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Radiation therapy after breast conserving surgery

Including partial breast irradiation and radiation omission

DCIS – Session 3



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8th Workshop in Breast Surgery

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Aarhus University Hospital, Denmark

COI

None disclosed



FONDAZIONE FIRENZE RADIOTERAPIA ONCOLOGICA

OVERVIEW

POSTOPERATIVE RADIATION AFTER BCS FOR DCIS

BCS FOR LOW-RISK SUBSETS OF DCIS

PARTIAL BREAST IRRADIATION FOR DCIS

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POSTOPERATIVE RADIATION AFTER BCS

Four prospective randomized **trials** compared **adjuvant RT to no RT** following BCS for DCIS (1985-1990)

Study name	Study dates	N	Median F/U ^a (years)	% positive/unknown margins	Local recurrence	
					No RT	RT
NSABP ^b B-17 (5) [†]	1985–1990	818	17.25	0%	35.1%	17.7%
EORTC ^c 10853 (4) [†]	1986–1996	1010	15.8	16%	31.0%	18.0%
SweDCIS ^d (6) [‡]	1987–1999	1067	17.5	20%	32.0%	20.0%
UK/ANZ DCIS ^e (3) [§]	1990–1998	1030	12.7	0%	19.4%	7.1%

POSTOPERATIVE RADIATION AFTER BCS

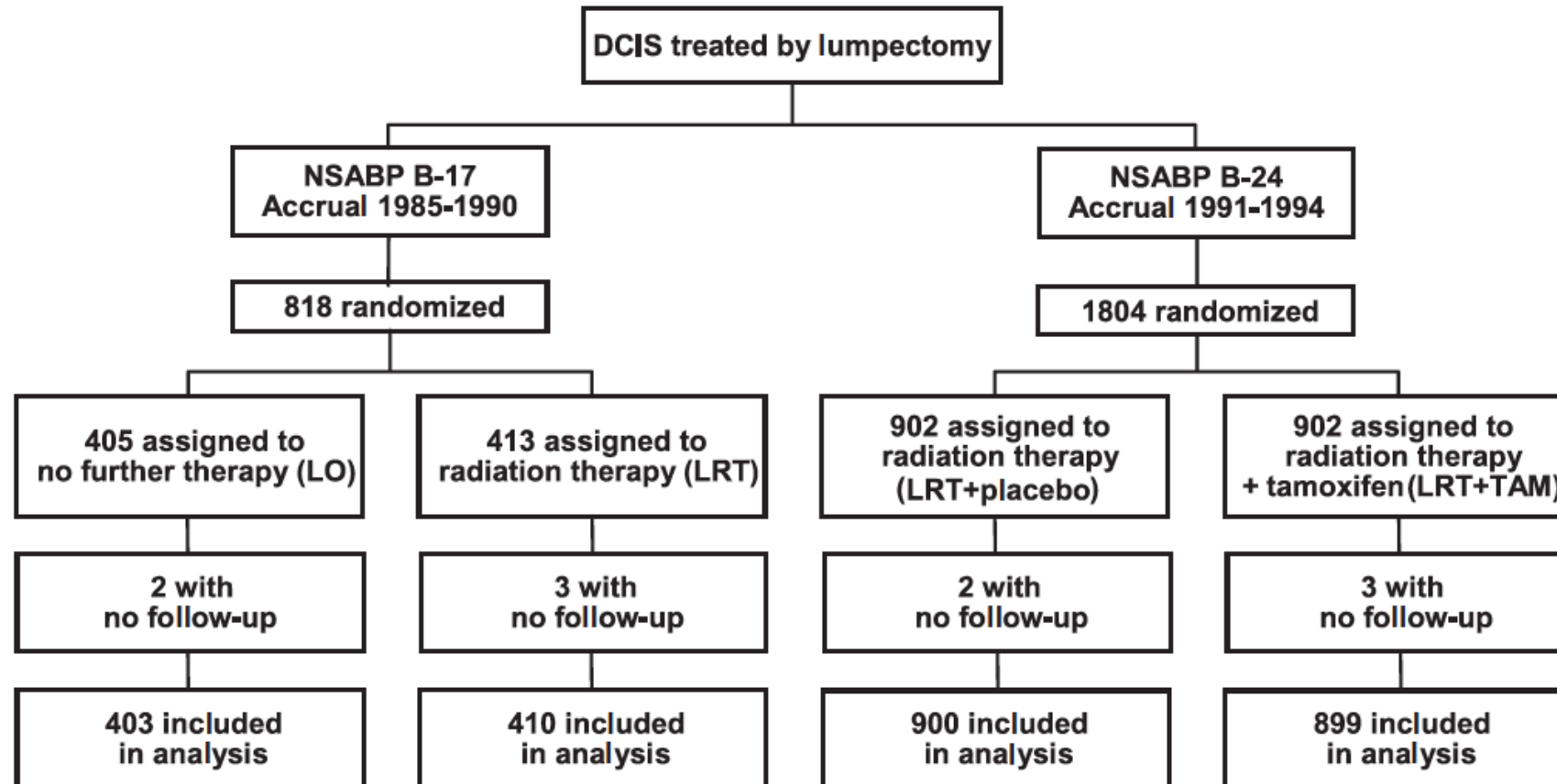
Ipsilateral breast tumor recurrence (IBTR) is the most common failure event after lumpectomy for DCIS

NSABP randomized trials for DCIS

- **NSABP B-17** trial (1985-1990) → lumpectomy only (LO, $n=403$) vs. lumpectomy followed by RT (LRT, $n=410$)
- **NSABP B-24** trial (1991-1994) → LRT+ placebo ($n=900$) vs. LRT + tamoxifen (LRT + TAM, $n=899$)

Endpoints → I-IBTR, DCIS-IBTR, contralateral breast cancers (CBC), overall and breast cancer–specific survival, and survival after I-IBTR

POSTOPERATIVE RADIATION AFTER BCS



POSTOPERATIVE RADIATION AFTER BCS

Median follow-up: 17.2 years (*B-17 trial, N=813 patients*) and **13.6 years** (*B-24 trial, N=1799 patients*)

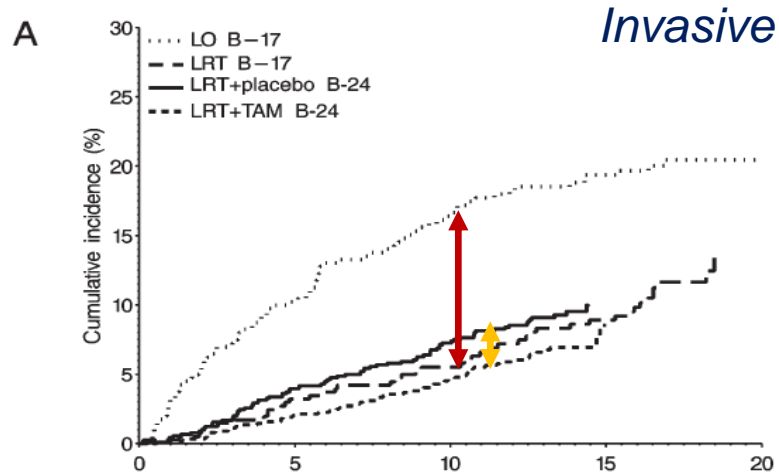
Overall 490 IBTR events → **263 (53.7%) invasive IBTR**

RT reduced I-IBTR by 52% in the LRT group vs. LO
(*B-17, HR 0.48; p<0.001*)

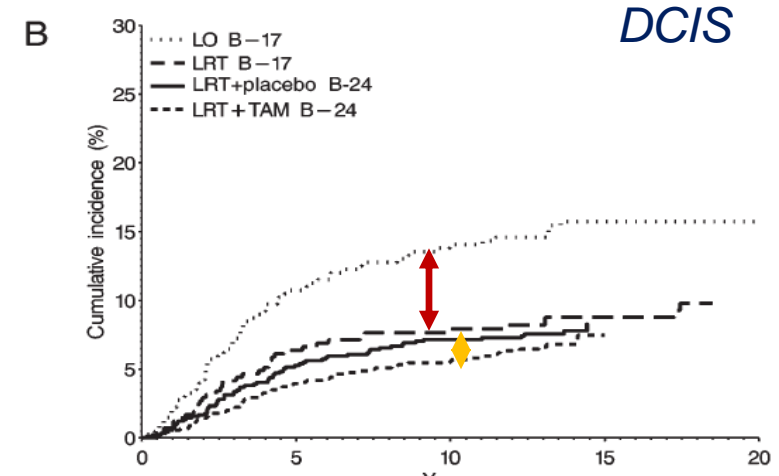
LRT + TAM reduced I-IBTR by 32% compared with LRT + placebo
(*B-24, HR 0.68; p=0.025*)

I-IBTR was associated with ↑ mortality risk (*HR 1.75; p<0.001*)

POSTOPERATIVE RADIATION AFTER BCS



	0	5	10	15	20
LO B-17 No. of patients at risk	403	288	207	153	10
Cumulative Incidence, % (95% CI)	0	10.2 (7.8 to 12.6)	16.4 (13.7 to 19.1)	19.4 (16.6 to 22.2)	20.4 (17.6 to 23.3)
LRT B-17 No. of patients at risk	410	335	256	186	13
Cumulative Incidence, % (95% CI)	0	3.2 (1.4 to 5.0)	5.5 (3.4 to 7.6)	8.9 (6.5 to 11.3)	13.5 (10.6 to 16.4)
LRT+placebo B-24 No. of patients at risk	900	731	563	41	
Cumulative Incidence, % (95% CI)	0	3.9 (2.4 to 5.5)	7.3 (5.4 to 9.1)	10.0 (7.9 to 12.1)	
LRT+TAM B-24 No. of patients at risk	899	764	621	54	
Cumulative Incidence, % (95% CI)	0	2.0 (0.7 to 3.4)	4.6 (3.0 to 6.3)	8.5 (6.2 to 10.8)	



	0	5	10	15	20
LO B-17 No. of patients at risk	403	288	207	153	10
Cumulative Incidence, % (95% CI)	0	10.7 (8.3 to 13.2)	14.1 (11.5 to 16.7)	15.7 (13.1 to 18.4)	15.7 (13.1 to 18.4)
LRT B-17 No. of patients at risk	410	335	256	186	13
Cumulative Incidence, % (95% CI)	0	6.4 (4.2 to 8.5)	7.9 (5.6 to 10.2)	8.8 (6.4 to 11.1)	9.8 (7.3 to 12.3)
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15-year I-IBTR rate

Adding **RT**: 19.4% → 8.9% (B-17)

Adding **also ET**: 10.0% → 8.5% (B-24)



POSTOPERATIVE RADIATION AFTER BCS



Significant RT benefit independently of AGE



POSTOPERATIVE RADIATION AFTER BCS

Long-term results **UK/ANZ DCIS trial**

1701 women (1990-1998)

Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial

Randomized **2x2 factorial trial** of RT, tamoxifen, or both

Median follow-up: **12.7 years**

376 events:

- **163 invasive** [122 ipsilateral vs 39 contralateral]
- **197 DCIS** [174 ipsilateral vs 17 contralateral]
- 16 of unknown invasiveness or laterality

POSTOPERATIVE RADIATION AFTER BCS

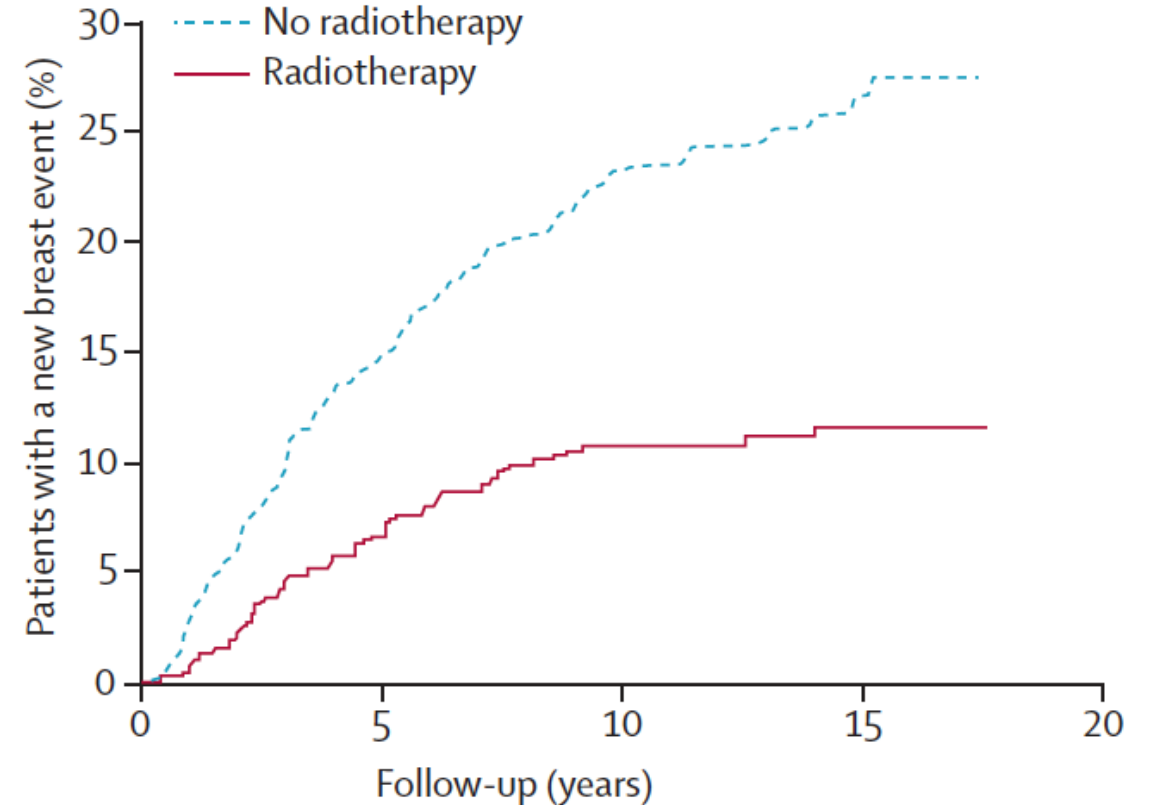
RT ↓ the incidence of:

- all new breast events ($HR\ 0.41; p<0.0001$)
- ipsilateral invasive disease ($0.32; p<0.0001$)
- ipsilateral DCIS ($0.38; p<0.0001$)

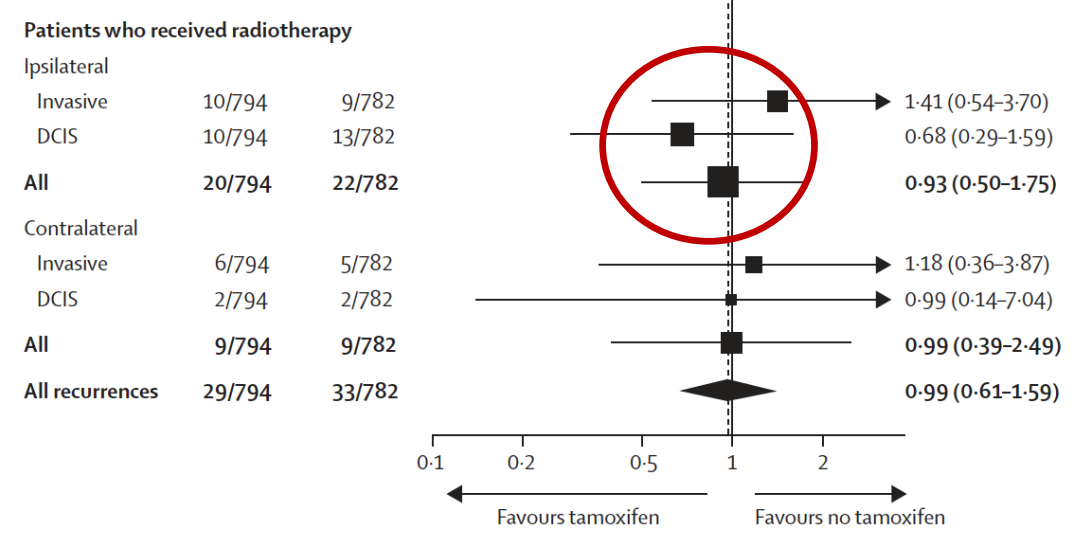
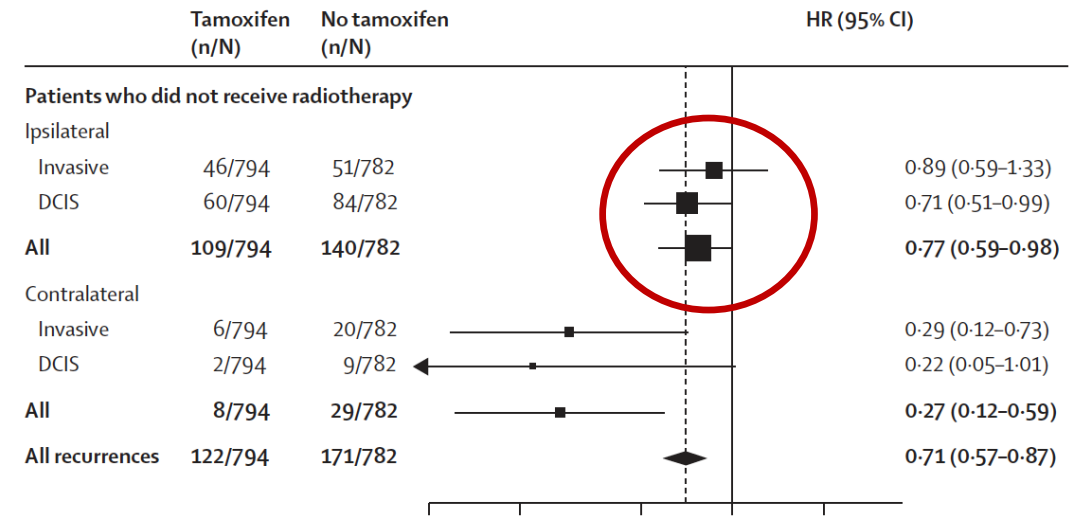
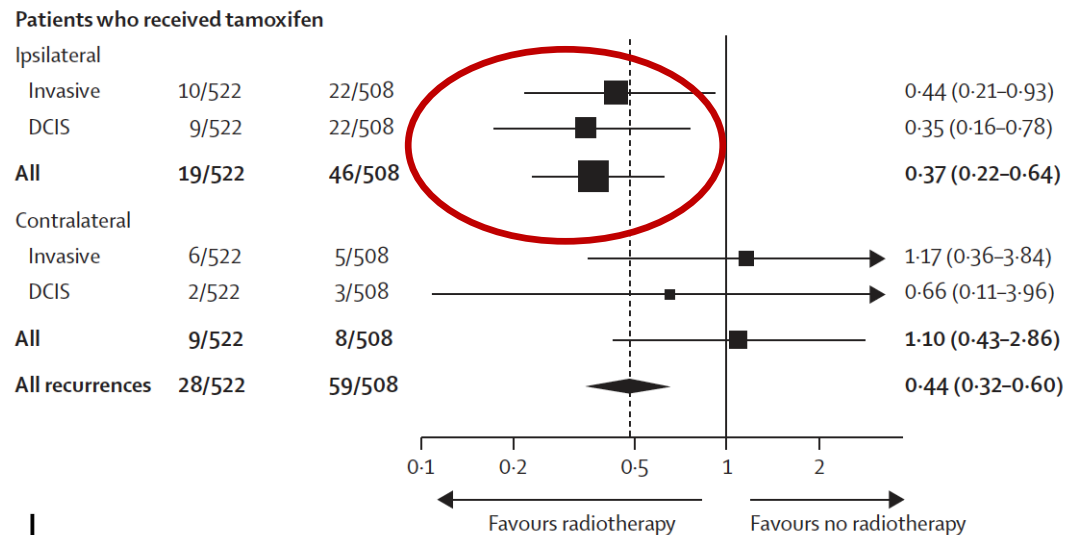
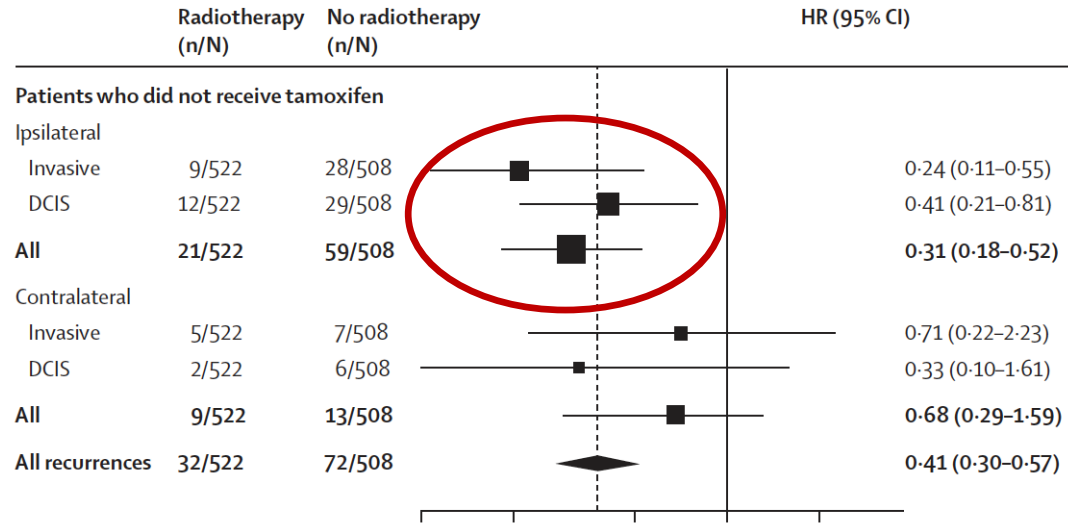
Tamoxifen ↓ the incidence of:

- all new breast events ($HR\ 0.71; p=0.002$)
- ipsilateral DCIS ($0.70; p=0.03$)
- contralateral tumors ($0.44; p=0.005$)

No effect on ipsilateral invasive disease ($0.95; p=0.8$)



POSTOPERATIVE RADIATION AFTER BCS



POSTOPERATIVE RADIATION AFTER BCS

1010 women with DCIS <5 cm complete LE (1986-1996)

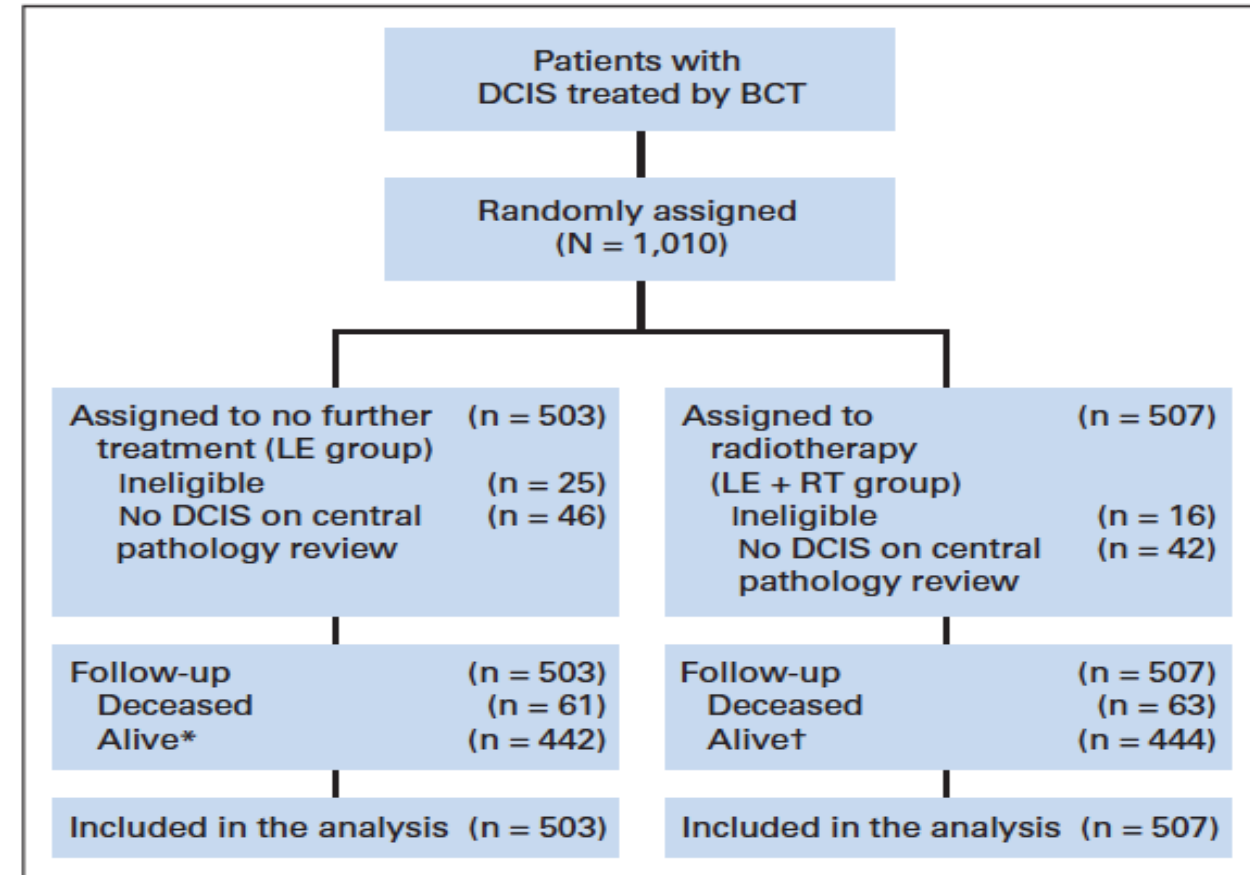
Complete LE (n=503) vs. **LE+RT** (n=507)

Median follow-up: **15.8 years**

Almost **one in three** nonirradiated women developed a LR after LE at 15-year

RT ↓ LR risk by a factor of 2

Breast-Conserving Treatment With or Without Radiotherapy in Ductal Carcinoma In Situ: 15-Year Recurrence Rates and Outcome After a Recurrence, From the EORTC 10853 Randomized Phase III Trial



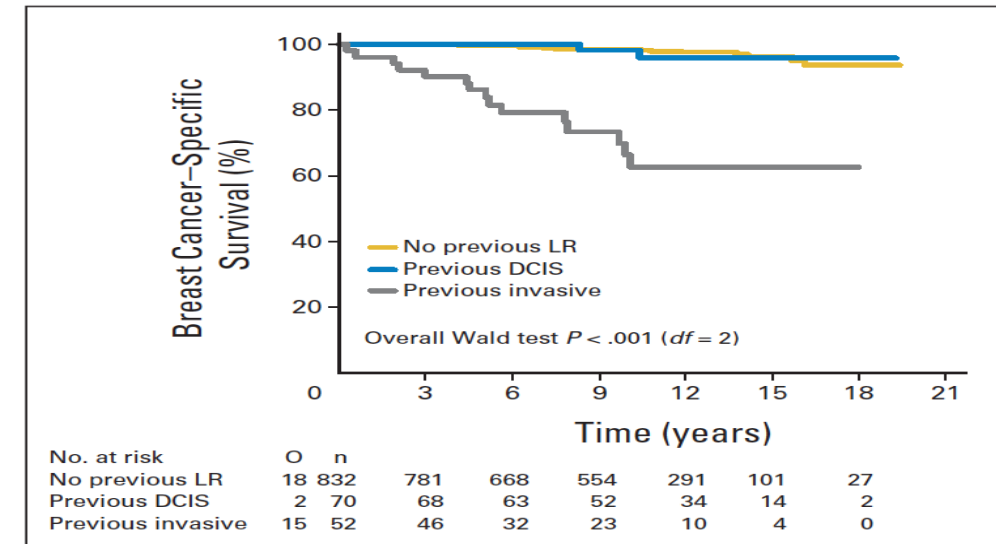
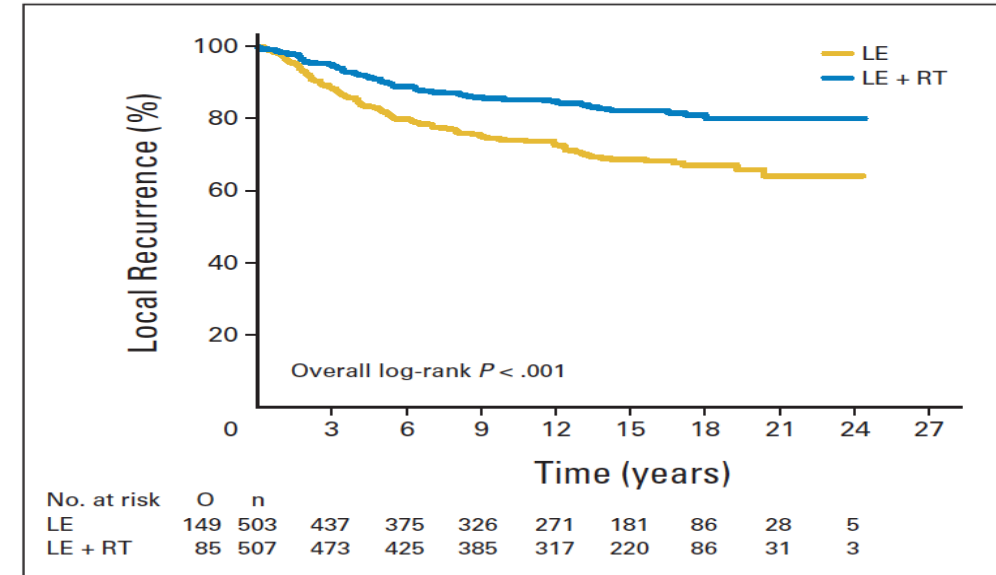
POSTOPERATIVE RADIATION AFTER BCS

RT ↓ the risk of **any LR** by **48%** (*HR 0.52; p=0.001*)

15-year **LR-free rate**:
69% (*LE*) vs. 82% (*LE+RT*) group

15-year **invasive LR-free rate**:
84% (*LE*) vs. 90% (*LE+RT*) group (*HR 0.61*)

Patients with **invasive LR** → significantly ↓ **BCSS**
(*HR 17.66*) and **OS** (*HR 5.17*)



POSTOPERATIVE RADIATION AFTER BCS

SweDCIS trial 20-year updated follow up

1046 women (1987-1999) assigned to RT or not after BCS

RT ↓ 20-year LR risk:

12% (relative risk ↓ 37.5%)

10% for DCIS

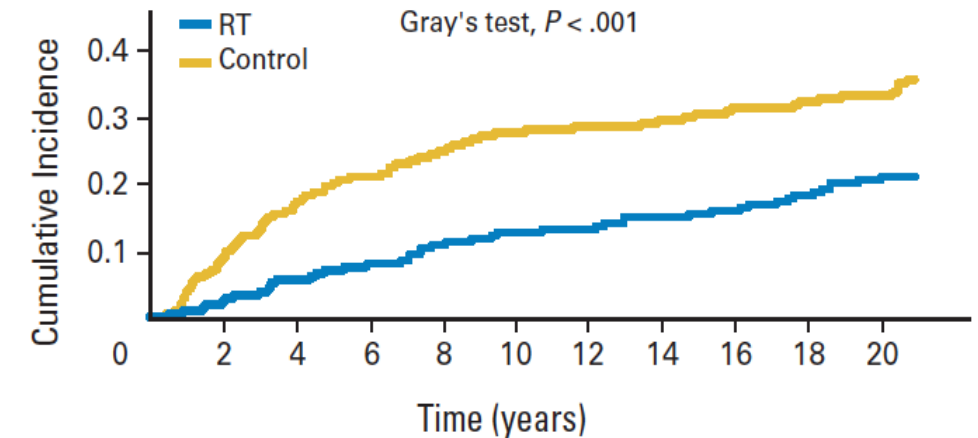
2% for invasive-IBTR

Non significant ↑ CBC in the RT arm (67 vs. 48 events; HR 1.38)

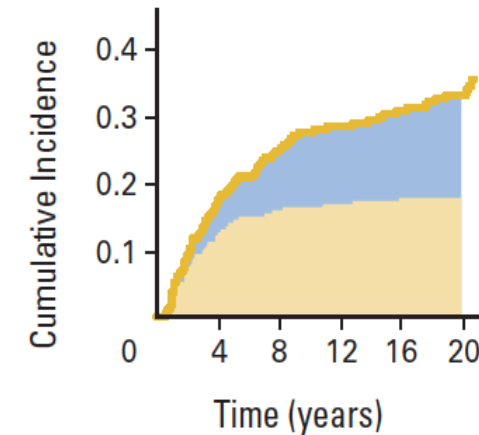
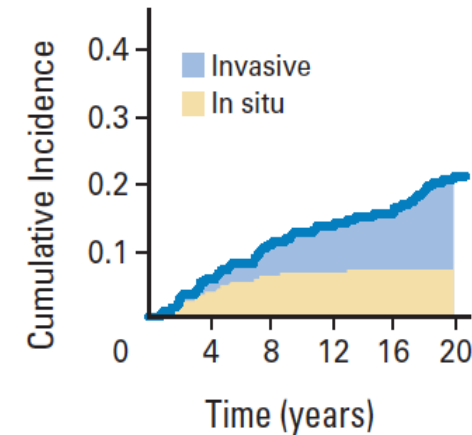
BCSS and OS not influenced

Use of adjuvant RT is supported by 20-year follow-up

Modest protection for I-IBTR and a possible ↑ in CBC call for groups of patients for whom RT could be avoided



No. at risk		Time (years)										
		0	2	4	6	8	10	12	14	16	18	20
RT	526	521	487	469	448	422	406	368	277	190	124	
Control	520	468	422	394	370	350	334	292	228	152	102	



POSTOPERATIVE RADIATION AFTER BCS

Individual patient-level **EBCTCG meta-analysis** (4 trials, 3729 women)

RT addition after local surgical excision ↓ **LR risk \approx 50%**

Absolute **10-year ↓ LR risk of 15.2%** (28.1% [no RT] vs. 12.9% [RT], $p < 0.00001$)

All patient subsets (*i.e.*, small, low-grade tumors, negative margins)

→ RT halves LR risk

POSTOPERATIVE RADIATION AFTER BCS

RT did not improve:

- breast cancer mortality/BCSS

3.7% [no RT] VS. **4.1%** [RT] $p=NS$

- all-cause mortality/OS

8.2% [no RT] VS. **8.4%** [RT] $p=NS$

EBCTCG, J Natl Cancer Inst 2010

With **no documented** \uparrow **in survival** with RT, later studies focused on a **subset of low-risk DCIS patients** identification

OVERVIEW

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BCS FOR LOW-RISK SUBSETS OF DCIS

PARTIAL BREAST IRRADIATION FOR DCIS

BCS FOR LOW-RISK SUBSETS OF DCIS

Randomized prospective trials of DCIS have demonstrated that **RT reduces LR risk** (*both DCIS and invasive*) by **≈50% in all subgroups**

LR rates for those treated **without RT** in the early randomized trials were **≈30% at 10 years**

EBCTCG, J Natl Cancer Inst 2010

LR rates following BCS for DCIS have *steadily declined over time*

Subhedar, Ann Surg Oncol 2015

*Identification of a **subset of patients with a low absolute LR risk** in whom RT may be omitted is an area of great interest*

BCS FOR LOW-RISK SUBSETS OF DCIS

143 patients (1995-2002) **BCS without RT**

low- to intermediate-grade DCIS

≤2.5 cm

margins ≥1 cm

10-year LR rate of **15.6%** (*without endocrine therapy*)

Wong et al, Breast Cancer Res Treat 2014

Significant and stable LR risk over time but **lower than 28.1%** 10-year risk reported from the ***earlier randomized trials***

EBCTCG, J Natl Cancer Inst 2010

BCS FOR LOW-RISK SUBSETS OF DCIS

ECOG-ACRIN E5194 single-arm study

BCS without RT (1997-2002)

Endocrine therapy 30% (*tamoxifen*)

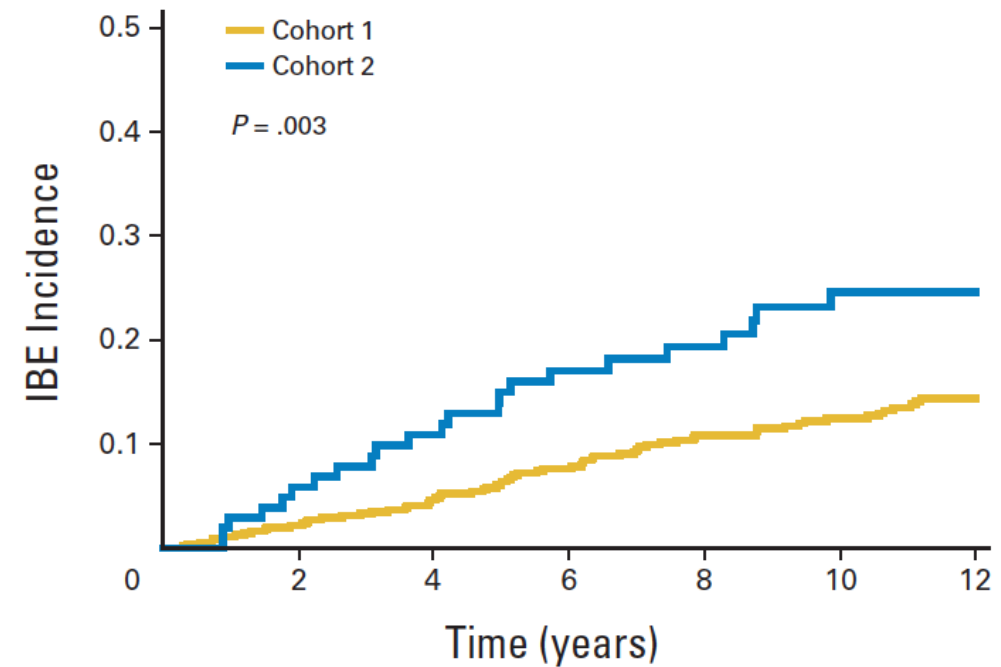
Low/intermediate grade

DCIS ≤ 2.5 cm, ≥ 3 mm margins

12-year LR rate **14.4%** (7.5% *invasive*)

High-grade DCIS ≤ 1 cm, ≥ 3 mm margins

12-year LR rate of **24.6%** (13.4% *invasive*)



Solin et al, JCO 2015

Is it acceptable an invasive LR rate >10% at 10-12 years?

BCS FOR LOW-RISK SUBSETS OF DCIS

RTOG 9804 randomized trial

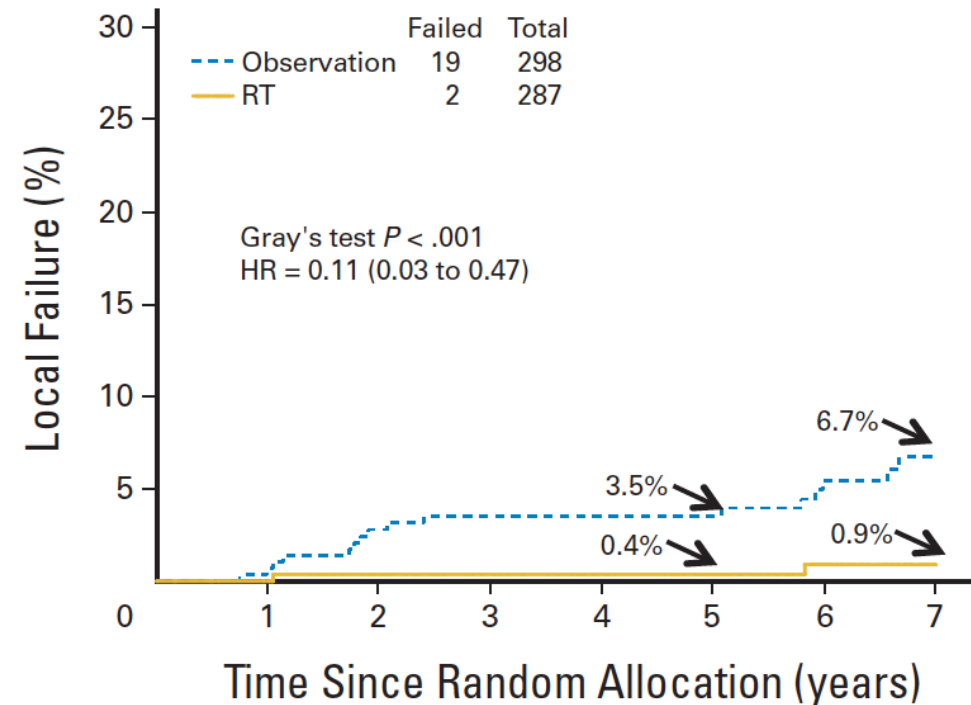
636 **BCS with or without RT** (1998-2006)

Endocrine therapy 62% (*tamoxifen*)

Low/intermediate grade (as cohort ECOG E5194)

7-year LR rate

0.9% (RT arm) vs. **6.7%** (observation)



McCormick et al, JCO 2015

Value placed on LR risk is paramount in making appropriate decisions regarding adjuvant RT omission

OVERVIEW

POSTOPERATIVE RADIATION AFTER BCS FOR DCIS

BCS FOR LOW-RISK SUBSETS OF DCIS

PARTIAL BREAST IRRADIATION FOR DCIS

PARTIAL BREAST IRRADIATION FOR DCIS

DCIS phase 3 trials confirmed the **long-term RT benefit**

→ **NO plateau over time**

McCormick et al, JCO 2015

Solin et al, JCO 2015

RT omission represents a **potential underestimation** of its real benefit

Cutuli et al, Radiother Oncol 2014

PBI is a safe and effective treatment with an **equivalent control** rate in **low-risk breast cancer**

Strnad et al, Lancet 2016

Polgar et al, Lancet Oncol 2017

Coles et al, Lancet 2017

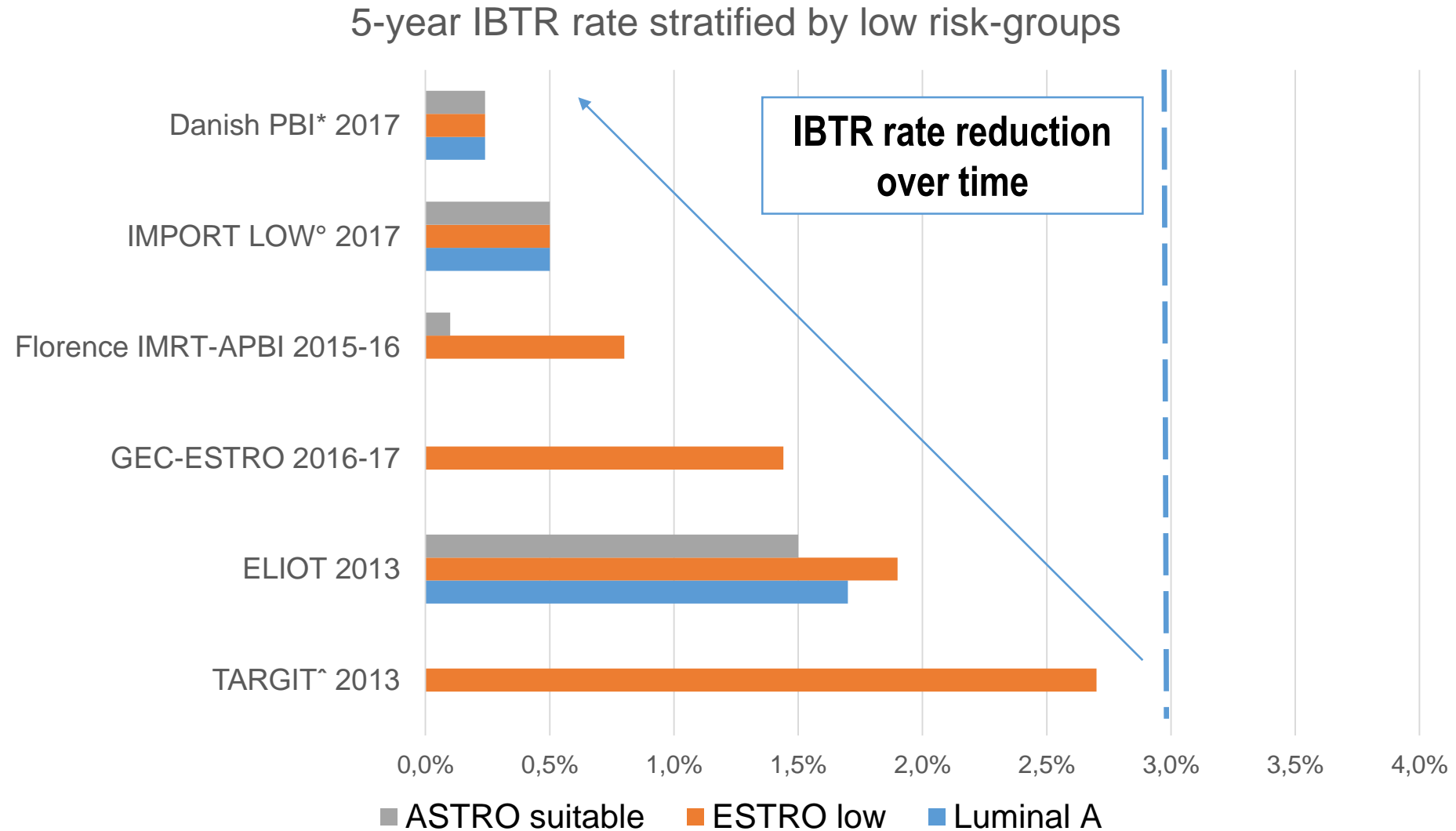
Highly debated in DCIS

→ **conflicting published results and intrinsic biological DCIS nature**

Krug et al, Radiat Oncol 2017

Local relapse in low-risk patients

Selection of patients



* 3-year IBTR rate; ° 5-year estimated rate; ^ Pre-pathology group

PARTIAL BREAST IRRADIATION FOR DCIS

Published studies

Authors, year	Patients, n	Technique	Schedule	Local relapse rate, %	Other outcomes, %	Follow-up time, y
Goyal et al., ²⁷ 2011	194	MammoSite™	34 Gy 10 twice daily fraction	1.98	DFS 92.6 OS 96.6	4.3
Vicini et al., ²⁸ 2013	300	MammoSite™	34 Gy 10 twice daily fraction	2.6	DFS 97.4 OS 96.4	4.7
Shah et al., ³⁰ 2012	99	Interstitial (<i>n</i> = 3) Balloon (MammoSite™ or Contura™) (<i>n</i> = 53) 3D CRT (<i>n</i> = 43)	Low-dose interstitial (50 Gy over 96 hours at 0.52 Gy/h) High-dose interstitial (32 Gy in 8 fractions or 34 Gy in 10 fractions, both delivered 2 times per day) 3D CRT: 38.5 Gy (10 twice daily fractions)	1.4	OS 94	3.0
McHaffie et al., ³¹ 2011	48	Balloon (MammoSite™)	32 to 34 Gy (8 to 10 twice-daily fractions)	0	No ipsilateral failure	5.0
Zauls et al., ³² 2012	183	Balloon (MammoSite™)	32 to 34 Gy (8 to 10 twice-daily fractions)	4.3		3.7
Abbott et al., ³³ 2013	41	Balloon (MammoSite™)	34 Gy (10 twice-daily fractions)	9.8	1-y excellent/ good cosmesis: 86.7 (physicians) 92.3 (patients)	5.2
Jeruss et al., ²⁹ 2011	194	Balloon (MammoSite™)	34 Gy (10 twice-daily fractions)	3.4	DFS 93.2	5.0
Israel et al., ³⁴ 2010	126	Balloon (Mammosite™ or Contura™)	34 Gy (10 twice-daily fractions)	2.4		2.0



PARTIAL BREAST IRRADIATION FOR DCIS

The *American Society of Breast Surgeons* (ASBS) Registry Trial (194 DCIS out of 1449 patients)

- **4-year** DCIS follow-up result **similar to invasive** cancer
- 5-year IBTR rate 3.4%

Keisch et al, Am J Surg 2009
Jeruss et al, Ann Surg Oncol 2011

41 patients in the ASBS Registry (met the low-risk group **ECOG 5194**)

- IBTR **5-year rate of 0%**

Goyal et al, Cancer 2011

99 patients (balloon, interstitial brachytherapy, or 3DCRT)

- IBTR **5-year rate of 1.4%**

Shah et al, Clin Breast Cancer 2012

PARTIAL BREAST IRRADIATION FOR DCIS

Largest pooled analysis - 300 women (*ASBS Registry + William Beaumont Hospital*)

- 5-year IBTR rate: **2.6%**
- 5-year BCSS rate: 99.5%
- 5-year OS rate: 96.4%

Cautionary DCIS ASTRO group vs. **suitable/cautionary invasive** group
→ 2.6% vs. 3.1% ($p=0.90$)

Vicini et al, Ann Surg Oncol 2013

Low rates low-risk DCIS treated with surgery only + early results PBI series

→ **ASTRO APBI task force update for suitable patients**

- *screen-detected*
- *low to intermediate nuclear grade*
- *≤25 mm size*
- *margins ≥3 mm*

ESTRO & ASTRO recommendations

Patient Group	Risk Factor	Original	Update	
ASTRO Suitable	Age	≥ 60	≥ 50	
	Margins	≥ 2 mm	≥ 2 mm	
	Nodal status	pN0		
	T stage	T1	Tis or T1	
	ER/PgR	Positive		
		DCIS	Not allowed	G1-2; ≤2.5 cm
		Lobular invasive	Not allowed	

Patient Group	Risk Factor	
ESTRO Low Risk	Age	≥ 50
	Margins	≥ 2 mm
	Nodal status	pN0
	T stage	T1-2
	ER/PgR	Any
		DCIS
	Lobular Invasive	Not allowed

*Polgar C, et al, R&O, 2010
Smith BD, et al, IROBP, 2009
Correa C, et al, PRO, 2016*



FINAL REMARKS - 1

Data from randomized trials on **PBI** vs. WBI (*including patients with DCIS*) are **limited**

APBI could reasonably represent a compromise between overtreatment and undertreatment (*as per ASTRO recommendations*)

No time for new specific **phase 3 trials** designed on DCIS and PBI in this fast era of **de-escalation of treatments**

Pooled analysis of available data from existing data is *strongly encouraged*

FINAL REMARKS - 2

Lack of knowledge on **biologic features** and **response to treatment**

RT after BCS halves the risk of LR without impact on overall survival

A very-low risk group of patients for whom avoid RT was not identified

Counseling with the patient on the **pros and cons** of each treatment option is strongly recommended

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Radiation therapy after breast conserving surgery

Including partial breast irradiation and radiation omission

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22-23, 2019

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