Faculty Biography

Jonathan B. Strauss, MD, is Assistant Professor in the Department of Radiation Oncology and Program Director of Residency in Radiation Oncology at Robert H. Lurie Comprehensive Cancer Center Northwestern University Feinberg School of Medicine.

Dr. Strauss received his medical degree from the Pritzker School of Medicine at the University of Chicago and his Master's in Business Administration from the University of Chicago Graduate School of Business. He later completed a residency at Rush University Medical Center. Dr. Strauss is board-certified in radiation oncology.

Dr. Strauss's clinical interests include breast and gynecological malignancies. He is an active and prolific clinical researcher and has focused more recently on adopting and studying new technologies in the treatment of breast and gynecological cancers to optimize cancer outcomes while minimizing the damage to normal tissues.

Dr. Strauss is a member of the American Brachytherapy Society (ABS), the American College of Radiology (ACR), the American Society of Clinical Oncology (ASCO), and the American Society for Therapeutic Radiology and Oncology (ASTRO). He also serves as Secretary/Treasurer/President-Elect of the Chicago Radiological Society and is an affiliate member of SWOG, an NCI-supported organization that conducts clinical trials in adult cancers. Additionally, Dr. Strauss has participated as an ad-hoc reviewer for a number of scientific publications, including the *American Journal of Clinical Oncology*, *Brachytherapy*, *Breast Cancer Research and Treatment*, the *International Journal of Gynecological Cancer*, the *International Journal of Radiation Oncology*, *Biology, and Physics*, and the *Journal of Thoracic Disease.*

2016

NCCN CONGRESS SERIES™

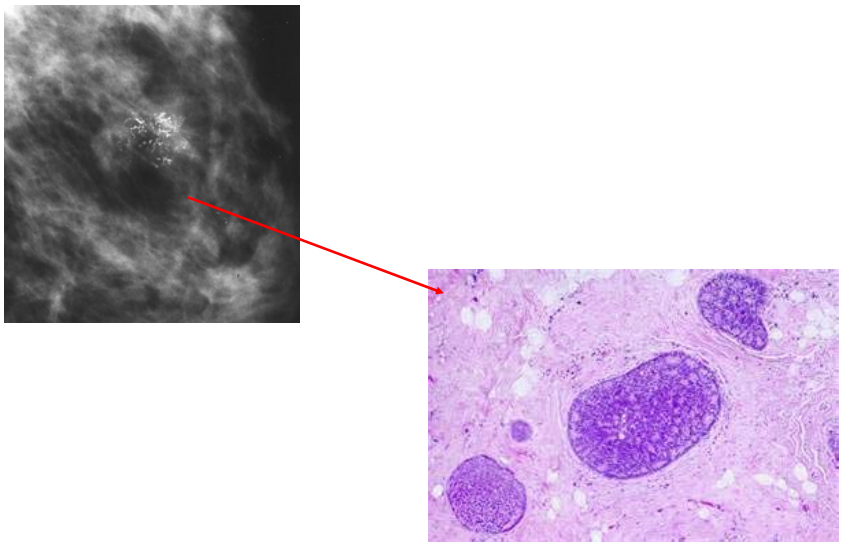
National Comprehensive Cancer Network

DCIS: Adjuvant Radiation Therapy & New Systemic Therapy Options

Jonathan B. Strauss, MD

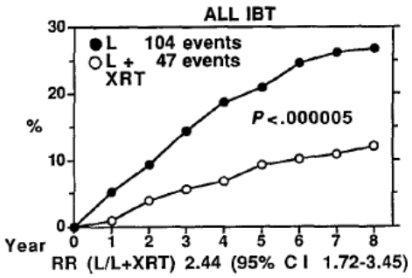
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

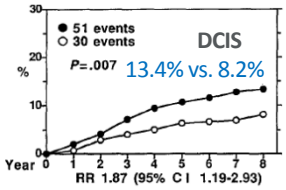
DCIS: Radiotherapy and Systemic Therapy

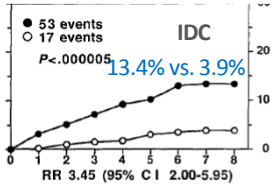


DCIS: RT Trial **NSABP B17**

- 818 women
  - 50 Gy/25 fx
  - No RT
- Excision and negative margins
- 17% palpable
- **8-year IBTR rate 27% vs. 12%**



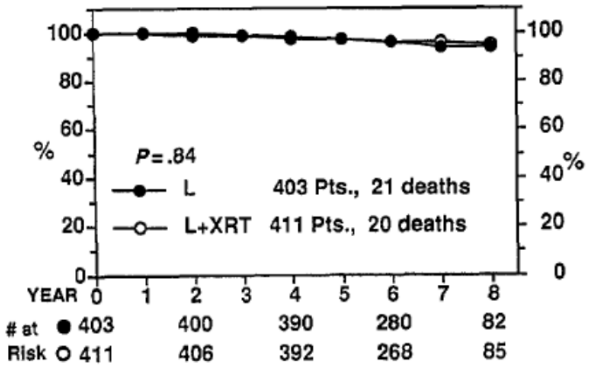




Fisher B, et al. N Engl J Med 1993;328:1581-1586
Fisher B, et al. J Clin Oncol 1998;16:441-452

DCIS: RT Trial **NSABP B17**

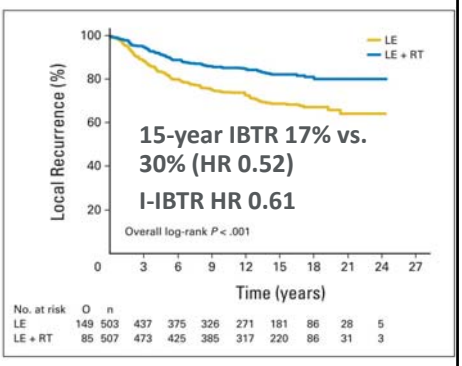
Overall Survival



Fisher B, et al. N Engl J Med 1993;328:1581-1586
Fisher B, et al. J Clin Oncol 1998;16:441-452

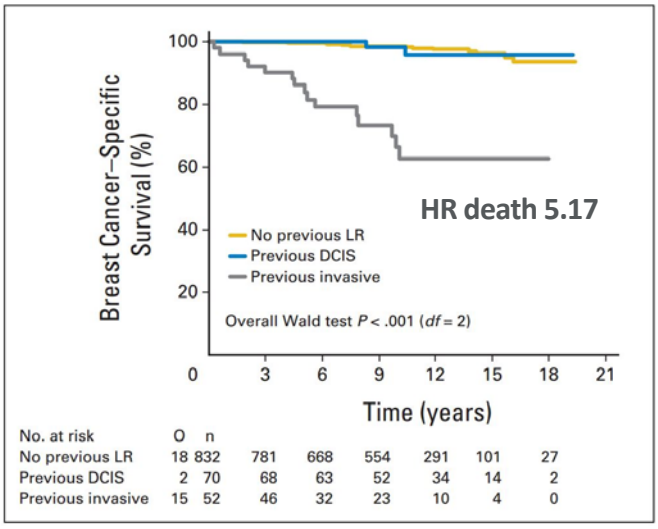
DCIS: RT Trial **EORTC 10853**

- 1,010 women <70 with DCIS <5cm
  - → 50 Gy/25 fx
  - → No RT
- Treated with excision
- In large subset 21% had close/+/NS margins
- 110 IBTRs: 48% DCIS and 52% invasive
- Prognostic Factors for IBTR
  - Age <40
  - Clinical detection (vs. mammographic)
  - + Margins
  - Solid or cribriform (vs. clinging or micropapillary)



Donker M, et al. JCO 2013;31(22):4054-4059

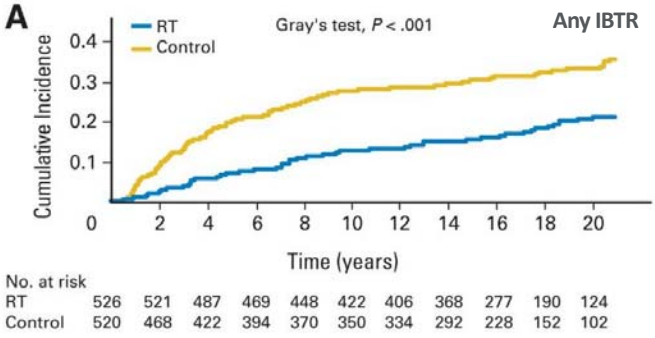
DCIS: RT Trial **EORTC 10853**



Donker M, et al. JCO 2013;31(22):4054-4059

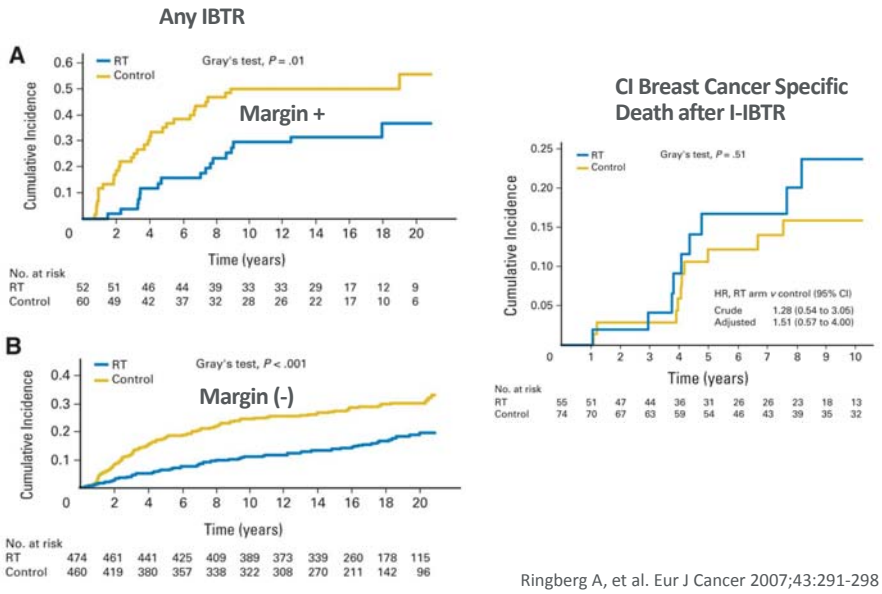
DCIS: RT Trial **SweDCIS**

- 1,046 women with DCIS → RT / No RT
- ~10% + margins and ~9% unknown margins
- 20-yr CI IBTR: 20% vs. 32% -- relative risk reduction 37.5%



Ringberg A, et al. Eur J Cancer 2007;43:291-298
Warnberg F, et al. J Clin Oncol 2014;32:3613-3618

DCIS: RT Trial **SweDCIS**



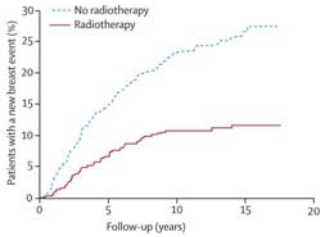
Ringberg A, et al. Eur J Cancer 2007;43:291-298
Warnberg F, et al. J Clin Oncol 2014;32:3613-3618

DCIS: RT Trial **UK/ANZ DCIS Trial (UKCCR)**

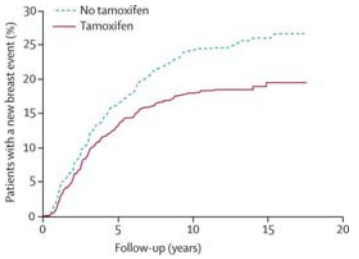
- 1,701 women with DCIS s/p excision
- Margins (-)
- Quasi 2X2 factorial design

→ 50 Gy/25 fx
→ No RT

→ Tam 20 mg qd x 5 year
→ No Tam

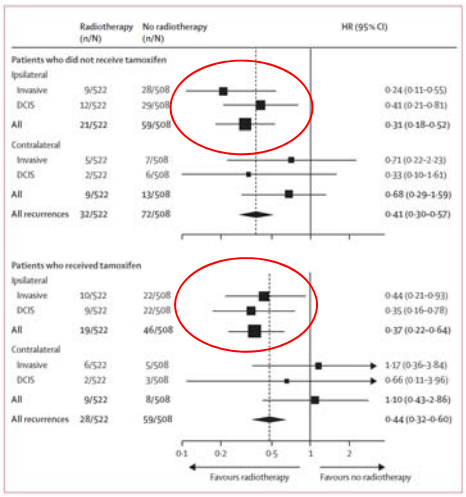


- RT reduced DCIS-IBTR (HR 0.38) and I-IBTR (HR 0.32)
- Tam reduced DCIS IBTR (HR 0.7) but not I-IBTR (HR 0.95)
- Tam reduced contralateral events (HR 0.44)



Cuzick J et al. Lancet Oncol 2011;12(1):21-29

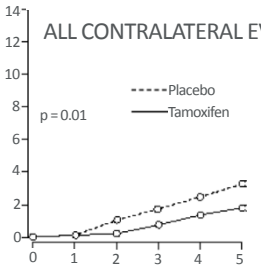
DCIS: RT Trial **UK/ANZ DCIS Trial (UKCCR)**

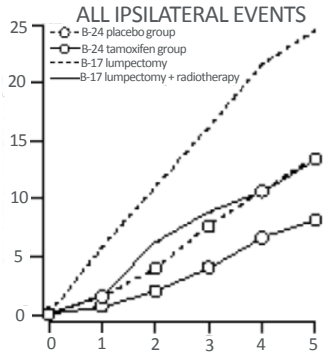


Cuzick J et al. Lancet Oncol 2011;12(1):21-29

DCIS: Endocrine Trial **NSABP B-24**

- 1,804 women with DCIS and 50 Gy/25 fx
  - → Tam 10 mg bid x 5 years
  - → Obs
- Treated with excision + or – margin
- 25% had + or unknown margins
- ER/PR status not specified
- **5-year breast cancer event 8.2% vs. 13.4%**

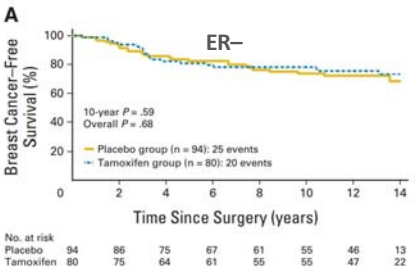


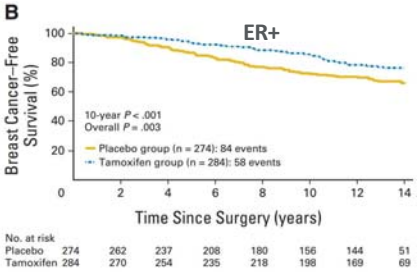


Fisher B, et al. Lancet 1999;353:1993-2000

DCIS: Endocrine Trial **NSABP B-24**

- Subset of patients for whom ER/PR status available
  - ER + 76%, PR + 66%





Allred D, et al. J Clin Oncol 2012;30(12):1268-1273

DCIS: **NSABP B-17 and B-24 Pooled Analysis**

- Median f/u 207 mo (B-17) and 163 mo (B-24)
- RT reduced I-IBTR by 52%
- Tam + RT reduced I-IBTR by 32% vs. RT alone

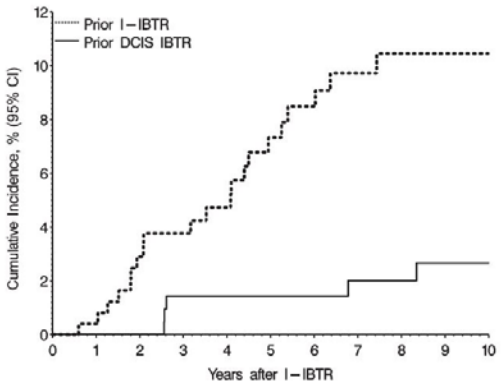
Table 3. Hazard ratios for invasive ipsilateral breast tumor recurrence (I-IBTR) or ductal carcinoma in situ (DCIS)-IBTR according to patient and disease characteristics*

	Ipsilateral breast tumor events			
	I-IBTR		DCIS-IBTR	
Characteristic	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis, y				
≥55	1.00 (reference)	.003	1.00 (reference)	<.001
<45	2.14 (1.40 to 3.26)		2.90 (1.84 to 4.56)	
45–54	1.80 (1.22 to 2.66)		1.81 (1.16 to 2.81)	
55–64	1.50 (1.00 to 2.26)		1.72 (1.10 to 2.70)	
Tumor size, cm				
≤1.0	1.00 (reference)		1.00 (reference)	
>1.0	0.94 (0.68 to 1.30)	.70	1.03 (0.73 to 1.44)	.89
Mode of detection				
Mammography only	1.00 (reference)		1.00 (reference)	
Clinically detected	1.37 (1.03 to 1.84)	.03	1.48 (1.09 to 2.01)	.01
Comedonecrosis†,‡				
Absent	1.00 (reference)		1.00 (reference)	
Present	0.87 (0.62 to 1.21)	.41	2.21 (1.52 to 3.20)	<.001
Treatment group, tumor margin status†,§				
LRT, margin-free	1.00 (reference)		1.00 (reference)	
LRT, involved/uncertain	2.61 (1.68 to 4.05)	<.001	1.65 (1.00 to 2.73)	.05
LRT + TAM, free	1.00 (reference)		1.00 (reference)	
LRT + TAM, involved/uncertain	1.27 (0.73 to 2.20)	.40	1.32 (0.77 to 2.28)	.31

Wapnir IL et al., JNCI 2011;103:478-488

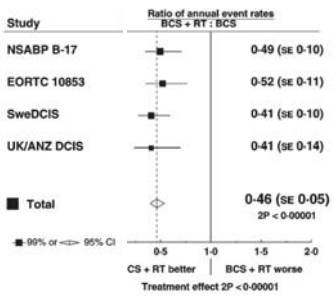
DCIS: **NSABP B-17 and B-24 Pooled Analysis**

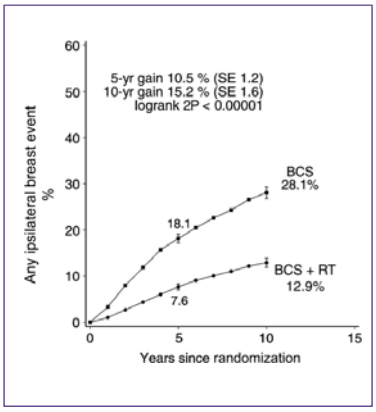
- 490 IBTR events (54% invasive)
- DCIS-IBTR not associated with increased mortality
- I-IBTR associated with increased mortality (HR 1.75)



Wapnir IL et al., JNCI 2011;103:478-488

DCIS: RT **Meta-Analysis**





- Every trial shows that RT cuts the risk of recurrence by at least half
  - Half of recurrences are DCIS – no compromise in survival
  - Half of recurrences are invasive – some decrease in survival

EBCTCG, JNCI 2010;41:162-177

DCIS: Clinical and Pathologic Risk Factors

- Imperfect information
- Some factors fairly consistent:
  - Age
  - Method of detection (clinical vs. mammographic)
  - Margin status (+ vs. -)
  - Histologic subtype/grade
  - Adjuvant therapy (RT, Tam)

DCIS: Risk Factors and RT

- MSKCC prospective database 1978-2010
- 2996 cases with 363 recurrences

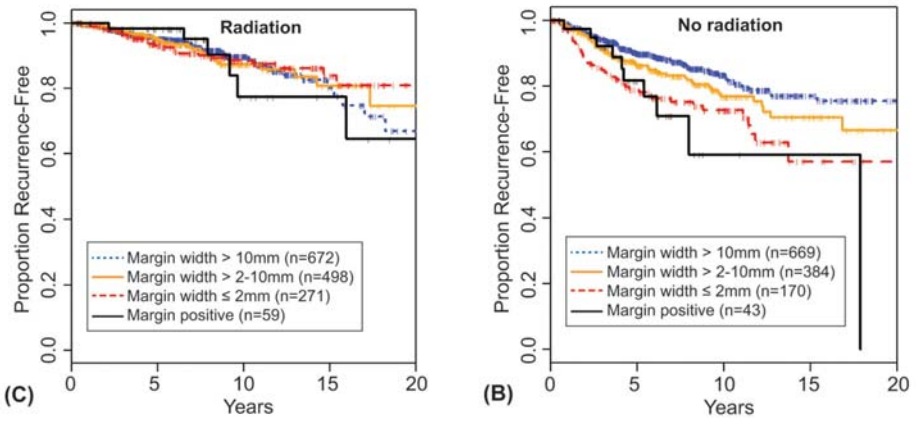
TABLE 5. Multivariable Cox Regression Analysis of Recurrence, Stratified by Use of Radiation

	No Radiation (N = 1225)*				Radiation (N = 1483)*			
Variable	**N**	**Events**	**HR**	***P***	**N**	**Events**	**HR**	***P***
Age at surgery								
Per year			0.987	0.02			0.956	<0.0001
Family history								
No	753	114	1	0.05	909	73	1	0.23
Yes	472	87	1.32		574	51	1.25	
Presentation								
Radiologic	1068	162	1	0.06	1326	102	1	0.43
Clinical	157	39	1.4		157	22	1.22	
Number of excisions								
1	688	100	1	0.0003	612	38	1	0.66
2	492	85	1.37		712	70	1.18	
≥3	45	16	3.18		159	16	1.30	
Endocrine therapy								
No	1026	180	1	0.003	1084	105	1	0.002
Yes	199	21	0.50		399	19	0.46	
Year of surgery								
1978–2000	459	123	1.60	0.003	367	65	1.18	0.44
2001–2010	766	78	1		1116	59	1	
Margin width								
Positive	40	10	1	<0.0001	58	6	1	0.95
Close (≤2 mm)	167	42	0.75		268	27	0.95	
>2–10 mm	369	62	0.58		492	35	1.00	
>10 mm	649	87	0.31		665	56	0.88	

*In entire population of 2996, 288 cases had at least one missing data point, resulting in population for multivariable analysis of 2708.

Van Zee KJ, et al. Ann Surg Oncol 2015;262:623-631

DCIS: Risk Factors and RT



Van Zee KJ, et al. Ann Surg Oncol 2015;262:623-631

Less is more ?

DCIS: Omission of RT: **Harvard Trial**

- Prospective single arm trial (BWH, MGH, BIDMC)
- DCIS, gr 1-2, size ≤ 2.5cm, margin ≥ 1cm or totally negative re-excision
- Planned accrual (n= 200); stopping boundary crossed at 158
- LR 1.9 % per patient-year (1.6% highest nuclear gr 1-2, 7.7% gr 3)

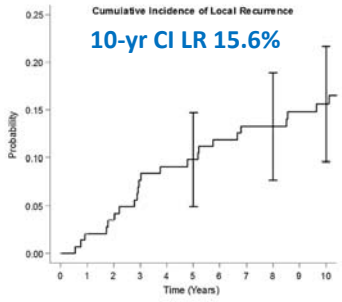


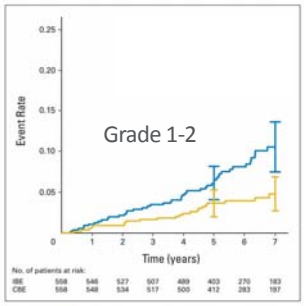
Fig. 1 Estimated cumulative incidence of LR

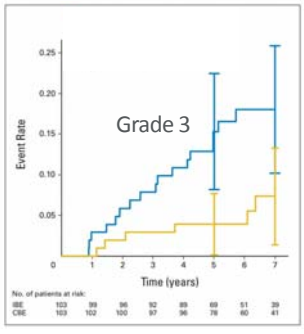
Wong J, et al. J Clin Oncol 2006;24(7):1031-1036
Wong J et al. Breast Cancer Res Treat 2014;143:343-350

DCIS: Omission of RT: **ECOG E-5194**

- Multi-institutional prospective single arm trial
- 665 women with DCIS s/p excision > 0.3cm margins
  - Gr 1-2: ≤ 2.5 cm (n=561)
  - Gr 3: ≤ 1 cm (n=104)
- Median size ~6mm
- Widely free margins (most >0.5cm)
- About 31% received tamoxifen

	5-year IBTR	12-yr IBTR	12-yr I-IBTR
Gr 1-2	6.1%	14.4%	7.5%
Gr 3	15.3%	24.6%	13.4%



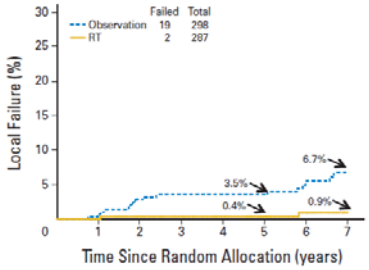


Hughes L, et al. J Clin Oncol 2009;27(32):5319-5324
Solin L, et al. J Clin Oncol 2015;33(33):3938-3944

DCIS: Omission of RT: **RTOG 9804**

- Closed due to slow accrual
- 636 women with DCIS treated with lumpectomy
  - Grade 1-2, >3mm clear margins, ≤ 2.5cm
- About 62% received tamoxifen → Whole breast RT ~ 50Gy
- Median size 5mm → No RT
- Widely free margins

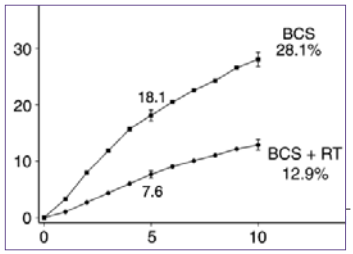
	5-yr	7-yr
RT	0.4%	0.9%
No RT	3.5%	6.7%



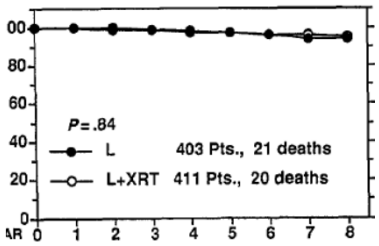
McCormick B, et al. J Clin Oncol 2015;33(7):709-715

DCIS: Should we omit RT in low risk cohort?

- **NO! RT is needed**
- RT reduces the risk of IBTR in half
- All subsets of patients benefit, clinical variables → imperfect risk stratification
- Half of all recurrences are invasive
- Invasive recurrences associated with reduced survival



- **YES! RT is optional**
- In some patients, baseline risk of recurrence is low
- Especially as imaging, surgery, endocrine tx improving
- No proven survival advantage for RT
- RT carries potential for late toxicity (cardiac, second cancers)



Fisher B, et al. N Engl J Med 1998;340:1381-1389

Donker M, et al. Lancet Oncol 2014;15:1303-1310

EBCTCG. Lancet Oncol 2012;13:1158-1160

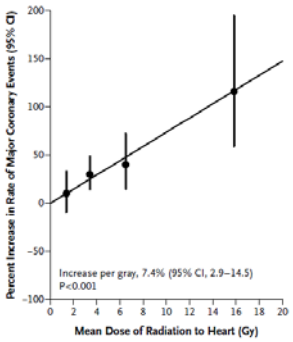
DCIS: Should we omit RT in low risk cohort?

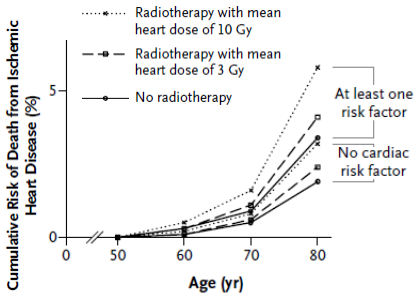
Better Radiotherapy

Better Patient Selection

DCIS: Late Toxicity of Radiotherapy

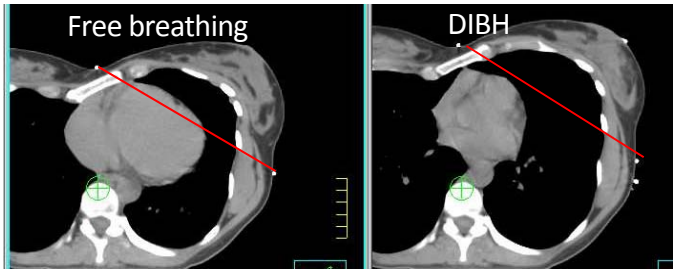
- 2168 women getting whole breast RT in Sweden/Denmark 1958-2001
- Major coronary events (MI, revascularization, death) increase linearly with mean heart dose – 7.4%/Gy for first 20 years
- Risk starts within 5 years, persists ≥ 20 years

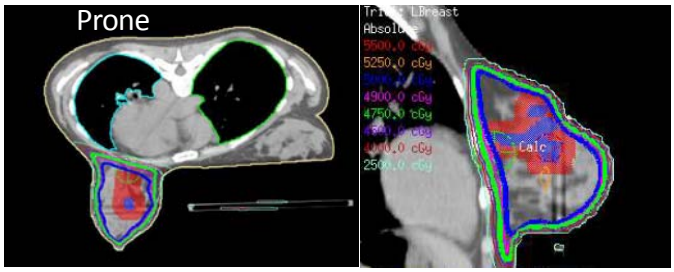




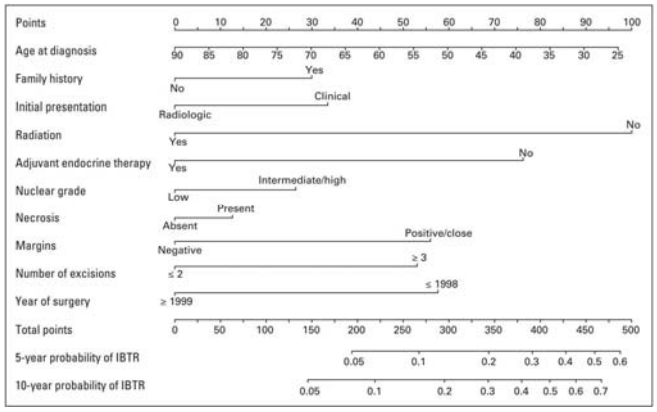
Darby S, NEJM 2013;368(11):987-998

DCIS: Better Radiotherapy





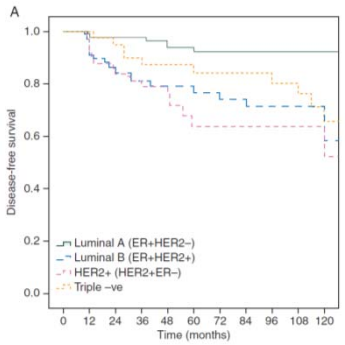
DCIS: Patient Selection via Nomogram



Rudloff U, et al. J Clin Oncol 2010;28(23):3762-3769

DCIS: Molecular Phenotypes

- 314 patients with DCIS screened for clinical trial
- Any surgery (~1/3 mastectomy), ~17% RT
- Molecular phenotypes determined by ER, PR, H2N staining



	HR IBTR	HR I-IBTR
Luminal B	5.1	13.4
Her-2	6.5	11.4
Triple (-)	3.3	10.3

Williams K, et al. Annals of Oncology 2015;26:1019-1025

DCIS: Genetic Profiling – **12-Gene RT-PCR Assay**

- Selected genes prognostic for LR in both ER+/ER- subsets
- Calculation of DS score:
  - 1) Expression of cancer-related genes normalized relative to ref genes
  - 2) Proliferation group score $(Ki67 + STK15 + Survivin + CCNB1 + MYBL2)/5$.
  - 3) $\text{DCIS Score}_u = +0.31 \times \text{proliferation group score} - 0.08 \times PR - 0.09 \times GSTM1.$
  - 4) DCIS Score = $(66.7 \times \text{DCIS Score}_u) + 10.0$

Proliferation group
Ki67
STK15
Survivin
CCNB1 (cyclin B1)
MYBL2

Hormone receptor group
PR

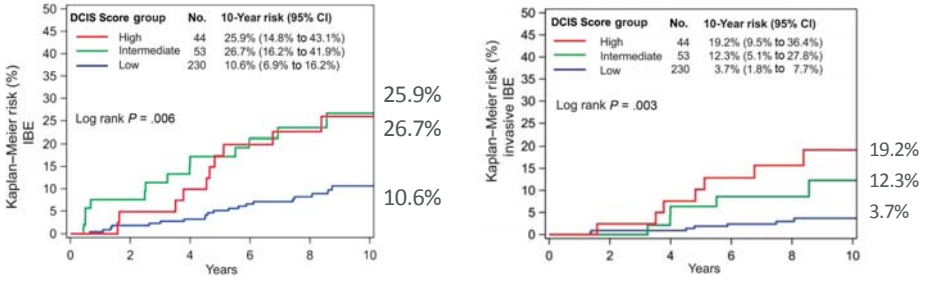
GSTM1

Reference group
ACTB (β-actin)
GAPDH
RPLPO
GUS
TFRC

Solin L, et al. JNCI 2013;105(10):701-710

DCIS: Genetic Profiling -- **ECOG E5194**

- Subset of highly selected ECOG E5194
- 12-Gene RT-PCR Breast Cancer Assay
- Continuous DCIS Score associated with risk of IBE (HR 2.31) and I-IBE (HR 3.68)



Solin L, et al. JNCI 2013;105(10):701-710

DCIS: Genetic Profiling -- **ECOG E5194**

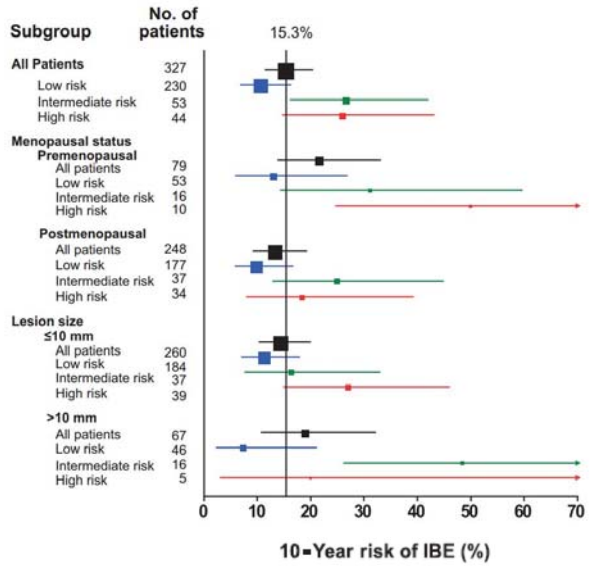
- Risk factors for IBTR: DCIS score, tumor size, menopausal status
- DS has independent prognostic value in addition to clinical variables
- DS is a compliment to, not a replacement for, clinical risk factors

Table 4. Multivariable Cox proportional hazards models for the risk of an ipsilateral breast event

Analyses and variables	Hazard ratio (95% CI)*	P†
Multivariable analysis of significant clinical and pathologic factors, including the DCIS Score		
Menopausal status		.02
Premenopausal	1.00 (referent)	
Postmenopausal	0.49 (0.27 to 0.90)	
Tumor size‡	1.52 (1.11 to 2.01)	.01
DCIS Score‡	2.37 (1.14 to 4.76)	.02

Solin L, et al. JNCI 2013;105(10):701-710

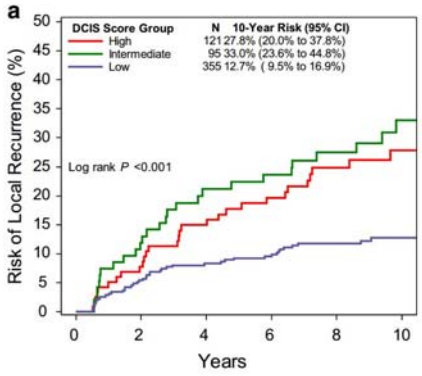
DCIS: Genetic Profiling -- **ECOG E5194**



Solin L, et al. JNCI 2013;105(10):701-710

DCIS: Genetic Profiling – **Ontario DCIS cohort**

- **Population-based cohort in Ontario, Canada**
- Not highly selected like ECOG E5194
- DCIS treated margin (-) excision (no RT) 1994-2003
- 12-Gene RT-PCR Breast Cancer Assay
- 571 pts, median f/u 9.6 years
- DS correlated to LR (HR 2.15)
  - I-IBTR: HR 1.78
  - DCIS-IBTR: HR 2.43



Rakovitch E, et al. Breast Cancer Res Treat 2015;152(2):389-398

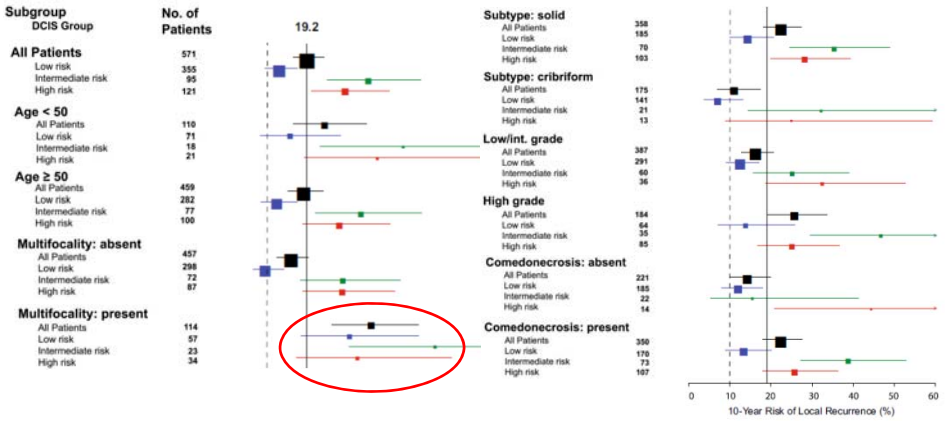
DCIS: Genetic Profiling – **Ontario DCIS cohort**

- DS independent prognostic info (adjusted HR 1.68) in addition to clinical variables

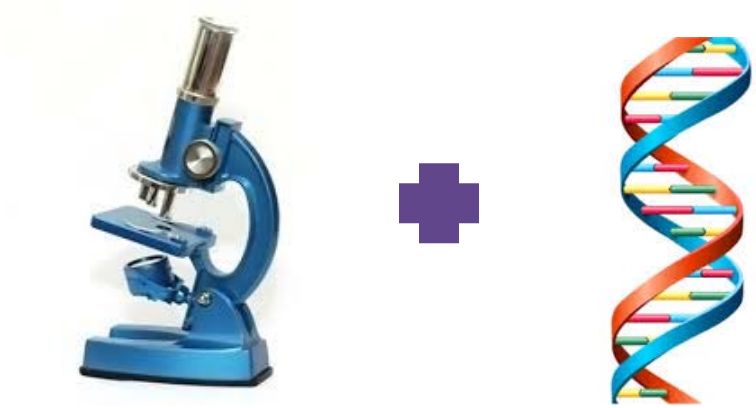
Characteristic	*N*	HR (95 % CI)*	*P* value*
DCIS Score (HR/50 U)	571	1.68 (1.08, 2.62)	0.02
Multifocality			0.003
Absent/unknown	457	1.0	
Present	114	1.97 (1.27, 3.02)	
Tumor size†			0.01§
≤10 mm	150	1.0	
>10 mm	140	2.07 (1.15, 3.83)	
Age			0.03
≥50	459	1.0	
<50	110	1.75 (1.07, 2.76)	
DCIS tumor subtype			0.04
Cribriform	175	1.0	
Solid	358	1.63 (0.97, 2.88)	
Other	38	2.75 (1.17, 6.04)	

Rakovitch E, et al. Breast Cancer Res Treat 2015;152(2):389-398

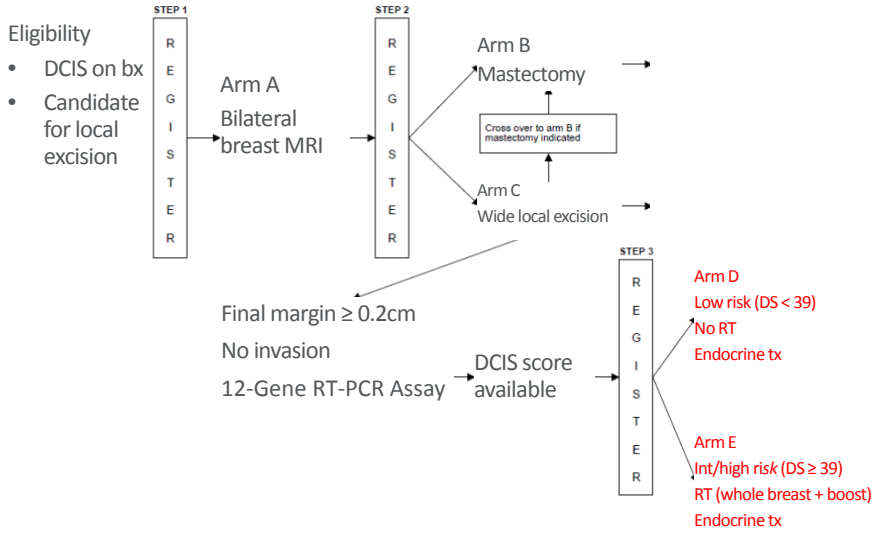
DCIS: Genetic Profiling – **Ontario DCIS cohort**



Rakovitch E, et al. Breast Cancer Res Treat 2015;152(2):389-398



DCIS: Genetic Profiling – **ECOG-ACRIN E4112**



DCIS: Endocrine Trial **NSABP B-35**

- 3,104 postmenopausal women with DCIS
  - Tam 20 mg qd x 5 yrs
  - Anast 1mg qd x 5 yrs
- ER or PR (+)
- Treated with excision (–) margin, 50 Gy RT
- Median follow-up 9 years
- AEs similar except thrombosis/embolism worse in tam group

(Await IBIS-II DCIS trial)

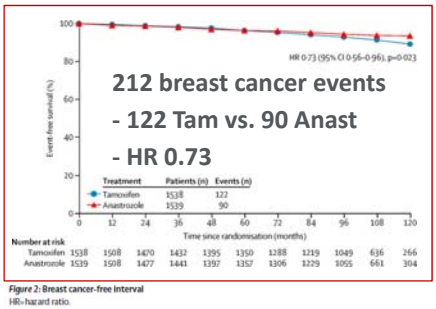


Figure 2: Breast cancer-free interval
HR=hazard ratio.

Margolese R, et al. Lancet 2015 Dec 10 [Epub ahead of print]

DCIS: Endocrine Trial **NSABP B-35**

- Anastrazole superior to Tam only in women <60

	Patients (n)	Tamoxifen (n=1538)	Anastrozole (n=1539)	Hazard ratio (95% CI)	p value
Breast cancer-free interval events					
<60 years	1447	63	34	0·53 (0·35–0·80)	0·0026
≥60 years	1630	59	56	0·95 (0·66–1·37)	0·78
Disease-free survival events					
<60 years	1447	104	74	0·69 (0·51–0·93)	0·0151
≥60 years	1630	156	161	1·03 (0·83–1·28)	0·79

Table 3: **Breast cancer-free interval and disease-free survival events by age group**

Margolese R, et al. Lancet 2015 Dec 10 [Epub ahead of print]

DCIS: Endocrine Trial **NSABP B-35**

- Of the 3,104 pts, 1,193 included in QoL substudy
- Tamoxifen worse for vasomotor sz, bladder control, gyne symptoms
- Anastrazole worse for M-skel pain, vaginal symptoms
- Younger age associated w/ more vasomotor, vaginal symptoms, weight problems, gyne symptoms

- **<60 years old: decision based on efficacy and toxicity profile**
- **>60 years old: decision on toxicity only**

Ganz P et al. Lancet 2015 Dec 10 [Epub ahead of print]

DCIS: Local Transdermal Endocrine Therapy

- Double-blind, Phase II, RCT
- 27 women with DCIS randomized
- Received tx for 6-10 weeks before surgery (med time 6 weeks)
- Oral tamoxifen vs. transdermal 4-hydroxytamoxifen gel (4-OHT)

	4-OHT	Oral Tam
Decrease in ki-67	3.4%	5.1%
Breast Adipose concentration (ng/g)	5.8	5.4
Mean Plasma concentration (ng/mL)	**0.2**	**1.1**
Effect on clotting factors	**No**	**Yes**

  - achieves therapeutic concentration in breast
  - exhibits anti-proliferative effect
  - Less systemic absorption

Lee O, et al. Clin Cancer Res 2014;20(14):3672-3682

DCIS: New Frontiers in Systemic Therapy

- **NSABP B-43**
  - 2000 women with DCIS Her-2 amplified
  - Treated with lumpectomy and RT
  - Endocrine tx if ER/PR +

→ Trastuzumab x 2 during RT

→ RT alone

- **CALGB 40903**
  - Phase II study neoadjuvant letrozole x 6 months in postmenopausal women with DCIS
  - Estimate mean change in MRI tumor volume, change in ki-67

DCIS: New Frontiers in Radiotherapy

- **EORTC 22085-10083**
  - DCIS, margin (-) excision, "high risk"
  - 2x2 factorial design:
    - Breast 50 Gy / 25 fx
      - Boost 16 Gy / 8 fx
      - No Boost
    - Breast 42.5 Gy / 16 fx
      - Boost 16 Gy / 8 fx
      - No Boost
- **BONBIS Trial**
  - DCIS, excision
  - 50 Gy to breast
    - Boost 16 Gy / 8 fx
    - No Boost
- **Multiple Trials of APBI in DCIS**

NCCN Guidelines