PREDICTORS OF DCIS RECURRENCE AND RISK OF INVASIVE CANCER:

OVERVIEW OF THE FIELD AND CURRENT CHALLANGES

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CLINICALLY RELEVANT ENDPOINTS

Important — **Risk to patient**

- Local recurrence
  - All (invasive plus DCIS) → Mastectomy
  - Invasive → Metastatic disease

Not important (too few events)

- Distant metastases
- Survival

GENERAL CONCEPTS

- Current predictors for local recurrence:

  - Based on patient and tumor characteristics

  - Not adequate for treatment decisions
    (Surgery, radiation, tamoxifen)

  - Similar for studies of excision with vs. without radiation

  - Need for new biologically based predictors for
    tailored treatments

RISK FACTORS FOR LOCAL RECURRENCE

Patient	Age
Tumor	Size
	Clinical presentation
	Margins
	Pathology
	Grade
	Necrosis
	Subtype
Biologic	Receptor status
Treatment	Surgery (none vs. lumpectomy vs. mastectomy)
	Radiation (none vs. yes)
	Hormones (none vs. tamoxifen vs. AI)

RANDOMIZED TRIALS OF RADIATION FOR DCIS

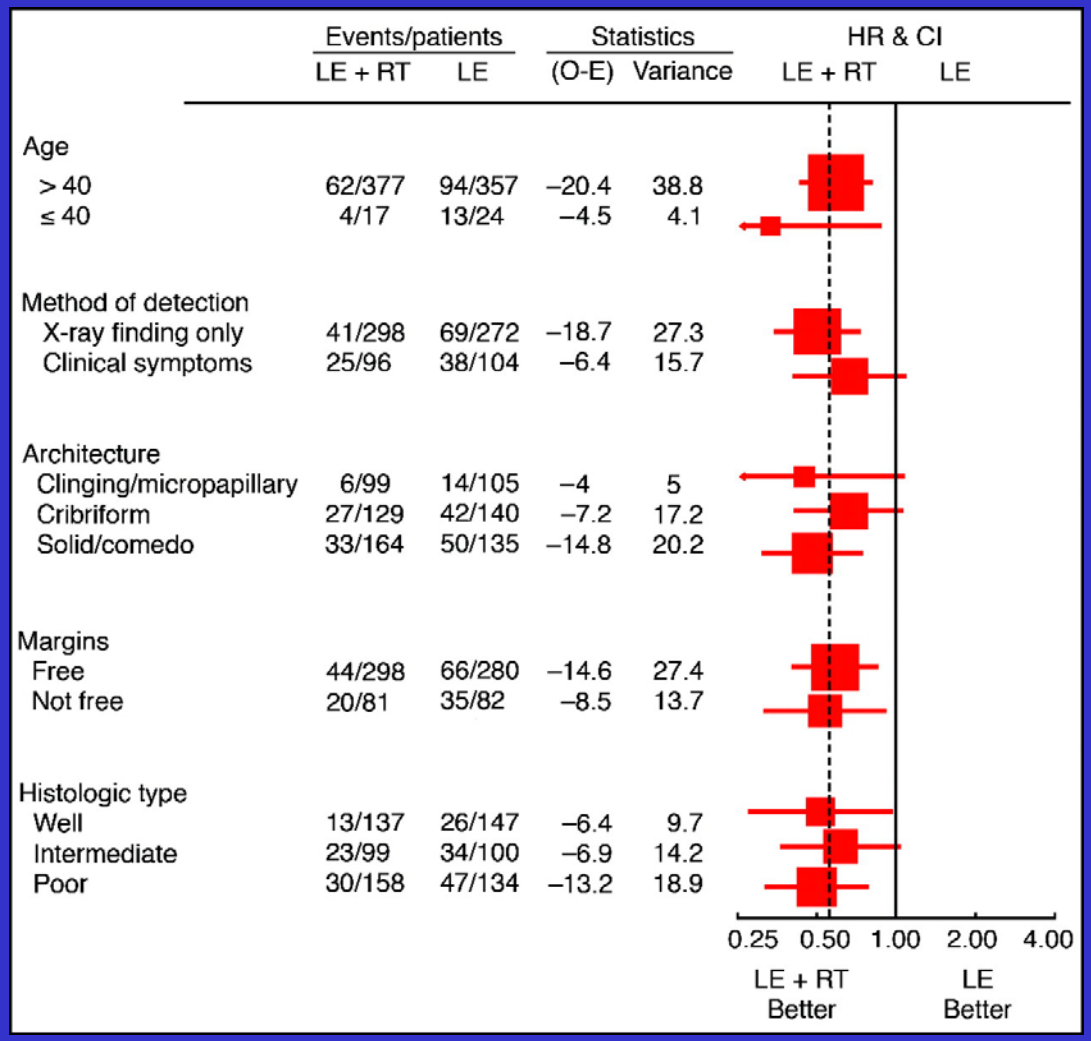
Study	Randomization	No. of patients	Median follow-up (years)
NSABP B-17 Fisher, 2001	Excision ± RT	813	10.8
EORTC 10853 Bijker, 2006	Excision ± RT	1,010	10.5
UK DCIS Trial Houghton, 2003	Excision ± RT ± Tam	1,030	4.4

EORTC DCIS TRIAL 10853
MULTIVARIATE ANALYSIS FOR LOCAL RECURRENCE

	Hazard ratio	p value
Age		
> 40 years	1	
≤ 40 years	1.89	.026
Method of detection		
Mammography only	1	
Clinical symptoms	1.55	.012
Margins		
Free	1	
Unknown/close/positive	1.84	.0005
Architecture		
Clinging/micropapillary	1	
Cribriform	2.39	.002
Solid/comedo	2.25	
Grade		
1	1	
2	1.85	.024
3	1.61	
Radiation treatment		
Yes	1	
No	1.82	.0002

Bijker, JCO, 2006

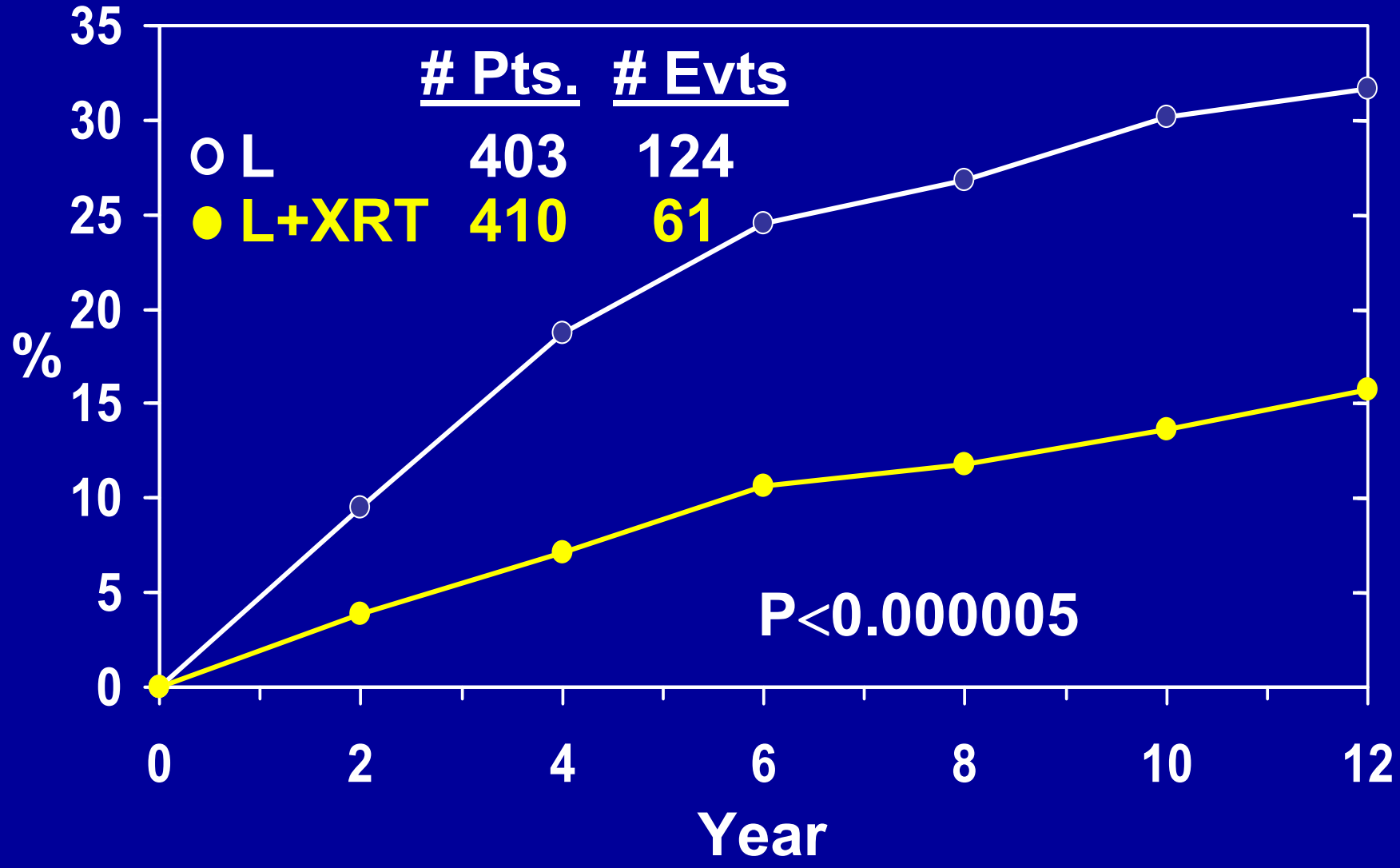
EORTC 10853: Effect of radiotherapy on local control by subgroup



Bijker, JCO, 2006

B-17

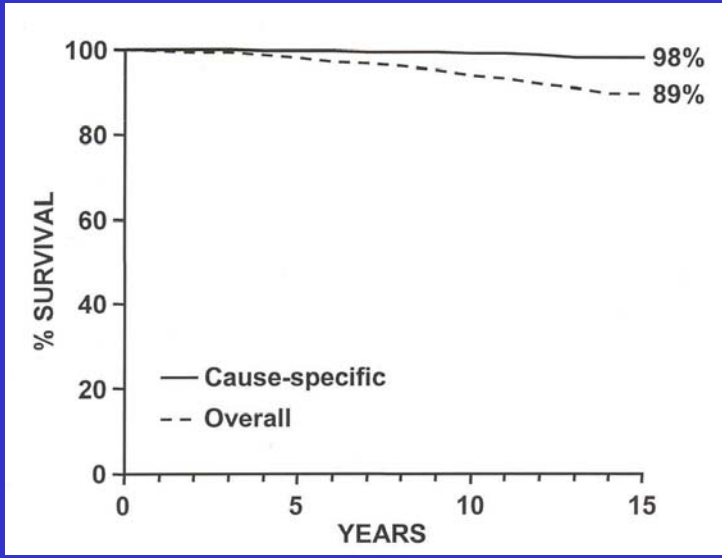
All Ipsilateral Breast Tumors

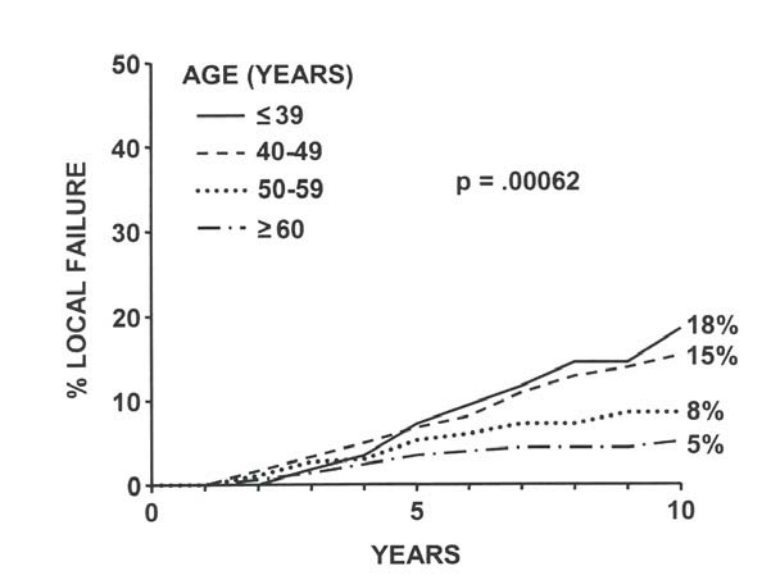


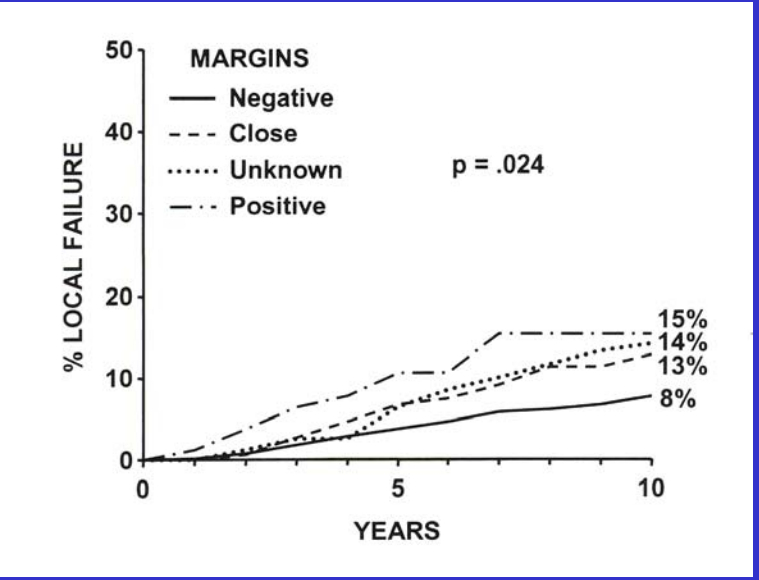
SUMMARY OF RANDOMIZED TRIALS OF RADIATION AFTER LUMPECTOMY FOR DCIS

	No. of patients	Ipsilateral local recurrence				Overall survival		
		Without RT	With RT	Risk reduction	P Value	Without RT	With RT	P Value
Fisher NSABP B-17	813	31.7% At 12 years	15.7%	50%	<.000005	86%	87%	.80
Bijker EORTC 10853	1,010	26% At 10 years	15%	42%	<.0001	95%	95%	.53
Houghton UK	1,030	14% Crude incidence	6%	62%	<.0001			

EXCISION PLUS RADIATION: COLLABORATIVE STUDY OF 1,003 PATIENTS WITH MAMMOGRAPHICALLY DETECTED DCIS







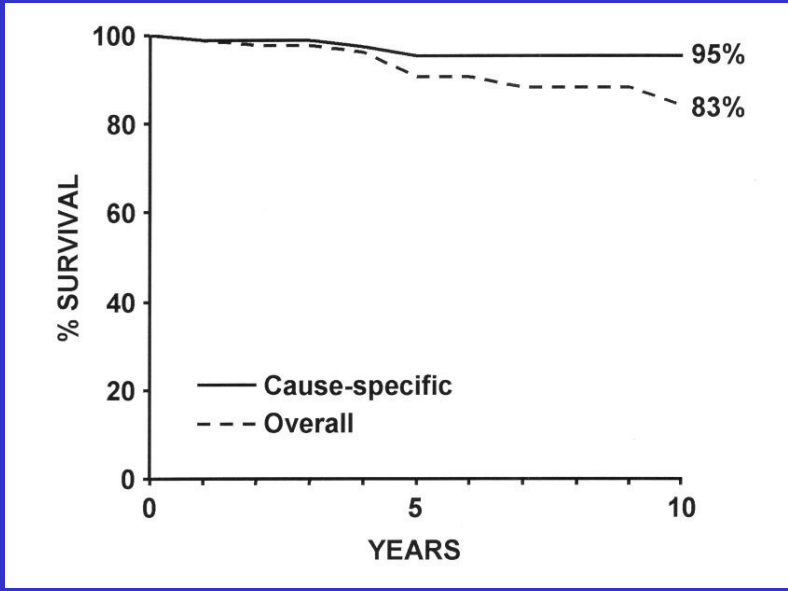
Solin, Cancer, 2005

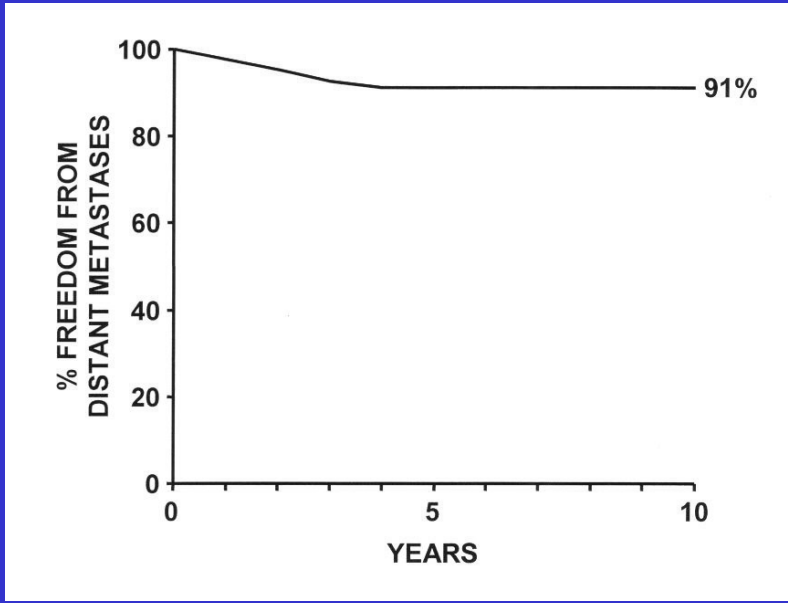
EXCISION PLUS RADIATION: COLLABORATIVE STUDY OF 1,003 PATIENTS

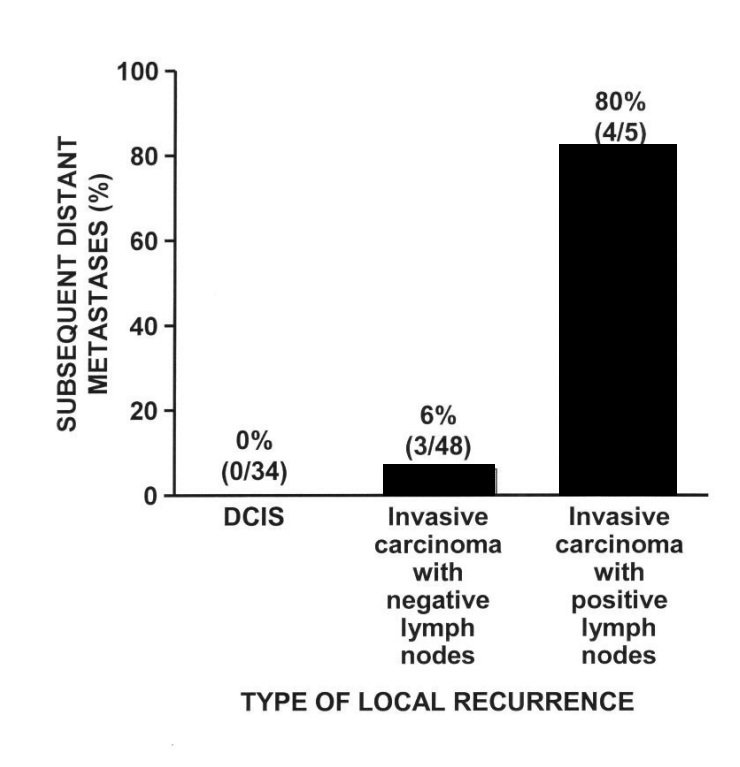
First event	No.		%	
None	756		75	
Local recurrence	85		8	
Invasive carcinoma		48		5
DCIS/Paget's disease		34		3
Angiosarcoma		1		<1
Unknown		2		<1
Regional recurrence	1		<1	
Local-regional recurrence	5		<1	
Distant	1		<1	
Contralateral breast cancer	71		7	
Second malignant neoplasm	56		6	
Deaths from causes other than breast carcinoma	21		2	
Other	7		<1	

Solin, Cancer, 2005

SALVAGE TREATMENT AFTER LOCAL OR LOCAL-REGIONAL RECURRENCE AFTER INITIAL LUMPECTOMY PLUS RADIATION





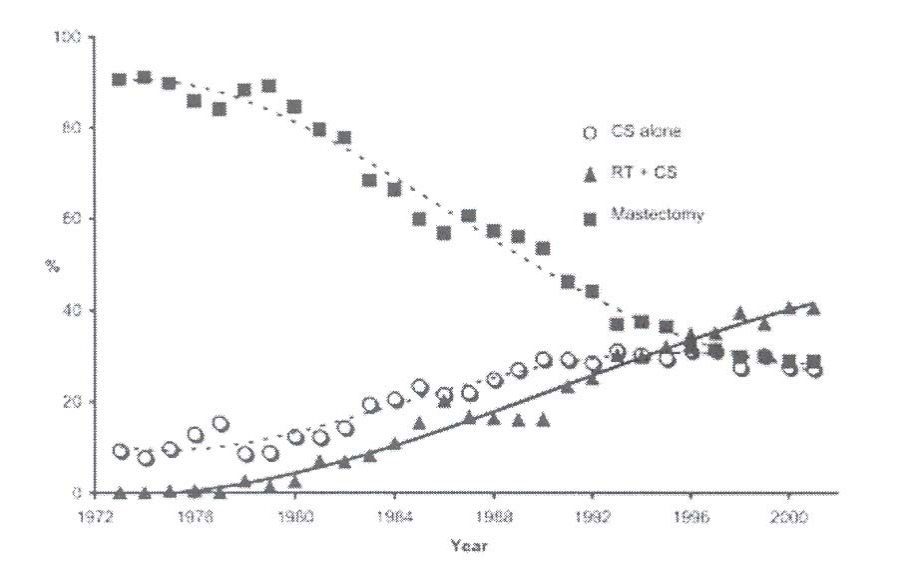


Solin, EJC, 2005

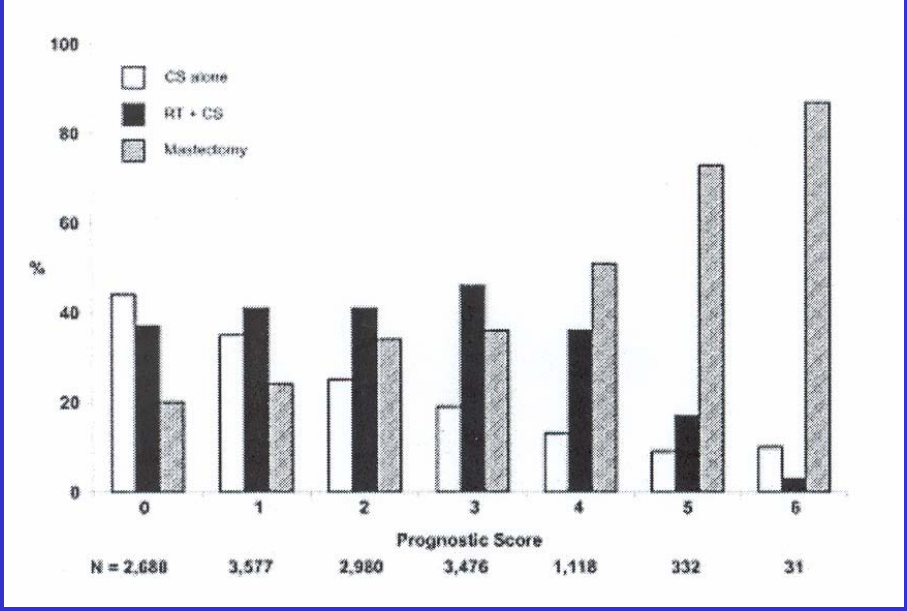
CHANGE IN RETROSPECTIVE SELECTION CRITERIA OVER TIME FOR TREATMENT WITH LUMPECTOMY ALONE

Year	Study	Criteria
1982	Lagios, Cancer	Mammo detection, neg. margins, grade I-II
1989	Lagios, Cancer	Mammo detection, neg. margins, grade I-II, size ≤2.5 cm
1992	Schwartz, Cancer	Mammo detection or incidental finding, neg. margins, size ≤2.5 cm, (?noncomedo)
1992	Silverstein, Eur J Ca	Patient refusal of radiation treatment
1995	Silverstein, Lancet	Grade I-II ± necrosis
1996	Silverstein, Cancer	Van Nuys Prognostic Index (VNPI) score 3-4
1999	Silverstein, NEJM	Negative margin width ≥10 mm
2002	Silverstein (Book)	Modified Van Nuys Prognostic Index score 4-6

TRENDS IN THE TREATMENT OF DCIS: SEER DATA 1996-2001



Choice of treatment over time



Choice of treatment according to prognostic score (based on age, size, grade, but not margins)

Smith G, IJROBP, 2006

REPORTED RESULTS OF LUMPECTOMY ALONE WITHOUT RADIATION FOR SELECTED DCIS

	No. of patients	Actuarial local recurrence (%) At 5 yrs	At 10 yrs	At 15 yrs
Retrospective				
Arnesson	169	16	22	--
Blamey	178	14*	22	--
Cataliotti	105	13	22	--
Cutuli	190	27*	44	--
Hughes	60	18*	--	--
Lagios	79	15*	20*	22
Schwartz	256	27*	41*	49*
Silverstein	346	19	28	--
Saunders	28	12*	19*	32*
Prospective				
NSABP B-17	405	23*	30*	--
EORTC	503	18*	26	--
JCRT study	59	12	--	--

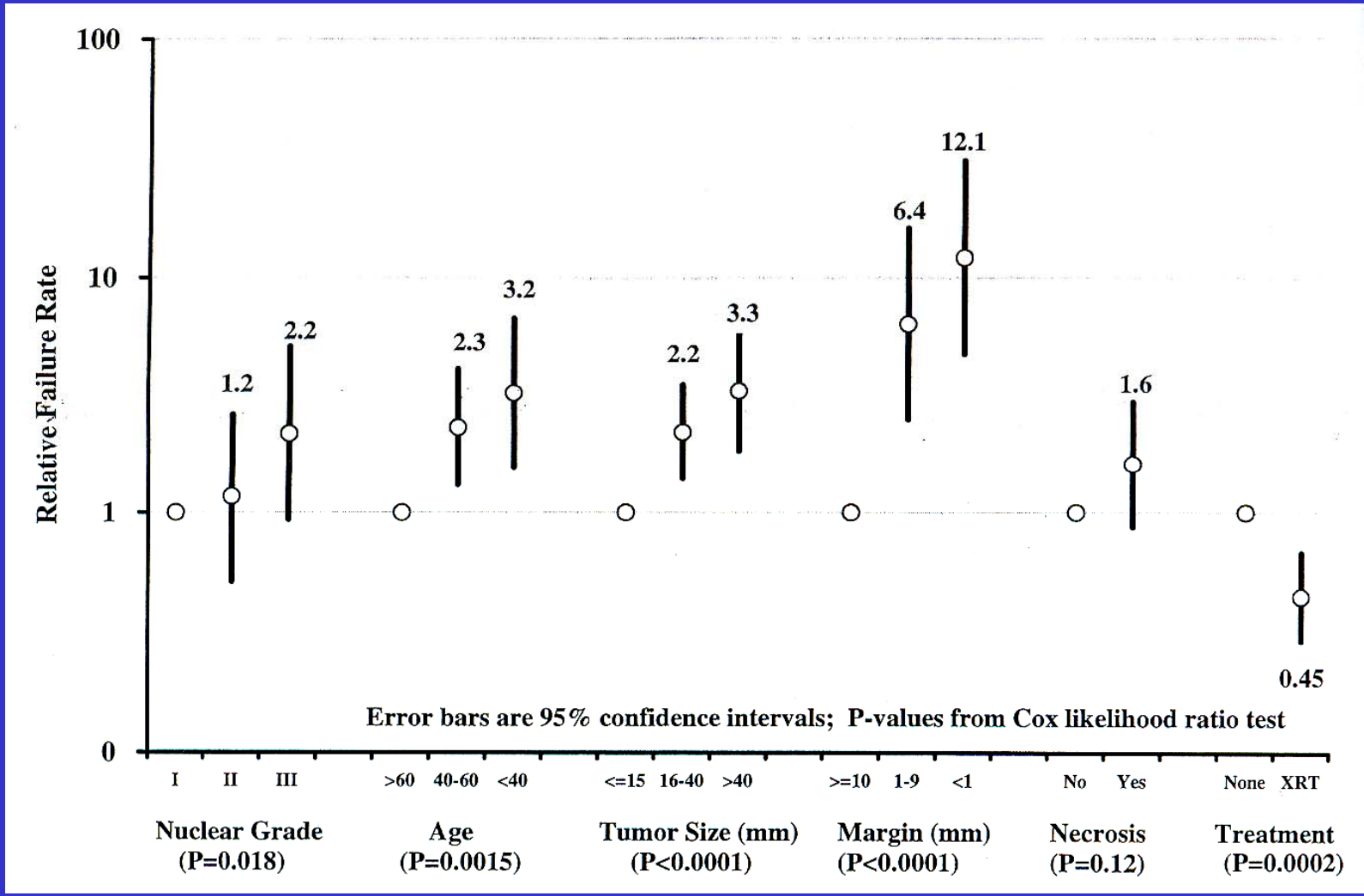
*Estimated from curve

ANALYSIS OF 909 CASES TREATED AT A SINGLE INSTITUTION

	Mastectomy	Excision plus RT	Excision alone
Mean tumor size (cm)	4.2	1.8	1.5
Margins			
≥1 mm	20%	65%	81%
≥10 mm	2%	19%	39%
Met Lagios criteria	21%	52%	69%
Nonpalpable presentation	76%	87%	94%
Mean follow-up (months)	81	106	70

Silverstein, DCIS Book, 2002

MULTIVARIATE ANALYSIS OF LOCAL RECURRENCE



Silverstein, Book, 2002

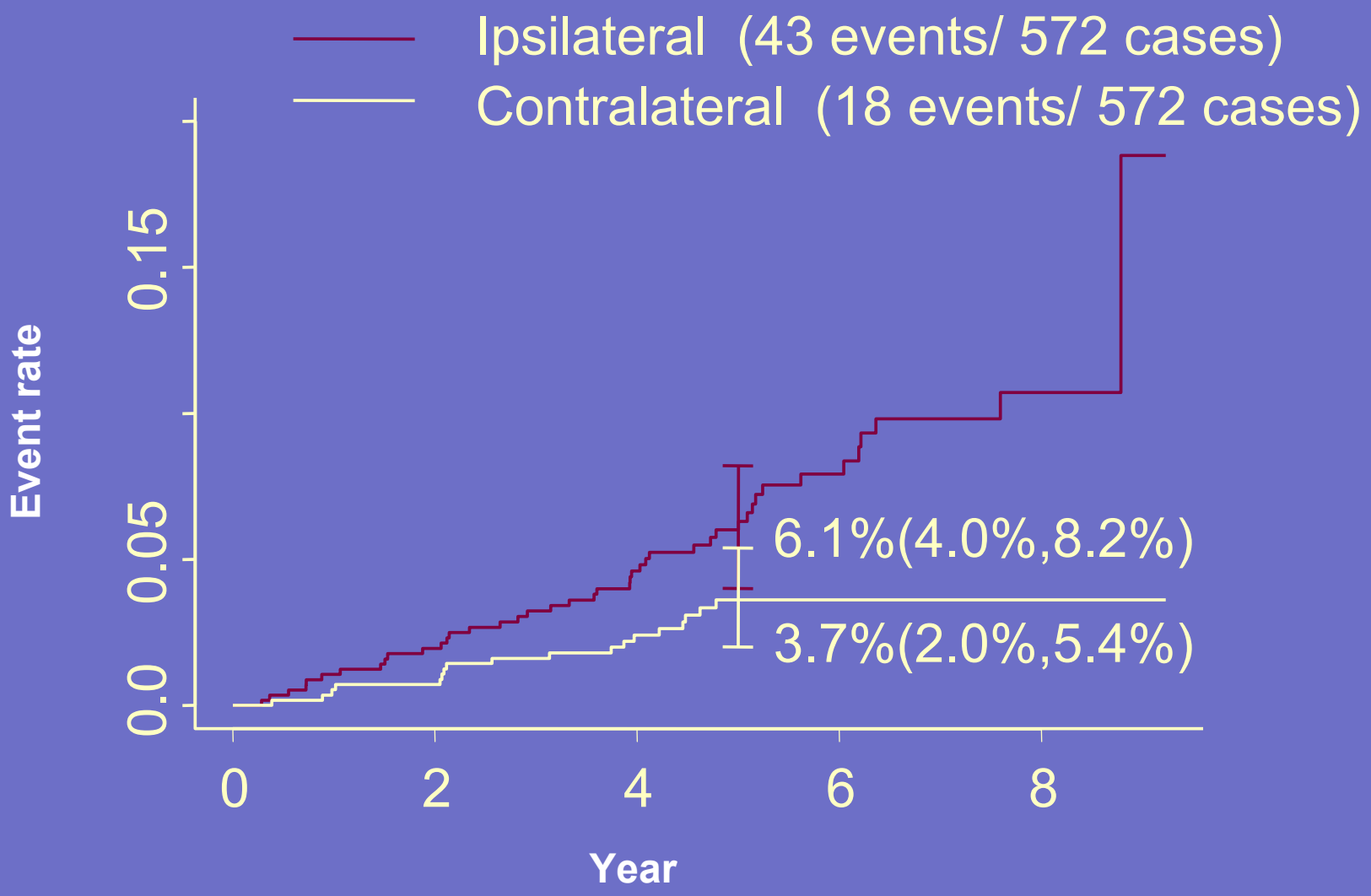
SUMMARY OF RISK REDUCTION WITH RADIATION FOR DCIS

	Local recurrence No RT	Local recurrence RT	Risk reduction	Outcome	P value
Randomized					
Fisher NSABP	32%	16%	50%	At 12 years	<.000005
Julien EORTC	26%	15%	42%	At 10 years	<.0001
Houghton UK	14%	6%	62%	Crude incidence	<.0001
Retrospective					
Silverstein	-	-	55%	Relative risk	.0002
Cutuli	44%	18%	58%	At 10 years	<.0001
SEER	6.2%	2.7%	57%	Invasive at 8 years	<.05

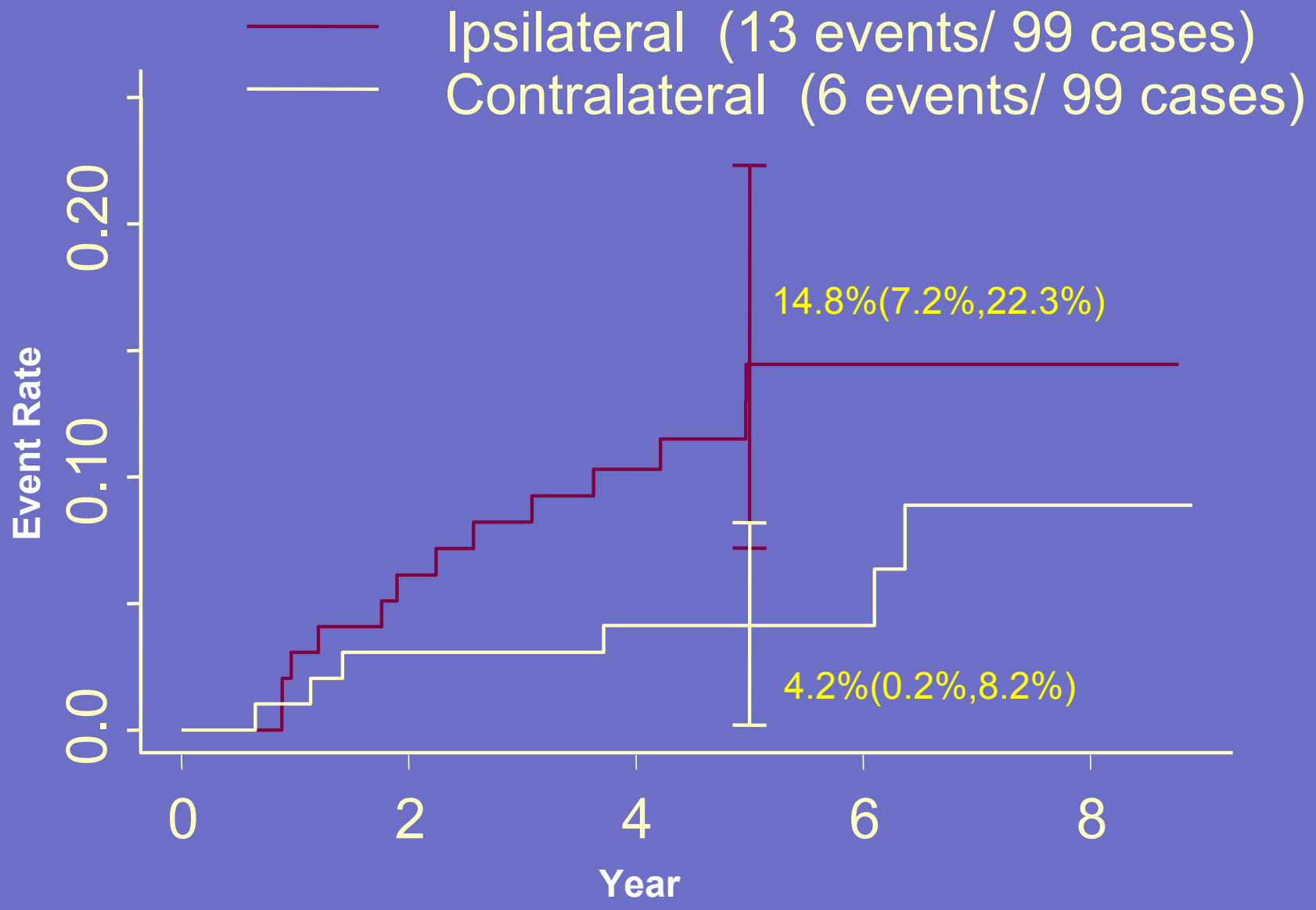
E5194 EXCISION ALONE WITHOUT RADIATION (+/-TAMOXIFEN): ELIGIBILITY

- DCIS, locally excised, ≥3mm in size
- Two arms:
  - Low or intermediate grade ≤2.5 cm
  - High grade ≤1cm (NG 3 + necrosis)
- Minimum margin width ≥3mm
- Specimen sequentially sectioned and completely embedded to determine grade, size, and margins
- Post excision mag mammo negative for microcalcifications

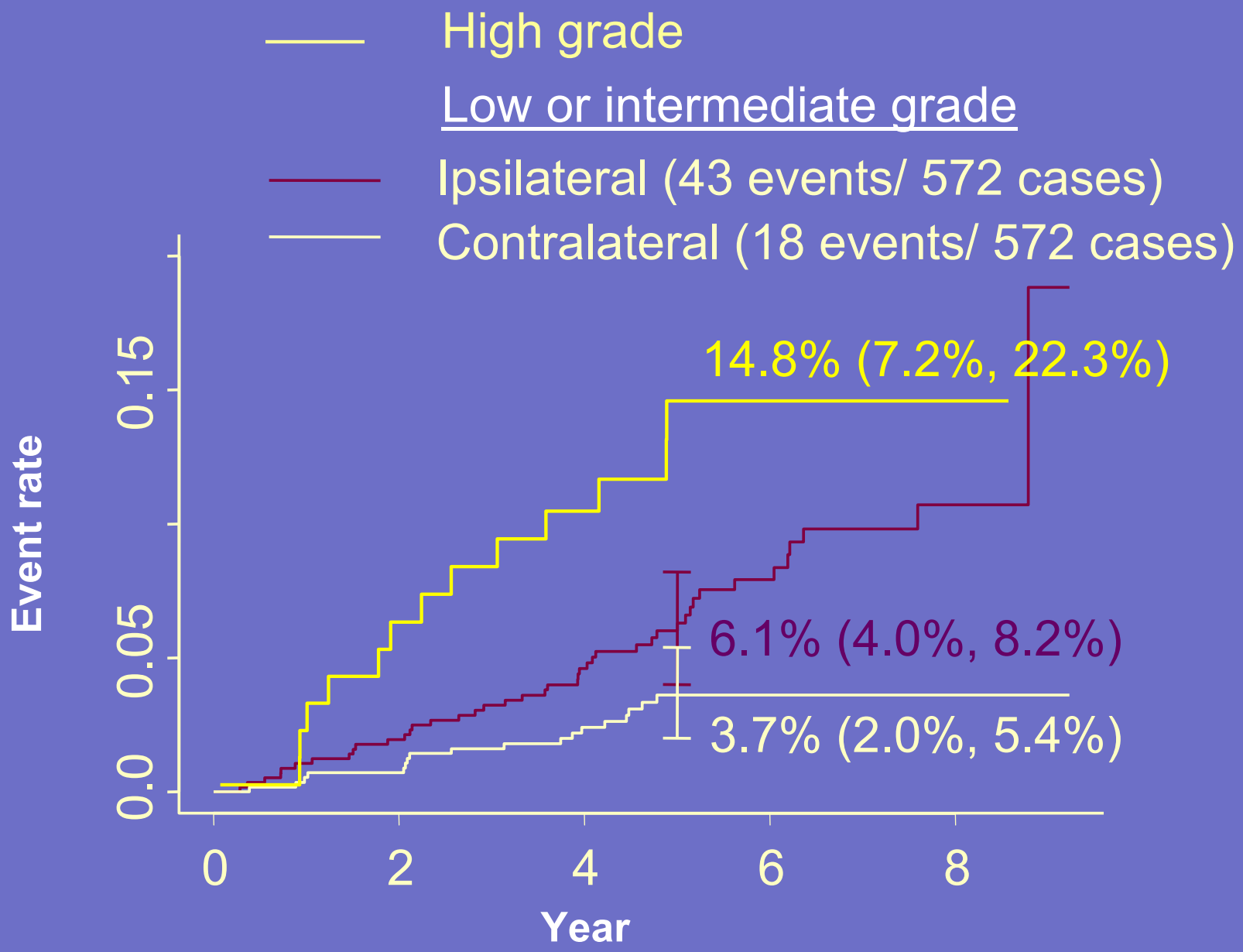
ECOG E5194: EXCISION WITHOUT RADIATION (+/-TAM): LOW OR INTERMEDIATE GRADE



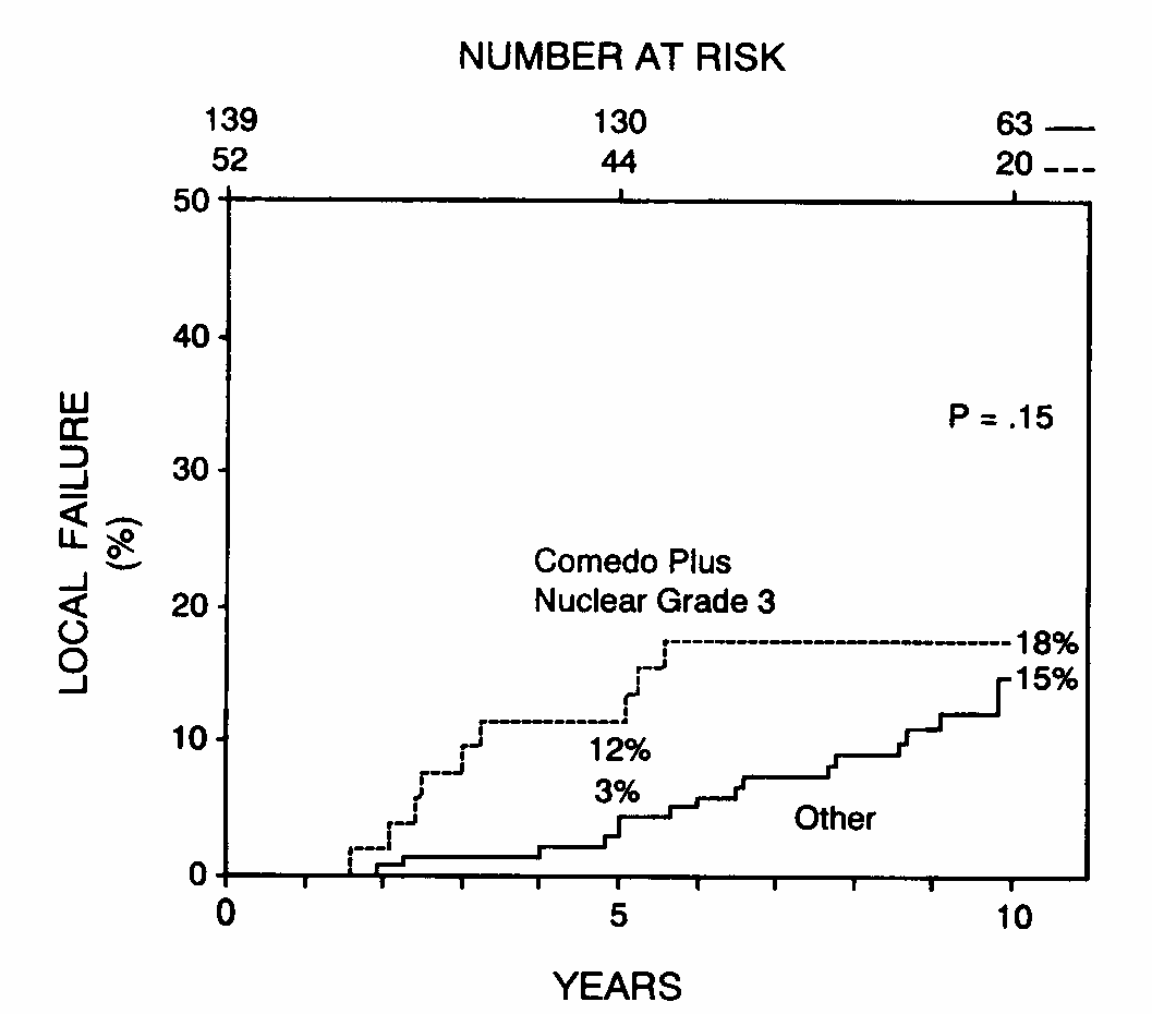
ECOG E5194: EXCISION WITHOUT RADIATION (+/-TAM): HIGH GRADE



ECOG E5194: EXCISION WITHOUT RADIATION (+/-TAM)

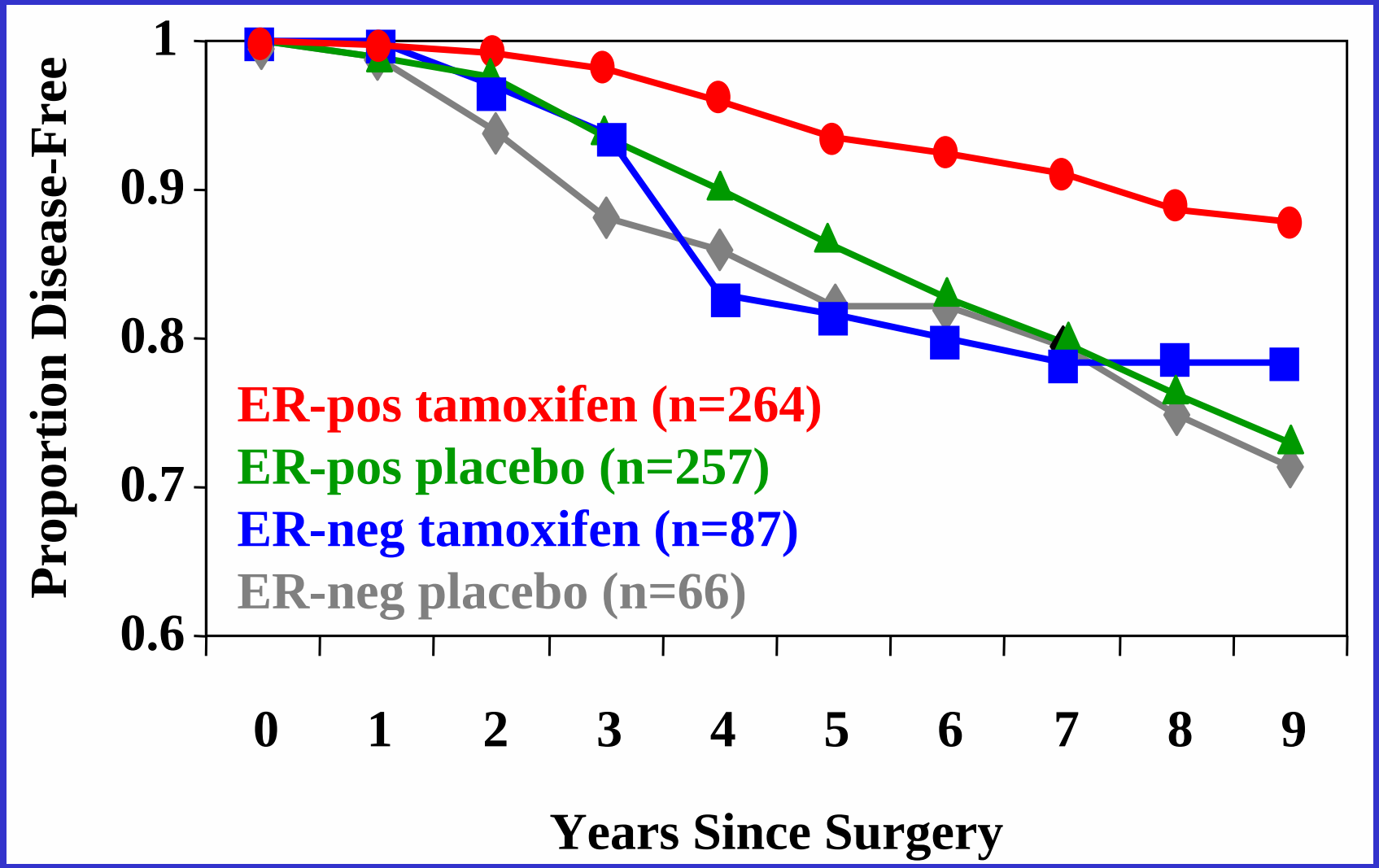


LOCAL FAILURE ACCORDING TO PATHOLOGY AFTER LUMPECTOMY AND RADIATION



Solin, JCO, 1996

TIME TO FIRST BREAST CANCER EVENT IN NSABP B24



Allred, San Antonio, 2002

SUMMARY OF RANDOMIZED TRIALS OF TAMOXIFEN FOR DCIS

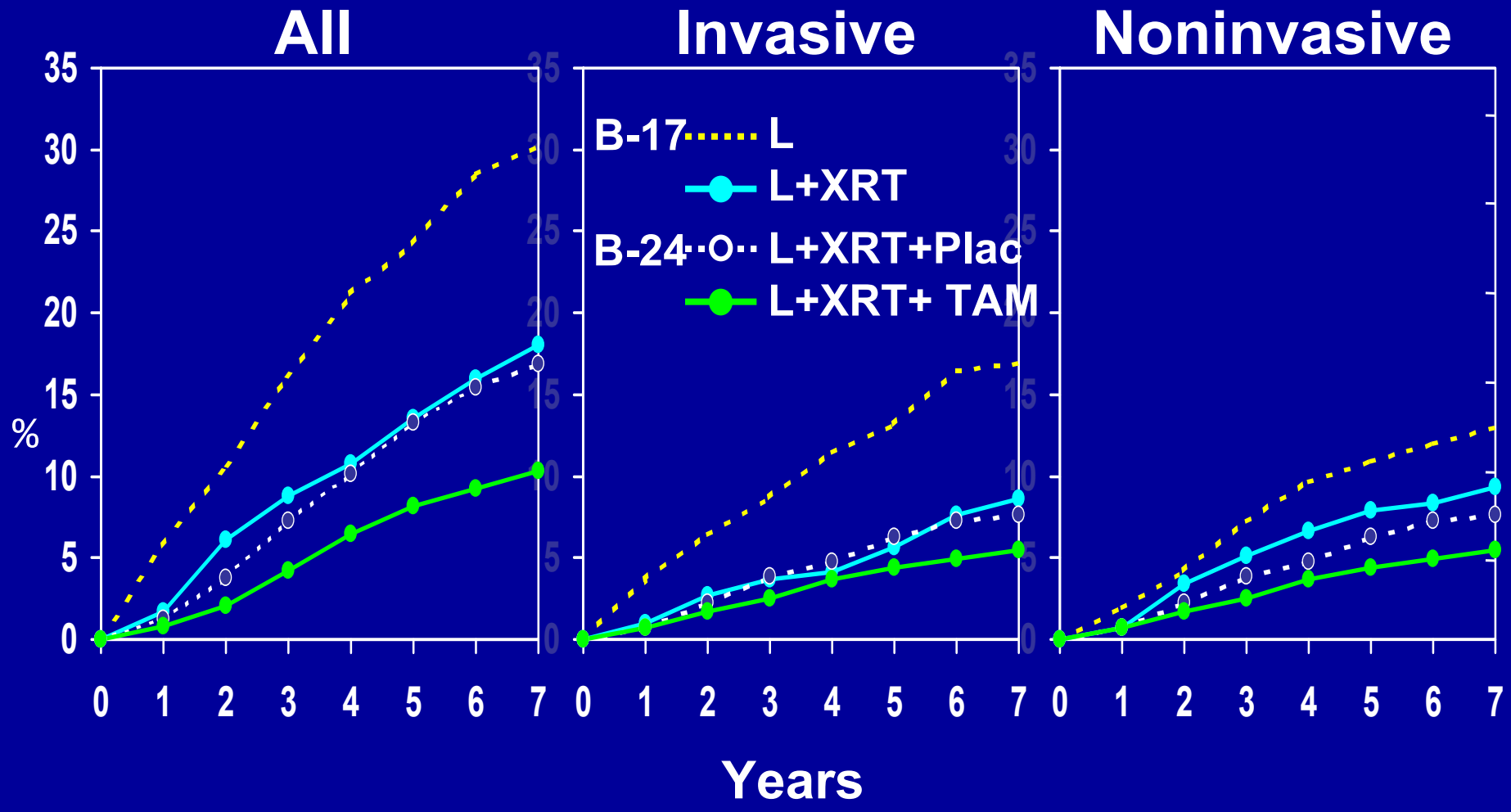
	No. of patients	All breast cancer events: No Tam	All breast cancer events: Tam	Risk Reduction	P Value	Median follow-up (years)
Fisher NSABP B-24	1,798	16.9% At 7 years	10.0%	41%	.0003	6.9
Houghton UK	1,576	18% Crude incidence	14%	22%	.13	4.4

RELATIONSHIP OF ER STATUS TO TAMOXIFEN USE

Feature	Tamoxifen Offered: No. of Patients (%)			
	Pre-ER Staining	P*	Post-ER Staining	P*
Grade		0.04		0.21
Low/intermediate	14/18 (78)		19/27 (70)	
High	9/20 (45)		15/28 (54)	
Treatment		0.03		0.34
Breast conservation	18/24 (75)		28/43 (65)	
Mastectomy	6/15 (40)		6/12 (50)	
Age, y		NS		0.13
50	19/32 (59)		19/35 (54)	
<50	5/7 (71)		15/20 (75)	
ER status				0.01
Positive	NA		30/42 (71)	
Negative	NA		4/13 (31)	
Family history		0.14		0.053
Positive'	6/7 (86)		11/13 (85)	
Negative	18/32 (56)		23/42 (55)	

Hird, Cancer, 2006

Cum. Inc. of Ipsilateral and Contralateral Breast Tumor Events in B-17 and B-24

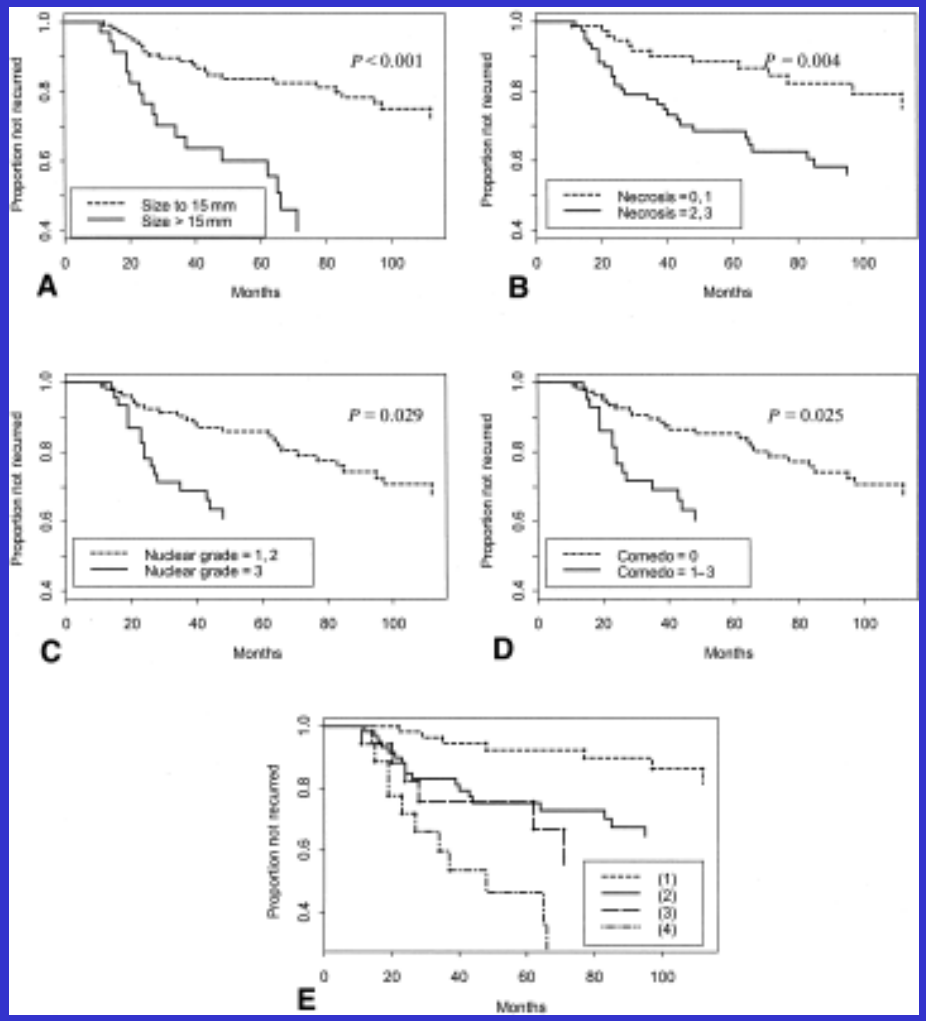


CORRELATION OF ER STATUS AND HER2 STATUS

DCIS grade	Number of cases	ER+/HER2-	ER-/HER2-	ER-/HER2+	ER+/HER2+
Low	18	18	0	0	0
Intermediate	56	56	0	0	0
High	74	26	6	28	14
TOTAL	148	100 (67.6%)	6 (4.1%)	28 (18.9%)	14 (9.5%)

Collins, Mod Path, 2005

PATHOLOGIC AND BIOLOGIC FEATURES CORRELATED WITH LOCAL RECURRENCE AFTER EXCISION ALONE

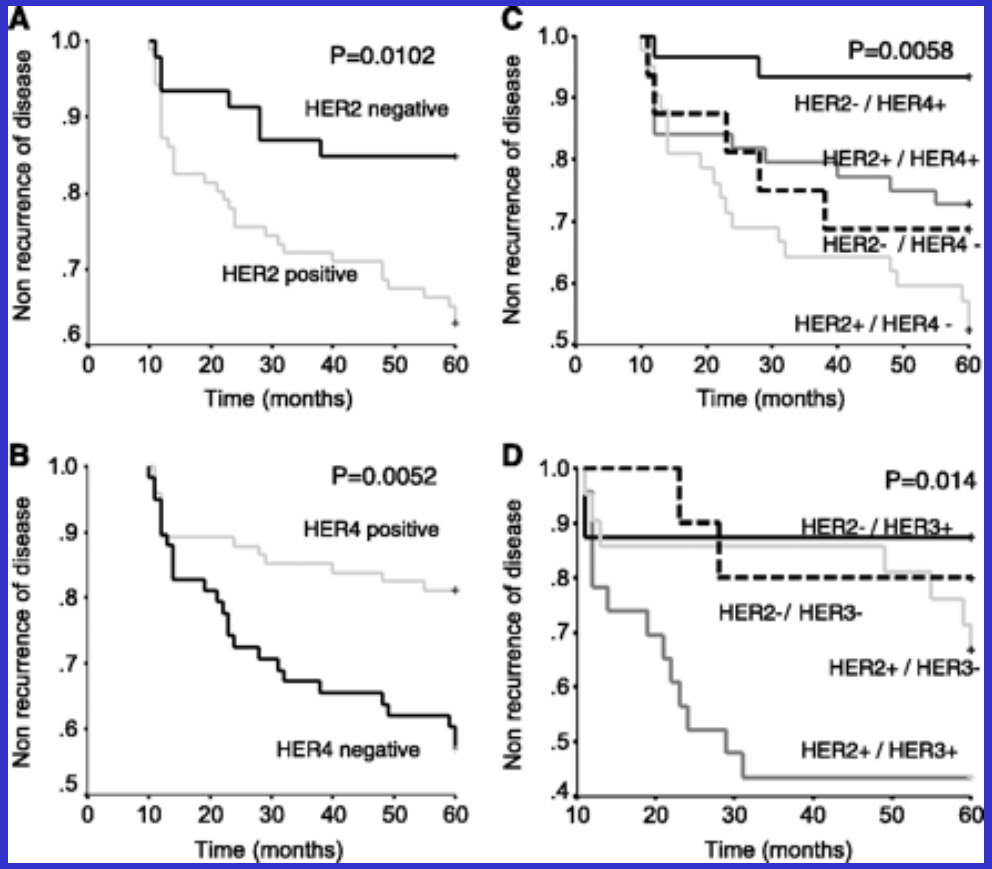


Not correlated with local recurrence:

- ER
- PR
- p53
- HER-2/neu
- Ki-67
- p21
- bcl-2

Cornfield, Cancer, 2004

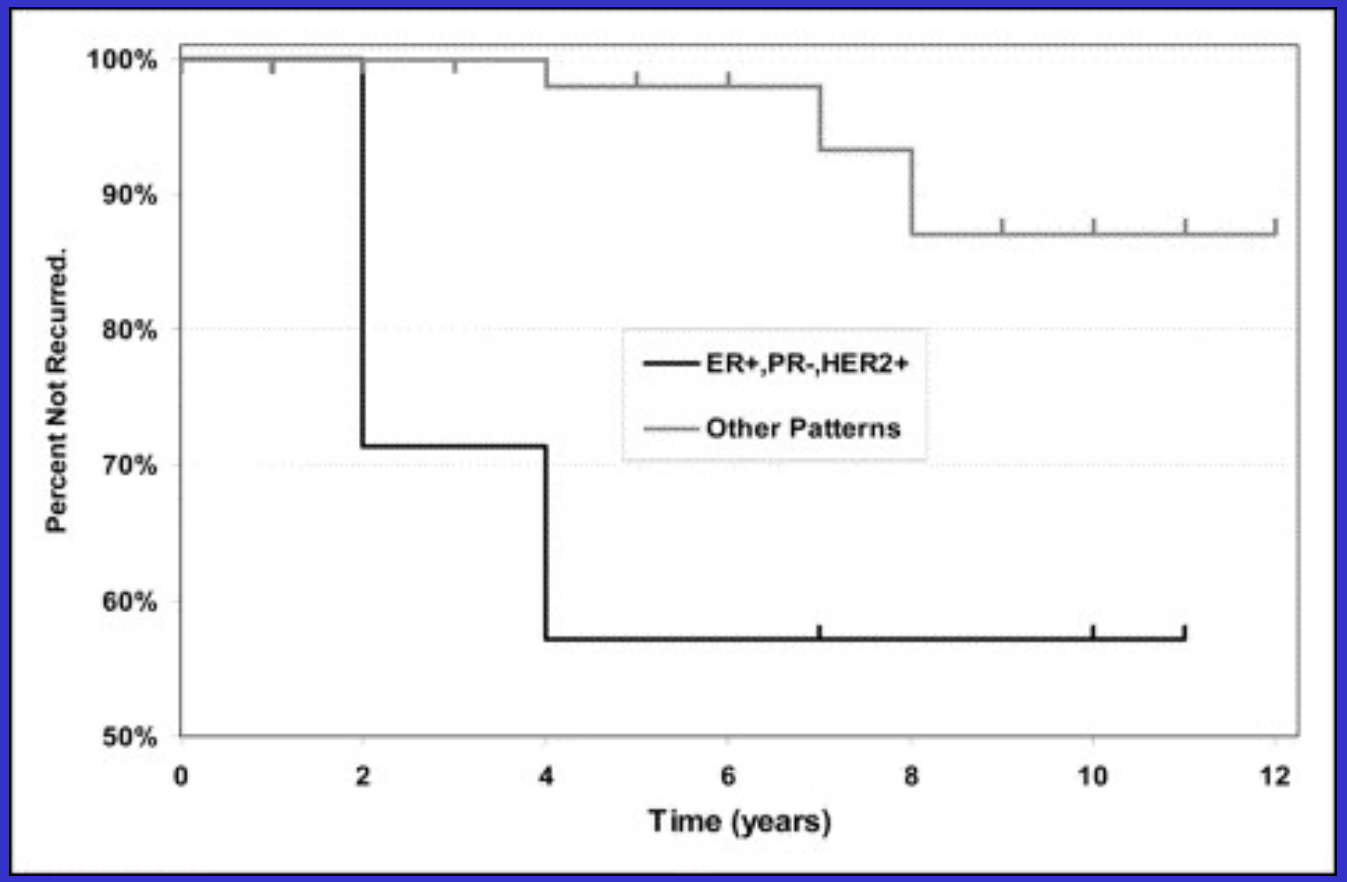
RELATIONSHIP OF BIOLOGIC MARKERS TO RECURRENCE



Barnes, Clin Cancer Res, 2005

Predictor	P value
Higher grade	0.003
Ki67	0.038
HER4 positivity	0.038
Age at diagnosis	0.144
BCS vs Mx	0.17
Involved/close surgical margins	0.449
HER2 positivity	0.99
HER3 positivity	0.322
ER status	0.77

BIOLOGIC MARKERS CORRELATED WITH DISEASE-FREE RECURRENCE AFTER VARYING TREATMENTS



Kepple, Am J Surg, 2006

MOLECULAR MARKERS AND THERAPEUTIC TARGETS

Molecular marker		Marker function or mutation	Expression frequency in DCIS	
			High grade	Low grade
Proliferation	Ki67	Cell proliferation	25%	10%
Apoptosis		Programmed cell death	High	Low
Tumor suppressor genes	p53	G1 cell cycle arrest	40%	0%
	p27	Cell differentiation	50%	50%
Oncogenes	bcl-2	Blocks apoptosis	33%	100%
Cell cycle regulator genes	cyclin D1	Over-expression	32%	8%
Cell surface receptors	ER	Cell signaling	16-50%	40-90%
	PR		10-50%	40-80%
	c-erbB-2		45-70%	10-50%
	EGFR		High	Intermediate
Loss of chromosomal heterozygosity	16p	Loss	Uncommon	Common
	17q/11p	Loss	Common	Uncommon

Modified from: Boland, Microscopy Research and Technique, 2002

CURRENT TRIALS

Lumpectomy alone (tamoxifen optional)
ECOG E5194 (not randomized)

Lumpectomy and tamoxifen ± RT
RTOG

Lumpectomy and RT – tamoxifen vs. anastrazol
NSABP B-35

Conventional whole breast RT vs. Accelerated partial breast irradiation (APBI) – NSABP/RTOG

CURRENT CHALLENGES

1. To develop predictive factors to tailor treatment for individual patients
   - Surgery – none vs. lumpectomy vs. mastectomy
   - Radiation – none vs. partial breast vs. whole breast
   - Hormones – none vs. tamoxifen vs. AI

2. To add biologically based factors to current models based on patient and tumor factors for tailored treatment