

How do clinical trials impact on practice of radiotherapy in breast cancer?



Alain Fourquet
Department of Radiation
Oncology

Assisi November 2013

Introduction

- ▶ **Several large phase III clinical trials conducted over the years have set up the scene for breast cancer irradiation**
- ▶ **To evaluate their impact of practice**
 - **Main trials, and metaanalyses**
 - **National guidelines**

Material

▶ Trials and metaanalyses

▶ Guidelines

- **NCCN (USA) 2013**
- **INCa (France) 2102**
- **REMAGUS (Institut Curie & Institut Gustave
Roussy) 2011**

Trials

- 1. Postmastectomy Radiotherapy**
- 2. Mastectomy vs Breast-conserving treatment with RT**
- 3. Whole-breast irradiation after breast-conserving surgery**
 - Invasive cancer**
 - DCIS**
- 4. Fractionation trials**
- 5. Toxicity**

Trials

- 1. Postmastectomy Radiotherapy**
- 2. Mastectomy vs Breast-conserving treatment with RT**
- 3. Whole-breast irradiation after breast-conserving surgery**
 - Invasive cancer
 - DCIS
- 4. Fractionation trials**
- 5. Toxicity**

Postmastectomy trials

▶ 20 trials

▶ 8266 women

▶ Adjuvant systemic treatments:

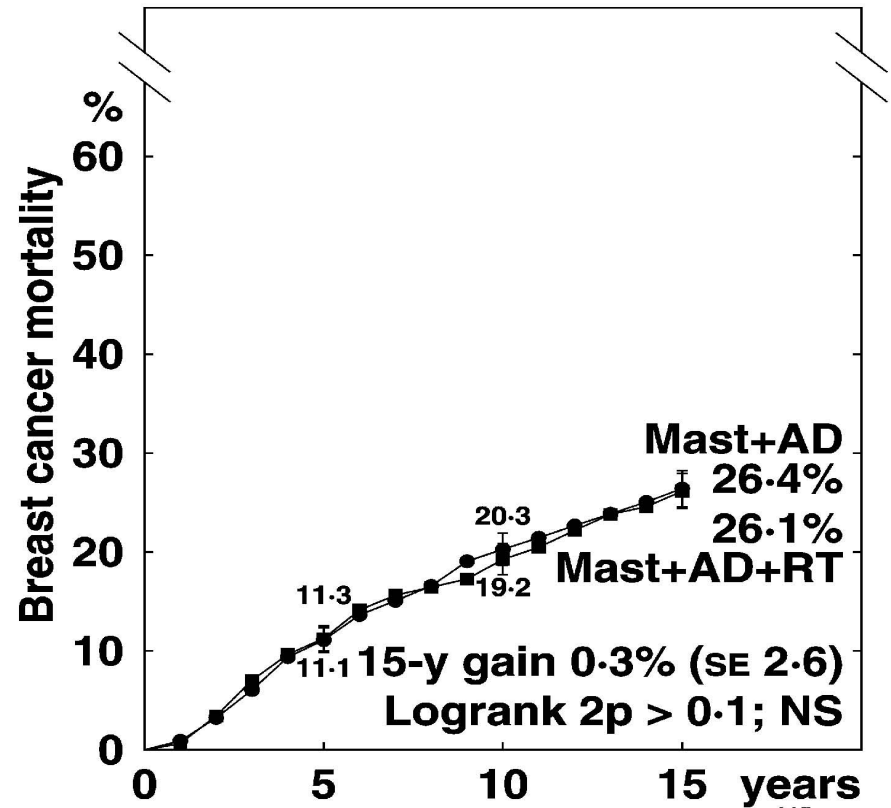
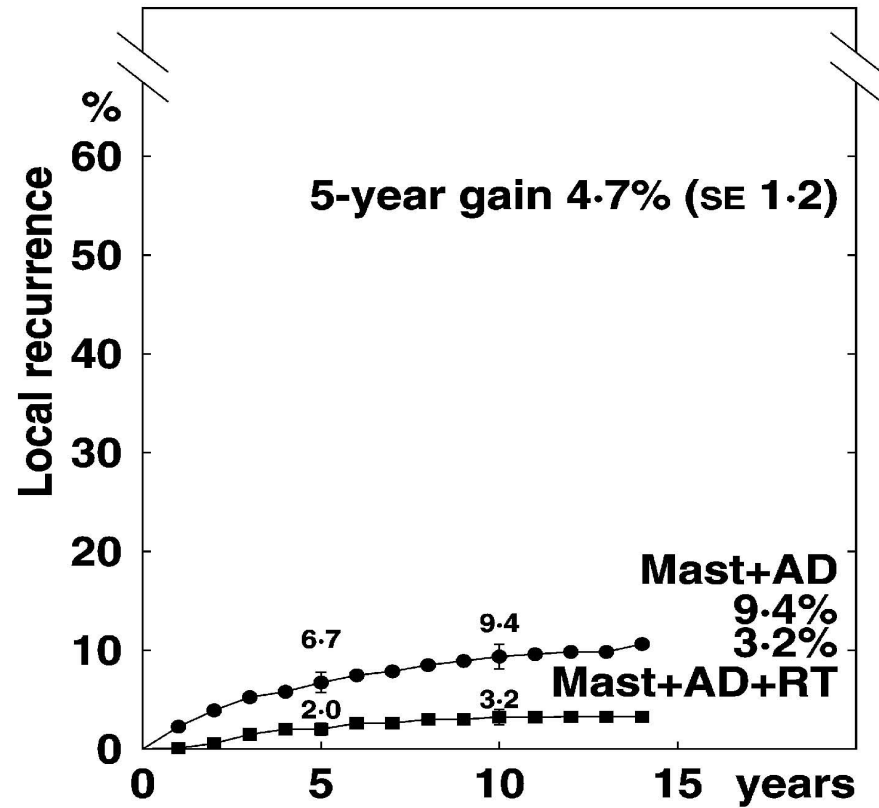
• pN0 34 %

• pN+ve 67%

▶ Median f/u: 8.6 years

pN0 in trials of Mast+AD ± RT: 15-year risks

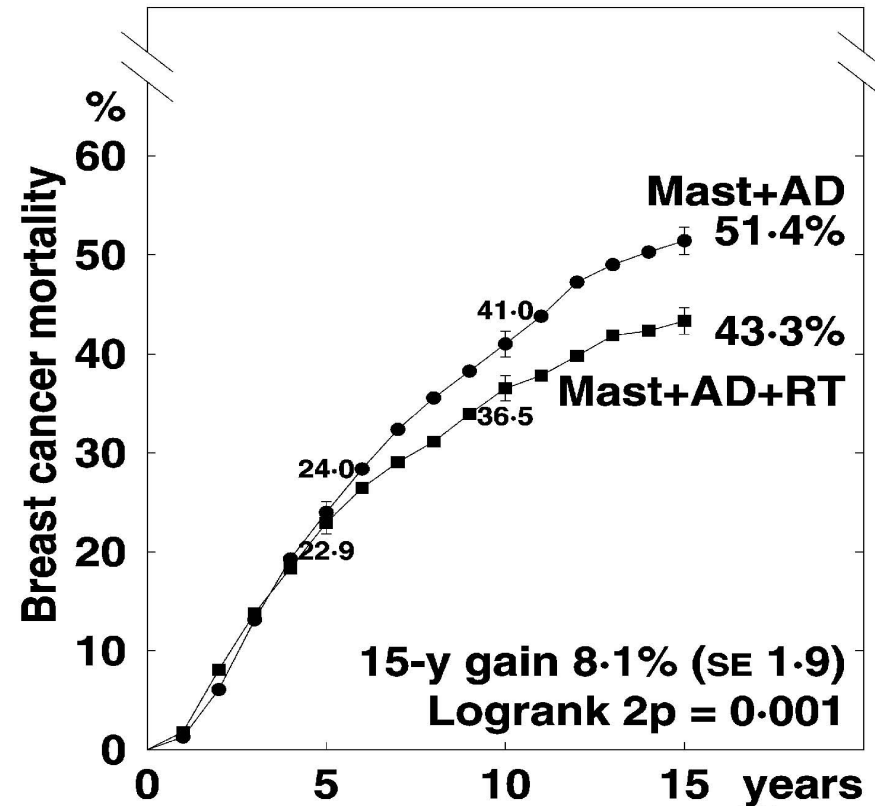
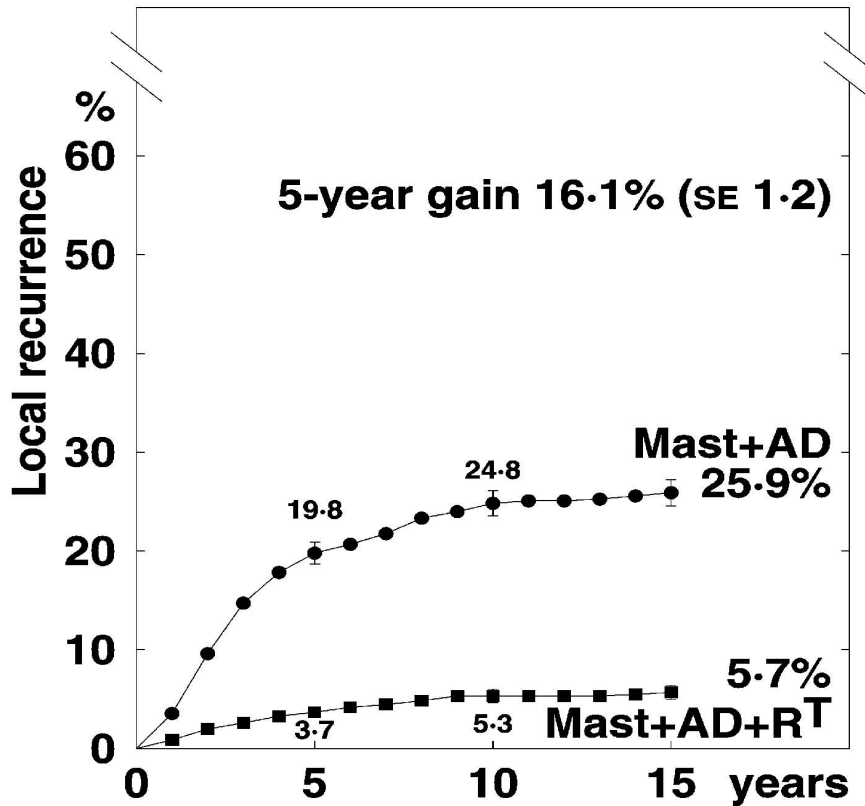
1296 women



Preliminary results: subject to revision

pN1-3 in trials of Mast+AD ± RT: 15-year risks

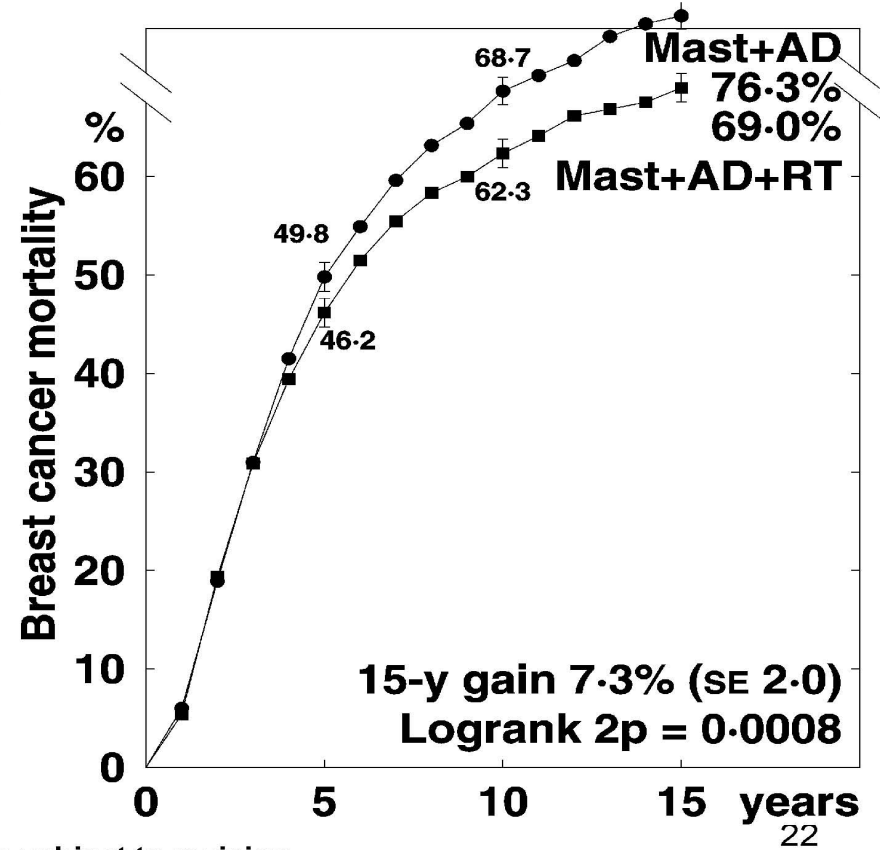
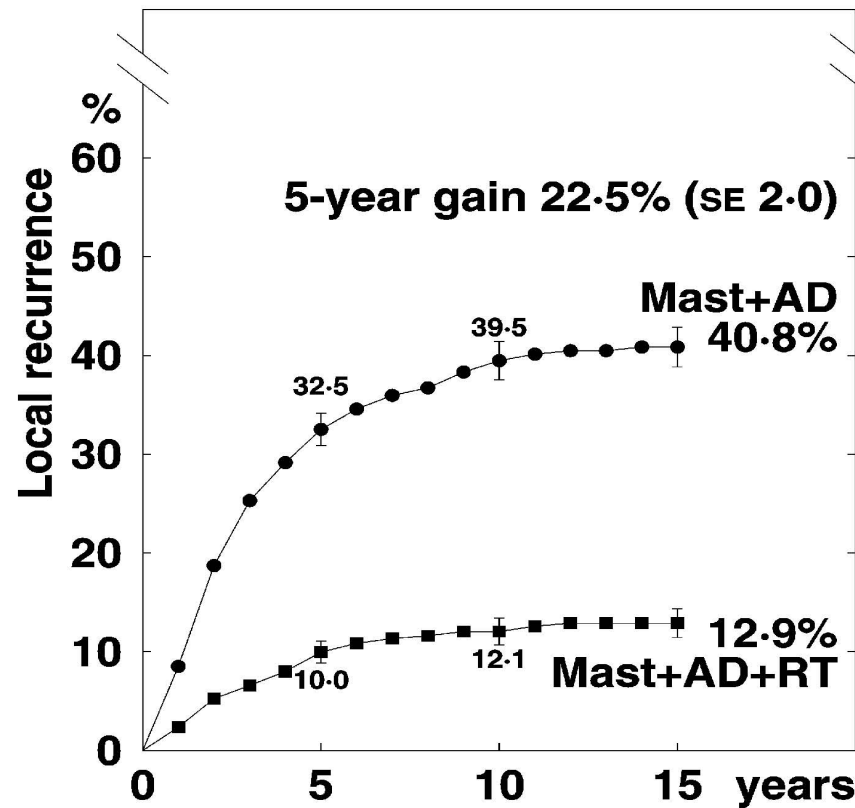
3222 women



Preliminary results: subject to revision

pN4+ in trials of Mast+AD ± RT: 15-year risks

2794 women



Preliminary results: subject to revision

Conclusion 1

- ▶ **A 70% locoregional risk reduction was achieved by PMRT, mostly during the first five years of follow-up**
- ▶ **In node positive cancer, PMRT significantly reduced mortality: this effect became apparent after 5 years**

PMRT. NCCN guidelines 2013

	Chest wall	Supra/Infra clavicular nodes	IMN
pN > 3	√	√	***
pN1-3	***	***	***
pN0 and pT > 5 cm or margins pos.	**	**	***
pN0 and pT < 5 cm and margins close (<1mm)	**	-	-
pN0 and pT < 5 cm and margins free	-	-	-

√: recommended

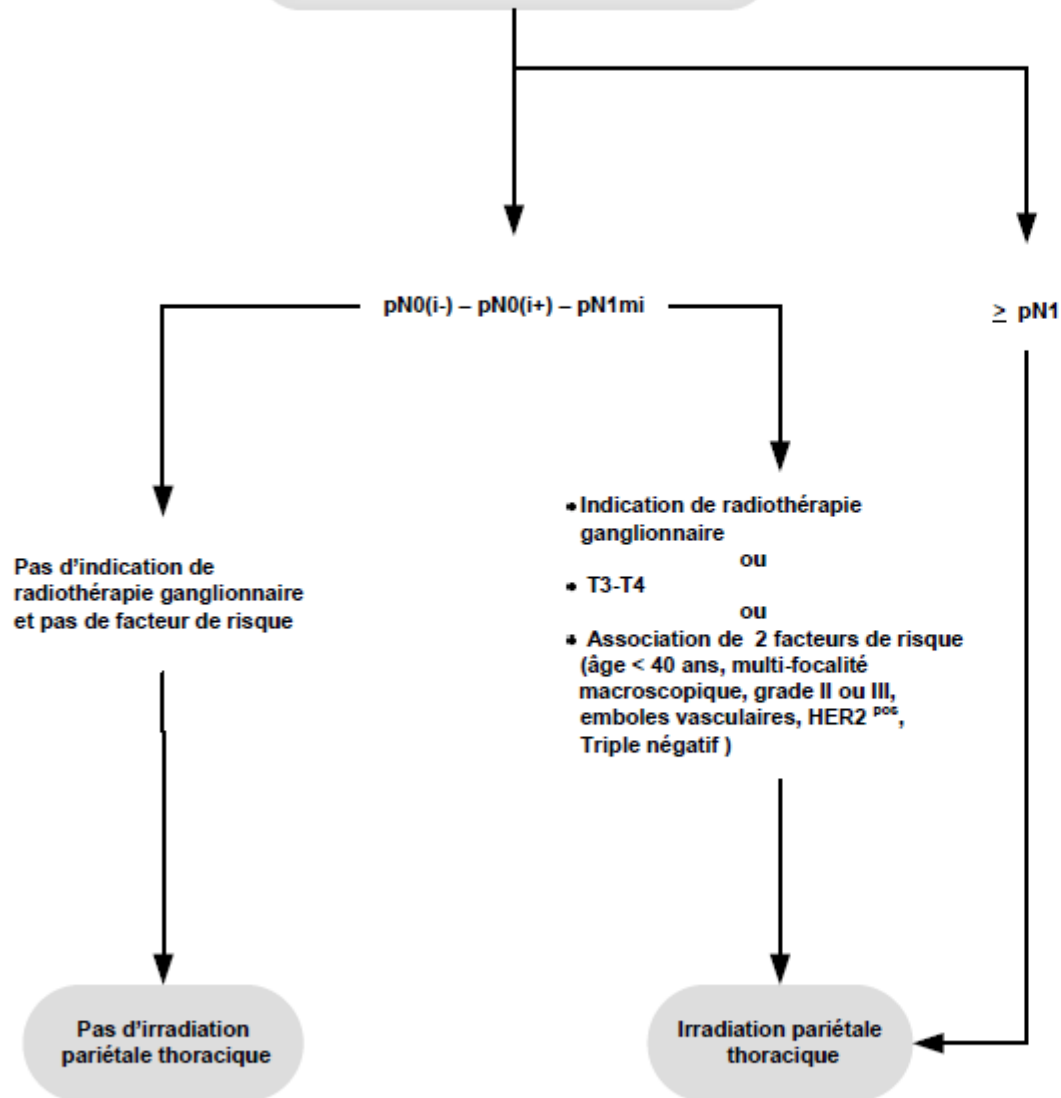
***: strongly consider

** : consider

Carcinomes infiltrants Traitement non conservateur

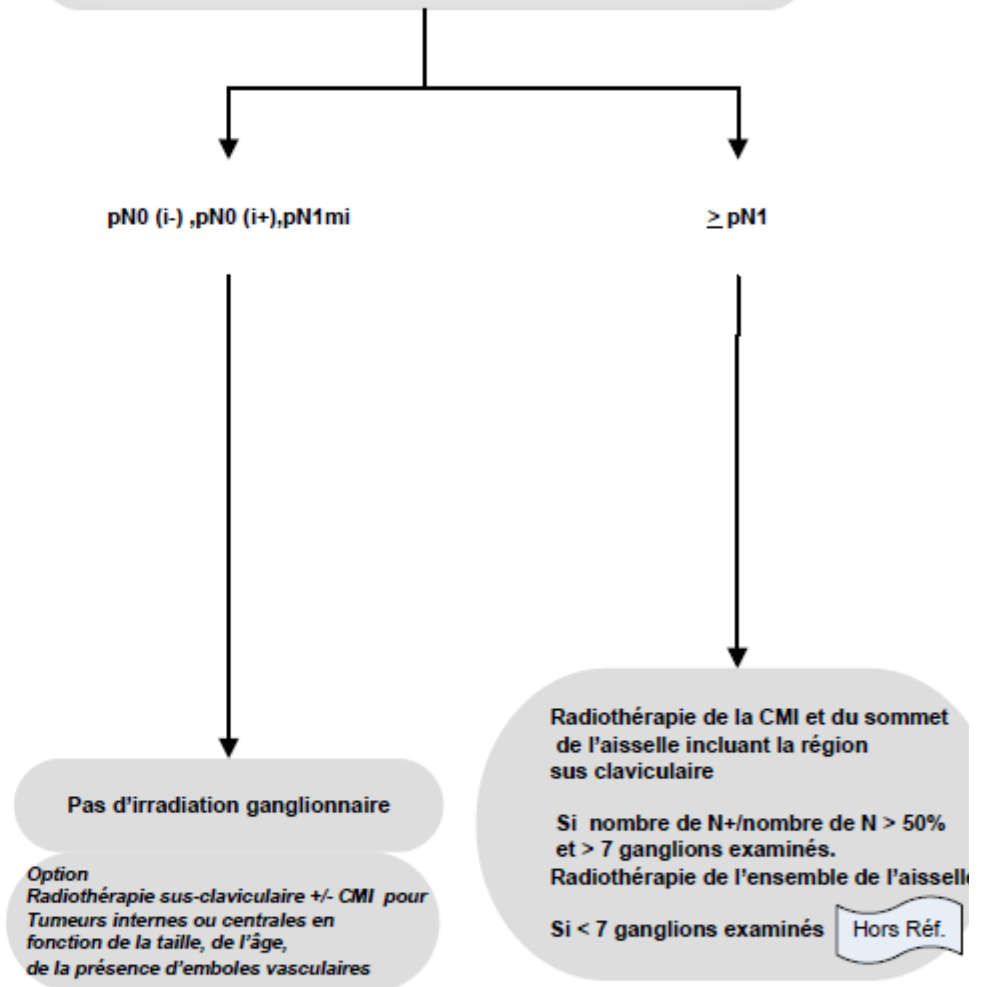
RADIOTHÉRAPIE DE LA PAROI THORACIQUE

MASTECTOMIE TOTALE SIMPLE



RADIOTHÉRAPIE DES AIRES GANGLIONNAIRES

STATUT GANGLIONNAIRE POST CHIRURGICAL



Trials

- 1. Postmastectomy Radiotherapy**
- 2. Mastectomy vs Breast-conserving treatment with RT**
- 3. Whole-breast irradiation after breast-conserving surgery**
 - Invasive cancer
 - DCIS
- 4. Fractionation trials**
- 5. Toxicity**

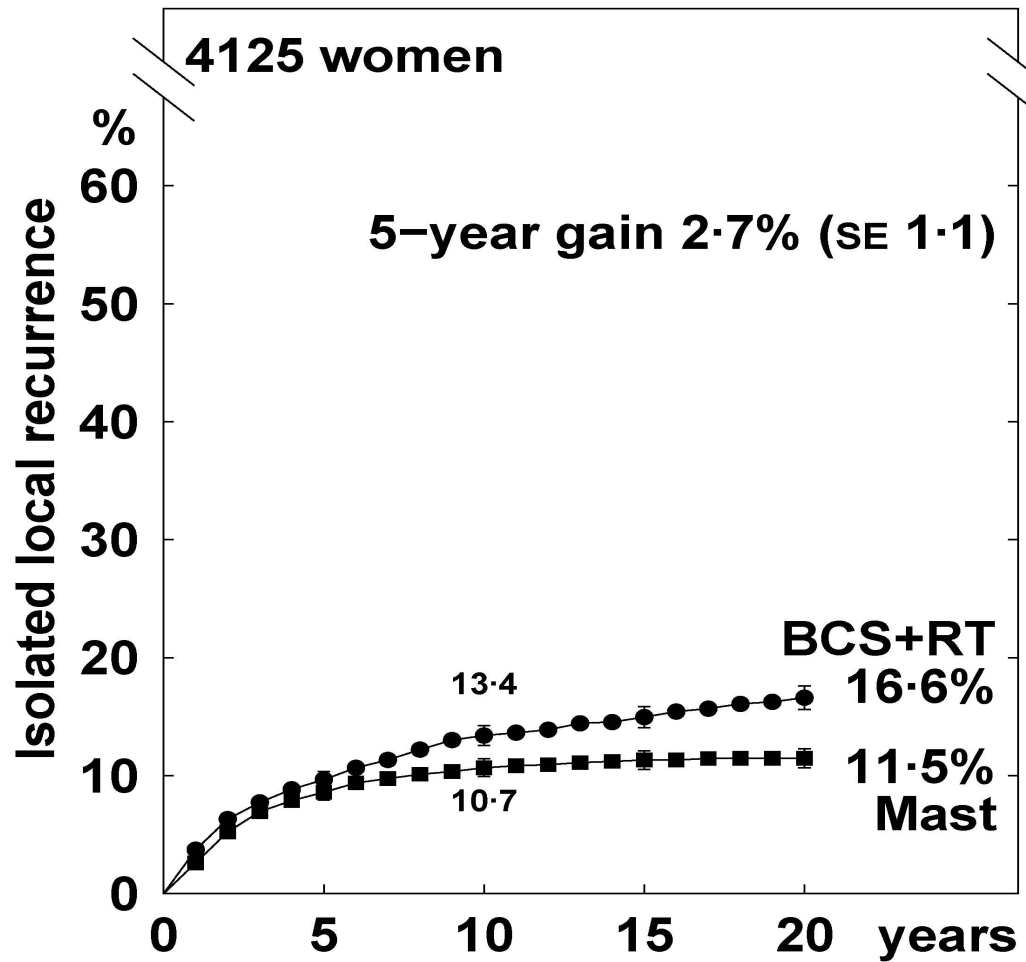
Breast-conserving surgery and WBRT vs. Mastectomy

- ▶ 1972-1986

- ▶ 7 trials

- ▶ 4125 women

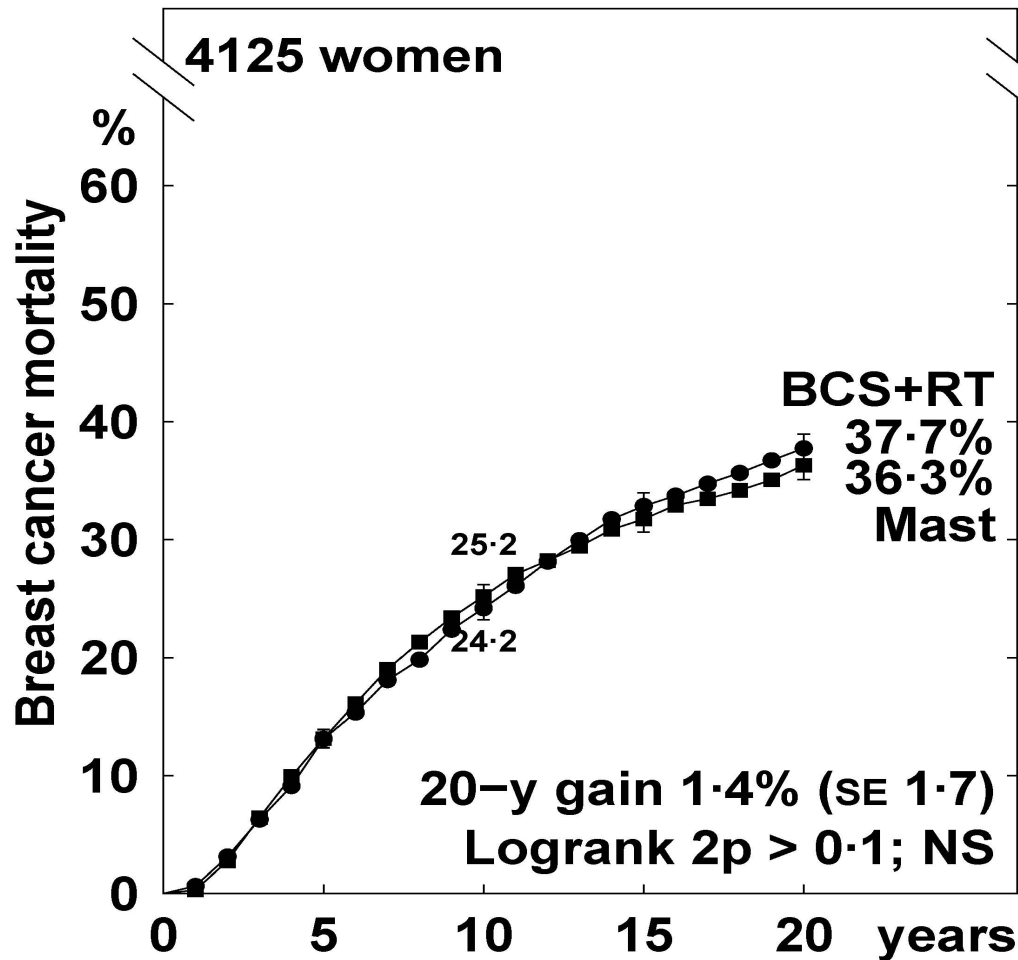
Mastectomy vs BCS + RT, both with AC ISOLATED LOCAL RECURRENCE



Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 - 9	Years 10 - 19	Year 20+
Mast	1.29 (187 / 14524)	0.10 (8 / 7731)	0.0(0/1163)
BCS+RT	1.60 (234 / 14626)	0.37 (29 / 7736)	0.43 (5 / 1157)
Rate ratio, from (O-E) / V	0.80 SE 0.09 -22.6 / 101.1	0.32 SE 0.20 -10.4 / 9.2	0.14 SE 0.45 -1.9 / 1.0

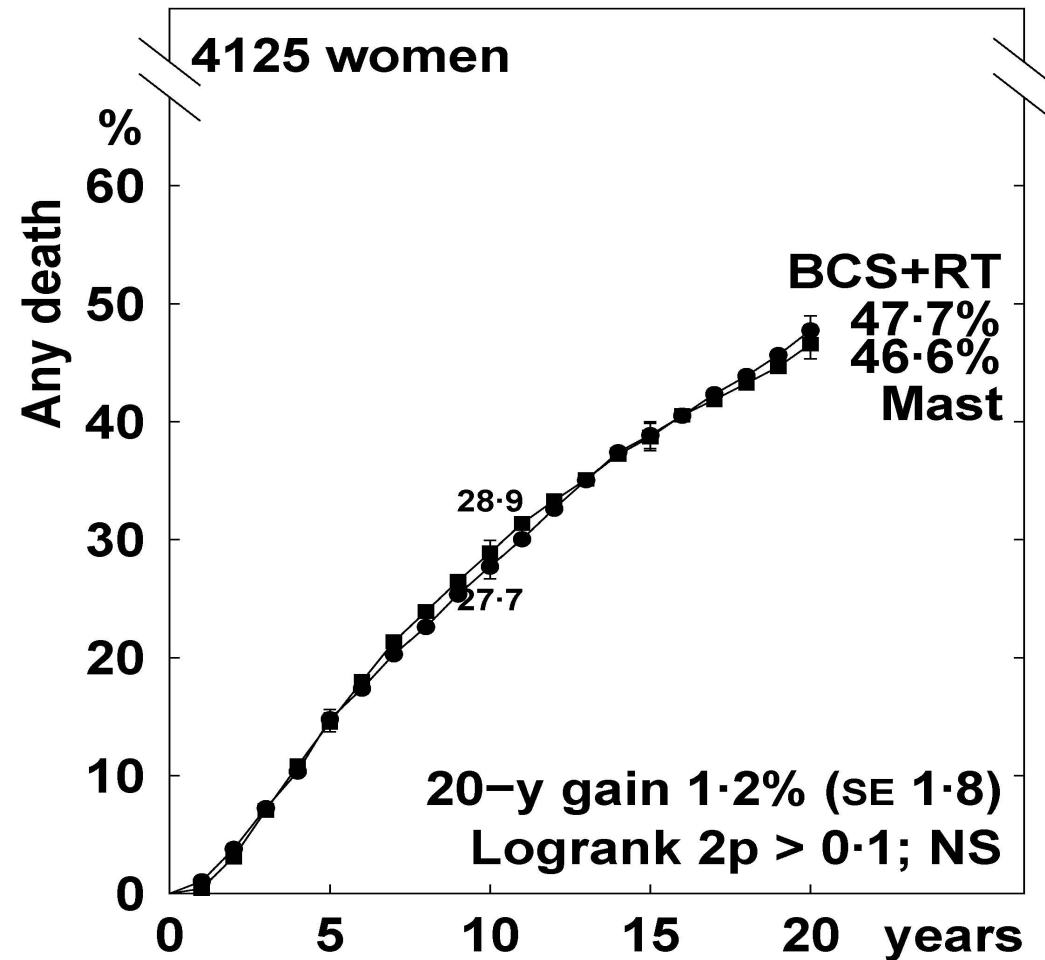
Mastectomy vs BCS + RT, both with AC BREAST CANCER MORTALITY



After-recurrence or possible-breast-cancer death rates (% / year) and logrank analyses

	Years 0 - 9	Years 10 - 19	Year 20+
Mast	2.84 (479 / 16842)	1.64 (154 / 9386)	1.15 (17 / 1473)
BCS+RT	2.77 (483 / 17437)	2.09 (209 / 10010)	1.99 (32 / 1612)
Rate ratio, from (O-E) / V	1.05 SE 0.07 10.7 / 227.9	0.80 SE 0.10 -19.2 / 85.8	0.63 SE 0.24 -5.3 / 11.5

Mastectomy vs BCS + RT, both with AC ANY DEATH



Death rates (% / year) and logrank analyses

	Years 0 - 9	Years 10 - 19	Year 20+
Mast	3.33 (561 / 16842)	2.90 (272 / 9386)	2.85 (42 / 1473)
BCS+RT	3.22 (562 / 17437)	3.25 (325 / 10010)	3.97 (64 / 1612)
Rate ratio, from (O-E) / V	1.05 SE 0.06 12.3 / 267.5	0.88 SE 0.08 -17.8 / 142.6	0.68 SE 0.17 -9.7 / 25.0

Conclusions 2

- ▶ **The long-term rate of local recurrence was higher following breast-conserving treatment than after mastectomy**
- ▶ **But long-term rates of specific and overall mortality were not increased**

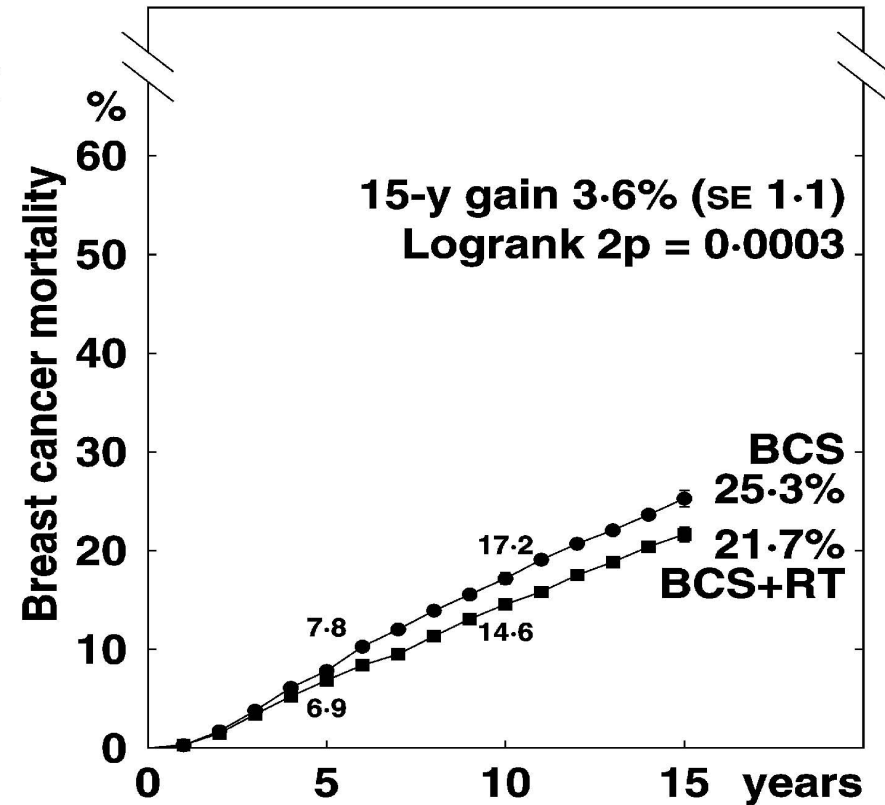
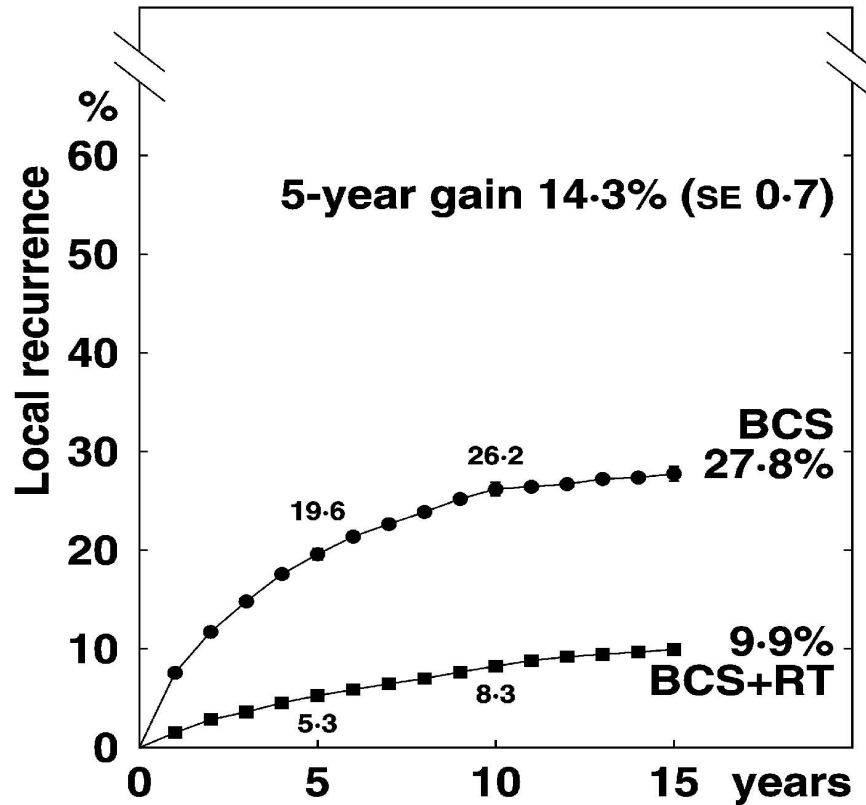
Trials

1. Postmastectomy Radiotherapy
2. Mastectomy vs Breast-conserving treatment with RT
3. Whole-breast irradiation after breast-conserving surgery
 - Invasive cancer
 - DCIS
4. Fractionation trials
5. Toxicity

EBCTCG Overview

- ▶ 17 trials
- ▶ 1976-1999
- ▶ 10801 women
- ▶ Median f/u: 9.5 years
- ▶ 25% with > 10 year F/U

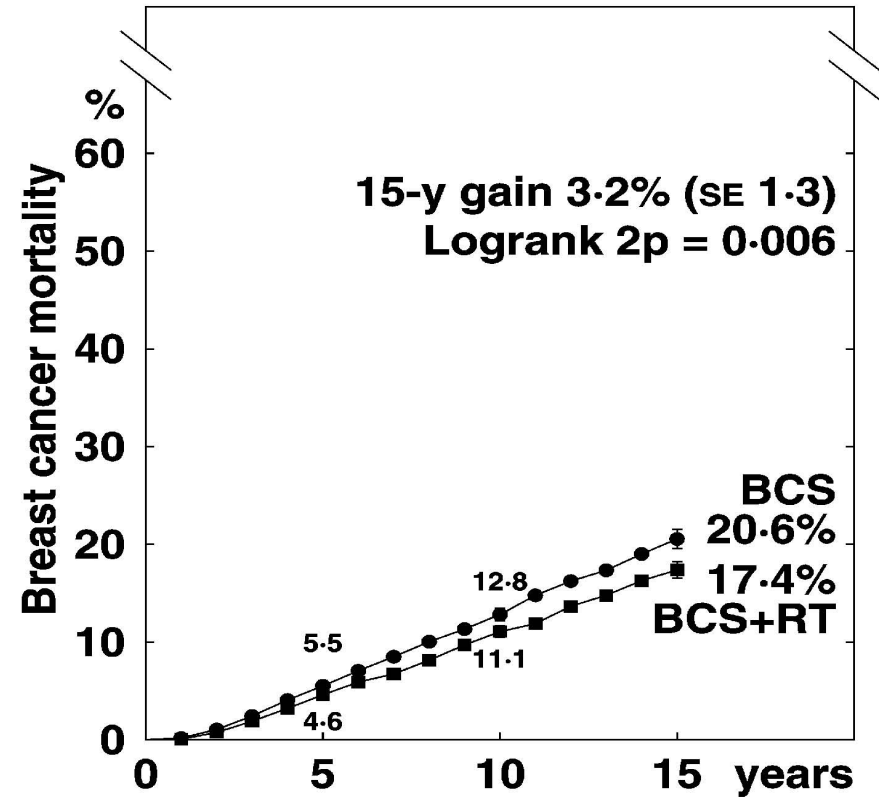
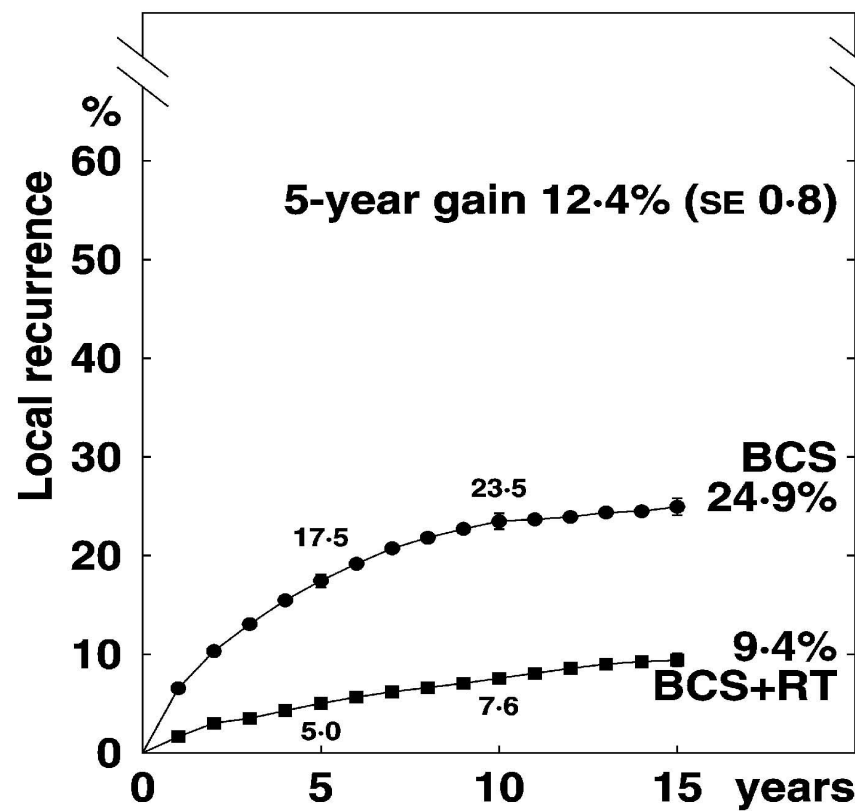
Trials of BCS ± RT: 15-year risks 10,906 women randomised in 17 trials



For every four local recurrences avoided by year 5
about one breast cancer death avoided by year 15

Preliminary results: subject to revision

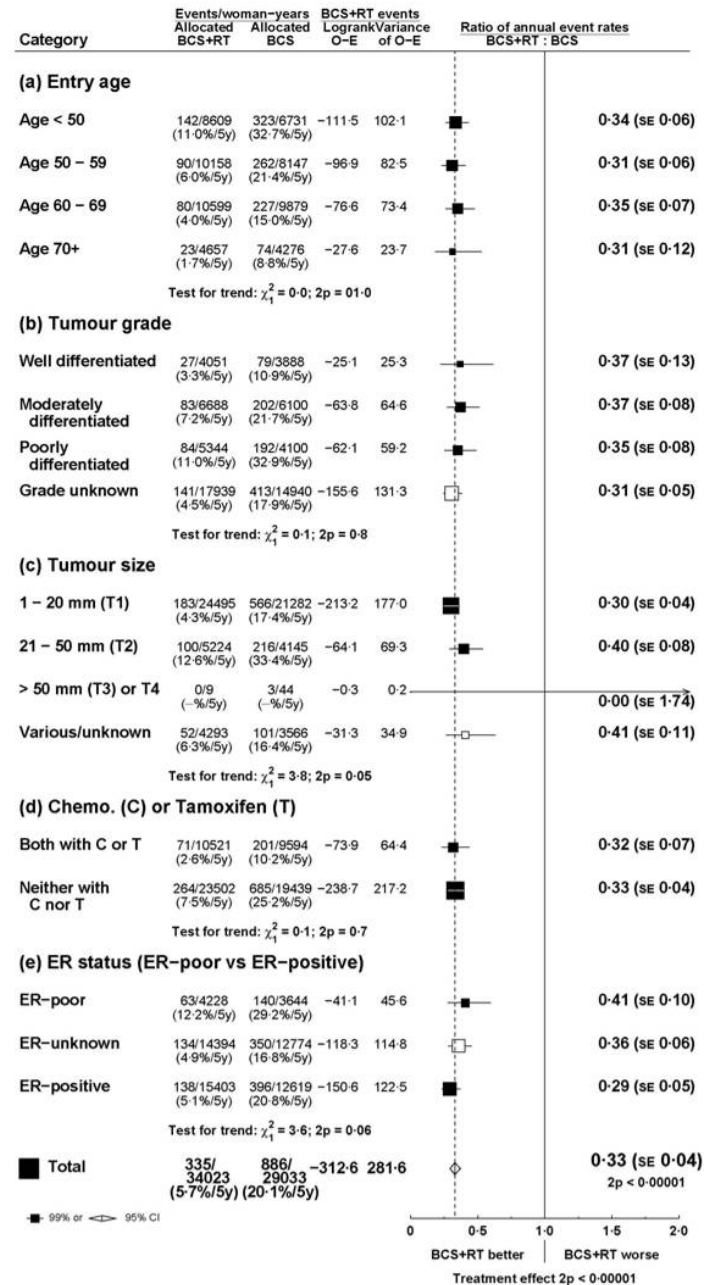
pN0 in trials of BCS ± RT: 15-year risks 7334 women



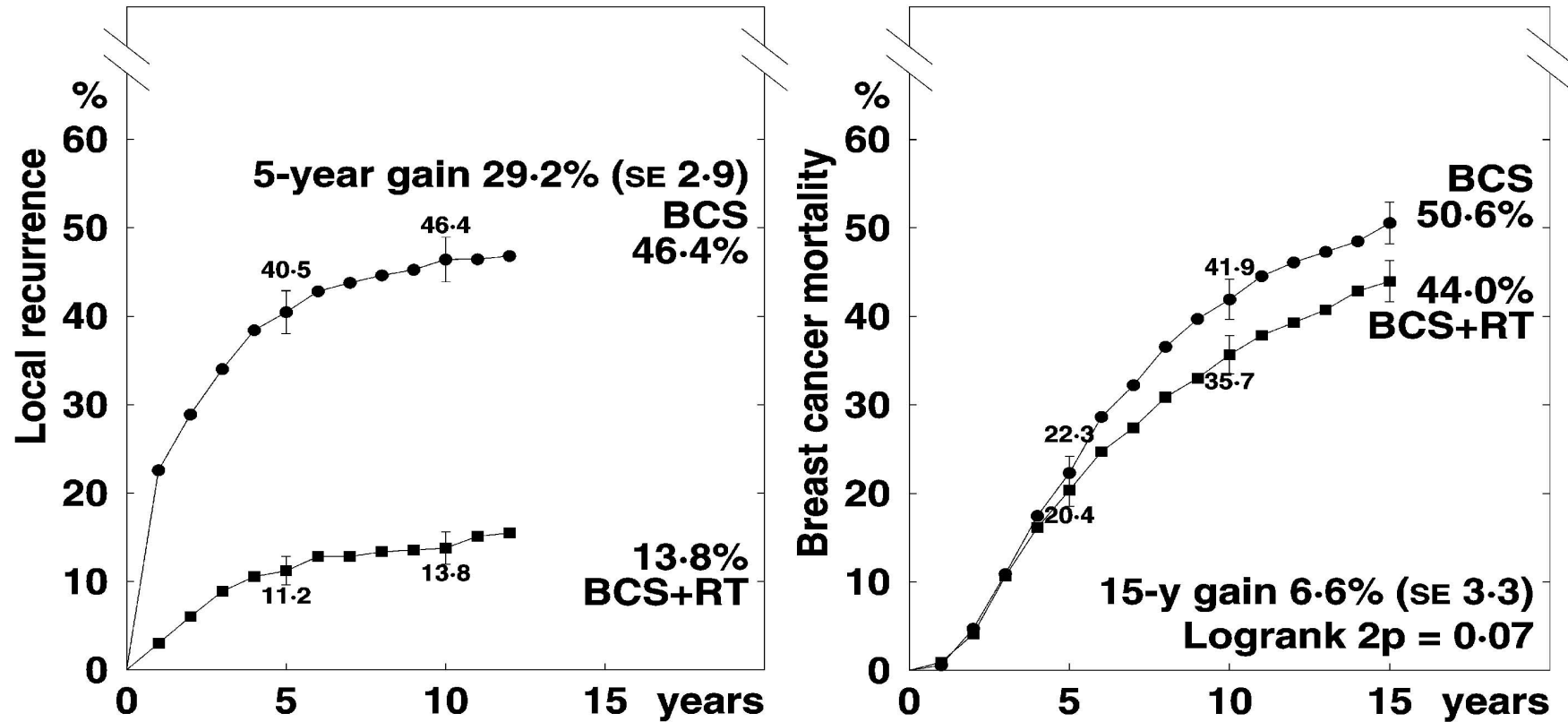
For every four local recurrences avoided by year 5
about one breast cancer death avoided by year 15

Preliminary results: subject to revision

N0/N-: BCS ± RT
ISOLATED LOCAL RECURRENCE



pN+ in trials of BCS ± RT: 15-year risks 1111 women



For every four local recurrences avoided by year 5
about one breast cancer death avoided by year 15

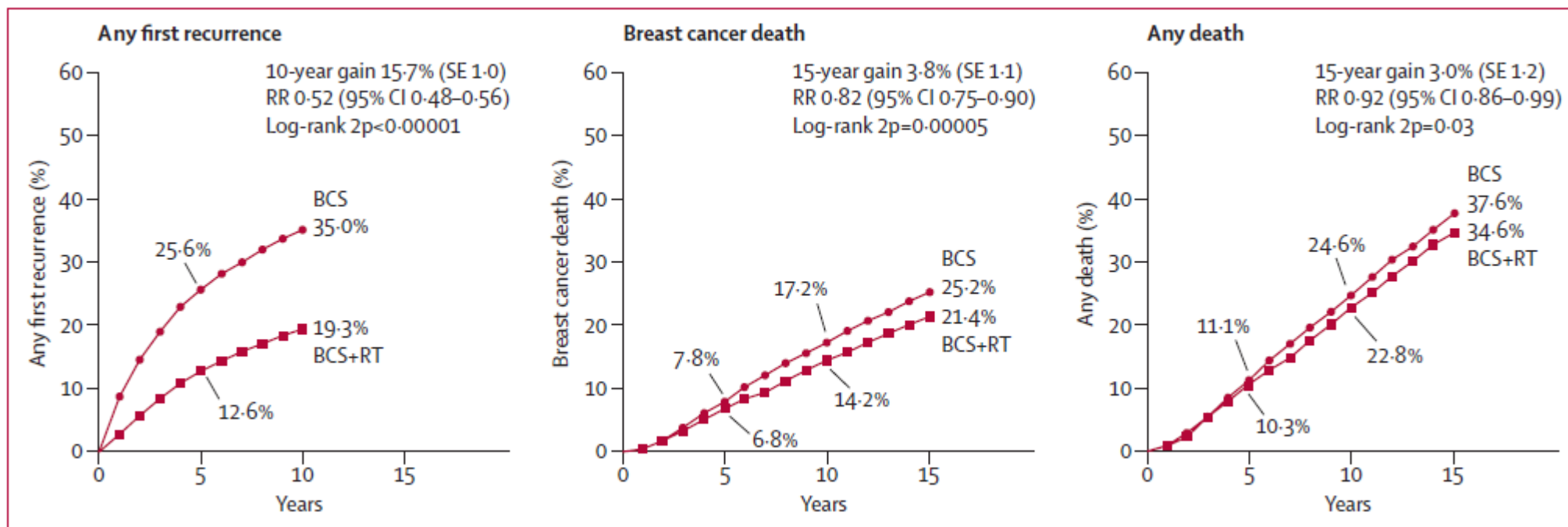
Preliminary results: subject to revision

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)*

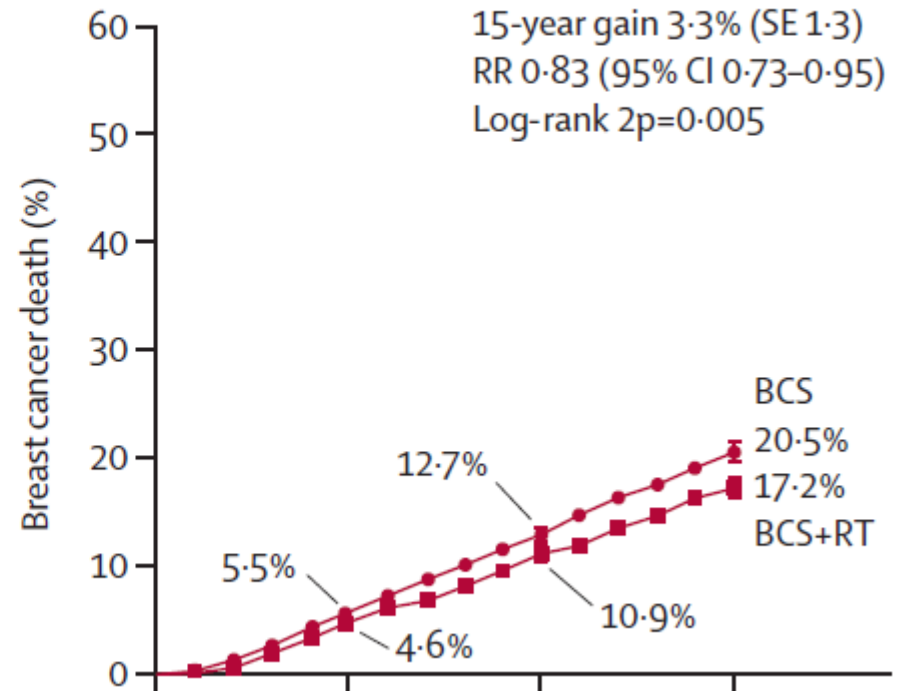
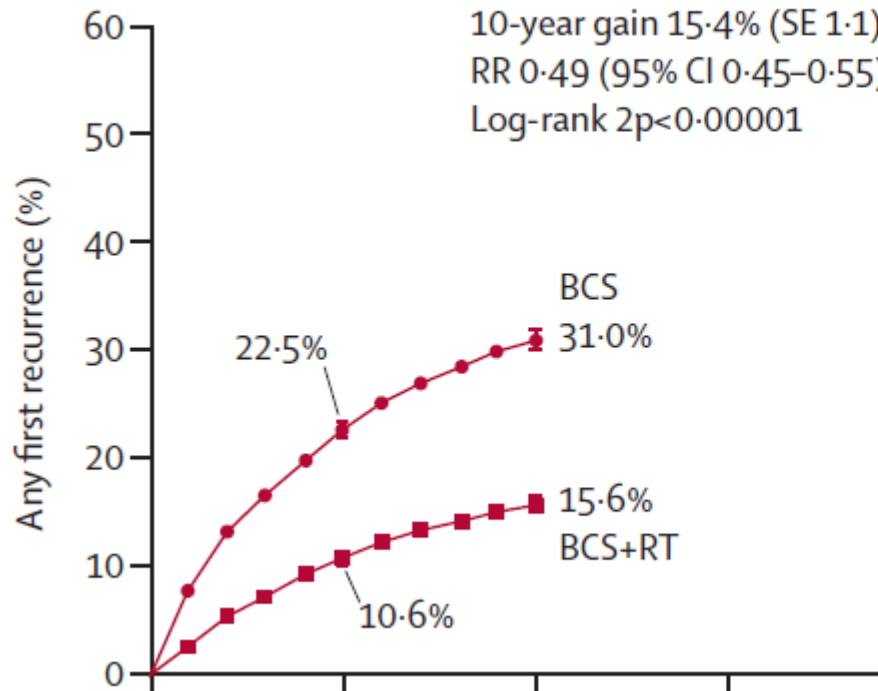
Recurrence: breast, nodes, metastasis,
or contralateral breast cancer *as first event*

EBCTCG



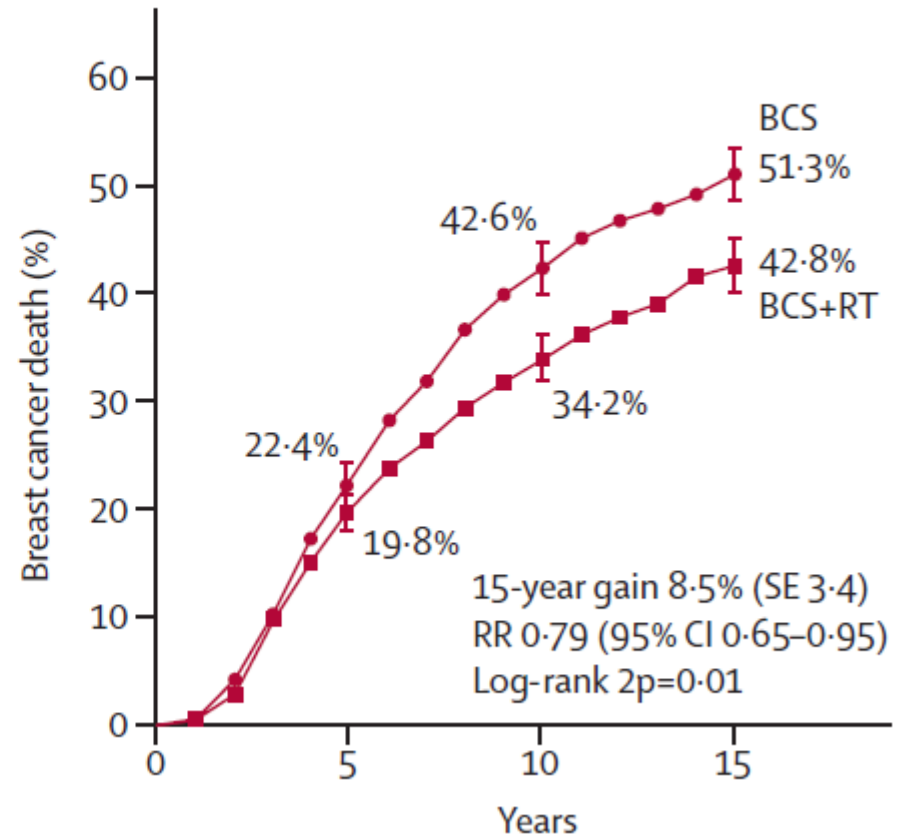
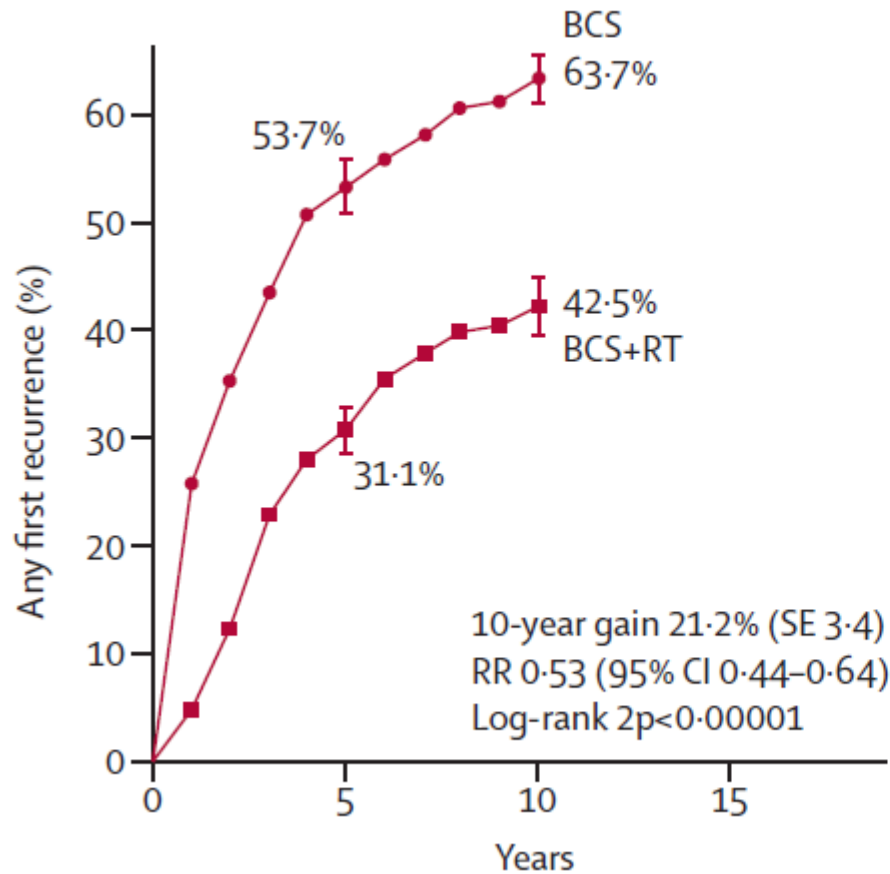
EBCTCG. pN0. 7287 ptes

Women with pN0 disease (n=7287)



EBCTCG. pN+. 1050 ptes

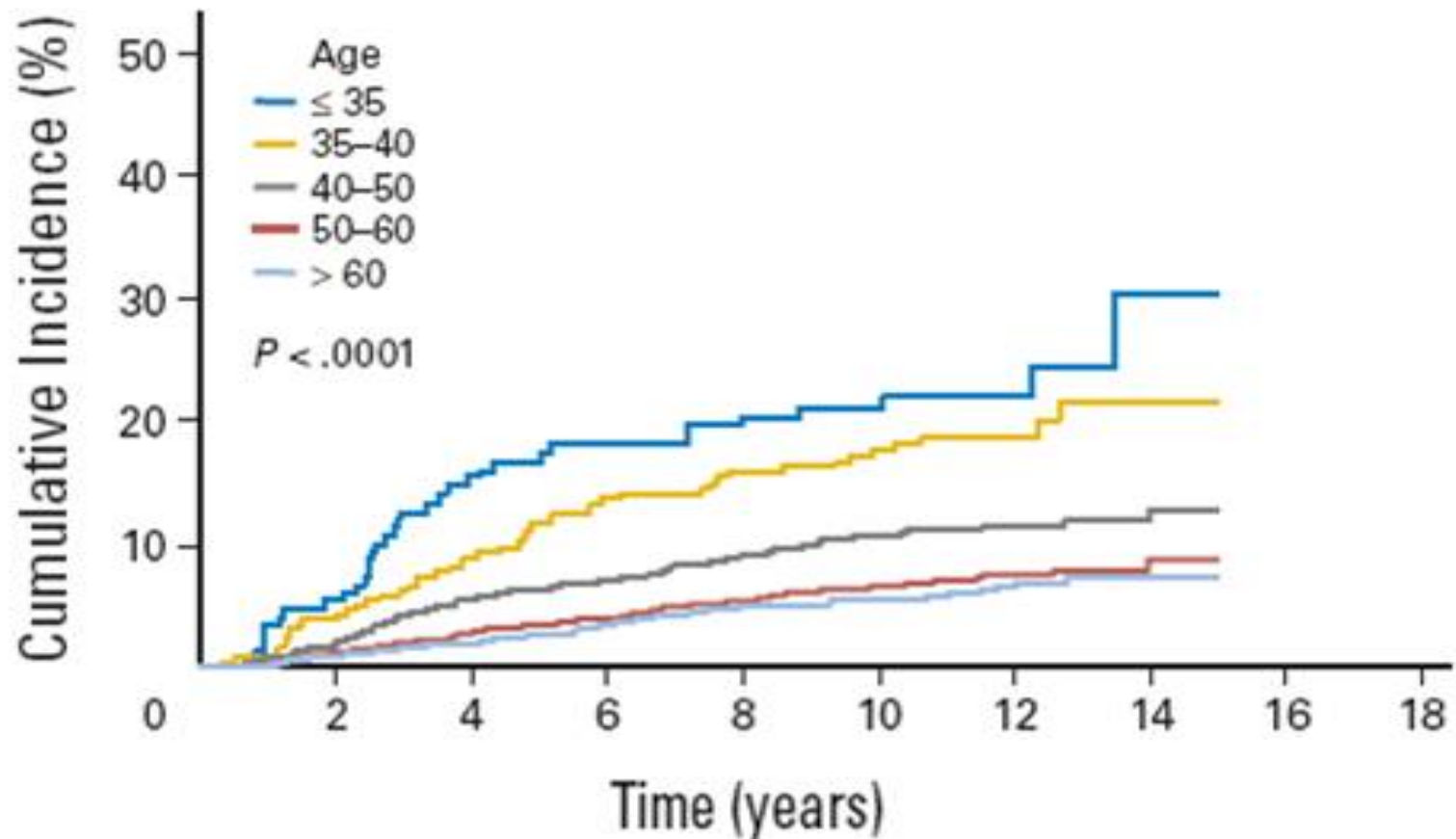
Women with pN+ disease (n=1050)



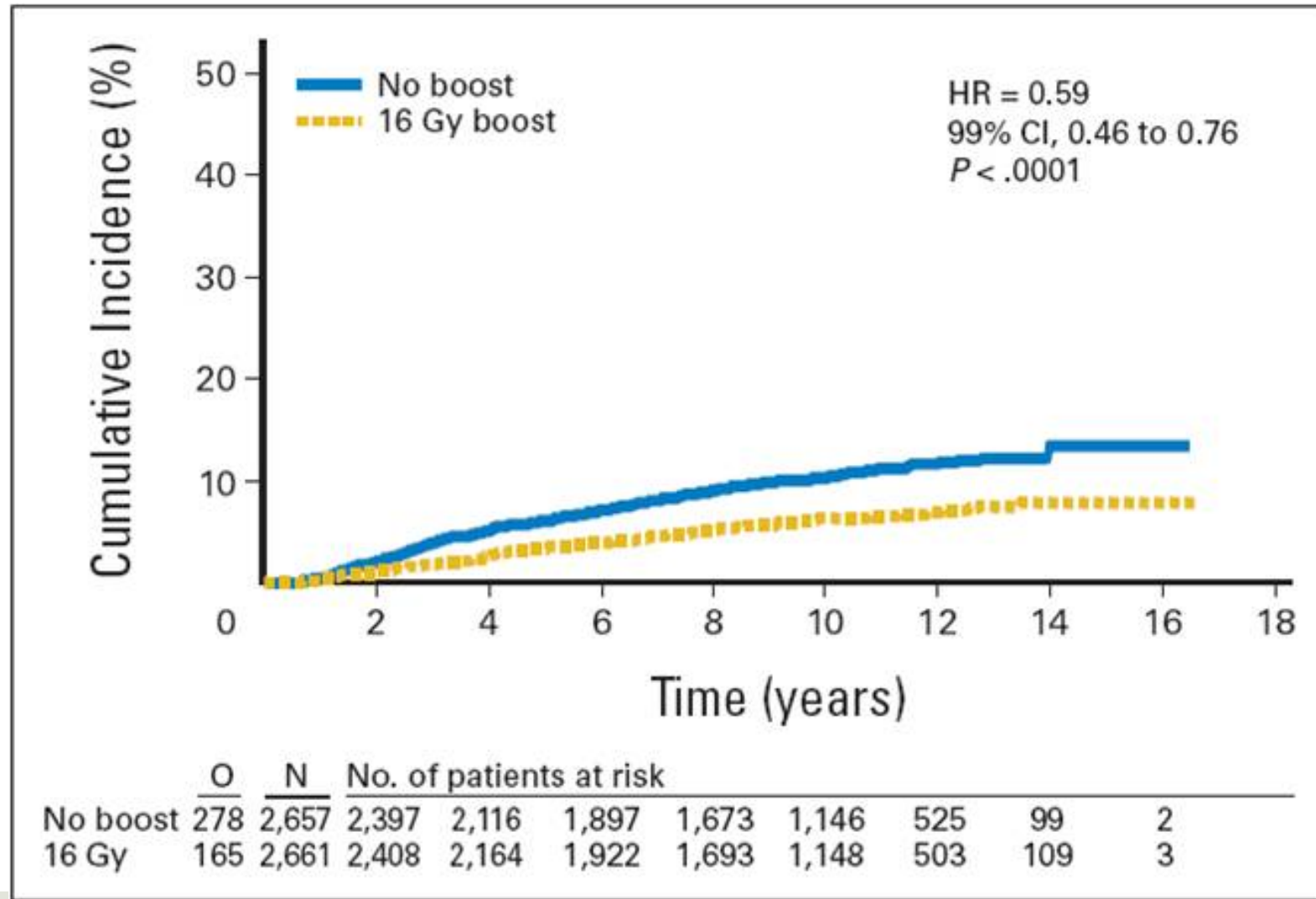
Conclusions 3

- ▶ **Following breast-conserving surgery, the rate of locoregional recurrence was reduced by 70% with radiotherapy.**
- ▶ **The rate of any recurrence (LRR, metastasis, CBC) as first event was reduced by 42 % with RT.**
- ▶ **Locoregional radiotherapy was associated with an 18% decrease in breast cancer mortality, after 5 years.**
- ▶ **The effects of radiotherapy were proportional, independent, from known risk factors: the higher the risk following surgery, the higher the benefit from RT.**

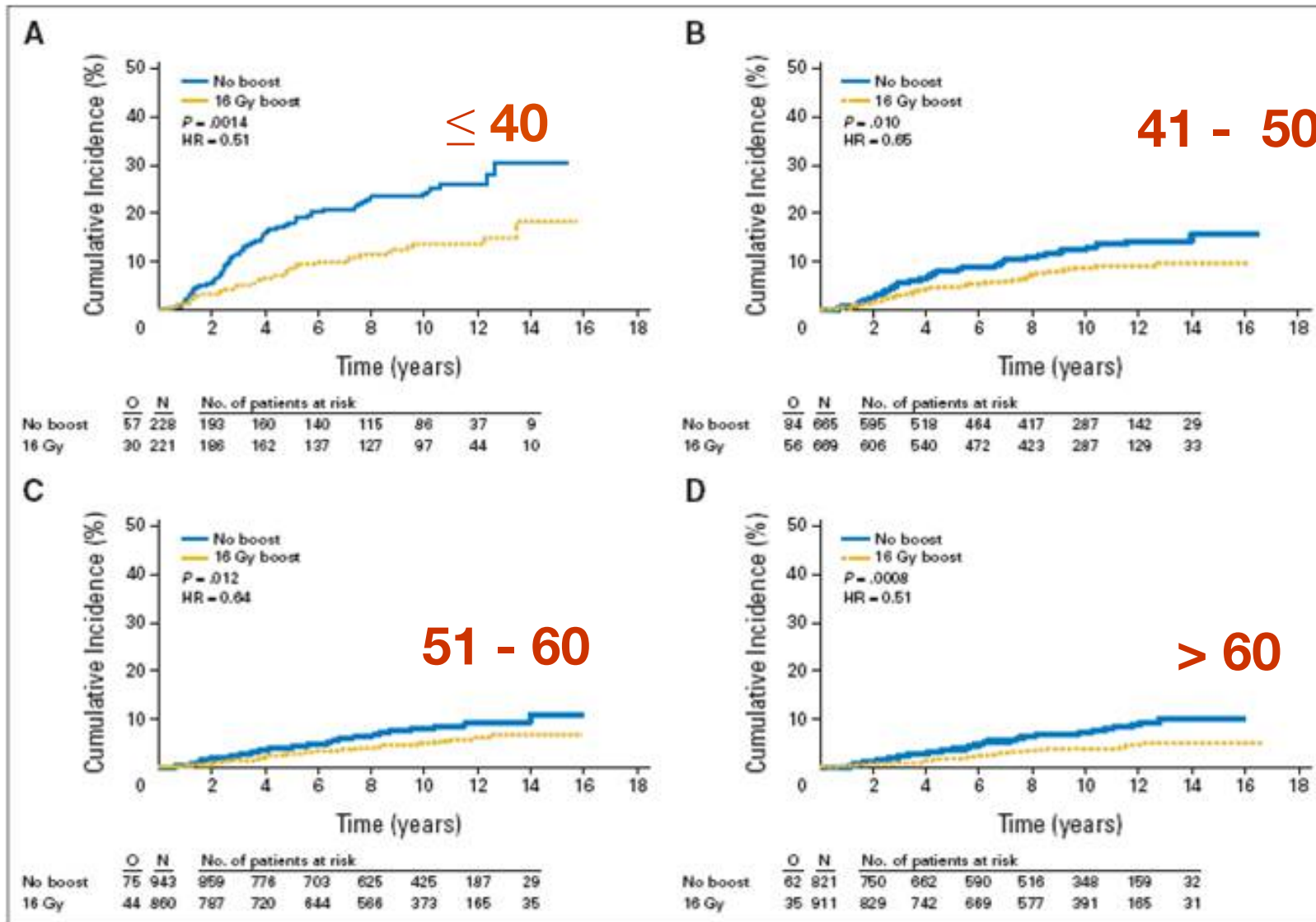
EORTC. Local recurrences in relation to age 5319 ptes. Median F/U: 10.2 years



EORTC Boost Trial. 10-year results Breast recurrences. First event



EORTC. Local recurrences per age groups and treatment

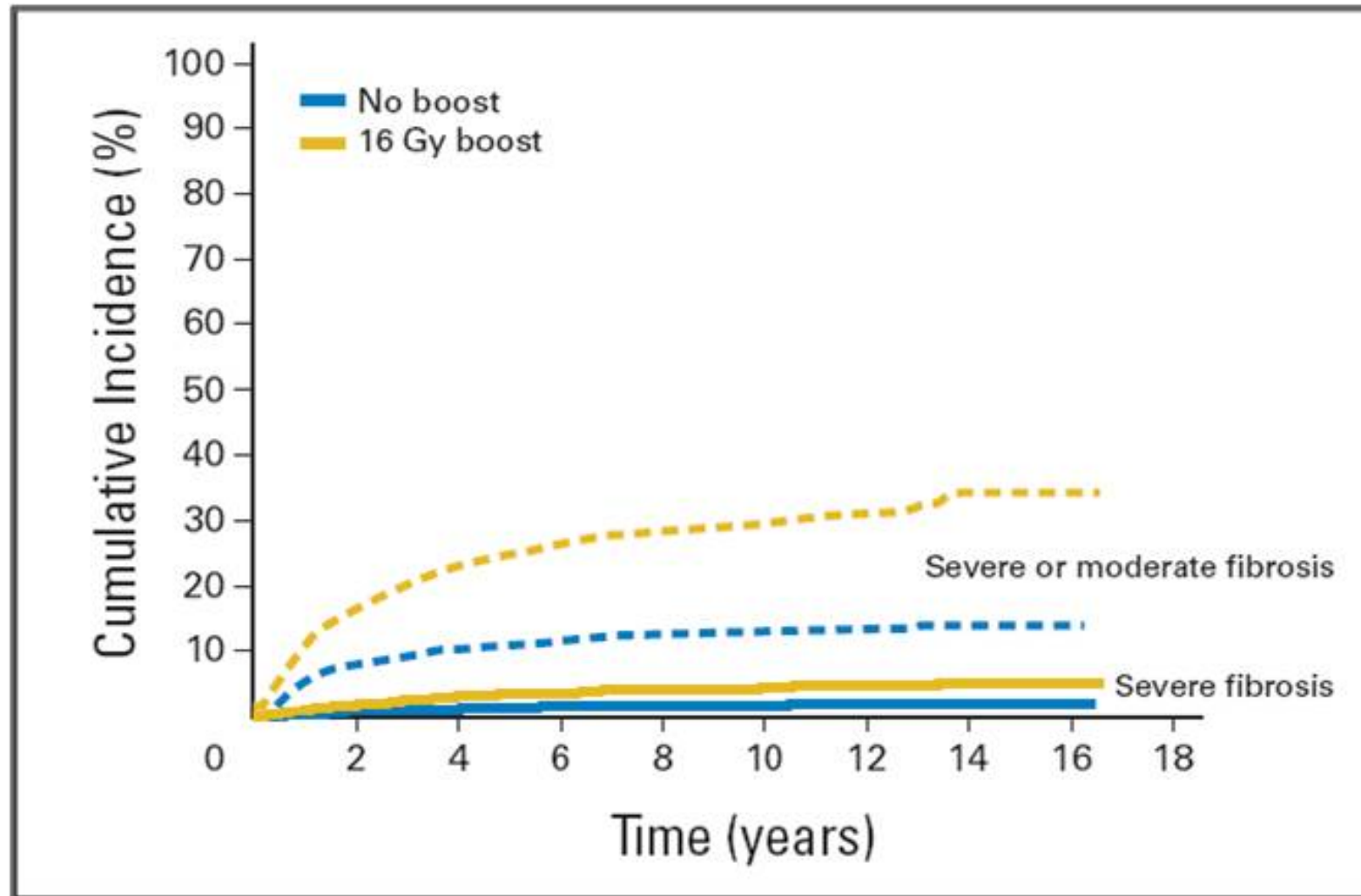


EORTC Boost Trial

Age (years)	% 10-year IBTR as first event	
	50 Gy	50 Gy + 16 Gy
≤ 40	23.9	13.5
41-50	12.5	8.7
51-60	7.8	4.9
>60	7.3	3.8



EORTC Boost Trial. 10-year results Fibrosis



Breast-conserving surgery. NCCN guidelines 2013

	Whole Breast	Tumor bed (Boost)	Supra/Infraclavicular nodes	IMN
pN > 3	√	±	√	***
pN1-3	√	±	***	***
pN0	√	±	-	-

√: recommended
 ***: strongly consider
 **: consider

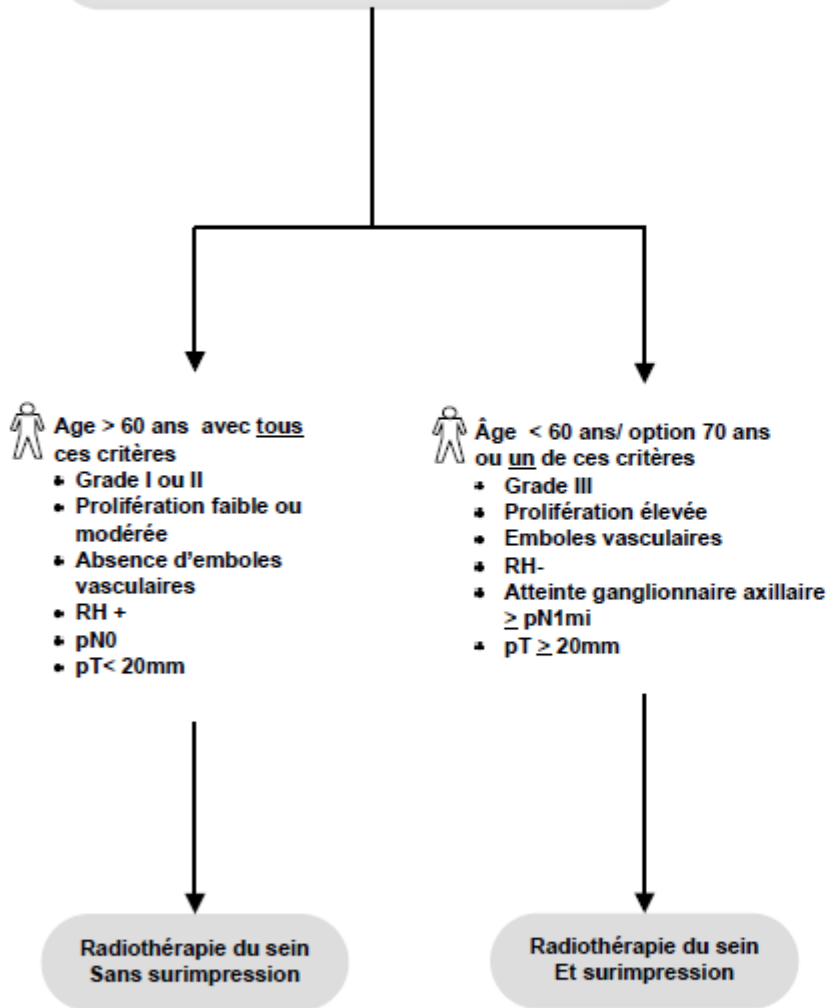
NCI France. Guidelines 2012

- ▶ **Following breast-conserving surgery and whole-breast irradiation to 50 Gy, a 16 Gy boost to the tumor bed is recommended**
- ▶ **Omission of a boost can be considered in women older than 70 years**

Carcinomes infiltrants Traitement conservateur

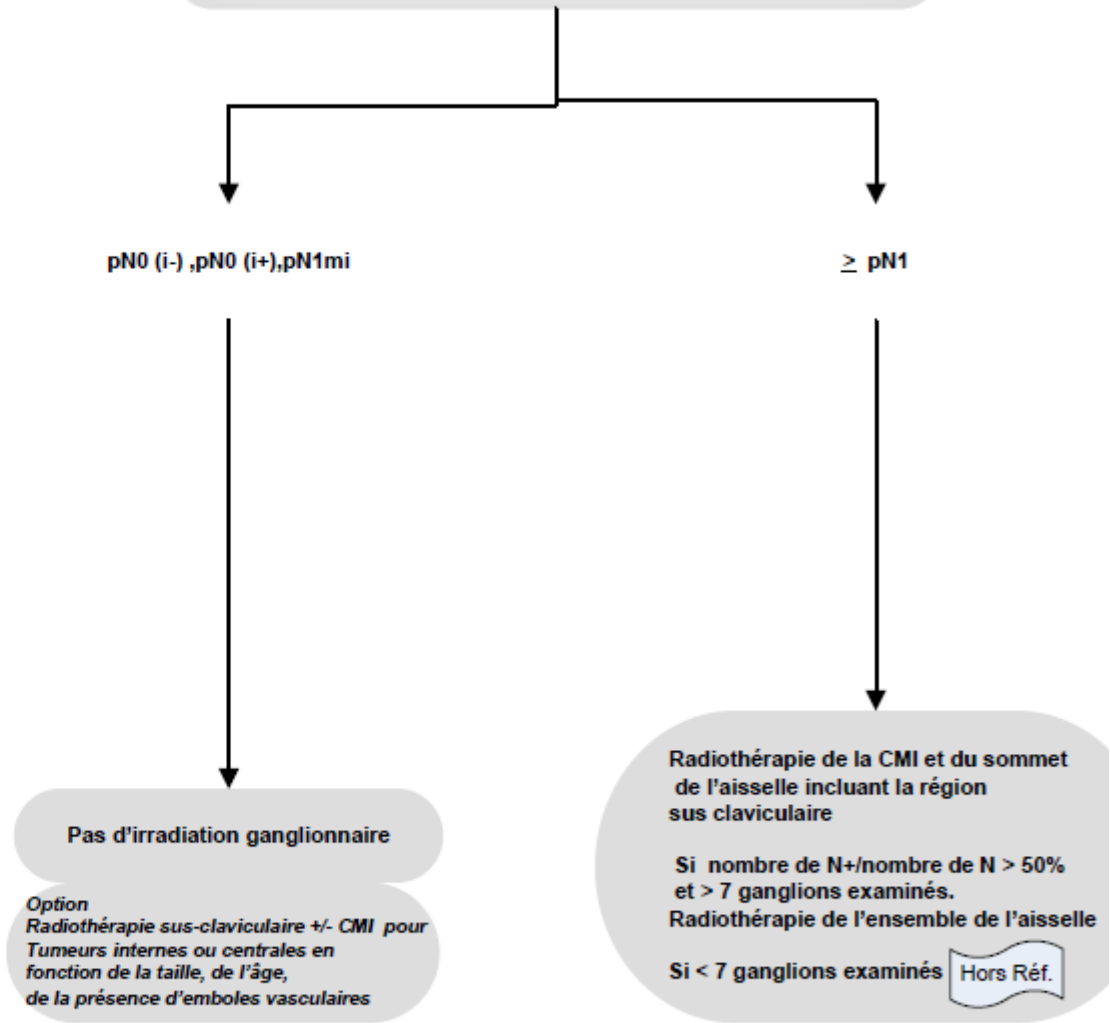
RADIOTHÉRAPIE MAMMAIRE

CHIRURGIE MAMMAIRE CONSERVATRICE
AVEC BERGES SAINES



RADIOTHÉRAPIE DES AIRES GANGLIONNAIRES

STATUT GANGLIONNAIRE POST CHIRURGICAL



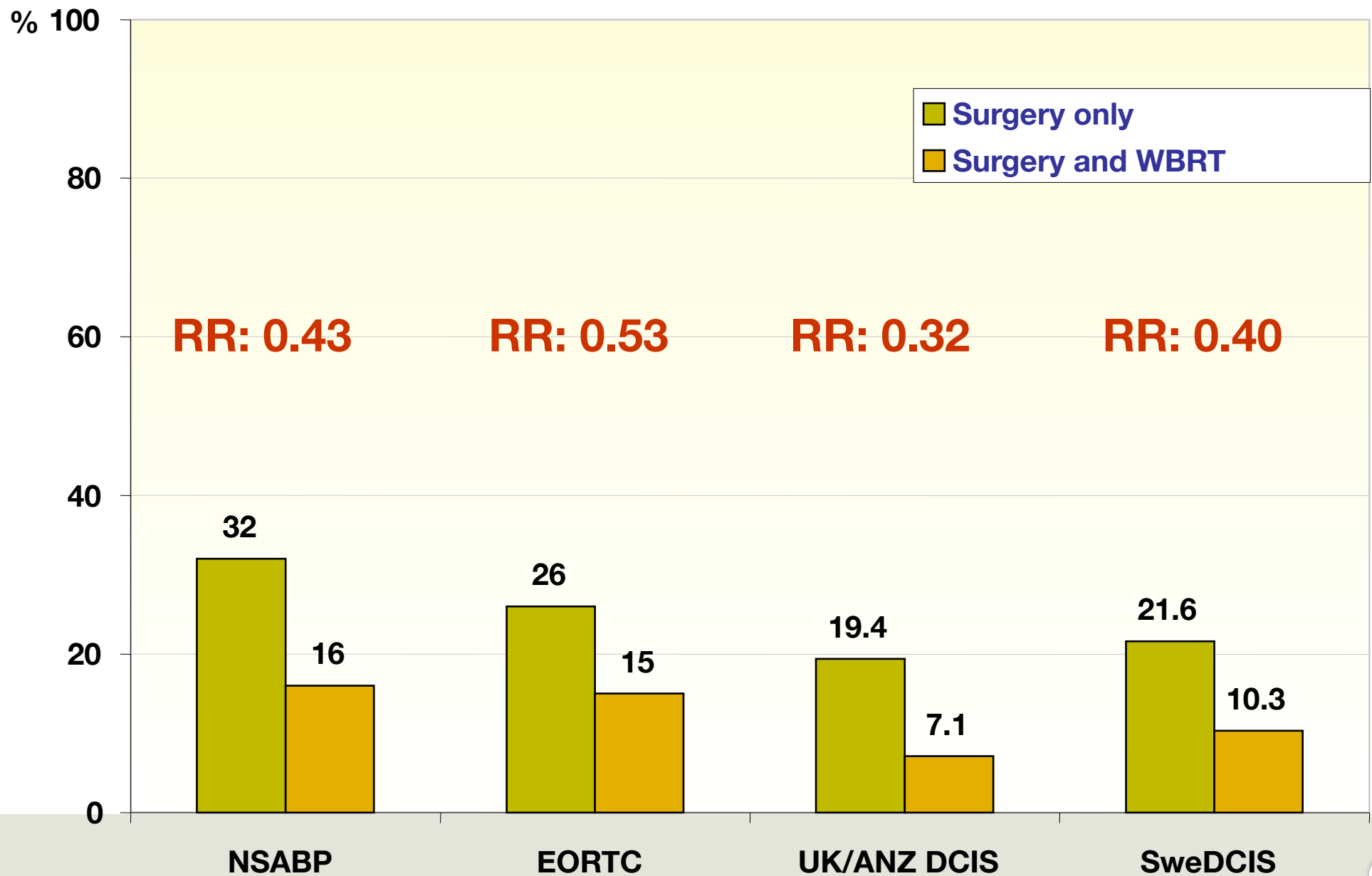
Trials

1. Postmastectomy Radiotherapy
2. Mastectomy vs Breast-conserving treatment with RT
3. Whole-breast irradiation after breast-conserving surgery
 - Invasive cancer
 - **DCIS**
4. Fractionation trials
5. Toxicity

Can radiotherapy be omitted in patients with DCIS who underwent breast-conserving surgery?

- ▶ Large retrospective studies
- ▶ Five trials
- ▶ Meta-analysis

10-year local recurrence rates

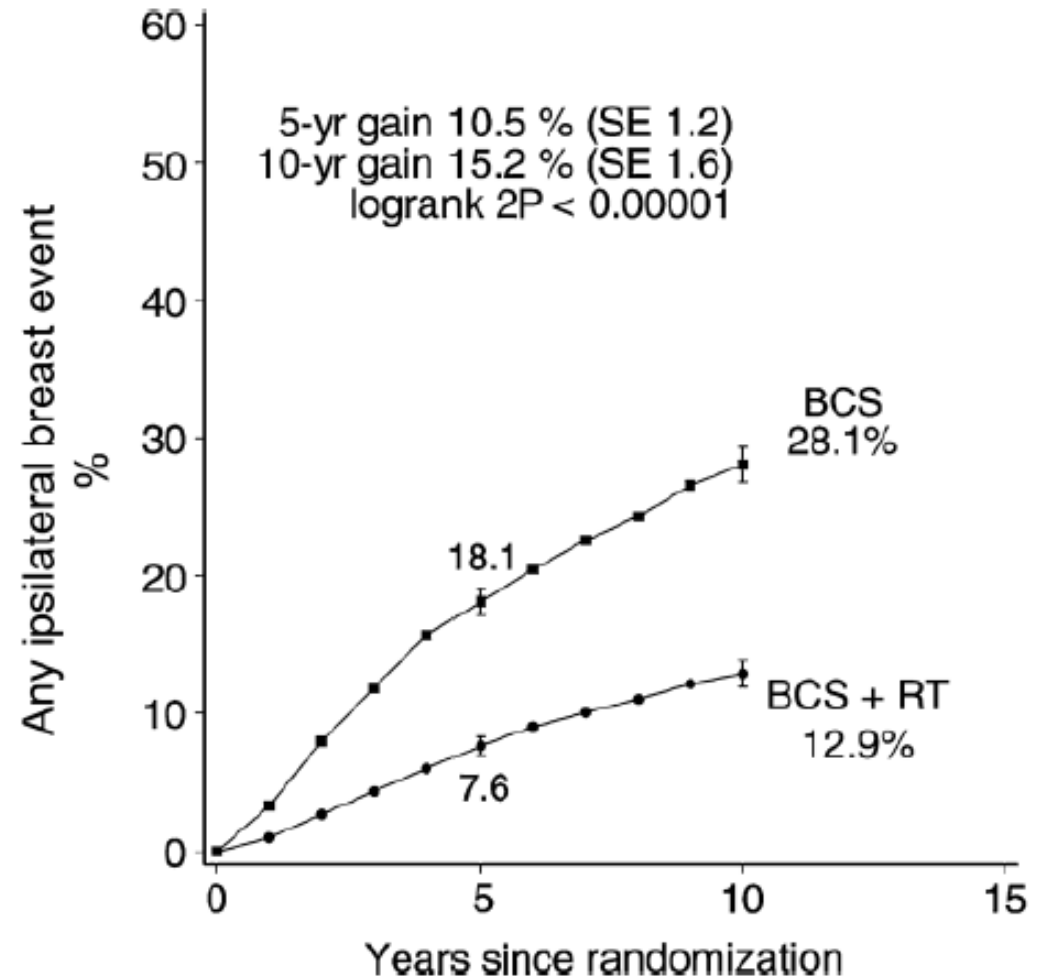


Overview EBCTCG

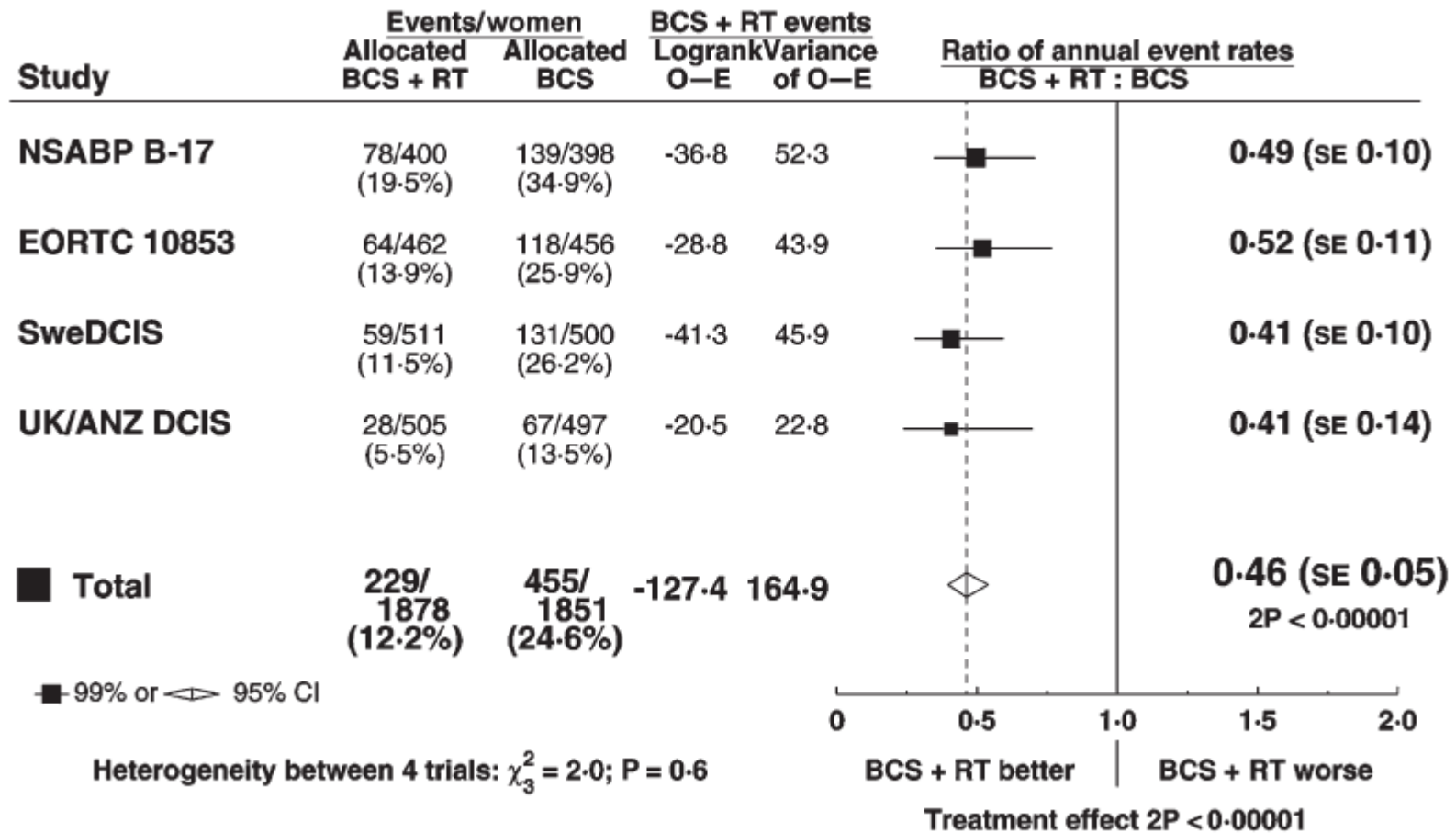
- ▶ **Ductal Carcinoma In Situ**
- ▶ **Breast-conserving surgery**
- ▶ **WBRT 50 Gy vs none**
- ▶ **4 trials**
- ▶ **1985-2000**

Overview DCIS

- ▶ **3729 patients**
- ▶ **Median F/U: 8.9 years**
- ▶ **RR= 0.46**



EBCTCG. DCIS Trials



Conclusions 4

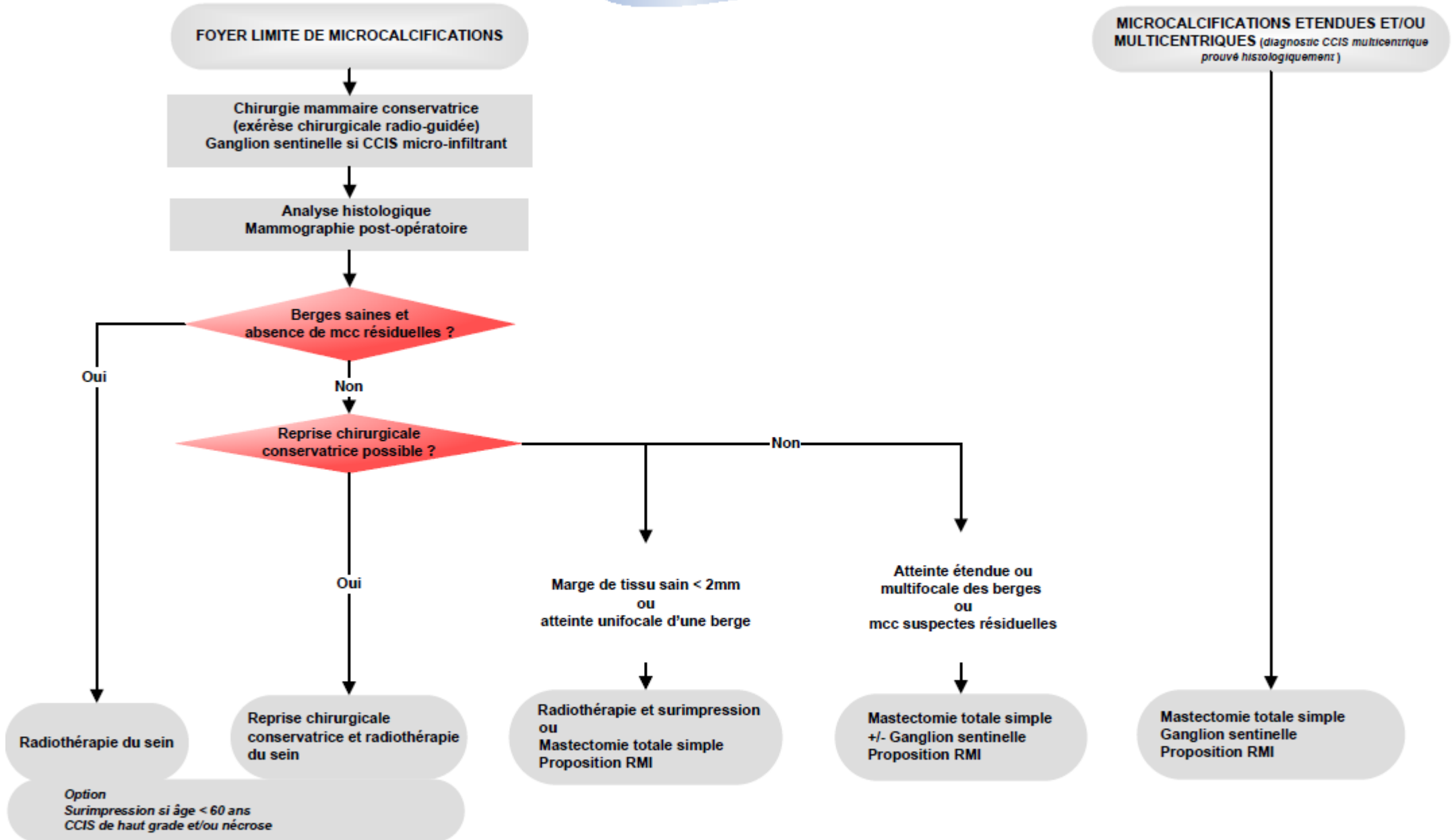
- ▶ **Following breast-conserving surgery of DCIS, WBRT reduces the rate of breast recurrence by 50-60%**
- ▶ **The effect is proportional**
- ▶ **No subgroups were identified where radiotherapy could be omitted**

DCIS. NCCN 2013 Guidelines

- ▶ Lumpectomy and WBRT
- ▶ or Total Mastectomy
- ▶ or Lumpectomy alone

*Radiotherapy reduces local recurrence risk by 50%,
but no differences in survival*

Carcinomes canaux In Situ (+/- micro infiltrant) Traitement loco-régional



Trials

- 1. Postmastectomy Radiotherapy**
- 2. Mastectomy vs Breast-conserving treatment with RT**
- 3. Whole-breast irradiation after breast-conserving surgery**
 - Invasive cancer
 - DCIS
- 4. Fractionation trials**
- 5. Toxicity**

Hypofractionation trials

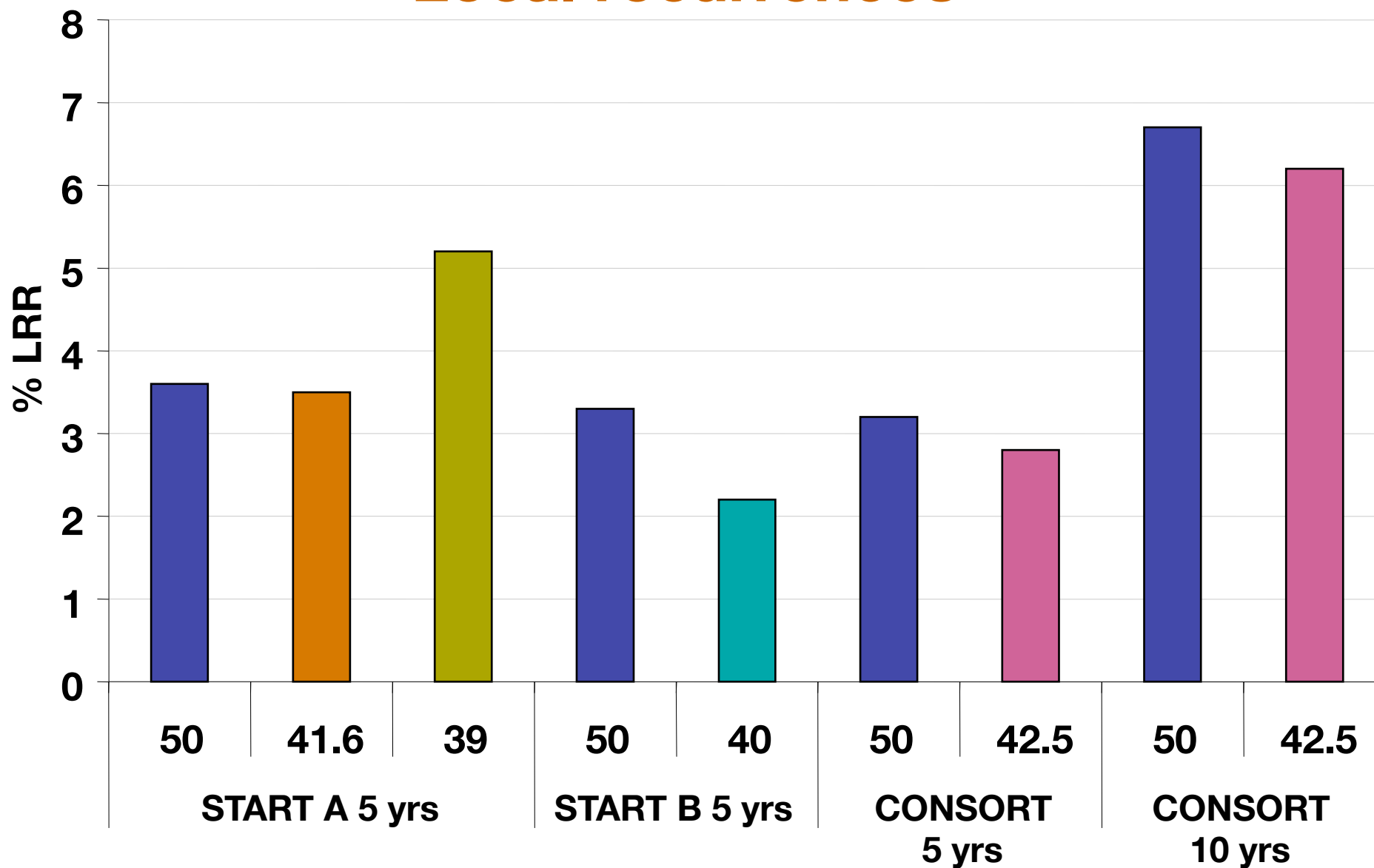
- ▶ **Canada**

- ▶ **UK**

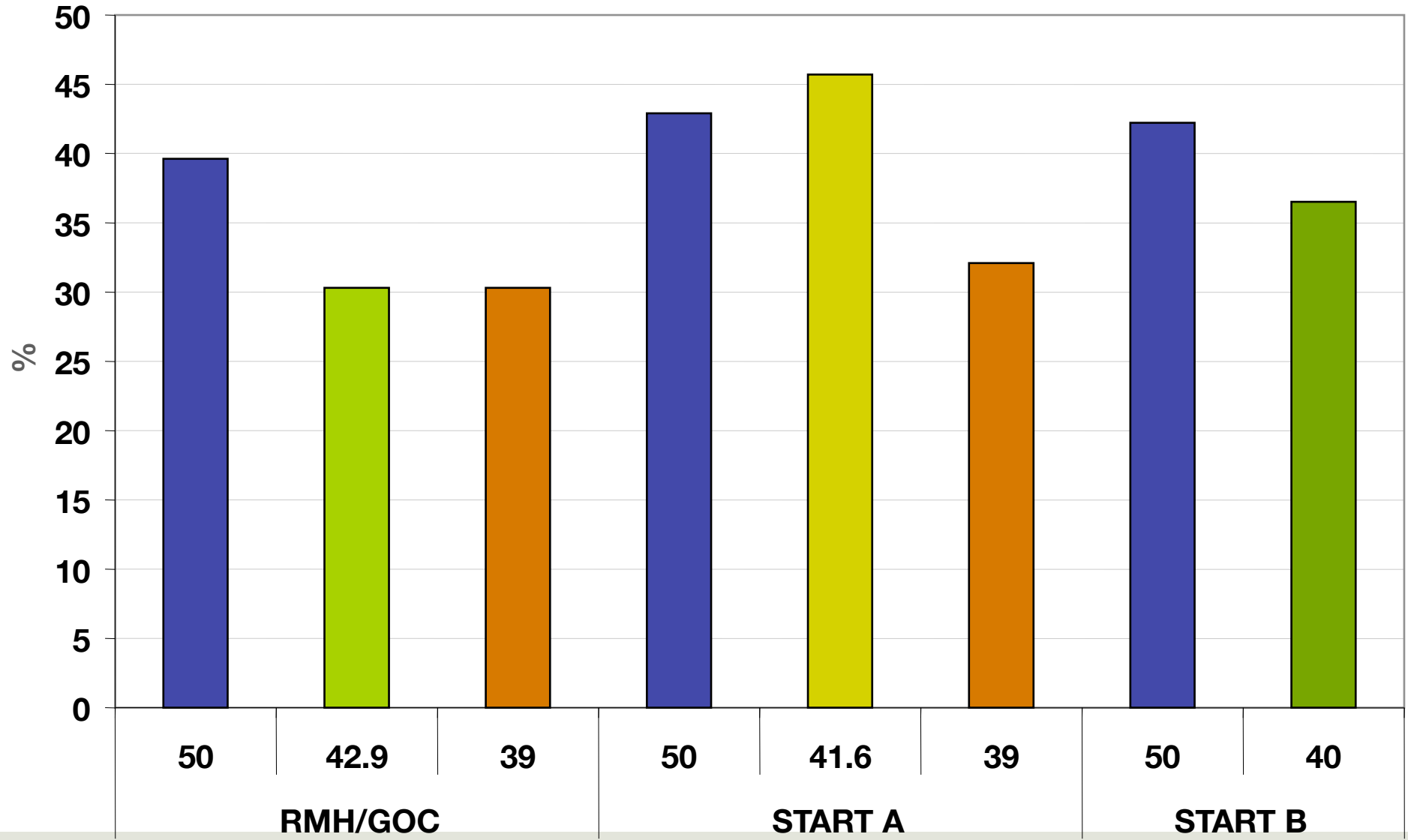
Irradiation schemes

Protocole	Dose (Gy)	No. fractions	Dose / fraction	No. weeks
Standard	50	25	2	5
RMH/GOC	42.9	13	3.3	5
START A	41.6	13	3.2	5
CONSORT	42.5	16	2.66	3
START B	40	15	2.67	3

Local recurrences



Toxicity



Local control: are HF schemes applicable in all patients?

1. Chest wall irradiation after mastectomy:

- **Subgroup of the START trials**
- **Insufficient statistical power**

2. Lymph nodes irradiation

- **Idem**

HF and Boost

- ▶ No boost delivered in the CONSORT trial
- ▶ Only some patients had a boost in the UK trials, *with a conventional 2 Gy per fraction regimen*

HF in high recurrence risk tumors?

- ▶ Young women
- ▶ High grade, high proliferation
- ▶ Basal-like or HER2+

NCCN 2013

- ▶ **The breast should receive a dose of 45-50 Gy at 1.8 – 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction.**

NCI France 2012

▶ Hypofractionation should be considered if all criteria are present:

- Age > 50 years
- pT1-2, pN0,
- Grade I-II
- HR +ve tumors
- Free margins

NCI France 2012

▶ HF is not recommended if either one is present

- Adjuvant chemotherapy
- Mastectomy
- Lymph nodes irradiation
- Grade III
- Lymphovascular involvement

NCI France 2012

- ▶ No recommendation for a boost
- ▶ Recommended fractionation regimen:
 - 42.5 Gy/16 fractions in 3 weeks
 - 41.6 Gy/13 fractions in 5 weeks
 - 40 Gy/15 fractions in 3 weeks
- ▶ Special care is advised to limit heart and lungs dose, and to ensure an homogeneous dose coverage of the breast

Trials

- 1. Postmastectomy Radiotherapy**
- 2. Mastectomy vs Breast-conserving treatment with RT**
- 3. Whole-breast irradiation after breast-conserving surgery**
 - Invasive cancer
 - DCIS
- 4. Toxicity**

EBCTCG. Second cancers 29 587 women RT vs no RT

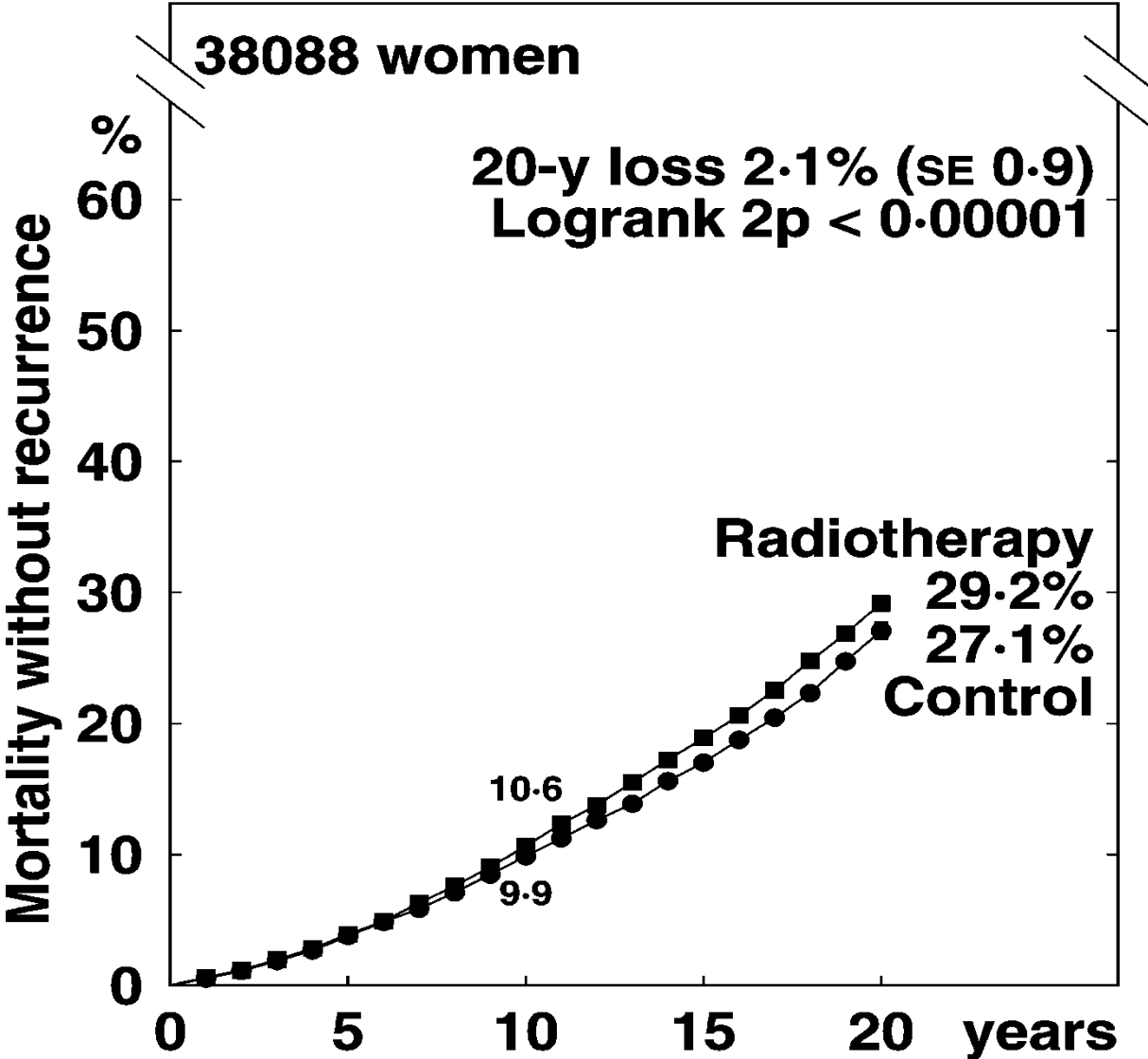
	Total event s	Excess events	Ratio of rates (se) ^a	2p
Contralateral breast cancer ^b	1316	122.4	1.22 (0.06)	0.0005
Cancer of other site ^c	1534	139.2	1.22 (0.06)	0.0002
Lung cancer	255	57.0	1.60 (0.16)	0.0002
Oesophagus cancer	32	10.0	1.89 (0.50)	0.08
Leukaemia	59	15.0	1.71 (0.36)	0.04
Soft-tissue sarcoma	26	10.8	2.34 (0.62)	0.03
Other specified sites	1020	31.6	1.07 (0.07)	NS

^a Ratio of annual event rates irradiated vs unirradiated

^b Contralateral breast cancer as the first or only site of recurrence.

^c Other than breast or non-melanoma skin cancer.

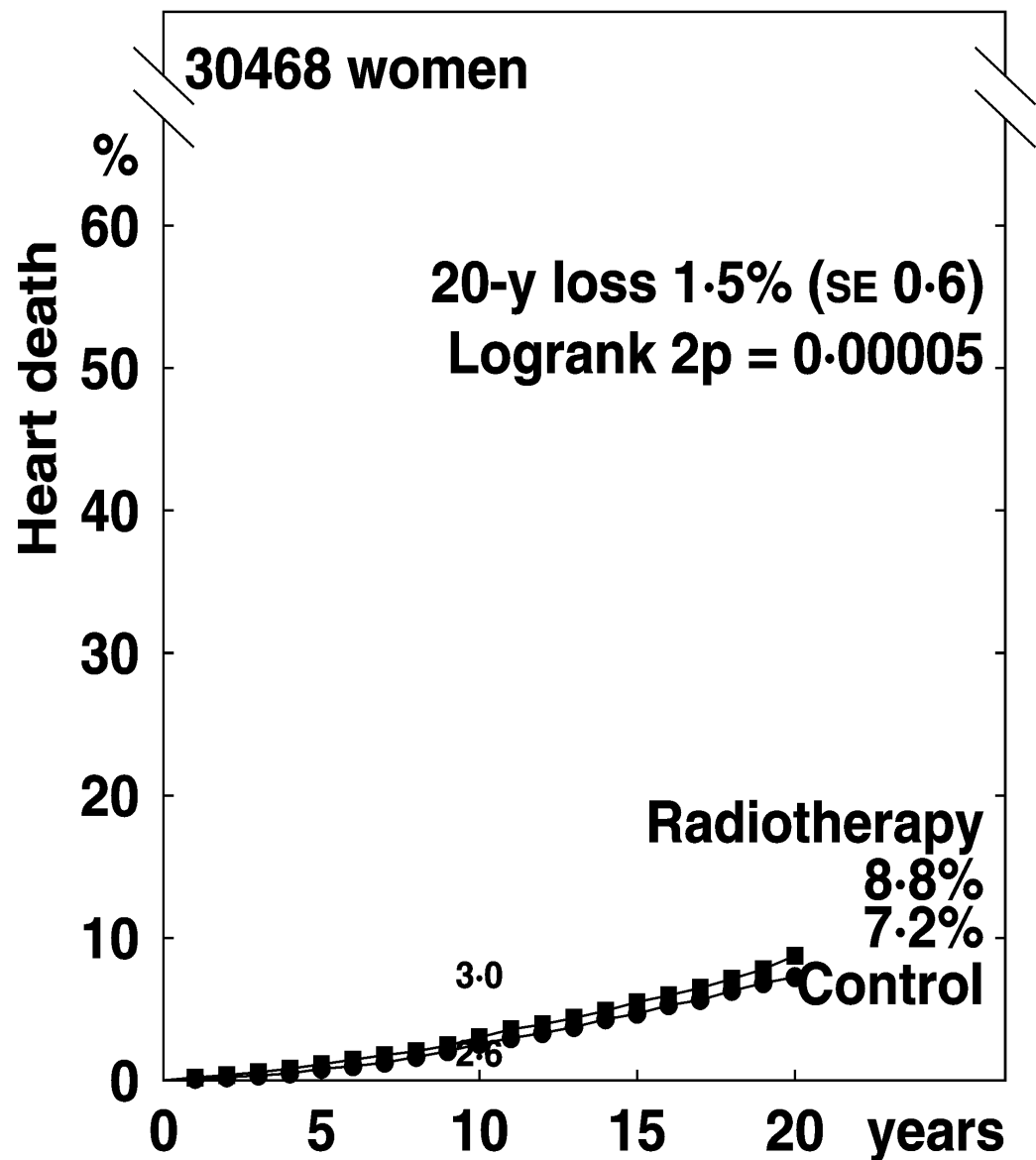
Mortality rates without breast recurrence



EBCTCG. Non-breast cancer mortality 25 500 women in 52 RT trials

	Total Events	Excess with RT	Ratio of rates RT/not	2p
Circulatory disease	1617	150	1.23 (0.06)	0.00009
Heart disease	1207	128	1.26 (0.07)	0.0001
Stroke	352	4	1.05 (0.11)	0.6
Pulmonary embolism	58	14	1.68 (0.36)	0.06
Other specified cause	1647	50	1.07 (0.05)	0.2
Unknown cause	2444	122	1.11 (0.04)	0.01
Total non-breast-cancer deaths	5708	322	1.13 (0.03)	<0.00001

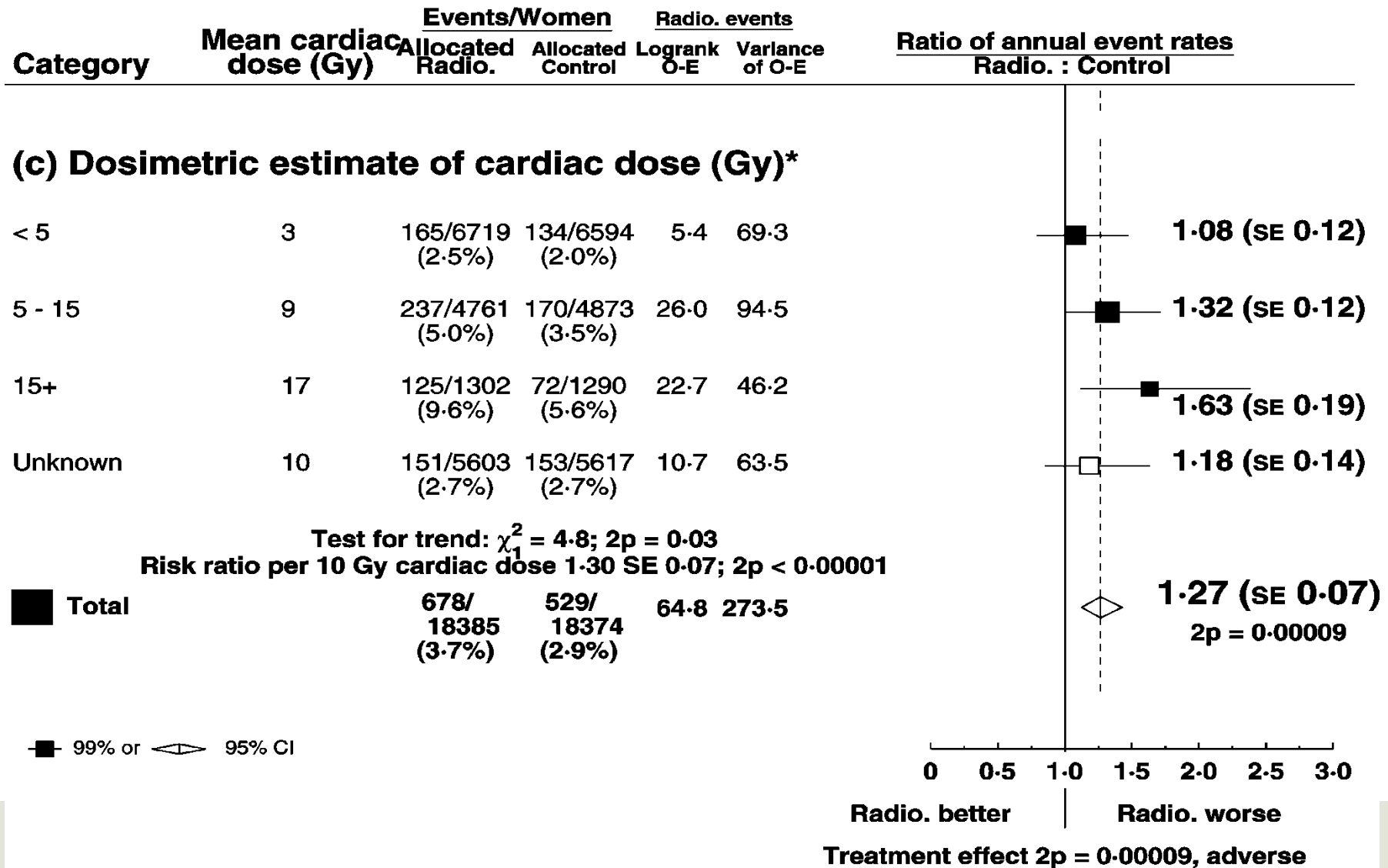
Heart disease mortality



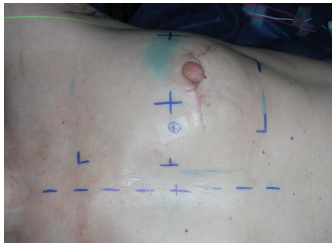
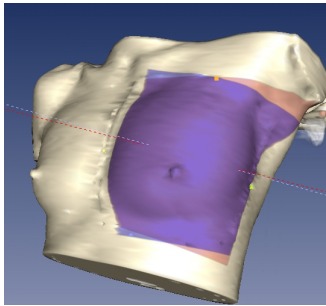
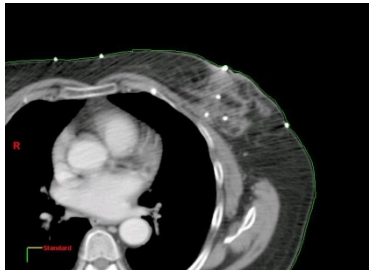
Heart disease death rates (% / year) and logrank analyses

	Years 0 - 9	Years 10 - 19	Year 20+
Radiotherapy	0.28 (280 / 100847)	0.58 (248 / 42890)	0.93 (141 / 15205)
Control	0.23 (204 / 89408)	0.47 (175 / 37137)	0.67 (98 / 14555)
Rate ratio, from (O-E) / V	1.24 SE 0.10 25.2 / 118.4	1.20 SE 0.11 18.5 / 99.6	1.55 SE 0.17 23.1 / 53.0

Retrospective evaluation of mortality in relation to cardiac dose



Treatment planning process



CT-scan in
treatment position

Virtual simulation

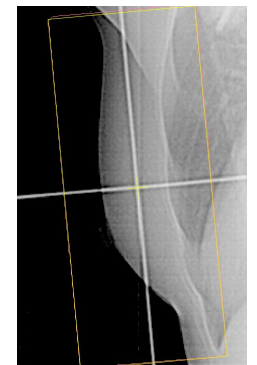
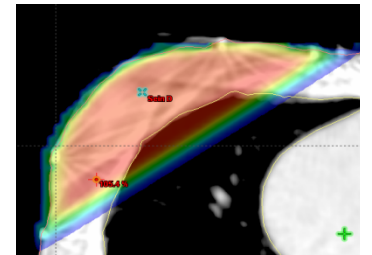
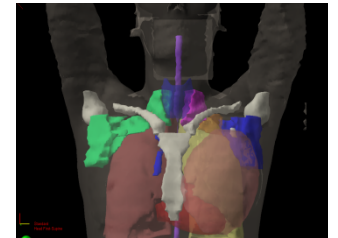
Skin marks
(mobile lasers)

Delineation

Dosimetry

Set up control:
images, clinical

Treatment



Conclusions

- ▶ **Clinical trials of radiotherapy over the past 40 years have significantly impacted the clinical practice by**
 - **Allowing a large number of women to preserve their breast**
 - **Demonstrating the relationship between local control and survival**
 - **Stimulating the improvement in RT delivery, thus reducing its potential toxicity**
- ▶ **They have contributed to continuously decrease the rate of recurrence of breast cancer**

Locoregional rates following BCT were reduced by 50% over a decade...

EBCTCG. 1972-1986

EORTC. 1989-1996

BCS + RT
5318 women

Mastectomy vs BCS + RT, both with AC
ISOLATED LOCAL RECURRENCE

