7–20%
Central	29–48%	0–12%
External	22–42%	3–13%
All	28–52%	4–16%

# IMN or no IMN irradiation?

## The clever Danish trial : the natural random !

### 3,089 early-stage node-positive breast cancers

Thorsen LB.JCO 2015, in press

- Mastectomy or conservative treatment with axillary dissection + systemic therapy
- **Natural random right breast vs left breast ; assessment in intent to treat**
- Chest wall irradiation for both groups ; with assurance quality of IMN dose coverage
- Median follow-up : 8.9 years

	IMNI = right breast 1492 pts	No IMNI = left breast 1597 pts	HR
<b>8-year overall survival</b> (first endpoint)	<b>75.9%</b>	<b>72.2%</b>	Death 0.8 [0.72 – 0.94] ; <b>p = 0.005</b>
<b>8-year breast mortality</b>	<b>20.9%</b>	<b>23.4%</b>	Death 0.85 [0.73 – 0.98] ; <b>p = 0.03</b>
<b>Distant recurrences</b>	<b>27.4%</b>	<b>29.7%</b>	0.89 [0.78 – 1.01] ; p = 0.07

# IMN or no IMN irradiation? Three randomized trials

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IB	Hennequin C. Red J2013. 86 : 860	Poortmans P. N Engl 2015. 373 : 317	Whelan TJ. N Engl 2015. 373 : 307
	French trial 1991-1997	EORTC 1996-2004	MA-20 (Canadian) 2000-2007
<b>N pts</b>	1334	4004	1832
<b>Surgery</b>	Mastectomy	Conservative (76%) Mastectomy	Conservative
<b>Inclusion criteria</b>	pN+	pN+	pN+
	pN0: internal/central	pN0: internal/central	pN0: High risk
<b>RT: control arm</b>	Chest wall Supraclav/axillary	Chest wall / Breast	Breast
<b>RT: experimental arm</b>	IMN	IMN Supraclav	IMN Supraclav/axillary
<b>Benefit</b>			
10-year overall survival	3.3% ; p = 0,8	<b>1.6% ; p= 0.05</b>	1% ; p = 0.38
10-year DFS	3.3% ; p = 0,35	<b>3% ; p = 0.04</b>	<b>5% ; p = 0.01</b>

# IMN or no IMN irradiation? One meta-analysis

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Budach et al. Radiat Oncol 2015. 10:258

## Comparison I: (MS+IM)+(WBI/CWI) vs. (WBI/CWI)

MA.20 [10]: n=1832; HR 0.91 (95% CL 0.72 - 1.13)

EORTC [12]: n=4004; HR 0.87 (95% CL 0.76 - 1.00)

Subtotal\*: n=5836; HR 0.88 (95% CL 0.78 - 0.99)

## Comparison II: IM+(WBI/CWI+MS) vs. (WBI/CWI+MS)

French [13]: n=1334; HR 0.94 (95% CL 0.79 - 1.11)

Subtotal: n=1334; HR 0.94 (95% CL 0.79 - 1.11)

## Comparison I+II

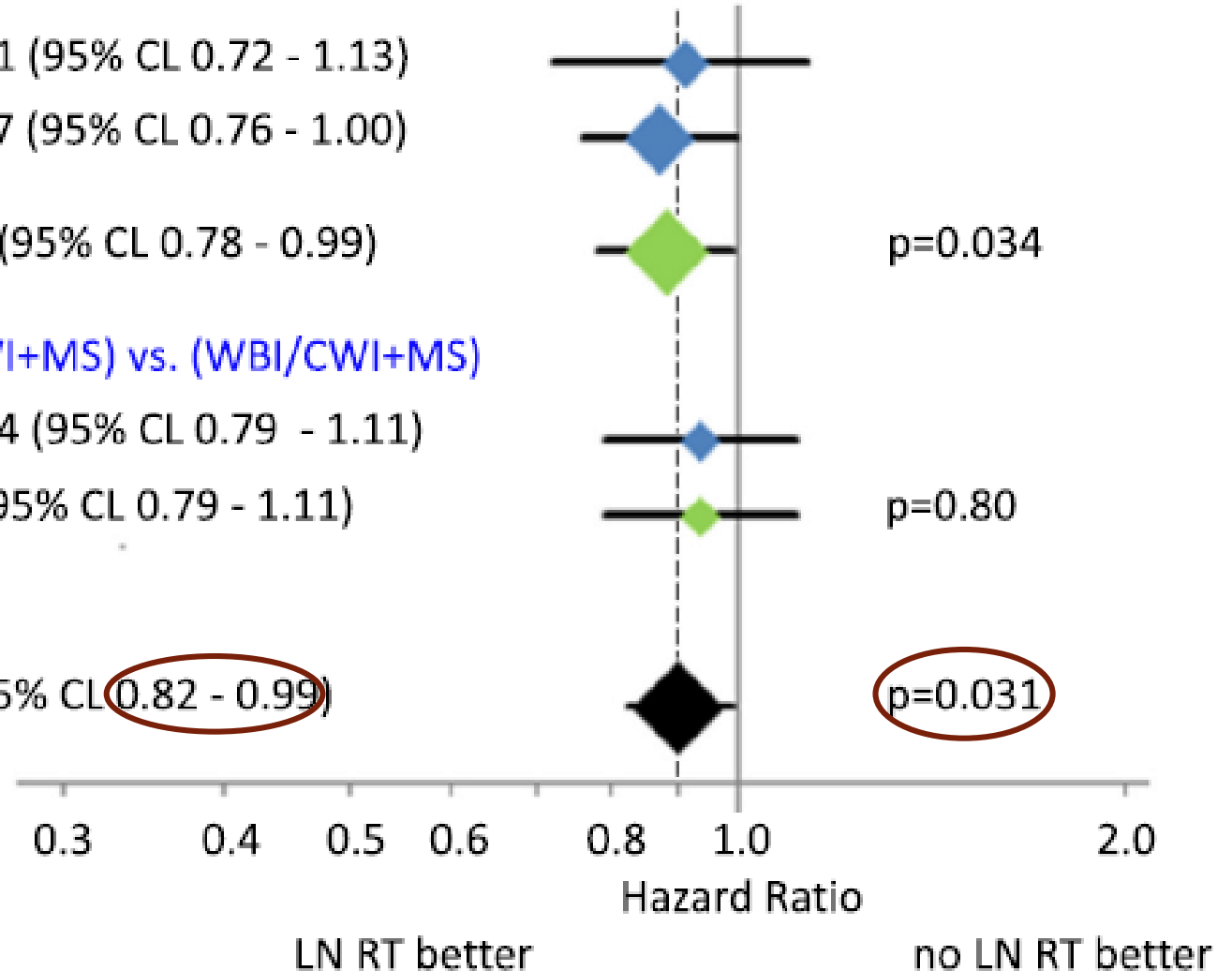
Total\*\*: n=7170; HR 0.90 (95% CL 0.82 - 0.99)

\* = fixed effect model

\*\* = random effect model

## Overall Survival

IA?



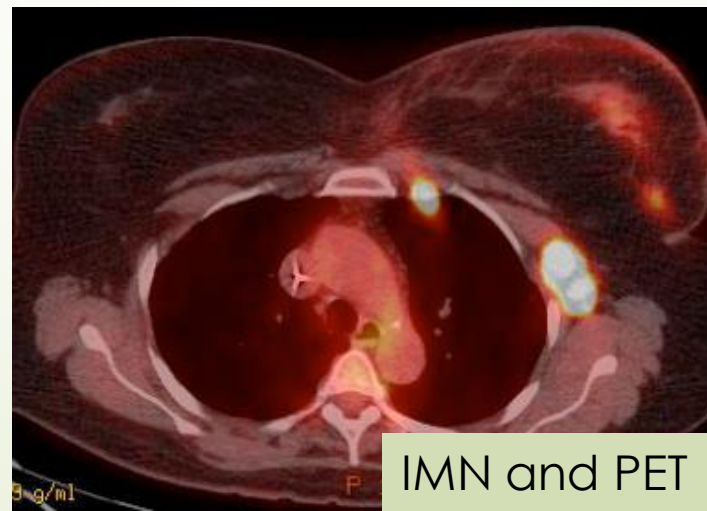
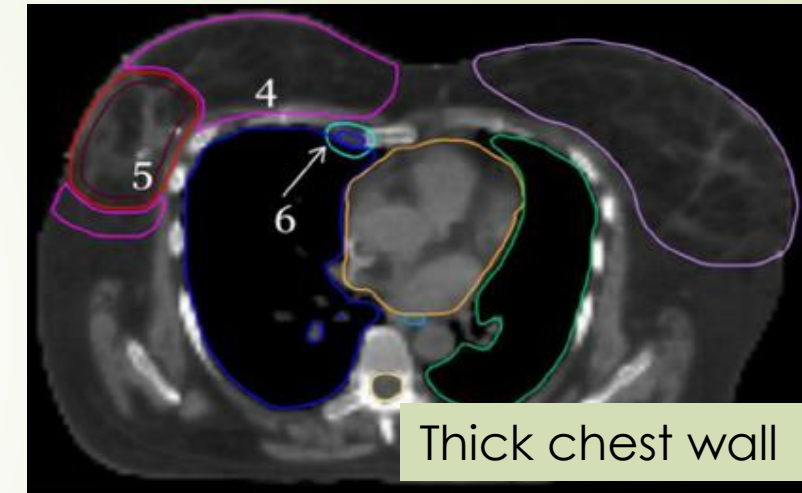
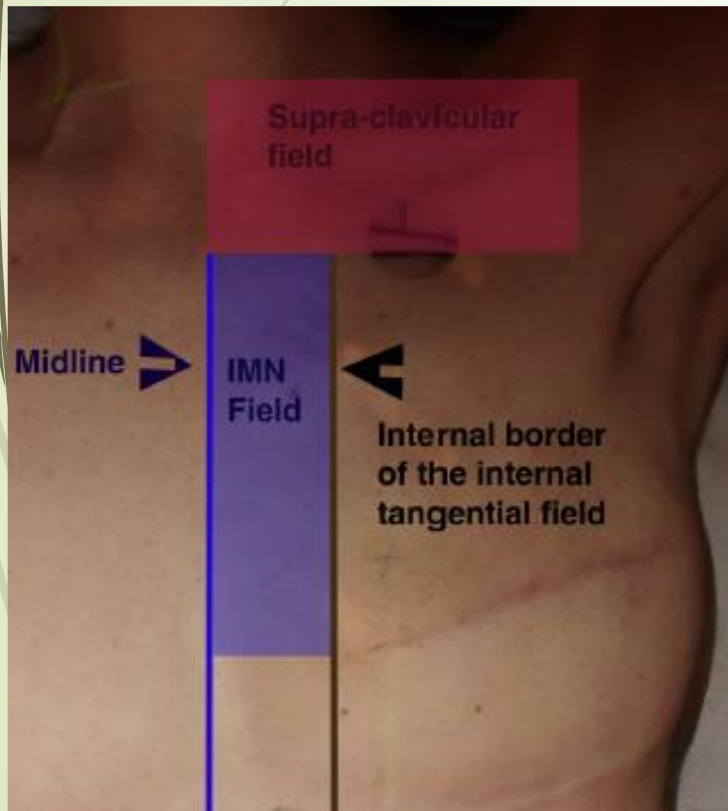
# IMN or no IMN irradiation?

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## Where is the IMN ?

3D technique

2D technique





# Axillary nodes : Surgery or radiotherapy ?

IB

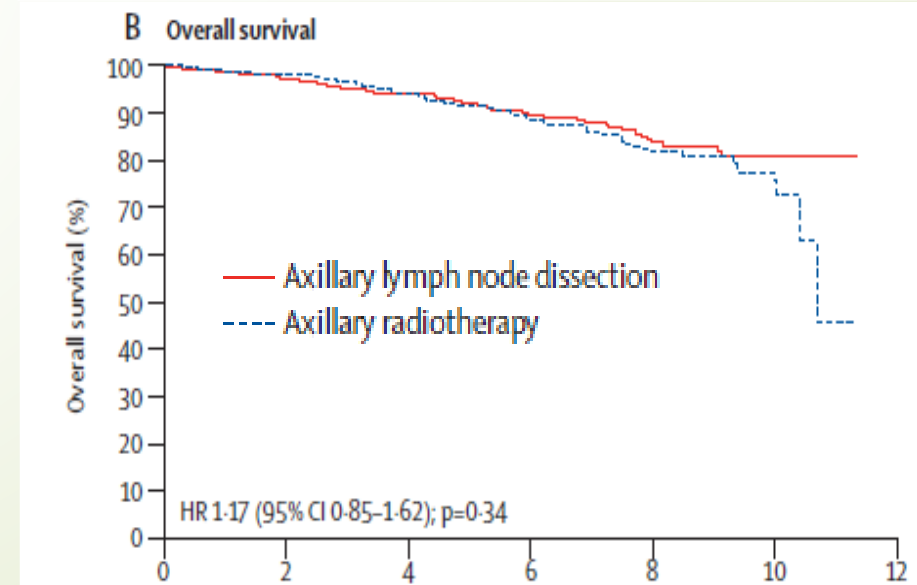
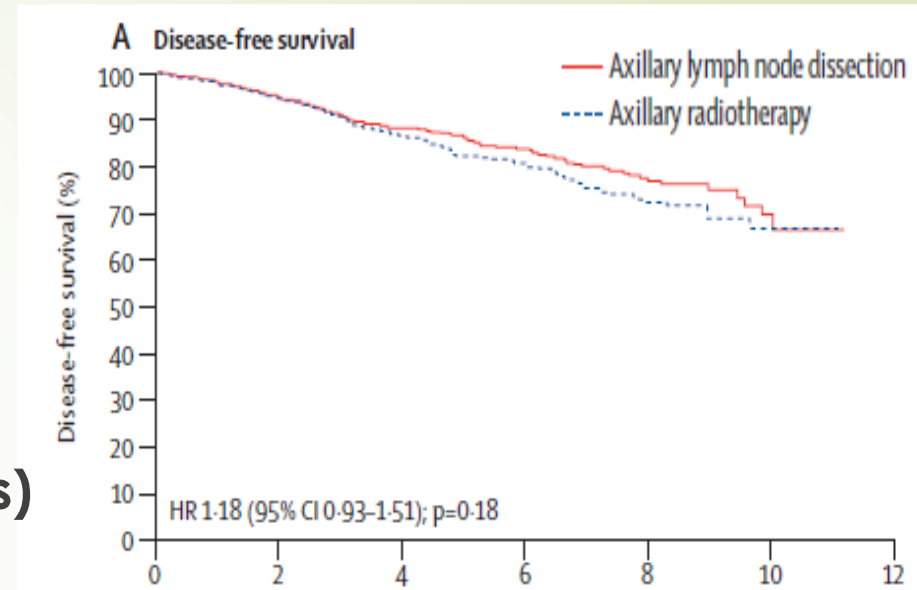
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## The AMAROS trial

Lancet Oncol 2014. 15 : 1303

### Phase III of EORTC 22 023-10 981

- Non-inferiority trial From 2001 to 2010
- 4,823 women with T1-T2
- 34 centers, 9 countries
- Comparing axillary dissection (2,402 pts) vs RT (2,404 pts)
- 1425 pts (30%) with positive sentinel nodes :
  - ✓ 704 pts = axillary dissection (median : 15 nodes)
  - ✓ 681 pts = RT
- Axillary RT = 50 Gy (5x2Gy) on levels I to III
- Axillary RT allowed if  $\geq 4$  positive nodes (41 pts)
- Median follow-up : 6.1 years



# Axillary nodes : Surgery or radiotherapy ?

IB

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## The AMAROS trial

Lancet Oncol 2014. 15 : 1303

	Axillary dissection 704 pts	Axillary RT 681 pts
pN+	220 (33%)	NA
Axillary recurrence	4	7
<b>NS</b> 5-year axillary recurrence rate	0.43 [0-0.92]	1.19 [0.31-2.08]

	Axillary lymph node dissection	Axillary radiotherapy	p value
<b>Clinical sign of lymphoedema in the ipsilateral arm</b>			
1 year	114/410 (28%)	62/410 (15%)	<0-0001
3 years	84/373 (23%)	47/341 (14%)	0-003
5 years	76/328 (23%)	31/286 (11%)	<0-0001
<b>Arm circumference increase ≥10% of the ipsilateral upper or lower arm, or both</b>			
1 year	32/410 (8%)	24/410 (6%)	0-332
3 years	38/373 (10%)	22/341 (6%)	0-080
5 years	43/328 (13%)	16/286 (6%)	0-0009

# What about fractionation ?

## Conservative treatment

- Hypofractionation : daily dose  $> 2\text{Gy}$
- Evidence-based guidelines **Task force of ASTRO**
- Randomized trials of whole breast irradiation comparing CF vs HF
- **Clinical eligibility criteria :**

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.
4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose ( $\pm 7\%$ ;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

# What about fractionation ?

## Conservative treatment

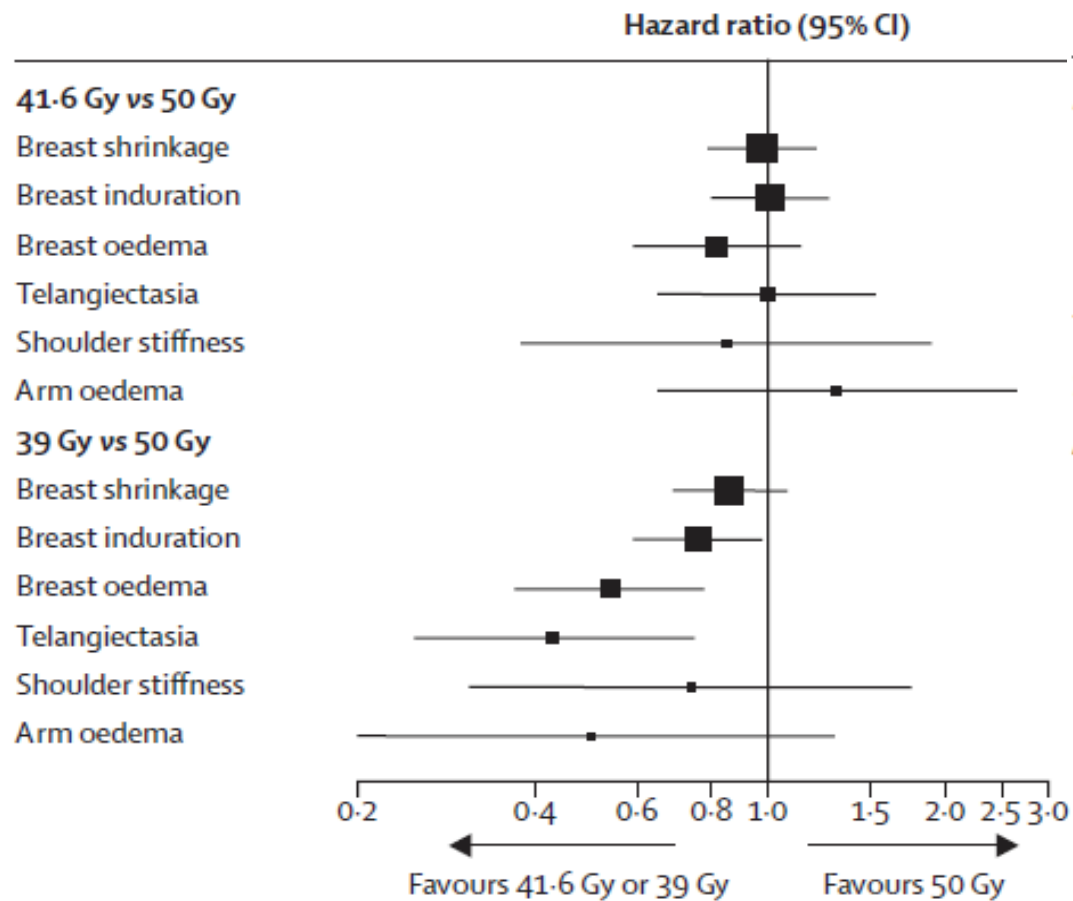
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	Canada 1234 pts		Royal Marsden 1410 pts		START A 2236 pts		START B 2215 pts	
Breast conserving	100%		100%		85%		92%	
T1-T2	100%		94%		< 2cm = 51%		< 2cm = 64%	
pN0	100%		40%		69%		74%	
No CT	89%		86%		65%		78%	
Boost (Gy)	-		14, 7f		10, 5f		10, 5f	
Nodal RT	0%		21%		14%		7%	
Doses (Gy)	42.5, 16f	50, 25f	42.5, 16f 39, 13f	50, 25f	41.6, 13f 39, 13f	50, 25f	40, 15f	50, 25f
Days	22	35	35		35		35	
Median FU (year)	12		9.7		9.3		9.9	
Time point	10		10		10		10	
Ipsi breast rec	6,2%	6,7%	9.6% 14.8%	12.1%	6.3% 8.8%	7.4%	4,3%	5,5%
			p=0.027					
Cosmetic results good	69.8%	71.3%	74.4% 58%	71.2%	Slide 28			
			p< 0.001					

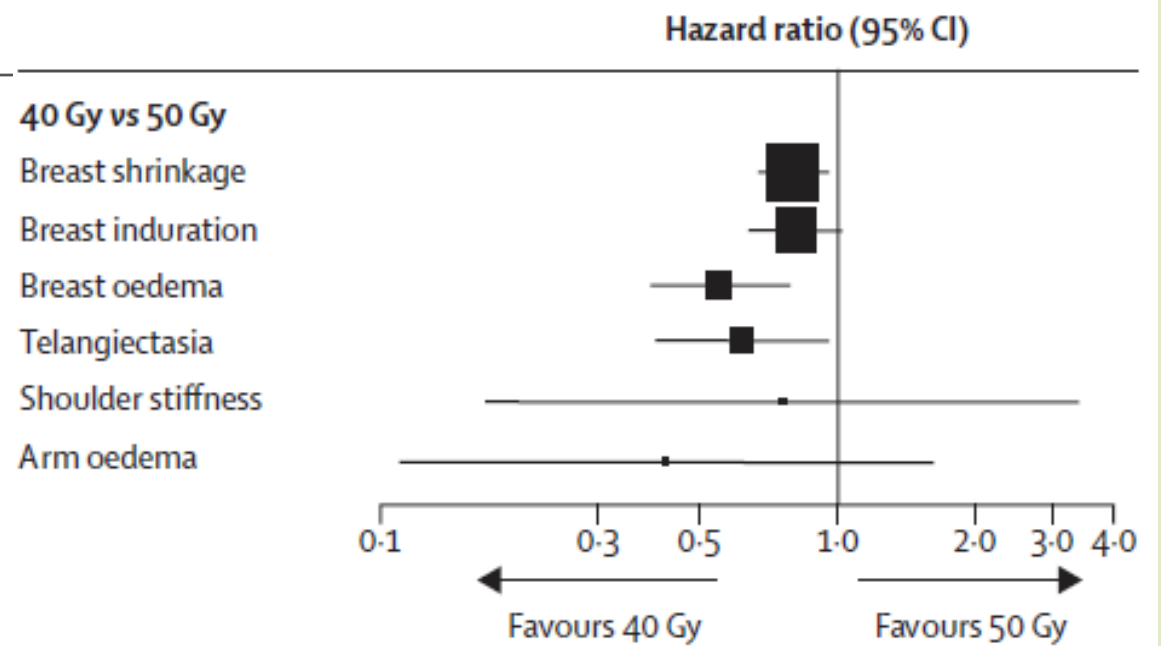
# What about fractionation ?

## START A and B : cosmetic results

A



B





# Conclusions



- In breast cancer, large part of our routine practice is based on level I of evidence for radiotherapy
- In breast cancer, the necessity of a long follow-up impacts on the conclusions of the phase III trials because of the constant technological progress.
- The quality of the techniques of irradiation must be assessed by expert committee for every randomized trial to validate the results of the trial
- Evidence based medicine stays mandatory to compare modern techniques and choose the best one