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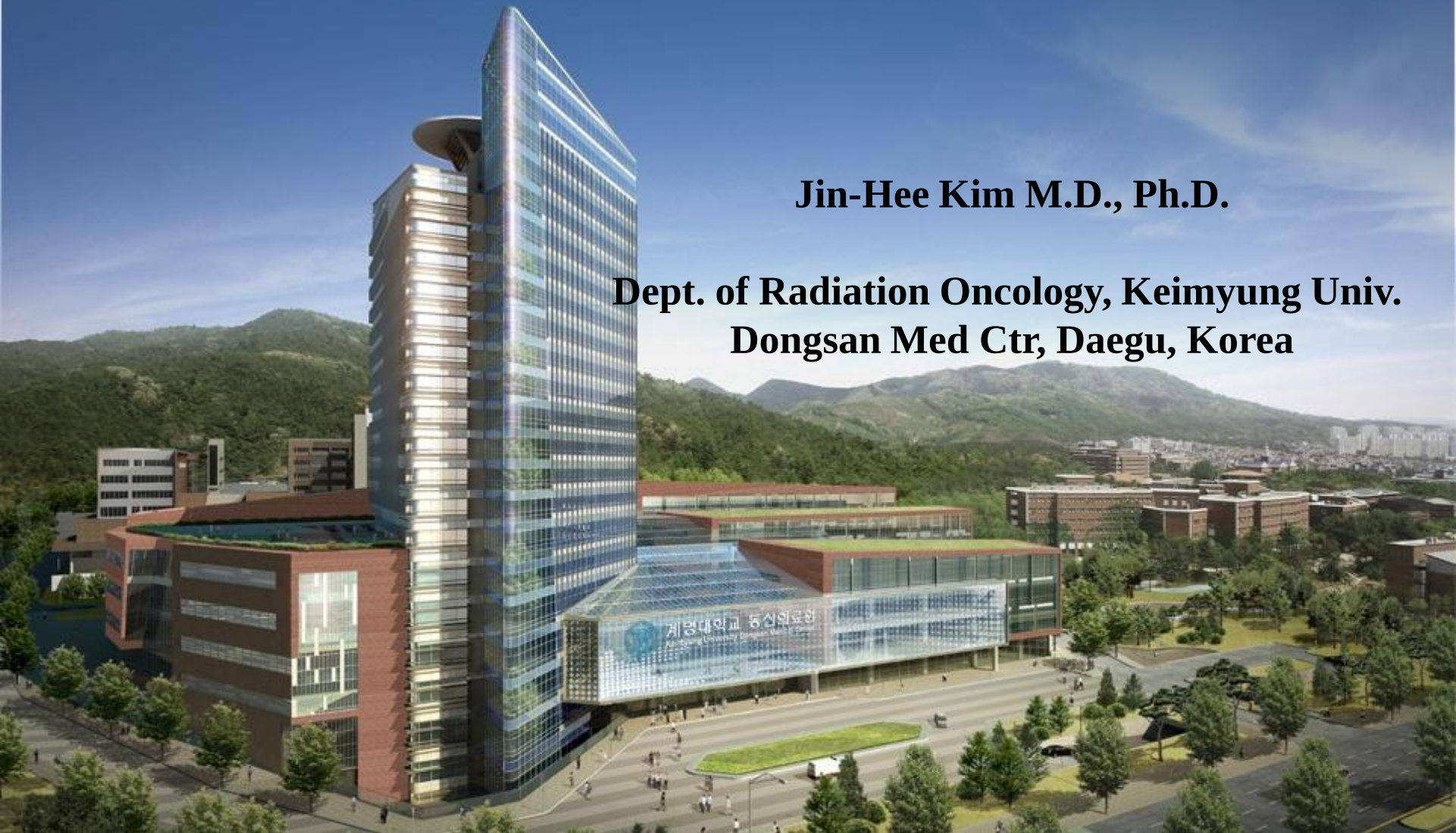
Radiotherapy in DCIS



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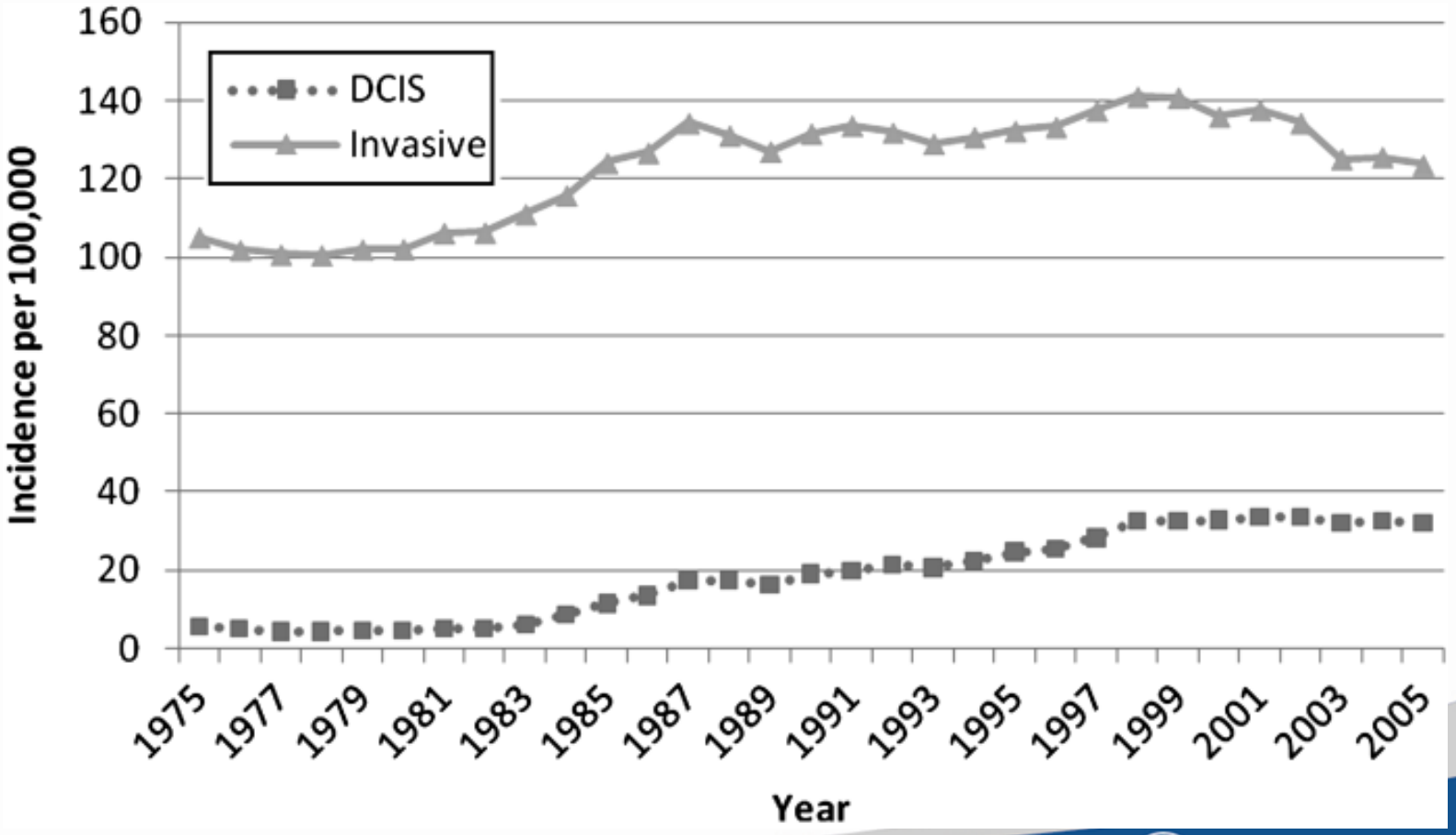
Incidences

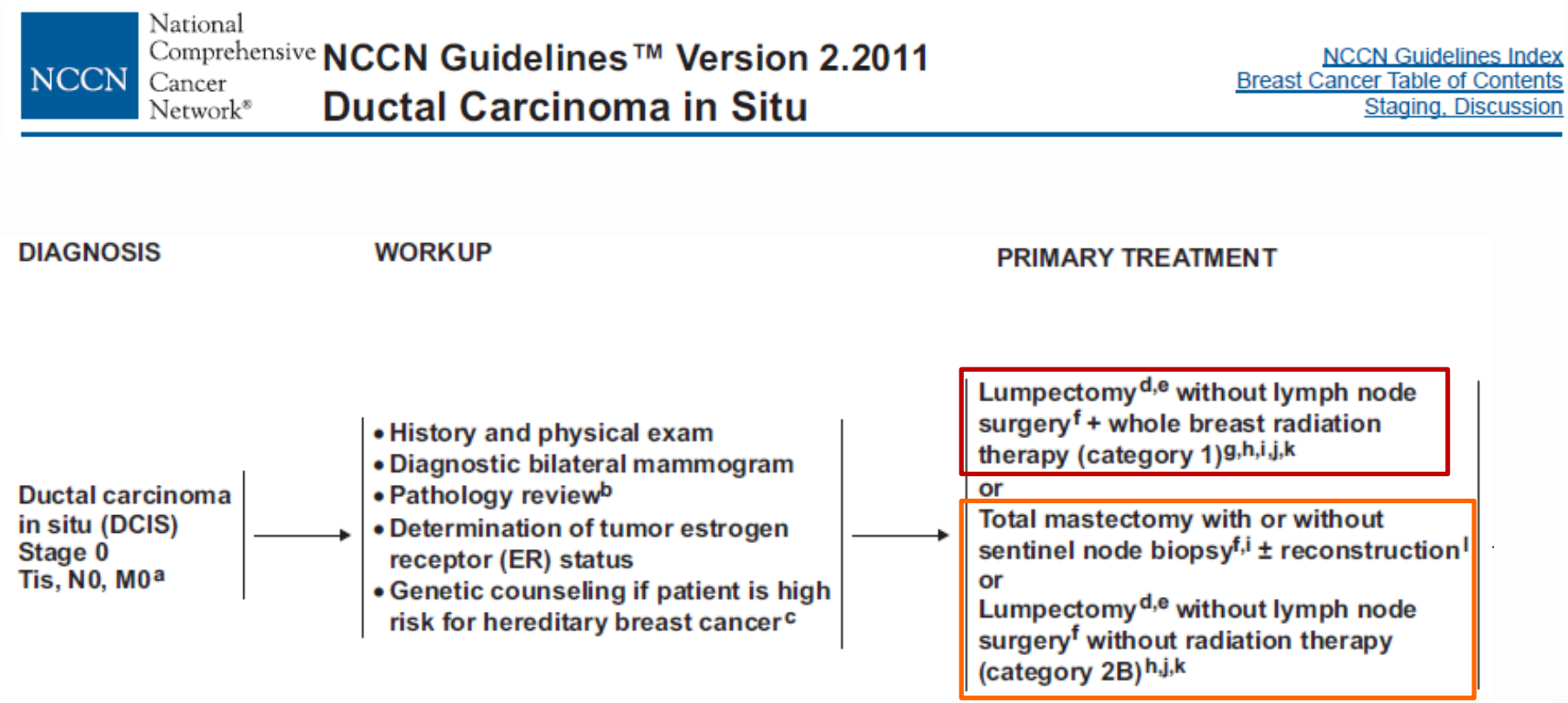
- Screening has led to a substantial increase in the incidence of DCIS over the past two decades.



Treatment Modalities of DCIS of breast

- *Total mastectomy +/- reconstruction*
  - *Excision + RTx*
  - *Excision alone*

NCCN guideline of DCIS



Margin

- Margins > 10mm --negative
  Margins <1mm -- inadequate

- Close surgical margins (<1mm) at fibroglandular boundary of the breast (chest wall or skin) do not mandate surgical re-excision but can be an indication for higher boost dose radiation to the involved lumpectomy site (category 2b)

Consensus Conference on the Treatment of DCIS of the Breast
(April 22-25, 1999)

- There was consensus that the goal of treatment for women with DCIS is breast conservation, with optimal cosmesis and with a minimum risk of subsequent invasive or in situ recurrence.

- There are some women for whom mastectomy remains optimal treatment, but most women with DCIS are candidates for breast conservation.

Cancer 2000; 88:946-954

Mastectomy is recommended for DCIS patients presenting with the following

1) Large areas of DCIS
2) Multiple areas of DCIS in the same breast that cannot be encompassed in a single incision
3) The inability to undergo radiation therapy because of other medical problems

Reconstruction should be offered to each patient who chooses mastectomy

DCIS of the Breast :

Wide Excision + Radiotherapy

1) The size of the areas of DCIS should be $\leq$ 5 cm in its greatest dimension

2) Margins preferably should be clear, but they are not absolutely required.

3) Any grade or subtype of DCIS is appropriate for radiation therapy.

DCIS of the Breast :

Wide Excision Alone without Radiotherapy

1) The size of the areas of DCIS should be small, preferably less than 2-3 cm in greatest dimension, less than 6 cm^2 in area.
2) Margins around any site of DCIS should be 10 mm or greater
3) The nuclear grade of the DCIS should be low or intermediate grade
4) The aesthetic appearance of the breast following local excision should be appropriate.

DCIS of the Breast : Radiotherapy

- After breast conserving surgery
- Whole breast , 50Gy, 1.8- 2.0Gy/ d
- A boost radiation (10-16Gy) at the tumor bed may be added for women with close surgical margins
- No role for postmastectomy or nodal irradiation

DCIS of the Breast : Margins

- Margin status was considered of crucial importance because it is the one variable that the physician can control

- Radiation oncologist are not entirely reluctant to treat patients with DCIS if the margin were “focally” close or “focally” positive.

- Widely clear (≥ 10 mm) margins are preferable.

- A 10 mm margin is the best compromise between removal of so much tissue that the cosmetic result would be less than desirable and the likelihood of local recurrence.

Breast Conservation in DCIS of the Breast

Majority of women with DCIS are candidates for breast conservation

Wide local excision ± Radiation ± Tamoxifen

No consensus could be reached on the selection of patients for treatment by local excision alone

Goal of Treatment of DCIS of breast

- Eradication of the initial DCIS
- Prevention of the recurrence of an invasive or non-invasive cancer in the ipsilateral breast
- Minimize the risk of death from breast cancer

Local Recurrence Rates by Treatment Modalities

Cancer. 1999 Feb 1;85(3):616-28

- By meta-analysis

  Conservative surgery(CS) alone 22.5%

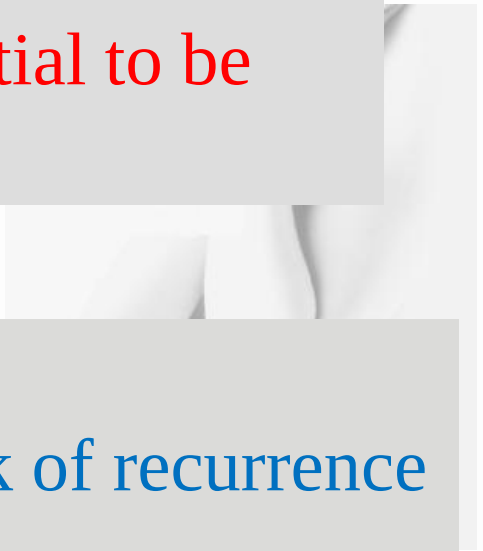
  CS + RT: 8.9%

  Mastectomy: 1.4%

* Mortality : < 5% , regardless of the treatment

Importance of Local Recurrence by Treatment Modalities

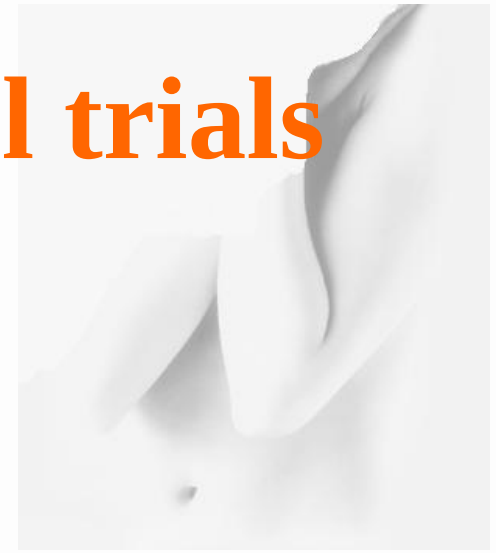
- Individual patient must face cancer again
- Subsequent treatment may not include BCS
- Invasive recurrence has the potential to be life threatening



Treatment decisions may reflect

- ✓ individual patient's acceptance of the risk of recurrence
- ✓ perceived benefit of treatment.

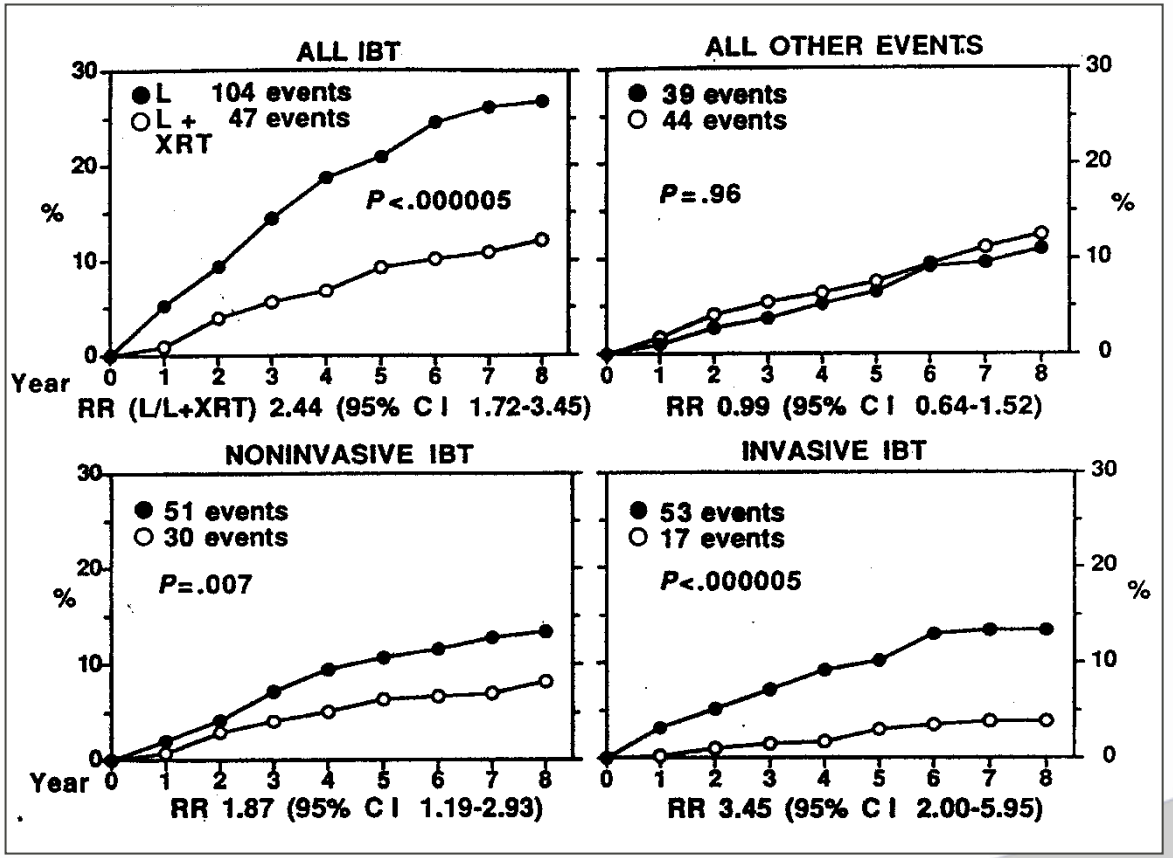
Review of past clinical trials



NSABP B-17 Trial (DCIS)

Conservative surgery(CS) alone vs. CS + RT

- 1985 - 1990
- n= 818
- 83 % : non-palpable lesion
- Wide excision with tumor free margin
- RTx : 50 Gy, No boost
- Mean F-U time : 90 Mo (67-130)

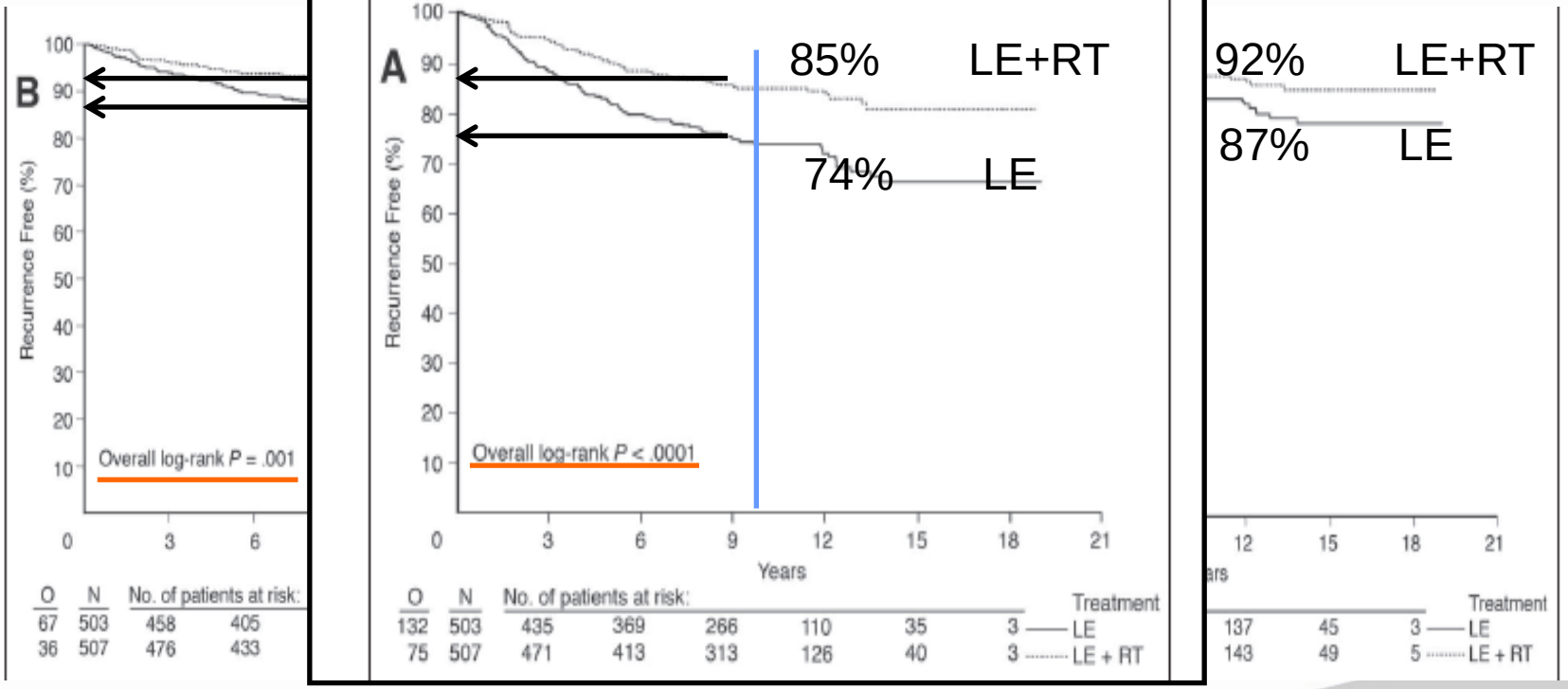


J Clin Oncol 1998;16:441–452.
Cancer 1999;86:429–438

Radiotherapy in BCT for DCIS: EORTC randomized phase III trial 10853 (10 yr results)

- 1986 -1996, N=1002 (500 vs 502), Local excision +/- RTx (50 Gy)
- Mammographic Dx 71%, Median F/U 10.5%

DCIS recurr … nce



Time to recurrence by treatment group

J Clin Oncol. 2006 Jul 20;24(21):3381-7

Risk factors related to local recurrence : EORTC trial 10853 (10 yr results)

J Clin Oncol. 2006 Jul 20;24(21):3381-7

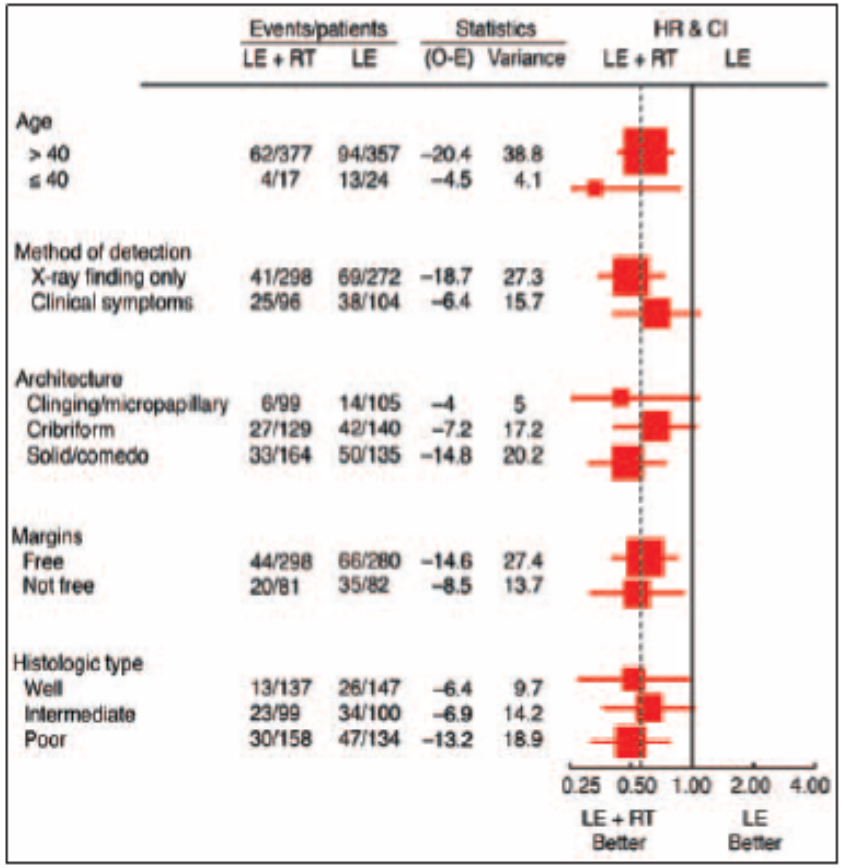


Fig 2. Effect of radiotherapy on local control by subgroup. LE, local excision; RT, radiotherapy; HR, hazard ratio; CI, 95% CI.

Table 3. Multivariate Analysis of Risk Factors Related to Local Recurrence

Variable	Hazard Ratio	95% CI	*P*
Age, years			
> 40	1		
≤ 40	1.89	1.12 to 3.19	.026
Method of detection			
X-ray finding only	1		
Clinical symptoms	1.55	1.11 to 2.16	.012
Histologic type			
Well	1		
Intermediate	1.85	1.18 to 2.90	.024
Poor	1.61	0.93 to 2.79	
Architecture			
Clinging/micropapillary	1		
Cribriform	2.39	1.41 to 4.03	.002
Solid/comedo	2.25	1.21 to 4.18	
Margins			
Free	1		
Not free	1.84	1.32 to 2.56	.0005
Treatment			
LE + RT	1		
LE	1.82	1.33 to 2.49	.0002

Abbreviations: LE, local excision; RT, radiotherapy.

Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomized trials

Gustavo A Viani*[1], Eduardo J Stefano[1], Sérgio L Afonso[1], Lígia I De Fendi[1], Francisco V Soares[1], Paola G Leon[2] and Flavio S Guimarães[3]

Radiat Oncol. 2007 Aug 2;2:28.

Address: [1]Department of Radiation Oncology, Faculty of Medicine of Marília (FAMEMA), Marília, São Paulo, Brazil, [2]Department of Radiation Oncology, Instituto Nacional de Enfermedades Neoplásicas, Lima, Perú and [3]Department of Radiation Oncology, Hospital A.C.Camargo, São Paulo, Brazil

Abstract

Background: To investigate whether Radiation therapy (RT) should follow breast conserving surgery in women with ductal carcinoma in situ from breast cancer (DCIS) with objective of decreased mortality, invasive or non invasive recurrence, distant metastases and contralateral breast cancer rates. We have done a meta-analysis of these results to give a more balanced view of the total evidence and to increase statistical precision.

Methods: A meta-analysis of randomized controlled trials (RCT) was performed comparing RT treatment for DCIS of breast cancer to observation. The MEDLINE, EMBASE, CANCERLIT, Cochrane Library databases, Trial registers, bibliographic databases, and recent issues of relevant journals were searched.

503 reports

↓

22 trials

↓

4 trials in review

Conclusion: The conclusion from our meta-analysis is that the addition of radiation therapy to lumpectomy results in an approximately 60% reduction in breast cancer recurrence, no benefit for survival or distant metastases compared to excision alone. Patients with high-grade DCIS lesions and positive margins benefited most from the addition of radiation therapy. It is not yet clear which patients can be successfully treated with lumpectomy alone; until further prospective studies answer this question, radiation should be recommended after lumpectomy for all patients without contraindications.

Cochrane review

http://www.thecochranelibrary.com

- Four RCTs, 3925 women
- Three trials compared the addition of RT to BCS.

One trial was a two by two factorial design comparing the use of RT and tamoxifen, each separately or together, in which participants were randomized in at least one arm.

•All the subgroups analyzed benefited from addition of radiotherapy.

• No significant long-term toxicity from radiotherapy was found.

• No information about short-term toxicity from radiotherapy or quality of life data were reported

Who could safely be treated by *lumpectomy alone* ?

The Factors that Influence the Selection of Treatment

- Size of the area of DCIS
- Pathology
  : nuclear grade, presence of comedo necrosis
- Margin status
- Age

J Natl Cancer Inst Monogr. 2010;2010(41):193-6.
Oncology (Williston Park) 2003; 17:1511-1533

New VNPI (Van Nuys Prognostic Index) for DCIS of the Breast

VNPI = pathologic classification score + margin score + size score + age score

Score	Age	Pathology	Margin	Size
3	<40	high grade	< 1mm	≥ 41 mm
2	40-60	low grade with necrosis	1-9 mm	16-40 mm
1	>60	low grade without necrosis	≥ 10mm	≤ 15 mm

Silverstein et al J Natl Cancer Inst Monogr. 2010;2010(41):193-6.

Table 2. New treatment recommendations to achieve a local recurrence rate of less than 20% at 12 years using the University of Southern California/Van Nuys Prognostic Index (USC/VNPI)

USC/VNPI	Treatment	12-yr recur, %
4, 5 or 6	Excision alone	≤6
7, margins ≥3 mm	Excision alone	16
7, margins <3 mm	Radiation	14
8, margins ≥3 mm	Radiation	15
8, margins <3 mm	Mastectomy	1
9, margins ≥5 mm	Radiation	19
9, margins <5 mm	Mastectomy	1
10, 11, or 12	Mastectomy	4

Silverstein et al J Natl Cancer Inst Monogr. 2010;2010(41):193-6.

Prospective Study of Wide Excision Alone for Ductal Carcinoma in Situ of the Breast

Julia S. Wong, Carolyn M. Kaelin, Susan L. Troyan, Michele A. Gadd, Rebecca Gelman, Susan C. Lester, Stuart J. Schnitt, Dennis C. Sgroi, Barbara J. Silver, Jay R. Harris, and Barbara L. Smith

JCO 2006;24:1031-1036 *(Dana Farber institute)*

A B S T R A C T

Purpose

It has been hypothesized that wide excision alone with margins ≥ 1 cm may be adequate treatment for small, grade 1 or 2 ductal carcinoma in situ (DCIS). To test this hypothesis, we conducted a prospective, single-arm trial.

Methods

Entry criteria included DCIS of predominant grade 1 or 2 with a mammographic extent of ≤ 2.5 cm treated with wide excision with final margins of ≥ 1 cm or a re-excision without residual DCIS. Tamoxifen was not permitted. The accrual goal was 200 patients.

Results

In July 2002, the study closed to accrual at 158 patients because the number of local recurrences met the predetermined stopping rules. The median age was 51 and the median follow-up time was 40 months. Thirteen pa[illegible]rrences was the first site of treatment failure 7 to 63 months after stu[illegible]eral local recurrence as first site of treatment failure was 2.4% per patient-year, corresponding to a 5-year rate of 12%. Nine patients (69%) experienced recurrence of DCIS and four (31%) experienced recurrence with invasive disease. Twelve recurrences were detected mammographically and one was palpable. Ten were in the same quadrant as the initial DCIS and three were elsewhere within the ipsilateral breast. No patient had positive axillary nodes at recurrence or subsequent metastatic disease.

Conclusion

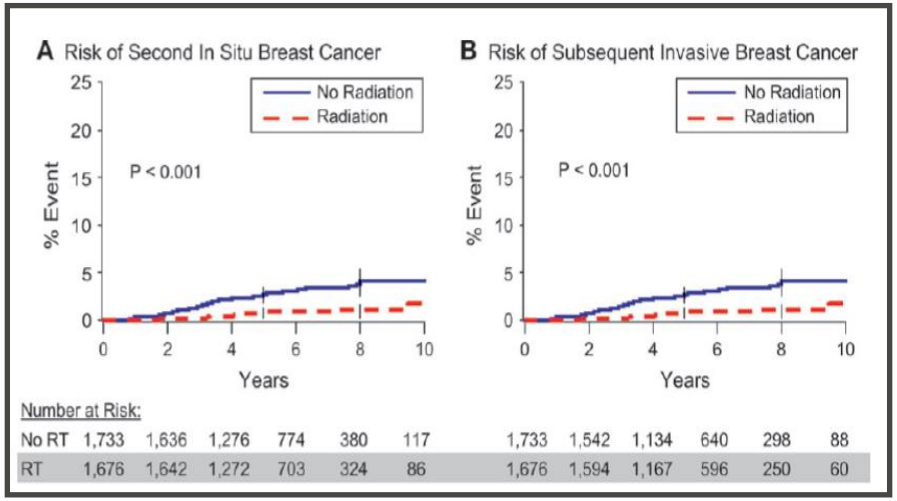
Despite margins of ≥ 1 cm, the local recurrence rate is substantial when patients with small, grade 1 or 2 DCIS are treated with wide excision alone. This risk should be considered in assessing the possible use of radiation therapy with or without tamoxifen in these patients.

Low risk group

Effectiveness of Radiation Therapy in Older Women With Ductal Carcinoma In Situ

Benjamin D. Smith, Bruce G. Haffty, Thomas A. Buchholz, Grace L. Smith, Deron H. Galusha, Justin E. Bekelman, Cary P. Gross

- Using SEER medicare database, 1992-1999, 3409 women, ≥ 66 years
- Low risk vs High risk (66-69, >2.5cm, comedo, high grade)



5Yr event risk(ipsilat. DCIS, invasive cancer)

RTx group lower risk ratio ;
HR=0.32(0.24-0.44)

	CS alone	CS+RT	p-value
High risk	13.6%	3.8%	p<.001
Low risk	8.2%	1.0%	p<.001

Conclusion: For older women with DCIS, radiation therapy appear to confer a substantial benefit that remains meaningful even among low risk patients. *(J Natl cancer inst 2006;98:1302-10)*

On-going Trials in DCIS

- RTOG 98-04: lumpectomy vs lumpectomy + RT

  - < 2.5cm, - low or intermediate-grade, - margin > 3 mm

  - 2006 closed

- ECOG 5194: lumpectomy alone

  - low to intermediate grade (LIG) ;

    size >0.3 cm but <2.5 cm, margins >3 mm

  - high grade (HG) ; size>0.3 cm but <1 cm, margins >3 mm

  - 1997- 2002

Local Excision Alone Without Irradiation for Ductal Carcinoma In Situ of the Breast: A Trial of the Eastern Cooperative Oncology Group

Lorie L. Hughes, Molin Wang, David L. Page, Robert Gray, Lawrence J. Solin, Nancy E. Davidson, Mary Ann Lowen, James N. Ingle, Abram Recht, and William C. Wood

See accompanying editorial on page 5303

JCO 2009;27:5319-5324

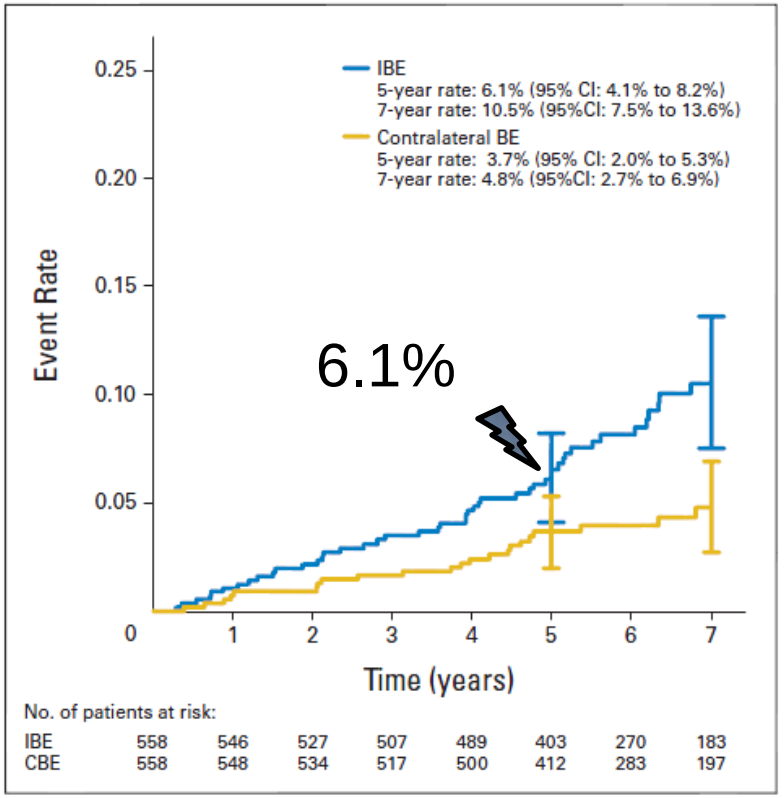


Fig 2. Ipsilateral breast events (IBEs) and contralateral breast events (CBEs) in patients with low-or intermediate-grade ductal carcinoma in situ. Vertical bars represent 95% CIs. Numbers at risk are given beneath the *x*-axis.

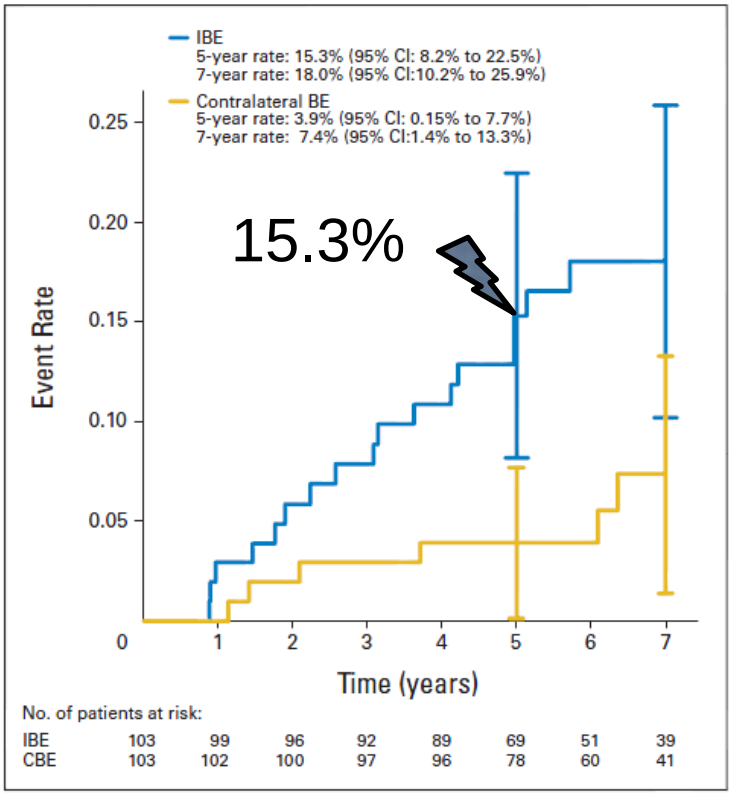


Fig 3. Ipsilateral breast events (IBEs) and contralateral breast events (CBEs) in patients with high-grade ductal carcinoma in situ. Vertical bars represent 95% CIs. Numbers at risk are given beneath the *x*-axis.

Ductal Carcinoma In Situ Treated With Breast-Conserving Surgery and Radiotherapy: A Comparison With ECOG Study 5194

Sabin B. Motwani, MD[1]; Sharad Goyal, MD[1]; Meena S. Moran, MD[2]; Arpit Chhabra, BS[3]; and Bruce G. Haffty, MD[1]

	5-Year Rate of Contralateral Breast Cancer
LIG: E5194	3.7%
LIG: current study	2.6%
HG: E5194	3.9%
HG: current study	2.7%
NSABP B-17	2.5%
EORTC	4%
UK/ANZ	2%
SweDCIS	3.3%

ECOG indicates Eastern Cooperative Oncology Group; LIG, low to intermediate grade; HG, high grade; NSABP, National Surgical Breast and Bowel Project; EORTC, European Organization for Research and Treatment of Cancer; UK/ANZ, DCIS Trialists in the United Kingdom, Australia, and New Zealand; SweDCIS, Swedish Breast Cancer Group.

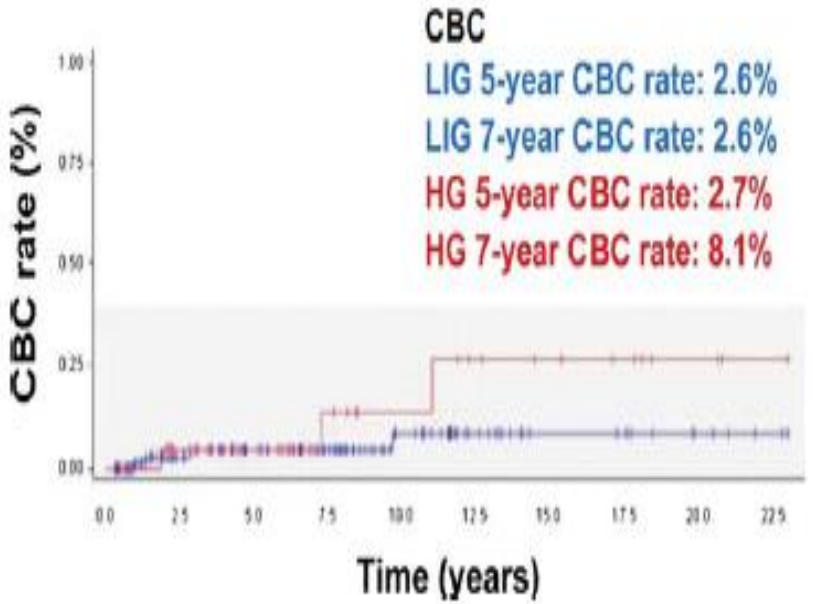


Figure 2. Contralateral breast cancer (CBC) rates in the low- to intermediate-grade (LIG) and high-grade (HG) groups.

Role of boost radiation on surgical bed

Comparison with previous studies on the effect of the boost

Studies	comparison	N	age	(+) margin	Necrosis	F/U	Recurrence
Omlin(2006)	Boost	150	All <45	7%	32%	72mo	10yLRFS 72%, 10yLR 14%
	No boost	166		4%	41%		10yLRFS 46% 10yLR28%
Yerushalmi (2006)	Boost	20	58			81.5mo	15%
	No boost	55					12.7%
Julian (abs 2008)	Boost	692	NSABP B-24 53	21%	52%	14y	13.8%
	No boost	877		15%	45%		14.3%
Monteau (2009)	Boost	147	53	50%	60%	89mo	7yLR 9.3%
	Reexcision (<2mm margin)	55		74%	64%		7yLR 9.6%
Wong(2011)	Boost	79	58	5%	56%	46mo	0%
	No boost	121		0.8%	49%		6%

Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network

Aurelius Omlin, Maurizio Amichetti, David Azria, Bernard F Cole
Marco Krengli, Cristina Gutierrez Miguelez, David Morgan, Hada
Dagmar Dohr, David Christie, Ulrich Oppitz, Ufuk Abacioglu, Gu

Lancet Oncol 2006; 7: 652–56

Published Online July 6, 2006
DOI:10.1016/S1470-2045(06)70765-3

See Reflection and Reaction page 615

Department of Radiation Oncology, University of Bern, Inselspital, Bern, Switzerland (A Omlin MD, G Gruber MD); Department of Radiation Oncology, Oncological Hospital A Businco, Cagliari, Italy (M Amichetti MD); Department of Radiation Oncology, INSERM Cancer Research Institut CRLC Val d'Aurelle, Montpellier, France (D Azria MD); Department of Community and Family Medicine, Dartmouth Medical School, Hanover, NH, USA

Summary

Background Outcome data in young women with
radiotherapy in this group are also unknown. We
with DCIS.

Methods We included 373 women from 18 institut
Tis and nodal status (N)0, age 45 years or younger
patients had no radiotherapy after surgery, 166 (45%)
and 150 (40%) had radiotherapy with boost (60 Gy [5

Findings Median follow-up was 72 months (rang
survival at 10 years was 46% (95% CI 24–67) fo
radiotherapy without boost, and 86% (78–93) for
groups, p<0·0001). Age, margin status, and radioth
Compared with patients who had no radiotherapy,
(without boost, hazard ratio 0·33 [95% CI 0·16–0·

Interpretation In the absence of randomised trials, boost radiotherapy should be considered in addition to surgery for breast-conserving treatment for DCIS.

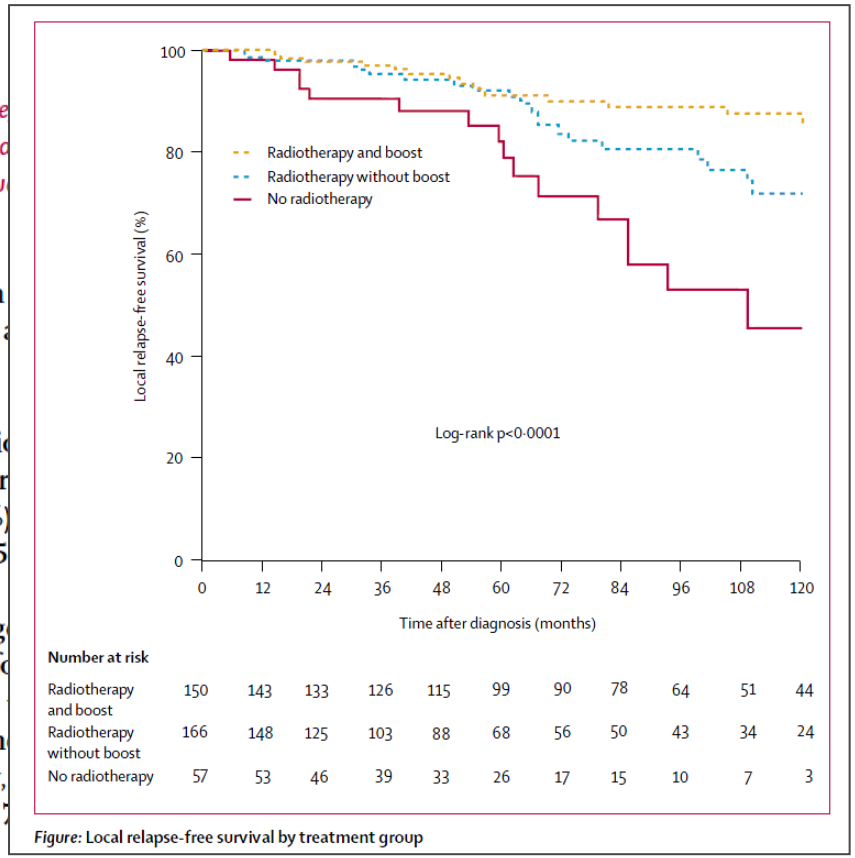


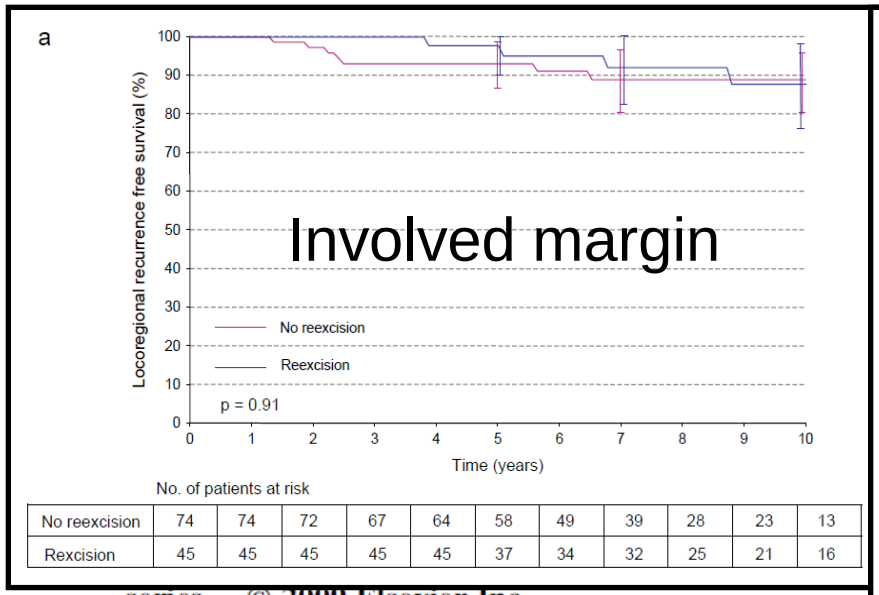
Figure: Local relapse-free survival by treatment group

Lancet Oncol 2006;7:652–656

DUCTAL CARCINOMA *IN SITU* OF THE BREAST WITH CLOSE OR FOCALLY INVOLVED MARGINS FOLLOWING BREAST-CONSERVING SURGERY: TREATMENT WITH REEXCISION OR RADIOTHERAPY WITH INCREASED DOSAGE

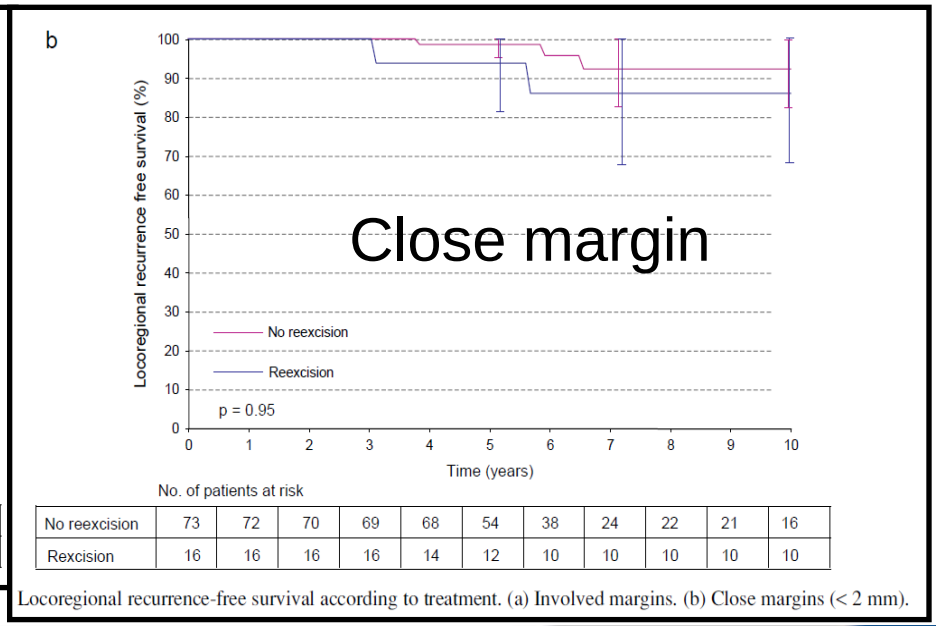
Amélie Monteau, M.D.,* Brigitte Sigal-Zafrani, M.D.,§ Youlia M. Kirova, M.D.,* Virginie Fourchotte, M.D.,† Marc A. Bollet, M.D., Ph.D.,* Anne Vincent-Salomon, M.D., Ph.D.,§ Bernard Asselain, M.D.,‡ Remy J. Salmon, M.D.,† and Alain Fourquet, M.D.*

Departments of *Radiation Oncology, §Pathology, †Surgery, and ‡Biostatistics, Institut Curie, Paris, France



No. of patients at risk

No reexcision	74	74	72	67	64	58	49	39	28	23	13
Rexcision	45	45	45	45	45	37	34	32	25	21	16



No. of patients at risk

No reexcision	73	72	70	69	68	54	38	24	22	21	16
Rexcision	16	16	16	16	14	12	10	10	10	10	10

Locoregional recurrence-free survival according to treatment. (a) Involved margins. (b) Close margins (< 2 mm).

Int J Radiat Oncol Biol Phys. 2009 ;15;75(4):1021-8

On-going trial of boost radiation to surgical bed after CS + WBRT in DCIS

- Trans-Tasman Radiation Oncology Group (from 2007)
  : BCS followed by

In Australia

Randomization A	42.5Gy /16fr to WBRT
Randomization B	50Gy /25fr to WBRT + 16 Gy boost
Randomization C	42.5Gy/16fr to WBRT + 16Gy boost

- French study (from 2008) DCIS : BCS followed by

Randomization 1	50Gy/25fr/ to WBRT
Randomization 2	50Gy/25/fr to WBRT + 16 Gy boost

Summary(I)

- Most women with DCIS are candidates for breast conservation. 50 Gy whole breast RT significantly decreased the 5-year LR rate.
- In a recent meta-analysis of randomized trials, the addition of RT to BCS resulted in a 60% risk reduction of both invasive and in situ recurrences.

- To date, no subgroups have been reliably identified that do not benefit from RT after BCS.
- In the NSABP-B-24 trial, the addition of tamoxifen(TAM) to RT reduced ipsilateral (11.1% vs. 7.7%) and contralateral (4.9% vs. 2.3%) breast events significantly.

Summary(II)

- Based on available evidence, all patients with DCIS have potential benefit from RT after BCS.
- Further prospective studies are warranted to identify subgroups of low-risk patients with DCIS for whom RT can be safely omitted.

- Until long-term results of ongoing studies, RT should be routinely recommended after BCS for all patients of DCIS except those with contraindications.
- Based on the currently available data on the efficacy of the boost, it is likely beneficial to patients who are young, have close or positive surgical margins, or with necrosis.


Thank you very much for your attention