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Policlinico Courlancy

REIMS

WORKSHOP SULL'IRRADIAZIONE MAMMARIA IPOFRAZIONATA

Il carcinoma duttale in situ

XXI° CONGRESSO AIRO

GENOVA 22.11.2011

INTRODUCTION

- **Due to wide diffusion of mammography, DCIS represent ≈ 20 % of all breast cancer (BC)**
- **In 2009 in US, we accounted 193 000 invasive BC and 62 000 DCIS (25%)**

  JEMAL Ca Cancer J Clin 2009, 59 : 225-249
- **In the French screening program, DCIS represent ≈ 15% of all new BC cases**

DCIS TREATMENTS

- **Mastectomy (M)**
- **Breast conserving surgery alone (BCS)**
- **BCS and radiotherapy (RT) +/- Tamoxifen**

TREATMENT MODALITIES (1) MASTECTOMY (M)

- **M provides a 98% local control rate, and can be indicated for multicentric DCIS large lesions (≥ 4-5 cm) or inadequate margins after breast-conserving surgery (BCS).**

- **Mastectomy rate varies from 26% to 39% in recent series**

British Journal of Cancer (2009) 00, 000 – 000

www.bjcancer.com

Full Paper

Breast-conserving surgery with or without radiotherapy *vs* mastectomy for ductal carcinoma *in situ*: French Survey experience

B Cutuli*[,1], C Lemanski[2], A Fourquet[3], B de Lafontan[4], S Giard[5], A Meunier[6], R Pioud-Martigny[7], F Campana[3], H Marsiglia[8], S Lancrenon[9], E Mery[4], F Penault-Llorca[10], E Fondrinier[11] and C Tunon de Lara[12]

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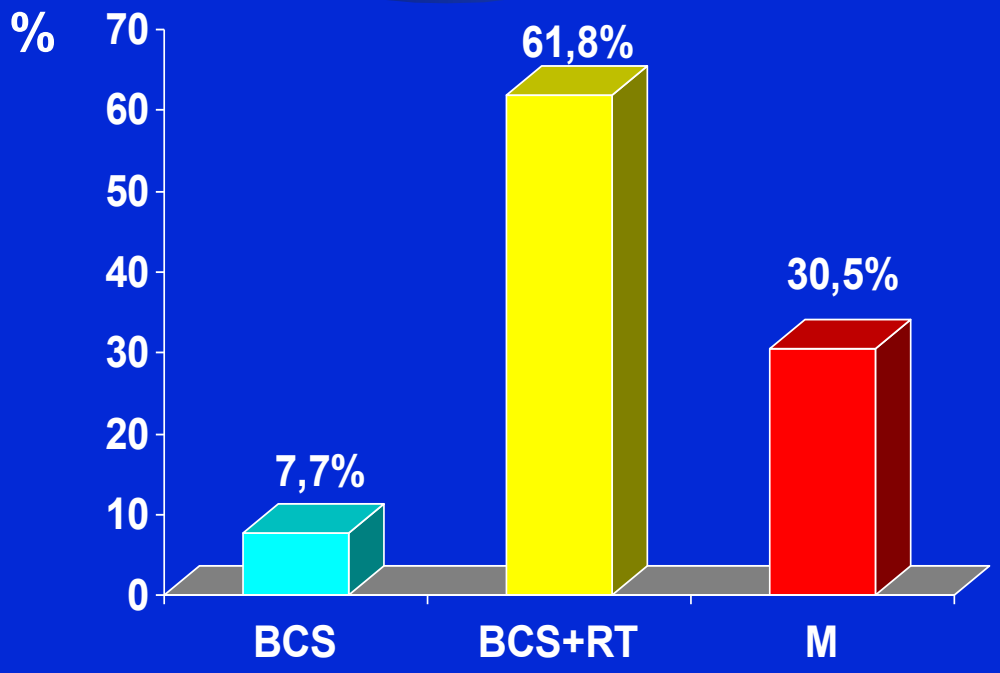
underwent mastectomy



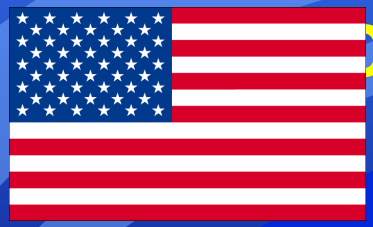
NB : Among women under 40 Y, 50% underwent mastectomy

(CUTULI et al BJC 2009)

TREATMENT MODALITIES (3)
BCS AND RADIOTHERAPY (RT)

- RETROSPECTIVE SERIES
- RANDOMIZED STUDIES
- META-ANALYSIS
- SPECIAL PROBLEMS
  - BOOST
  - HYPOFRACTIONATION

LONG-TERM OUTCOME AFTER BCT WITH RADIATION FOR MAMMOGRAPHICALLY DETECTED DCIS OF THE BREAST



SOLIN L, FOURQUET A, VICINI F et al
CANCER 2005, 103 : 1137-46

- Analysis of 1003 patients treated from 1973 to 1995 in 10 institutions in North America and Europe

Median F.U	8.5 years
Median Age	53 years
< 40 y :	7%
40-60 y :	52%
> 60 y :	31%

- All women underwent BCS + RT
- 470 (47%) had reexcision
- The median WBD was 50 Gy
- 722 (72%) received a boost (79% : e^-) with a 10 Gy median dose
- Definition of margins : (8/10 centers)
  - Negative : ≥ 2 mm
  - Close : < 2 mm

RESULTS

• **Local failure** (invasive LF 46 : 51%)	90	9%
• **Contralateral BC**	71	7%
• **Second Neoplasms**	56	5.6%
• **Metastases**	15	1.5%

- Median time to local failure : 5.3 Y
  - Invasive LF : 5.9 y
  - DCIS LF : 4.5 y

- Risk factors of LR
  - Patient age (<40 y) p=0.00062
  - Final pathology margin p=0.024
  (< 2 mm vs ≥ 2 mm)

THE SOUTHERN CALIFORNIA EXPERIENCE

- *583 patients treated from 1970 through 2000 with (237) or without RT (346) after lumpectomy*
- *Main RT use before 1989 (40-50 Gy + Ir^{192} Boost 10-20 Gy)*

	BCS (n=346)	BCS+RT (n= 237)	p
Average FU (Months)	70	106	<0.001

SILVERSTEIN DCIS Book 2d Ed 2002, 482-93

10-year probability of LR :

LR rates : L : 28% p= 0.06

L+RT : 21 %

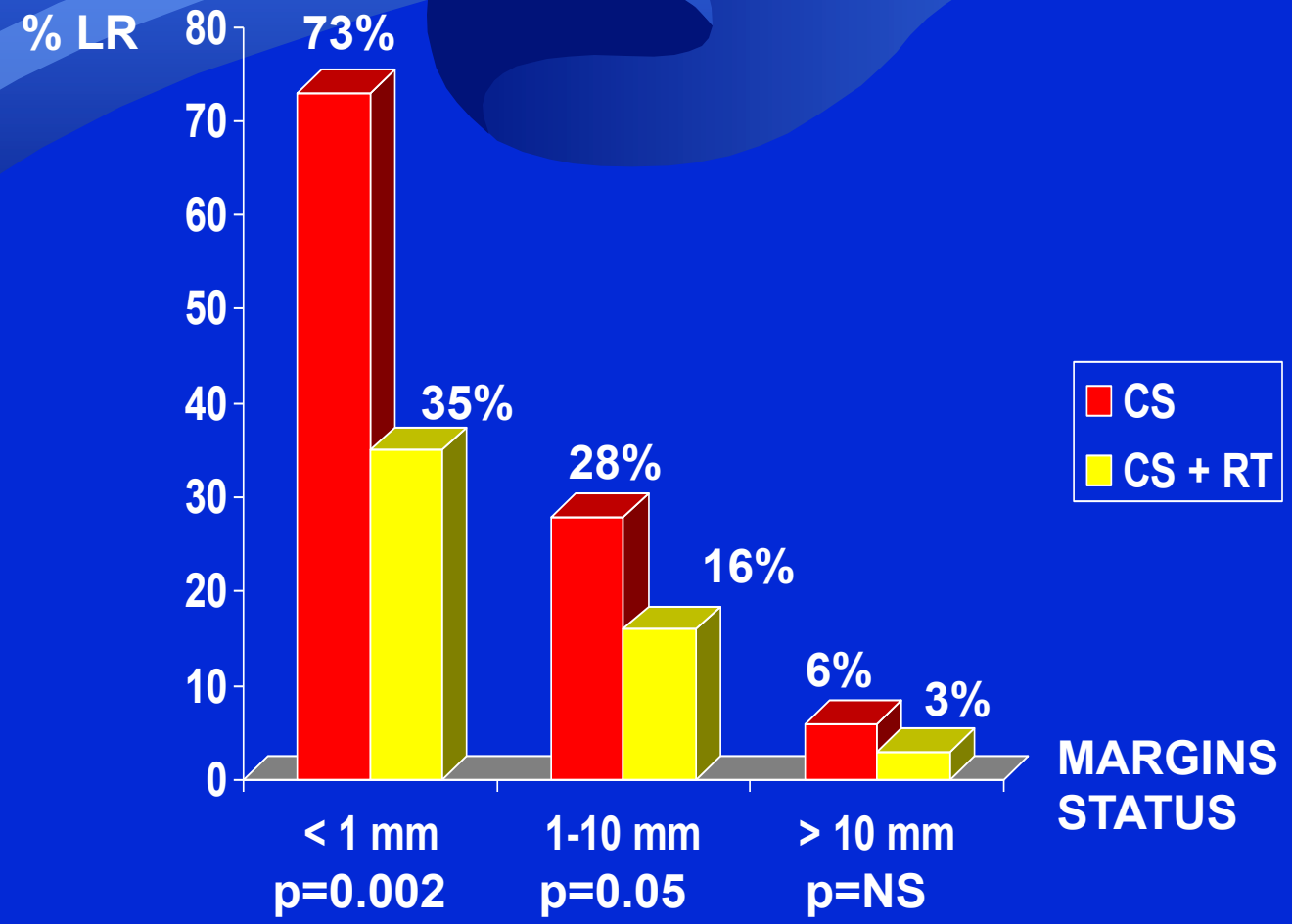
But :

Several unfavorable features were more frequent in RT group

	L	L + RT	p
Median size (mm)	10	15	0.01
Comedo subtype	61%	73%	0.003
Margins < 1 mm	19%	35%	< 0.001

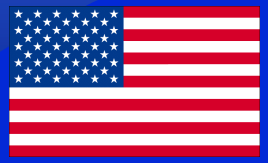
Despite all these facts, RT clearly decreases LR rates

THE SOUTHERN CALIFORNIA EXPERIENCE
Analysis of 583 patients treated with (237) or without RT (346) after lumpectomy



SILVERSTEIN, DCIS BOOK 2d ED, 2002 : 482-93

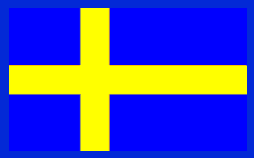
PUBLISHED RANDOMIZED TRIALS



NSABP B-17 — **1985-1990**

EORTC 10583 — **1986-1996**

UK-ANZ – DCIS TRIAL — **1990-1998**



SWEDISH TRIAL — **1987-1999**

NB : 4560 included patients

OVERVIEW OF THE RANDOMIZED TRIALS OF RADIOTHERAPY IN DUCTAL CARCINOMA IN SITU OF THE BREAST

EARLY BREAST CANCER TRIALIST COLLABORATIVE GROUP (EBCTCG)

JNCI MONOGRAPH 2010, 41 : 162-177

… RT reduced the ABSOLUTE 10-year risk of any ipsilateral breast event (recurrent DCIS or invasive) by 15.2%
(12.9 vs 28.1%, 2p<0.0001)…

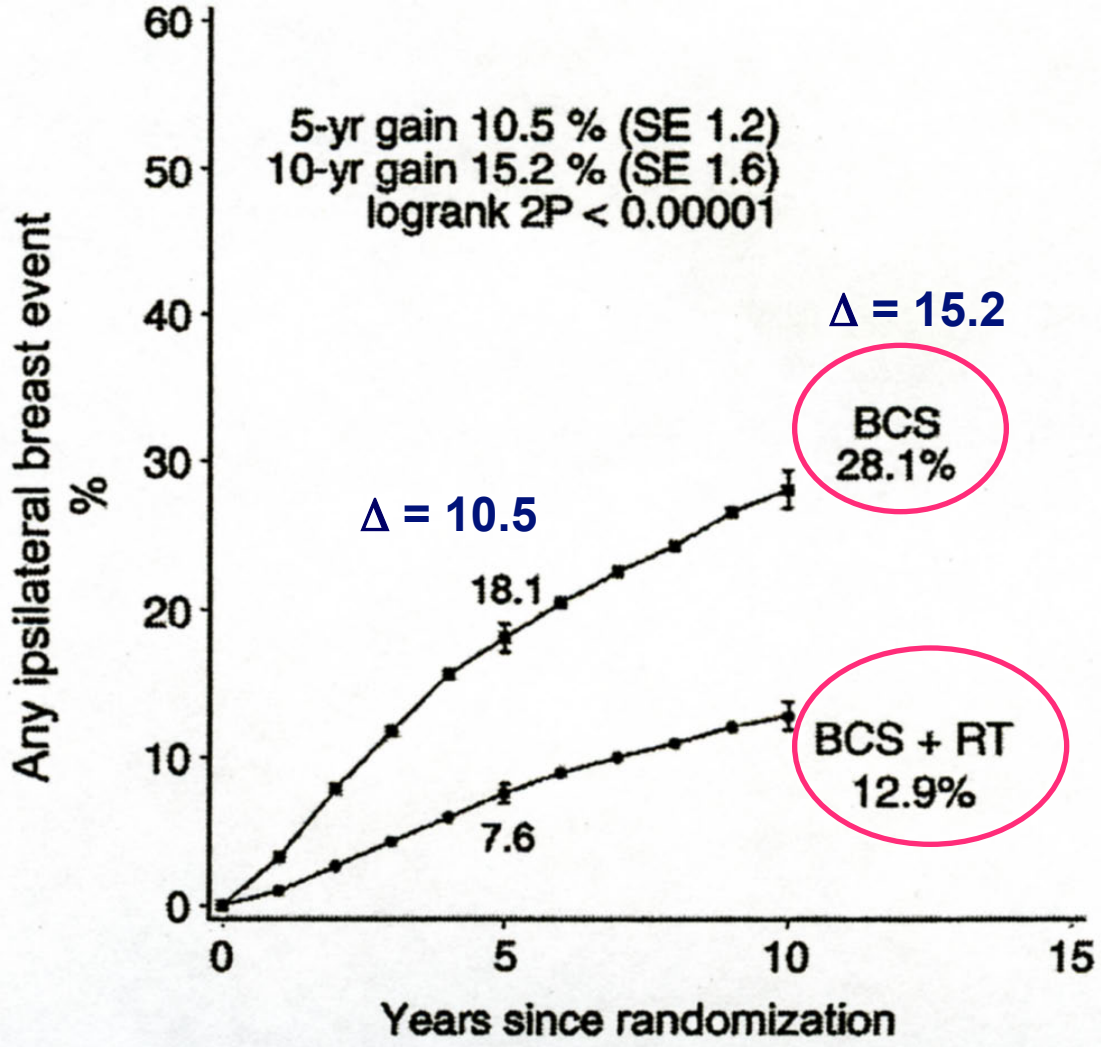


Figure 1. Effect of radiotherapy (RT) after breast-conserving surgery (BCS) (four trials, start dates 1985–1990, 3729 women): 10-year cumulative risks of any ipsilateral breast event (ie recurrent DCIS or invasive cancer).

Vertical lines indicate 1 SE above or below the 5 and 10 year percentages.

JNCI MONOGRAPH 2010, 41 : 162-177

REDUCTION ABSOLUE DU RISQUE : 54%

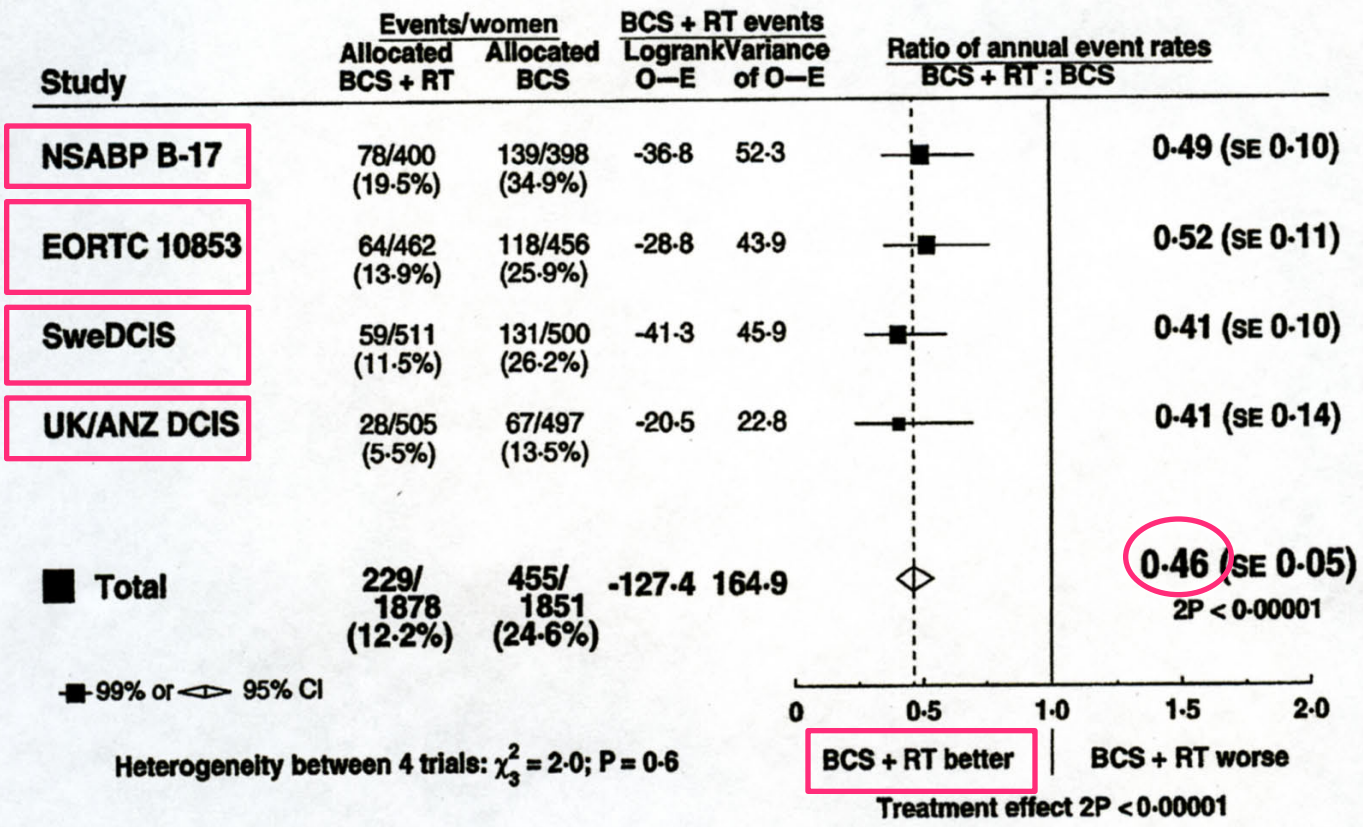


Figure 2. Effect of radiotherapy (RT) after breast-conserving surgery (BCS): ratio of annual event rates of any ipsilateral breast event by trial.

SE = standard error; CI = confidence interval.

JNCI MONOGRAPH 2010, 41 : 162-177

… RT was effective regardless of the age at diagnosis, extent of breast conserving surgery, use of tamoxifen, method of DCIS detection, margin status, focality, grade, comedonecrosis, architecture or tumor size

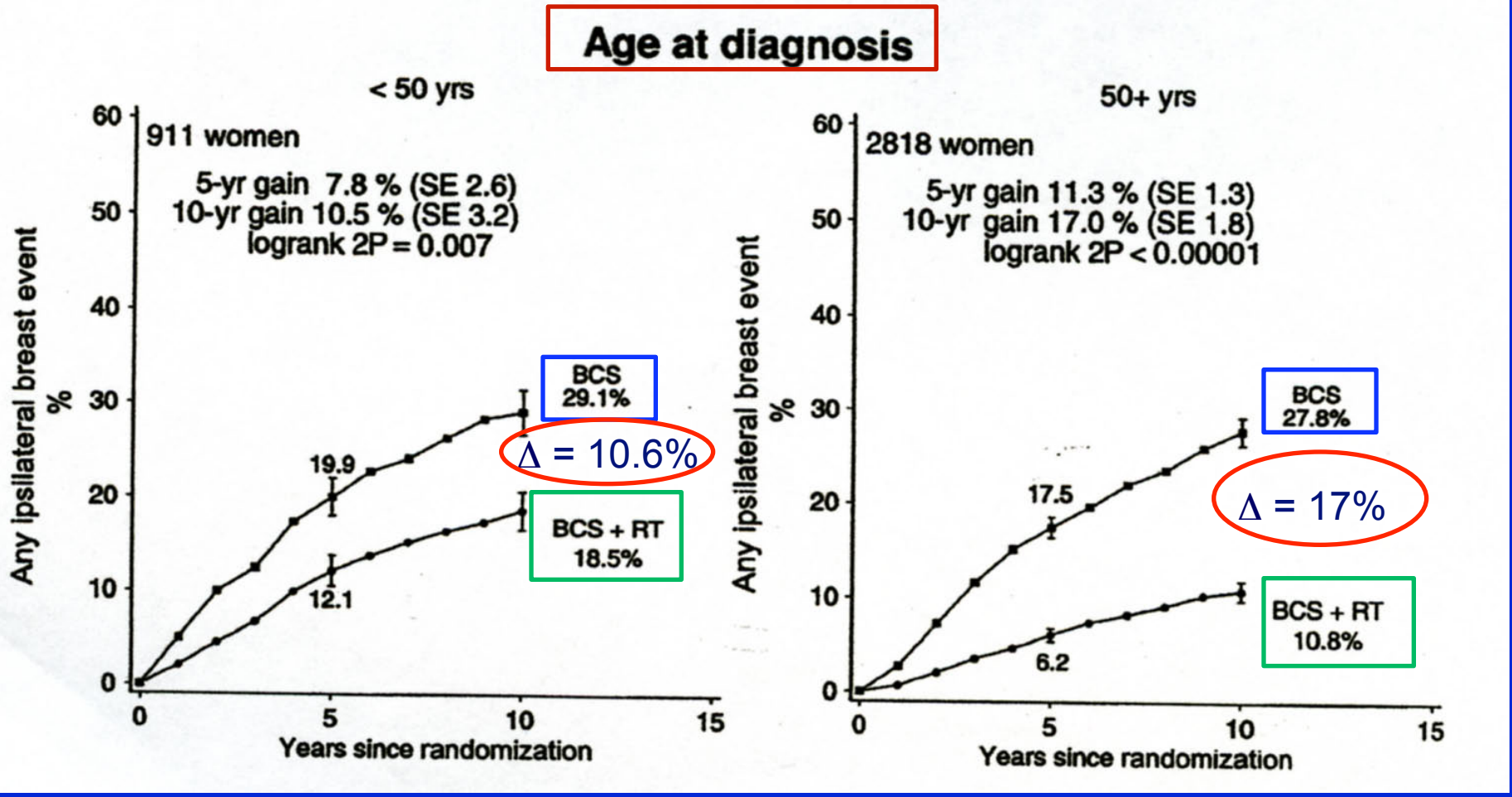
The proportional reduction in ipsilateral breast events was greater in older than younger women :

10-year ABSOLUTE risk :

< 50 y	18.5%	vs	29.1% (-10.6%)
			2p<0.004
> 50 y	10.8%	vs	27.8% (-17%)

JNCI MONOGRAPH 2010, 41 : 162-17

EBCTCG OVERVIEW : IMPACT OF RT



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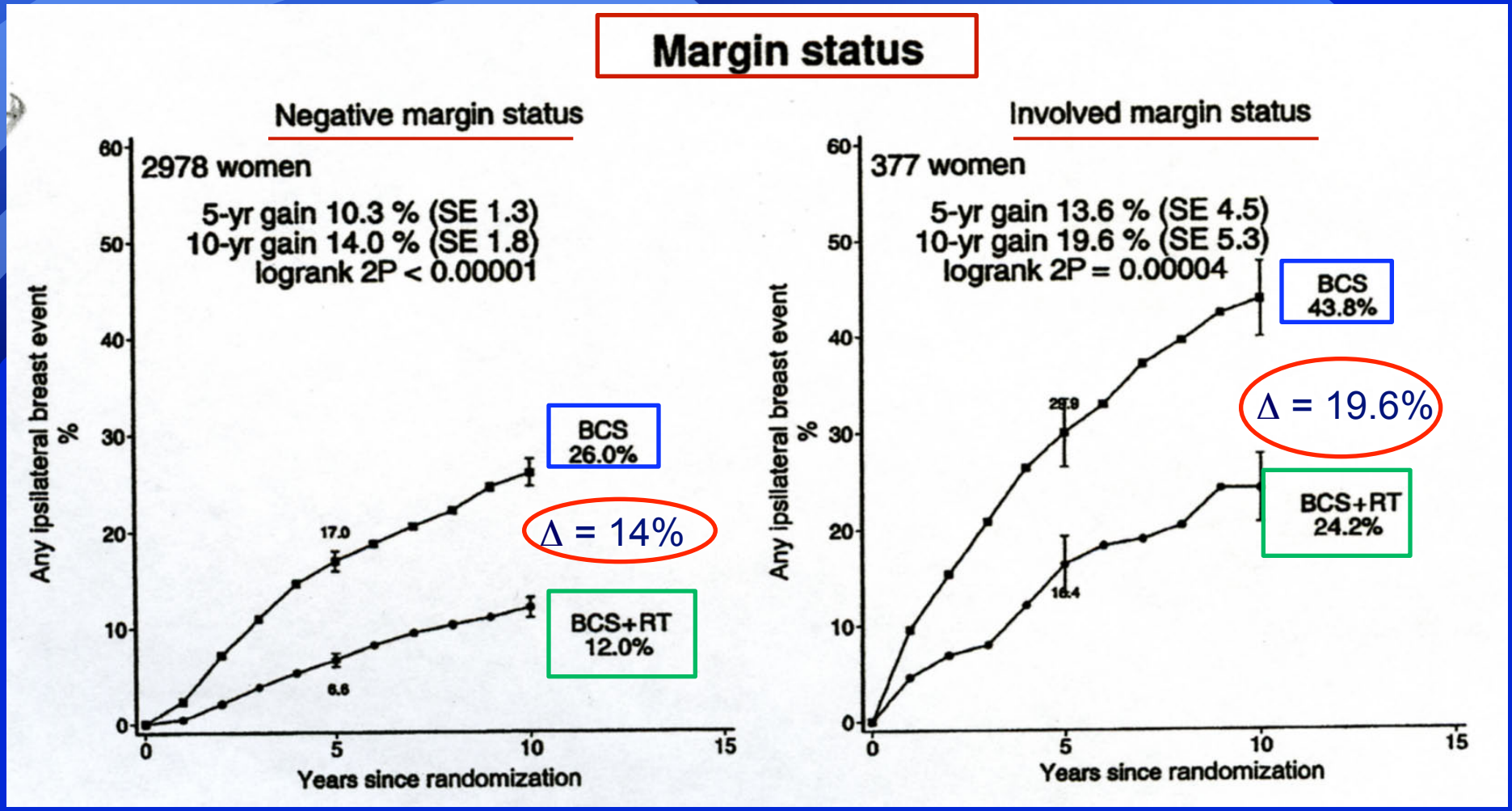
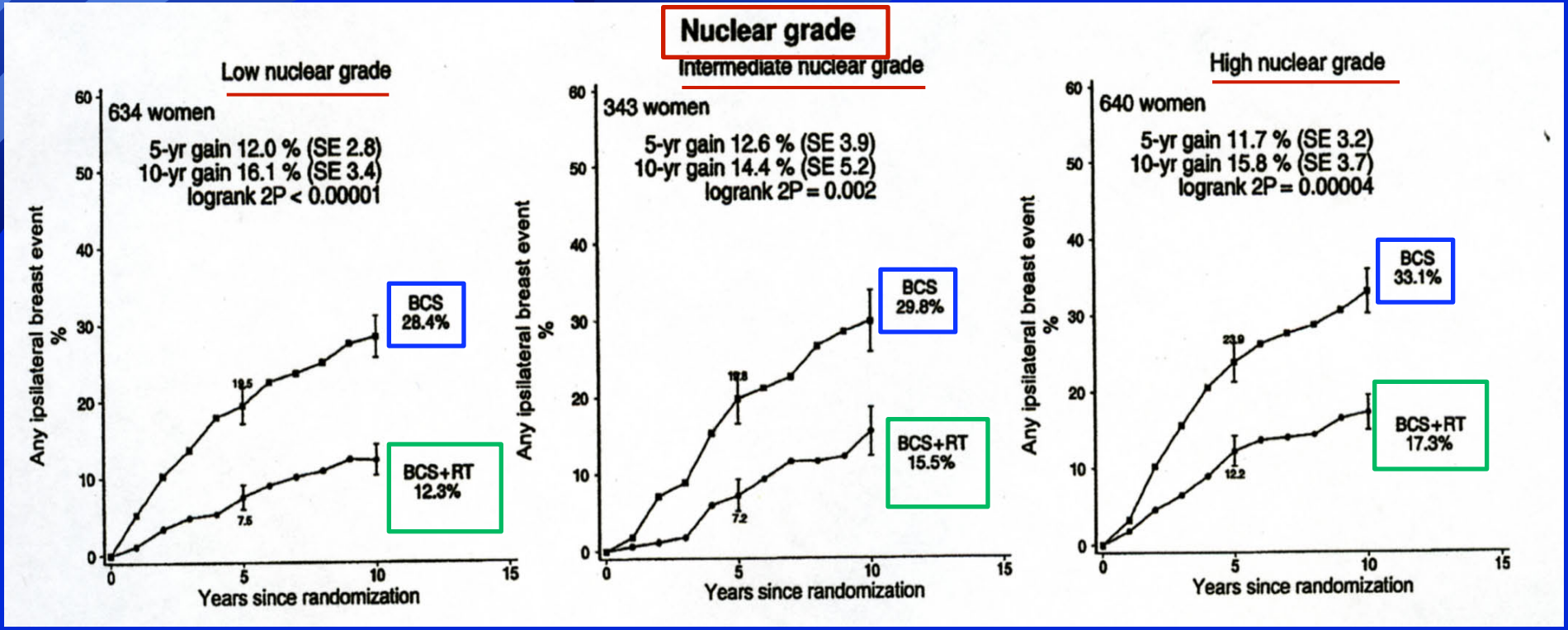


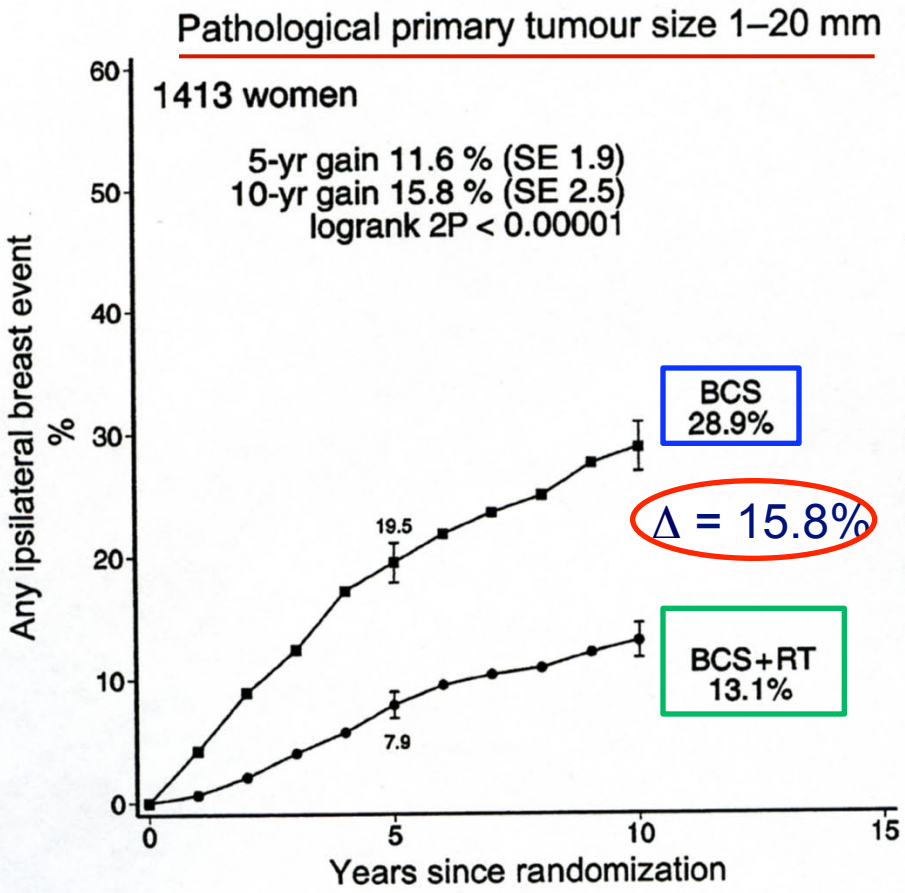
EBCTCG OVERVIEW : IMPACT OF RT

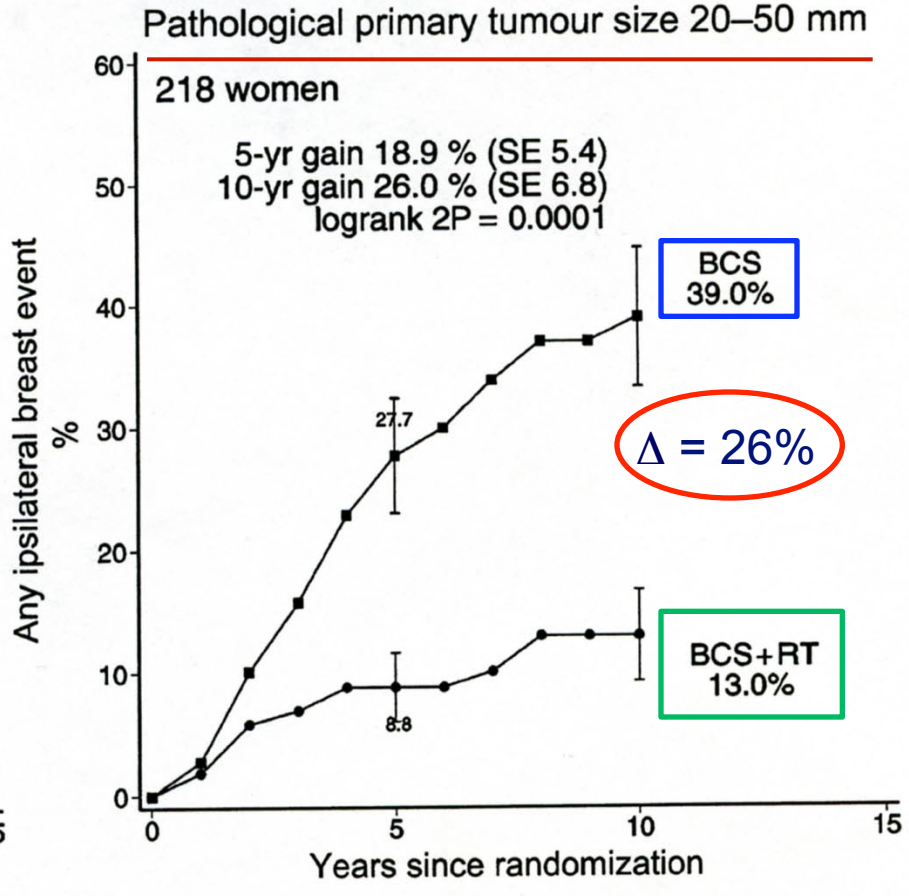


JNCI MONOGRAPH 2010, 41 : 162-17

EBCTCG OVERVIEW : IMPACT OF RT

Pathological primary tumor size





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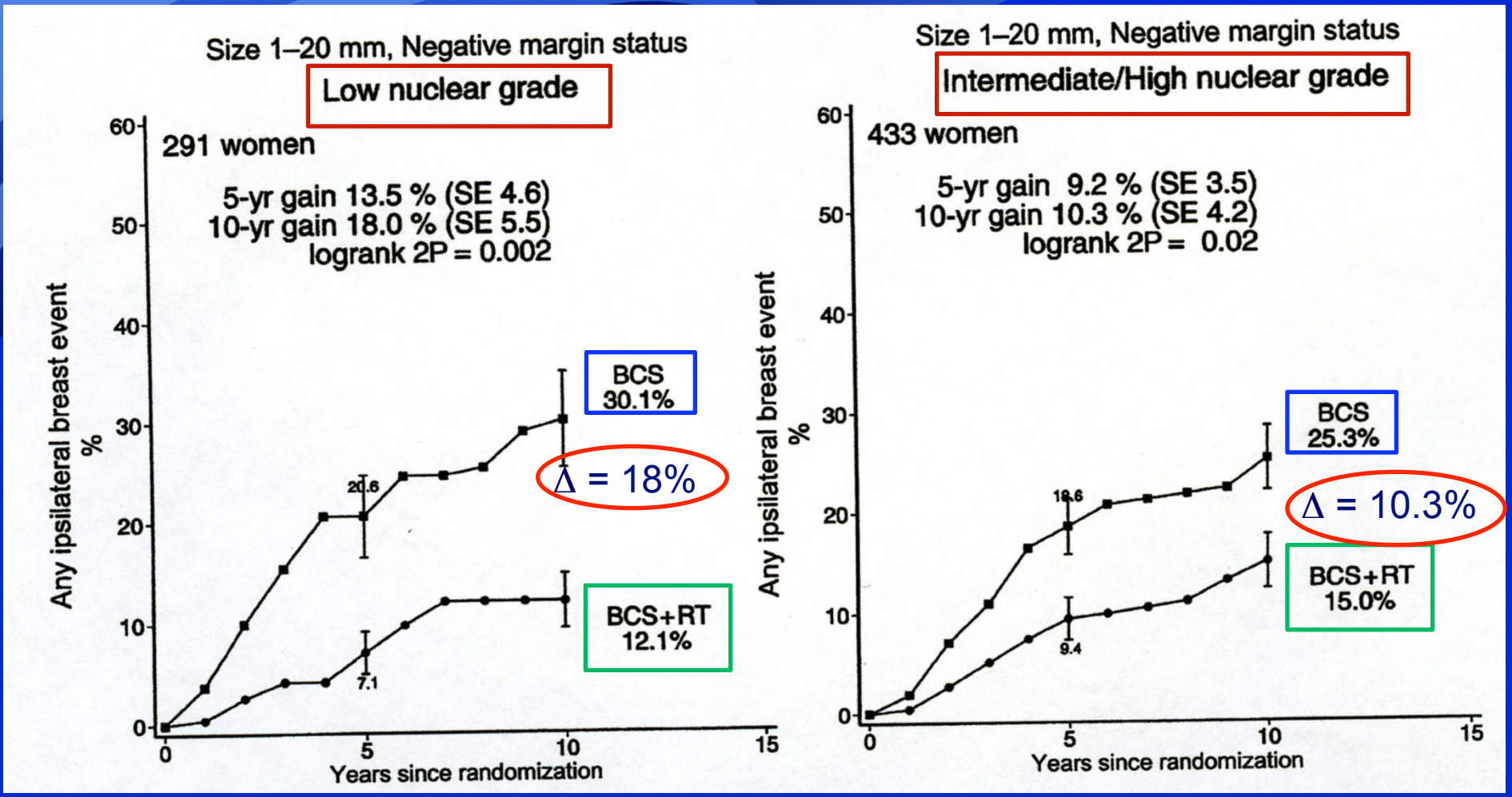
EBCTCG OVERVIEW : IMPACT OF RT



DCIS : FREQUENCE OF BOOST USE IN RETROSPECTIVE SERIES OF BCS +RT (SERIES WITH ≥ 100 CASES)

AUTHORS	N	FU (years)	% BOOST	% LR
SOLIN (2005)	1003	8.5	72	$9^{(10)}/16^{(15)}$
CUTULI (2002)	515	7	80	12.6
VARGAS (2005)	313	7	95	8
NAKAMURA (2002)	260	8.8	100	$18^{(1)}$

(1) : Whole breast dose : 1979-90 : 46-50 Gy 8 Gy/w

1990-02 : 45-50 Gy 9 Gy/w

+ 10-20 Gy Ir ^{192} boost

BOOST RADIOTHERAPY IN YOUNG WOMEN WITH DCIS : A MULTICENTRE, RETROSPECTIVE STUDY OF THE RARE CANCER NETWORK

OMLIN A et al LANCET ONCOL 2006, 7 : 652-56

- *Analysis of 373 women (18 institution) younger than 45 years, treated from 1978 to 2004, with three treatment modalities*

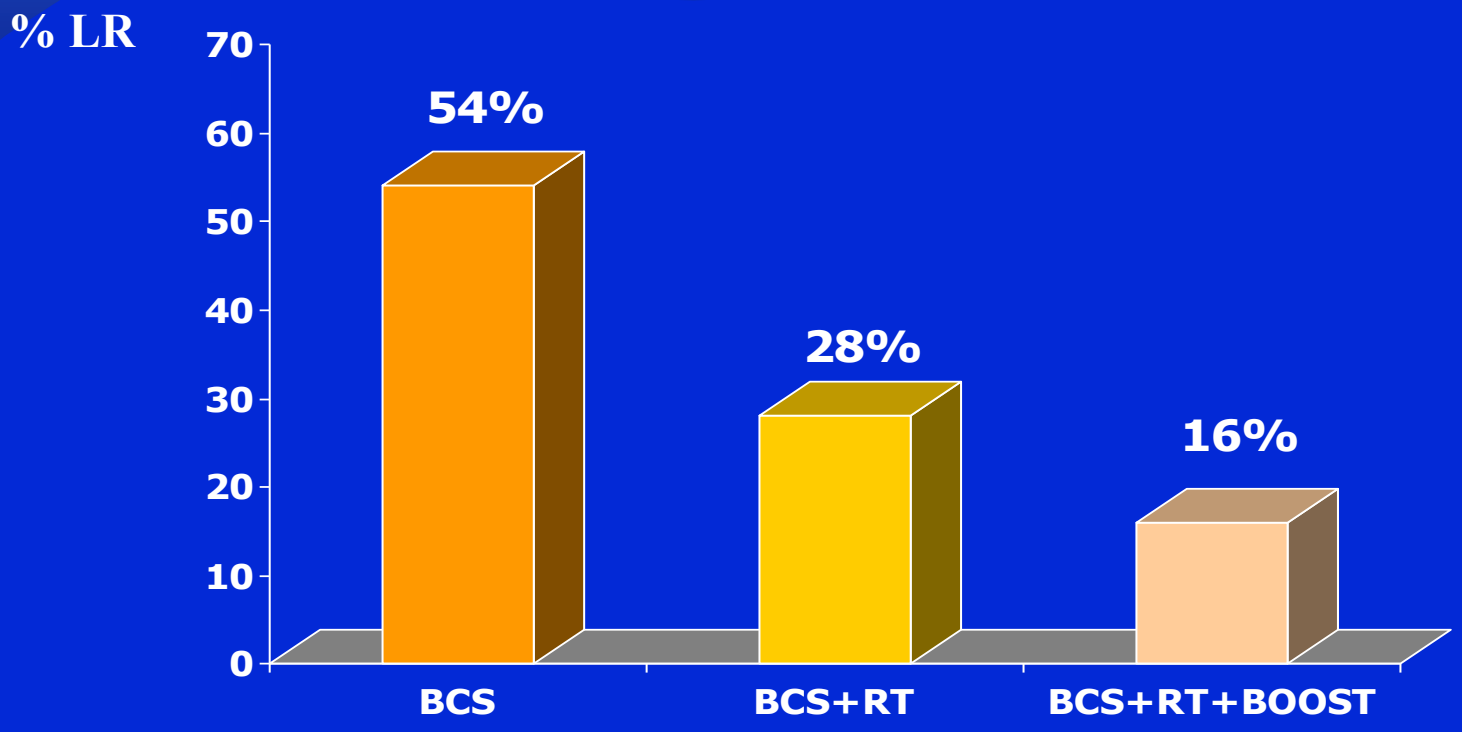
  BCS (n=57)

  BCS + RT (n=166)

  BCS + RT + boost (n=150)

  Median follow up : 72 monts

RESULTS



OMLIN A et al LANCET ONCOL 2006, 7 : 652-56

- ***This study suggest that boost should be considered in this high risk group of women.***

- ***However the clinico-pathological features of each group are different and tumor size margin width and hormonal receptor status were not reported***

Local Control with conventional and hypofractionated RT after CS for DCIS

Williamson D et al. Radiother Oncol 2011

- *Retrospective analysis of 266 patients treated in Toronto from 1999 to 2004*
- *Median FU: 3.7 years*
- *Median age: 56 years*

- *Analysis according to three RT schemes:*
- *50 Gy/25 F (104 = 39%)*
- *42.4 Gy/16F (119 = 45%)*
- *40 Gy/16F + 12.5 Gy/5F (43 = 16%)*

- *N.B. 48 (16%) received tamoxifen*

Results: actuarial risk of LR at 4 years

- *50 Gy:* *7%*
- *HF WBRT (40Gy/42.4Gy):* *6%*

- *LR according to grade:*
- *G1 = 0*
- *G2 = 4%* P = 0.029
- *G3 = 11%*

CONCLUSIONS

- *…..The results of our retrospective study in a non randomized population of women with DCIS are encouraging , with no difference between conventional and hypofractionated WBRT, and similar low (!) local recurrence rates to published series……*

- *But….the three fractionated schemes were selected according to individual physician preference ……*

- *12 patients (4.5%) had microinvasive disease ……..*

- *The role of boost remains unclear…..*
  (BOMBIS and TROG Trails)

Effect of Radiotherapy Boost and hypofractionation on outcomes in DCIS WAI E, Cancer 2011; 117: 54 - 62

Retrospective analysis of 957 patients treated in British Columbia from 1985 to 1999

MEDIAN FU : 9,3 years

Analysis according to treatment types :

BCS :	**475**	**(50%)**
BCS + RT (B) :	**338**	**(35%)**
BCS + RT + boost (C) :	**144**	**(15%)**

NB: → **542: mastectomy (33%)**

…during the study era, the use of adjuvant RT, RT dose-fractionation, and a partial breast boost were at the discretion of the treating oncologist…

At the start of the study era, RT was not routinely recommended for patient with DCIS…

After the publication of the NSABP B17 study in 1993, adjuvant breast RT was recommanded for patients with DCIS > 1cm, comedocarcinoma, or margins < 5 mm who underwent BCS…

…tamoxifen was not recommanded during the study era outside of available clinical trial…
Partial breast boost was generally recommanded for women with close or positive margins…

Short fractionation was considered standard practice in B.C during the study era, with extended fractionation if the patient had noticeable postopérative edema, hematoma, infection or larger breast size. Choice of fractionation was at the discretion and preference of the treating oncologist…

Boost RT was delivered by direct en-face electron beam (9-16 Mev)

Evolution importante des traitements au fil du temps (I)

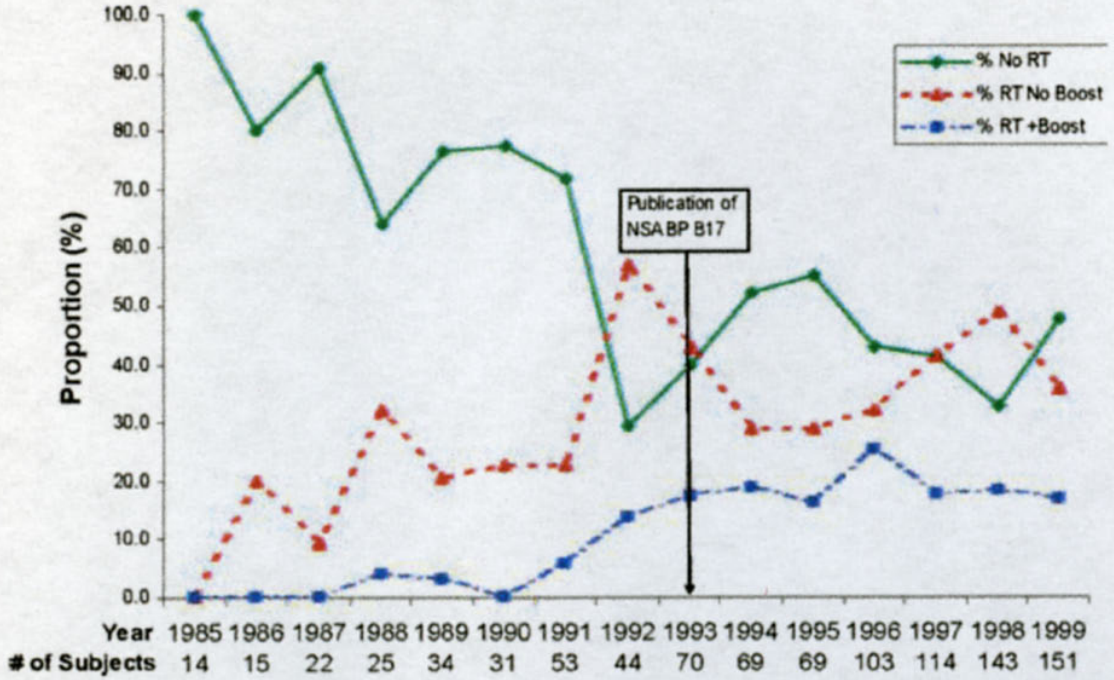


Figure 1. Depicted is the proportion of patients not treated with radiotherapy (No RT), treated with adjuvant whole breast RT with boost (RT+boost), and without a partial breast RT boost (RT No Boost) between January 1, 1985 and December 31, 1999.

Evolution importante des traitements au fil du temps (II)

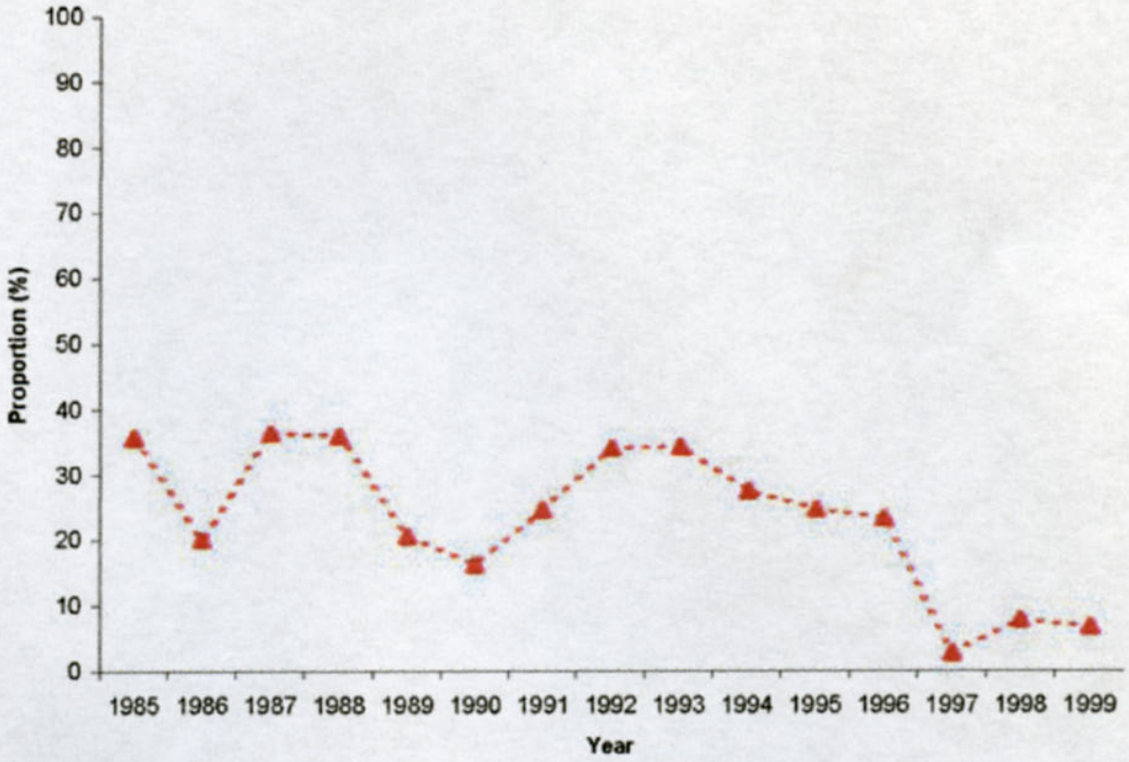


Figure 2. Proportion of patients treated with positive or close margins after tumor resection between January 1, 1985 and December 31, 1999 is shown.

Treatment modalities :

77 % — 44 Gy / 16 fr

17 % — 50 Gy / 25 fr

If dose < 45 Gy _____ boost 32%

> 45 Gy _____ boost 16%

Boost dose = **7.5 Gy (64%)**

CLINICO-PATHOLOGICAL FEATURE ACCORDING TO TREATMENT GROUP

AGE	BCS	BCS+RT	BCS+RT+ BOOST	p
< 50	30	31	31	
50-69	49	58	52	0.004
> 69	21	11	17	
GRADE				
1	36	16	16	<0.001
2	38	38	40	
3	12	38	41	
NP	14	8	3	

CLINICO-PATHOLOGICAL FEATURE ACCORDING TO TREATMENT GROUP

SIZE (1)	BCS	BCS+RT	BCS+RT +BOOST	p
< 1.5 cm	72	53	52	
1.5 – 4 cm	19	39	39	< 0.001
> 4 cm	6	6	7	
COMEDOCARCINOMA	25	55	46	< 0.001
MARGINS (1)				
POSITIVES	9	12	29	
« CLOSE »	5	5	8	<0.001
NEGATIVE	79	82	62	

10-YEAR RESULTS (%)

	BCS	BCS+RT	BCS+RT +BOOST	p
LR	13	6	9	0.65
SPECIFIC SURVIVAL	98	99.7	100	0.16
OVERALL SURVIVAL	88	96	94	0.013

NB : **50%** OF LR : **INVASIVES**

Multivariate analysis showed that RT, with or without boost, was indipendently associated with better LC… with no differences in LC according to different fractionation schemas, or use of the boost…

Intermediate or high grade, comedo histology, re-excision, and close, positive or unknown surgical margins were associated with an increased risk of L.R

Analyse multivariée: facteurs thérapeutiques de RL

	HR	p
RE-EXCISION		
NON	1	< 0.001
OUI	2.4 (0.4 - 2.4)	
TRAITEMENT		
CHIR CONS. SEULE	1	
RT ≤ 45 Gy	0.4 (0.2 – 0.7)	0.004
RT > 45 Gy	0.3 (0.1 – 0.8)	
RT ≤ 45 Gy + boost	0.5 (0.2 – 0.9)	
RT > 45 Gy + boost	0.8 (0.2 – 3.5)	

LOCAL RECURRENCE AND SPECIFIC SURVIVAL

The 10-year absolute difference in LC between subjects receiving RT or no RT was 6% (93% vs 87%, p= 0.065)

This was associated with a 1.7% absolute difference in 10-year BCSS (p=0.16)

The ratio of LR to deathes from breast cancer (1: 3.5) is similar to the ratio of LR to BC deathes reported from randomized trials of patients with invasive BC

POSSIBLE HYPOFRACTIONATED SCHEMES :

CANADIAN TRIAL

42.5 Gy / 16 fr (2,65 Gy) / 22 d

START A TRIAL

41.6 Gy / 13 fr (3,2 Gy) / 35 d

START B TRIAL

40 Gy / 15 fr (2,67 Gy) / 21 d

FINAL QUESTIONS

- It is possible to omit RT in some selected DCIS ?
- What is the acceptable LR rate ?
- What is the impact of invasive LR on survival ?

LOCAL EXCISION ALONE WITHOUT IRRADIATION FOR DCIS OF THE BREAST : A TRIAL OF EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)

HUGHES L, JCO 2009, 27 : 5319-24

- Analysis of two cohorts of patients (1997-2002) :

  A) Grade 1-2 DCIS ≤ 2.5 cm (n=565)

  B) Grade 3 DCIS ≤ 1 cm (n= 105)

- In all cases :

  - Complete excision (≥ 3 mm)
  - Post Op. mammogram
  - Central pathology review (90%)

LOCAL EXCISION ALONE WITHOUT IRRADIATION FOR DCIS OF THE BREAST : A TRIAL OF EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)

HUGHES L, JCO 2009

- Median :

  Age : 60y

  F.U : 6.5 y

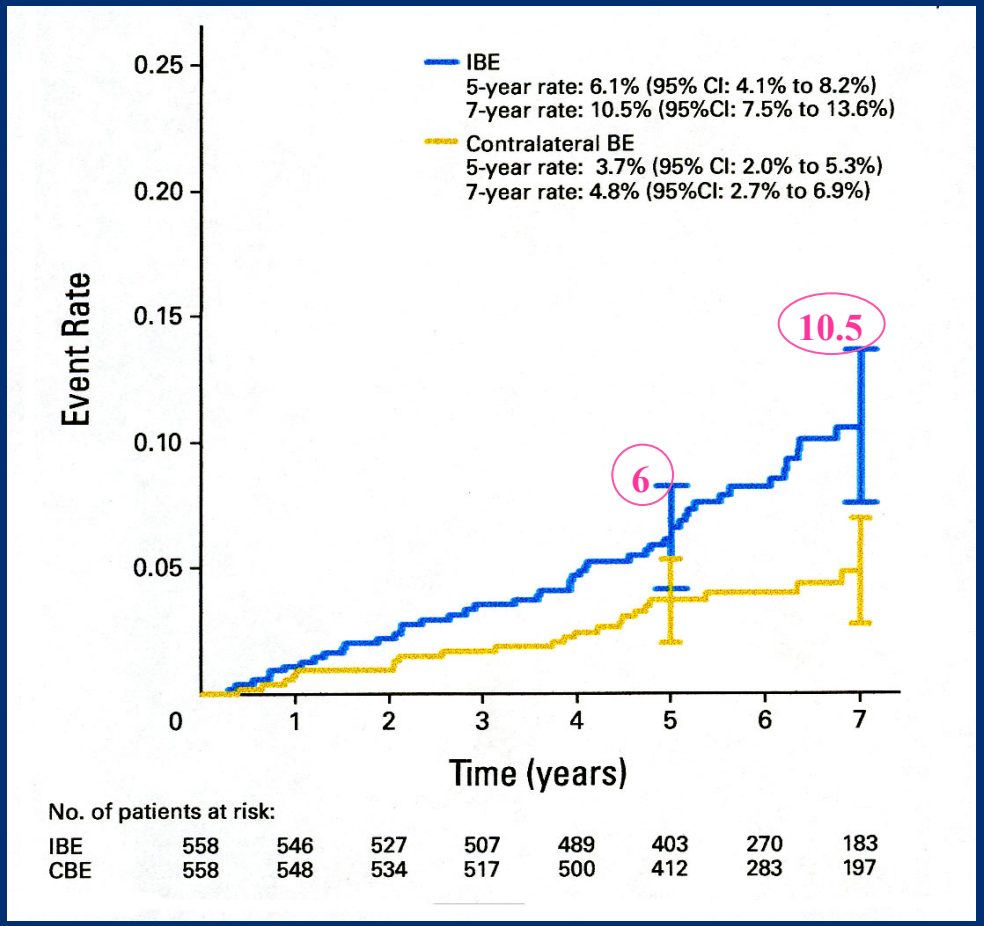
Tumor sizes

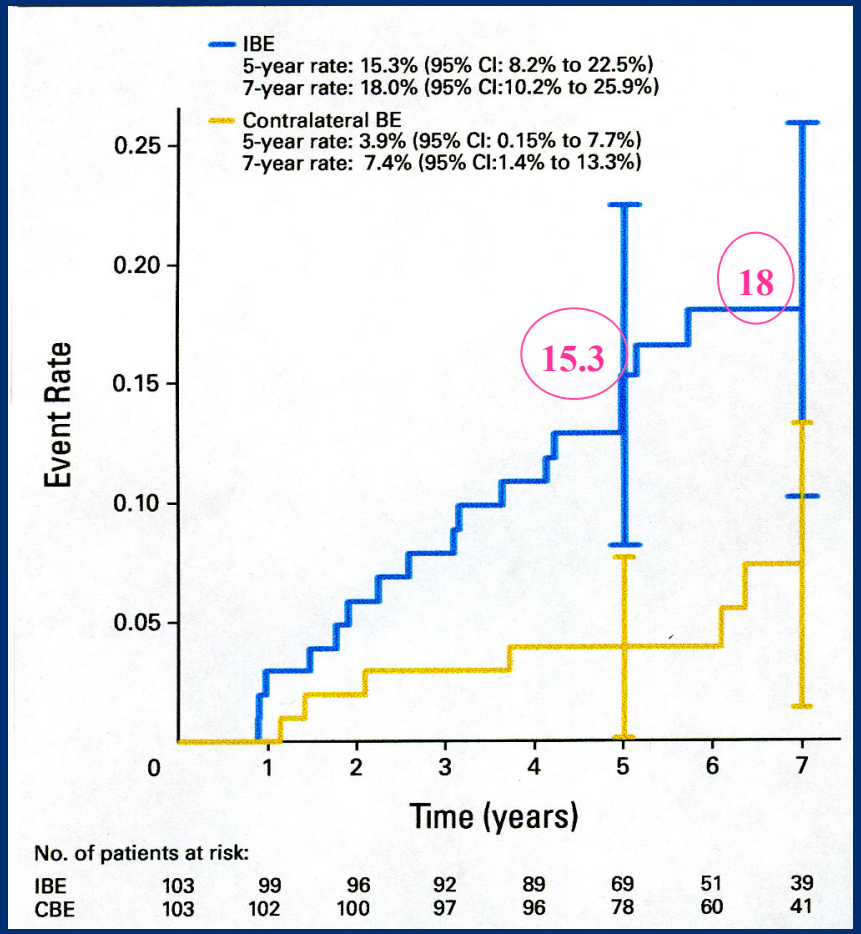
- A) 6 mm (76% < 10 mm) (low / Int. Grade)
- B) 5 mm (88%) < 10 mm) (High Grade)

NB : 1) margins { ≥ 5 mm : 83%
                 ≥ 10 mm : 53%

2) ≅ 30% received Tamoxifen (> 2000)

IPSILATERAL BREAST EVENTS (IBEs) AND CONTRALATERAL BREAST EVENTS (CBEs) IN PATIENTS WITH LOW-OR INTERMEDIATE-GRADE AND HIGH GRADE DCIS





53% of IBE were invasive

HUGHES L. JCO 2009

LOCAL RECURRENCES (LR) AND METASTASES AFTER CONSERVATIVE TREATMENT OF DCIS LITERATURE RESULTS (RETROSPECTIVE STUDIES AND RANDOMIZED TRIALS)

	St Louis series	International Collaborative Group	Southern California group	French Series	NSABP B17[3]	EORTC 10583[3]
Number of cases	177	1003[2]	583	1215	814	1010
Period	1985-96	1973-95	1971-00	1985-96	1985-90	1986-96
Treatment: CS CS+RT	 - 177	 - 1003	 346 237	 403 812	 403 411	 503 507
Median FU (months)	84	102	106 (CS+RT) 70 (CS)	80	90	126
LR: total LR: in situ LR: invasive	16[1] (9%) 4 (25%) 12 (75%)	90 (9%) 34 (38%) 56 (62%)	109 (18.7%) 62 (57%) 47 (43%)	195 (17%) 82 (42%) 113 (58%)	151 (18.5%) 81 (54%) 70 (46%)	207 (20.5%) 103 (50%) 104 (50%)
Axillary recurrence	1	5	5	23	6	NS
Metastases	1 (0.5%)	8 (0.7%)	7 (1.2%)	16 (1.3%)	6 (0.7%)	32 (3.2%)
MIR[4]	8.3%	14.3%	14.9%	14.2%	8.6%	24.3%

(1): one case of angiosarcoma excluded
(2): all cases mammographically detected
(3): randomized trials
(4): metastasis/invasive recurrence ratio

CONCLUSIONS

- **BCS + RT remains the standard treatment for limited DCIS**
- **Mastectomy is mandatory in case of large lesions with incomplete excision**
- **A subgroup of DCIS in which RT could be safely omitted is not yet identified**
- **Boost and hypofractionation should be tested in future trials**

2ème COLLOQUE FRANCOPHONE SUR LES CANCERS DU SEIN IN SITU

REIMS - PALAIS DES CONGRÈS

VENDREDI 29 JUIN 2012

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Int. J. Radiation Oncology Biol. Phys., Vol. 53, No. 4, pp. 868–879, 2002

0360-3016/02/$–see front matter

ELSEVIER

PII S0360-3016(02)02834-1

CLINICAL INVESTIGATION **Breast**

BREAST-CONSERVING THERAPY FOR DUCTAL CARCINOMA *IN SITU* OF THE BREAST: THE FRENCH CANCER CENTERS' EXPERIENCE

Bruno Cutuli, M.D.,* Christine Cohen-Solal-le Nir, M.D.,† Brigitte de Lafontan, M.D.,‡ Hervé Mignotte, M.D.,§ Virginie Fichet, M.D.,‖ Renaud Fay, Ph.D.,¶ Véronique Servent, M.D.,# Sylvia Giard, M.D.,# Claire Charra-Brunaud, M.D.,** Claire Lemanski, M.D.,†† Hugues Auvray, M.D.,‡‡ Stéphane Jacquot, M.D.,†† and Jean-Christophe Charpentier, M.D.¶

- **Analyse de 705 patientes traitées de 1985 à 1995 par chirurgie conservatrice seule (190) ou chirurgie conservatrice + RT (515) avec un recul médian de 7 ans**

PATIENTS CHARACTERISTICS (%)

	BCS N= 190	BCS + RT N= 515	p
AGE			
< 40	6	8	
40-60	64	65	0.61
> 60	30	27	
MEAN SIZE (mm)	10	14.5	0.003
COMEDO SUBTYPE	17	37	<00001

TREATMENT RESULTS
(7-year median FU)

	BCS N= 190	BCS + RT N= 515	
LR Total	*59 (31%)*	*66 (13%)*	*<0.0001*
LR (in situ)	*28 (15%)*	*26 (5%)*	*<0.0001*
LR (invasive)	*31 (16%)*	*40 (8%)*	*<0.0001*
MEAN TIME TO LR (Months)	*41*	*55*	
NR	*6 (3%)*	*9 (2%)*	*NS*
M+	*5 (3%)*	*7 (1%)*	*NS*