

Therapeutic Implications of Ductal Carcinoma in Situ

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Changes in Therapy of DCIS

- Mastectomy
- Lumpectomy with radiation
- Lumpectomy alone

DCIS Before Mammography

- rare before 1970
- large palpable lesions
- high grade “comedo” histology
- many not strictly “non-invasive”
- DCIS: “Single disease resulted in single treatment”

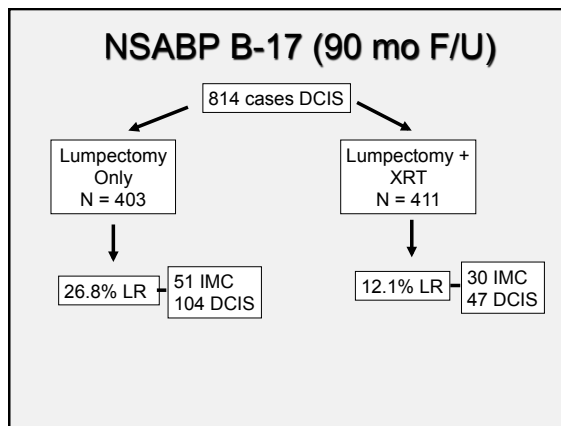
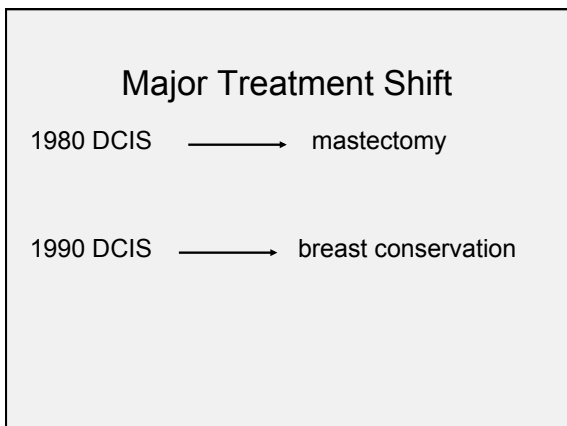
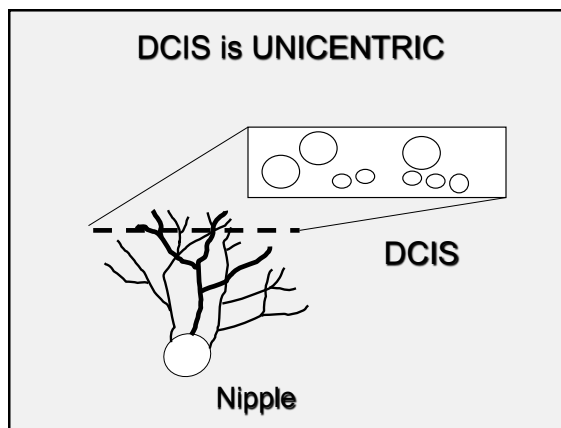
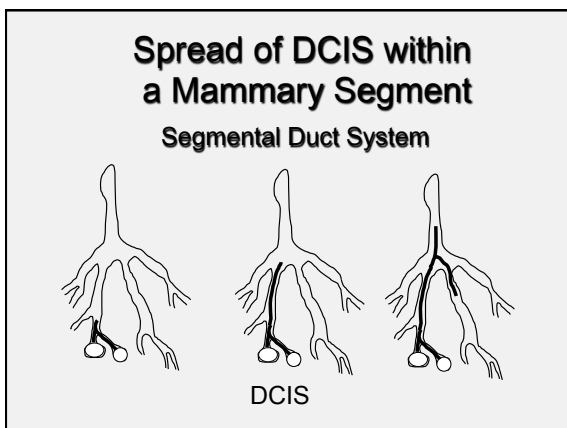
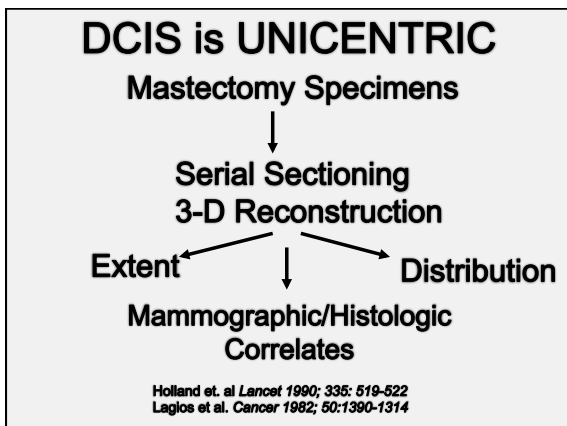
DCIS -Mammography

- 15-40% of breast cancers (45,000 cases in 2010)
- palpability < 20%
- 10% < age 40; average age 55
- low grade and limited extent

DCIS-Mammography

- size range 5-15 mm (vs. 3.5 cm palpable cases)
- occult invasion extremely rare
- treatment protocols based on pre-mammographic DCIS obsolete

Misconception of Multicentricity



Criticisms of NSABP B-17

- No central review for admission to trial
- No careful case definition
- Margin status not meaningfully defined
- Proved effectiveness of XRT, did not define group who could be spared XRT

Diversity of DCIS

Opportunity to identify subsets of patients whose tumors demonstrate features that allow rational therapy stratification

Subset analysis of DCIS

Risk of recurrence and progression related to:

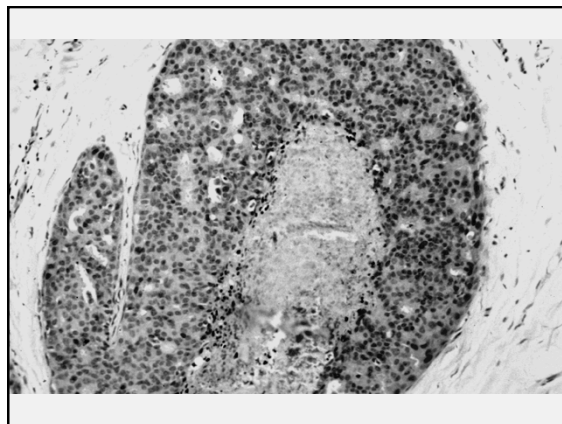
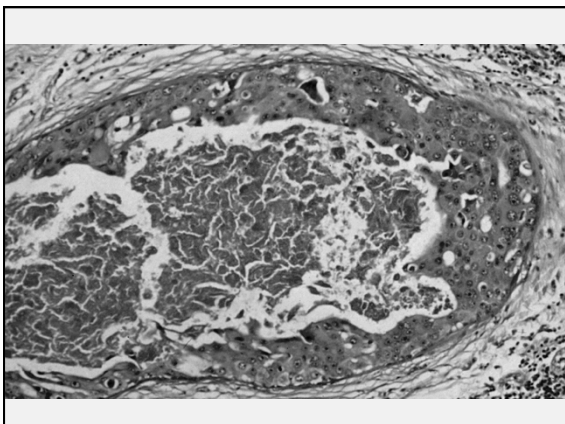
- * histologic type
- * size (extent)
- * grade
- * adequacy of margins

Protocol for Examination of Specimens from Patients (DCIS) of the Breast

* Architectural Patterns (select all that apply) (Note E)

- * Comedo
- * Paget disease (DCIS involving nipple skin)
- * Cribriform
- * Micropapillary
- * Papillary
- * Solid
- * Other (specify: _____)

*optional

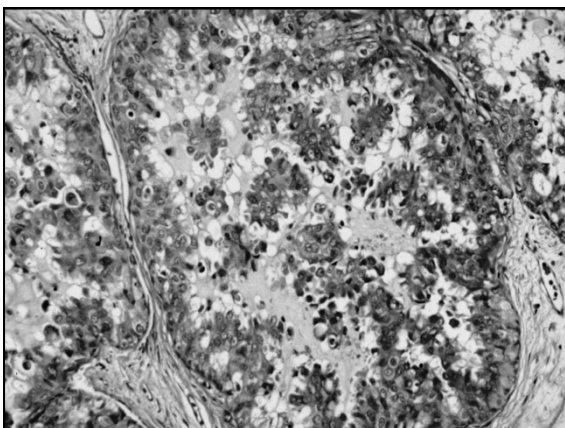
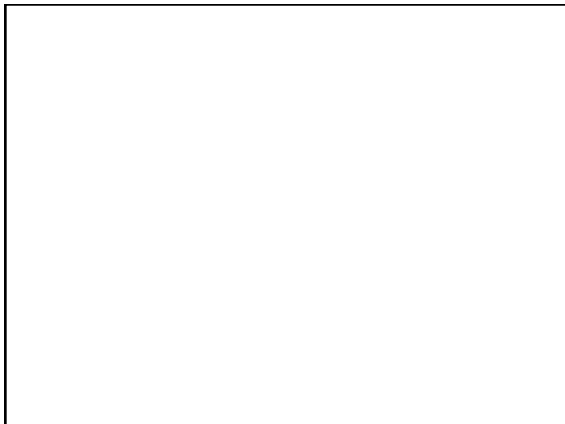


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Micropapillary = Diffuse Disease

Micropapillary	10/14	} # Cases Multiquadrant Disease/Total
Comedo	2/26	
Solid, cribriform	6/49	

Bellamy et al. *Hum Path* 1993; 24:16-23

Micropapillary	289	} Avg # Involved Acini or Ducts/Case
Comedo	45	
Solid, cribriform	20	

Patchefsky et al. *Cancer* 1989; 63:731-741

Pure micropapillary DCIS

- May be extensive
- May have positive margins, after several re-excision attempts
- May require total mastectomy

Natural History of DCIS

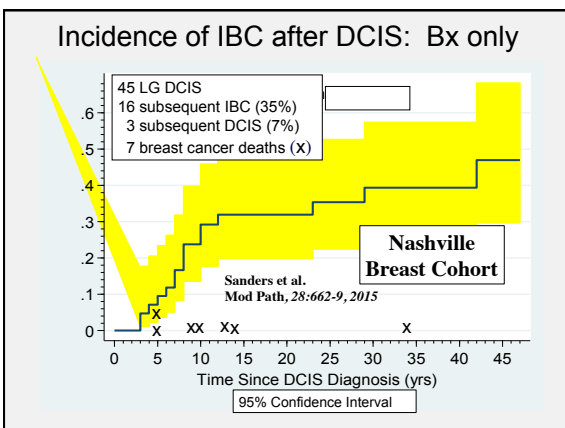
**Long-Term Follow-Up
High Grade DCIS
after biopsy only**

Dean & Geschickter (1938)

**Large, High Grade, Comedo
75% (6/8) ipsilateral IMC
same site in < 4 years**

**Long-Term Follow Up DCIS After Biopsy
Alone in Pre-Mamographic Era**

Betsill <i>JAMA</i> 239:1863, 1978 Rosen <i>Cancer</i> 46:919, 1980	Page. <i>Cancer</i> 49:751, 1982 Page. <i>Cancer</i> 76:1197, 1995
Memorial Hospital, NY >10,000 bx 1940-1950 18 yrs avg F/U 87% Local Recurrence 9.7 yrs avg interval 54% IMC (8) 13% DCIS (2) same side & site	Nashville Breast Cohort, TN >11,000 bx 1950-1968 23 yrs avg F/U 36% Local Recurrence 10 yrs avg interval IMC (all) same side & site



**Natural History of DCIS
Nurses' Health Study**

- 13 of 1877 cases reclassified as DCIS
- 6 of 13 developed invasive carcinoma (all ipsilateral)
- Invasive carcinoma after high grade DCIS occurred within 5 years

Collins et al, Cancer 2005

**Grade of DCIS influences time to
recurrence or progression**

- Low grade DCIS---10+ years
- High grade DCIS---within 5 years

**Lessons from Long-Term Follow
Up Studies of Small DCIS**

- **Recurrence in same breast and same site validates unicentric nature of DCIS (3-D reconstructions)**
- **Suggested lesser examples of DCIS could be locally excised**

Histologic Grade and the Amount of Necrosis Predicts Local Recurrence

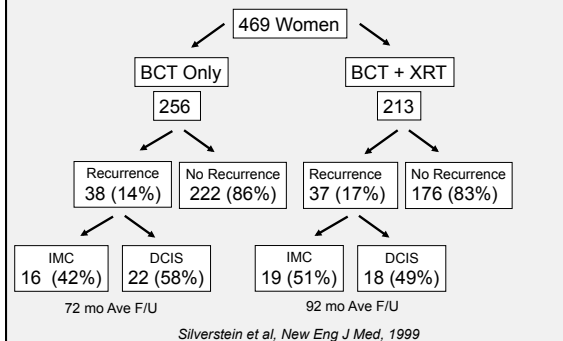
- 79 Women: Mammographically detected DCIS
- Treated by lumpectomy alone
- ≤ 25 mm with negative margins
- Negative post-operative mammogram

Lagios Cancer 63: 618-624, 1989

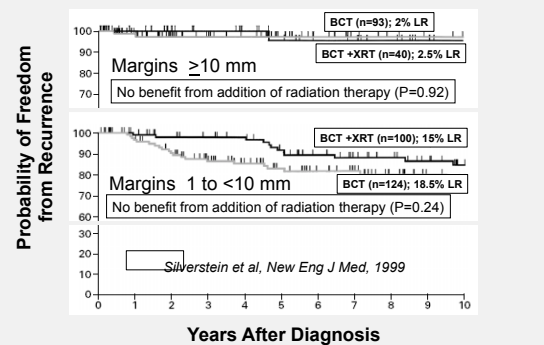
Lagios 1990; Schwartz 1992;
Silverstein 1998, 1999; Chan 2001

- Single center series support local resection of small low grade DCIS (esp if <1.0 cm) without XRT
- No recurrences in 5 years with careful case definition and attention to margin status
- Recurrences occur in vicinity of biopsy site (50% IMC & 50% DCIS)

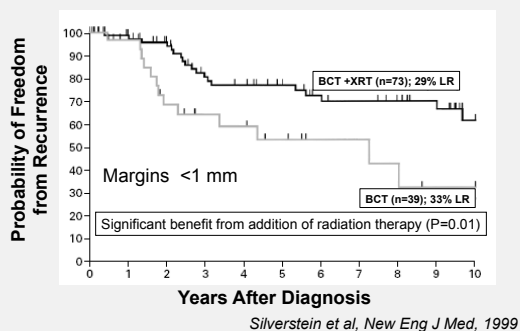
Influence of Margin Width on Local Control of DCIS



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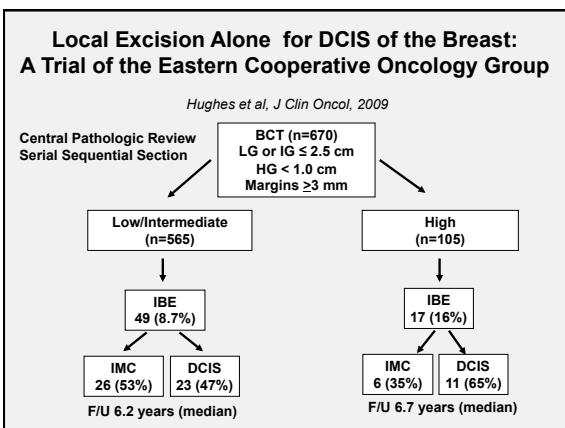
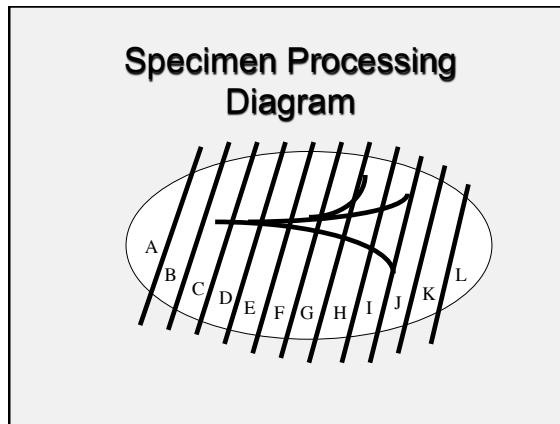


Lagios 1990; Schwartz 1992;
Silverstein 1998, 1999; Chan 2001

- Invasive recurrences occur faster following HG DCIS; in longer follow up, LG recur
- Extensive HG comedo lesions not easily cured and recurrences common even after XRT
- XRT does not compensate for inadequate surgical margins especially if HG

ECOG Trial 5194: Excision only for DCIS

- **Accrual - 600 Cases:**
 LG & IG DCIS ≤ 2.5 CM
 HG < 1.0 CM
- ≥ 3.0 mm margins
- Complete tissue submit
 by sequential sections
- Central review



5 Year Ipsilateral Breast Event Rates

	Low/Intermediate Grade		High Grade	
	# women	rate	# women	rate
Margin size				
< 10 mm	284	5.6%	48	14.8%
≥ 10 mm	274	6.7%	55	15.9%
Lesion size				
< 10 mm	426	5.5%	90	12.7%
10 mm	132	8.1%	13	32.9%

Hughes et al, J Clin Oncol, 2009

ECOG Conclusions

- Combination of lesion size, grade and surgical margin width defines subset of patients at low risk for local failure without XRT
- Rigorously evaluated and selected patients with LG to IG DCIS with margins ≥ 3.0 MM have acceptably low rate of IBE without radiation
- Patients with HG DCIS have much higher rate suggesting XTR may still be necessary

2 Prospective Randomized Trials Breast-Conserving Therapy for DCIS

Lumpectomy only vs. Lumpectomy + XRT

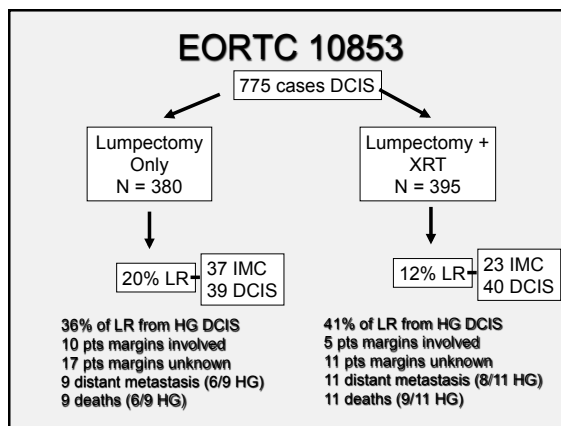
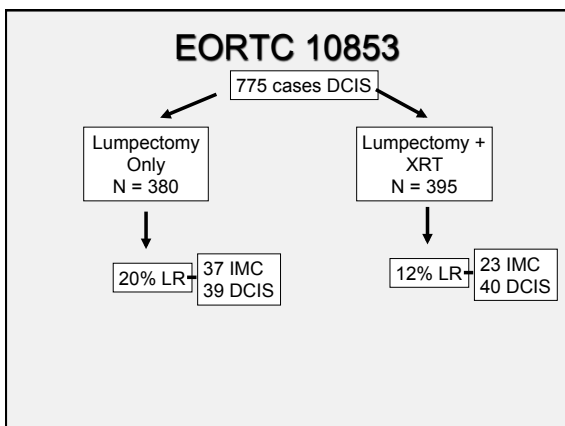
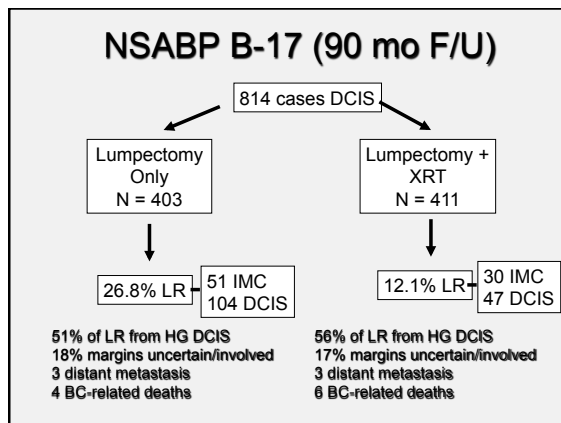
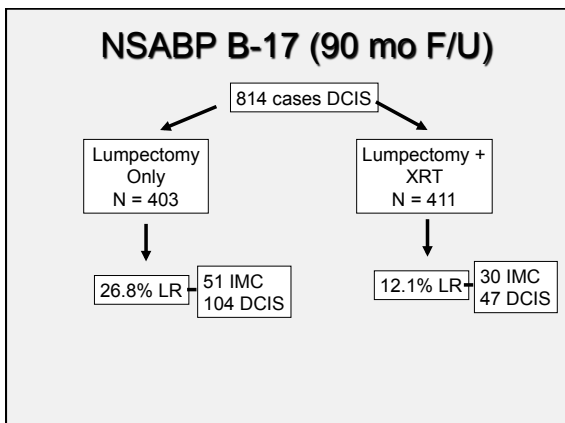
NSABP B-17 Trial

Fisher et al. J Clin Oncol 16:441-452, 1998

EORTC Trial 10853

Bijker et al. J Clin Oncol 19:2263-2271, 2001

Design: Evaluate efficacy of XRT only



10853/B-17 Summary #1

- Ipsilateral failure rates (20% EORTC and 26.8% B-17) same as studies documenting the natural history of DCIS (30-50%) = ? residual disease
- Some recurrences accompanied by metastatic disease = ? unsampled invasion in or near the original biopsy
- Real effect of XRT to reduce invasive recurrences

10853/B-17 Summary #2

- short term benefit from XRT but... inability to stratify results by grade or margin status... ?? who did and did not benefit from XRT (and by how much)?
- Neither EORTC nor B-17 showed that XRT had beneficial effect on:
 - *Distant metastasis
 - *Breast cancer-related mortality

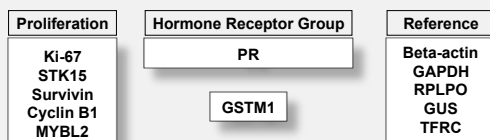
Current Understanding DCIS

- Non-obligate precursors of IMC
- Risk of recurrence and progression related to:
 - * histologic type
 - * size (extent)
 - * grade
 - * adequacy of margins
 - * molecular analysis????

Molecular Analysis of DCIS

- ECOG 5194
- DCIS without XRT
- Multigene assay (OncotypeDX)

DCIS Score™: Gene Selection



- DCIS Score:
- Continuous variable
 - Number between 0 – 100

DCIS Score™ Pre-specified for Validation

- All aspects of the study were pre-specified in a final protocol prior to initiation of sample processing for the E5194 clinical validation study. This included:
 - Pre-analytical and analytical methods
 - Gene coefficients for DCIS Score
 - Scaling and centering coefficients
 - DCIS Score risk groups
 - Low < 39, Intermediate 39 – 54, High ≥ 55

Solin et al. JNCI, May 2013

ECOG E5194 (PARENT STUDY)

Prospective multicenter study 1997-2000 (n = 670)
 Cohort 1: Low/intermediate grade, size ≤ 2.5 cm
 Cohort 2: High grade, size ≤ 1 cm

Study treatment

- Surgical excision
- Minimum 3 mm negative margin width
- No radiation
- Tamoxifen option beginning May 2000

Reported outcomes at 5 and 7 years (Hughes, JCO, 2009)
 - Currently 10-year outcomes

Solin et al. JNCI, May 2013

METHODS FOR DCIS SCORE VALIDATION STUDY

Prospective-retrospective study design

Pre-specified: Study objectives, population, laboratory assays, endpoints, statistical methods

Oncotype DX assay performed (n = 327; 49%)

Standardized methods for 21 gene assay
 Calculated: DCIS Score and Recurrence Score

Study endpoint: Ipsilateral breast events (IBE)

- 1° Endpoint: Any IBE (DCIS or invasive carcinoma)
- 2° Endpoints: Invasive IBE
DCIS IBE

Solin et al. JNCI, May 2013

PATIENT AND TUMOR CHARACTERISTICS

Characteristic*	Number
Patient age	61 years (Median)
Postmenopausal	248 (76%)
Tumor size	7 mm (Median)
Tumor size ≤ 10 mm	280 (89%)
Negative margins ≥ 5 mm	214 (65%)
Tamoxifen use	96 (29%)
ER positive (RT-PCR)	318 (97%)
Study cohort:	
Cohort 1	273 (83%)
Cohort 2	54 (17%)

*Similar to parent trial for all variables except for tumor size

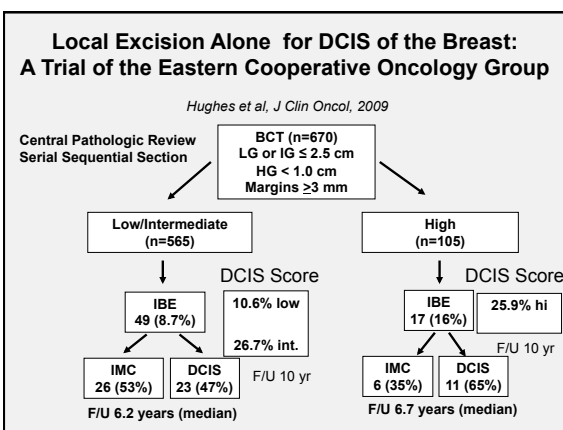
Solin et al. JNCI, May 2013

PRIMARY ANALYSES OF THE RISK FOR AN IPSILATERAL BREAST EVENT (IBE)

	Hazard Ratio* (95% CI)	P value
Primary Analysis		
DCIS Score	2.34 (1.15, 4.59)	0.02
Tamoxifen use	0.56 (0.24, 1.15)	0.12
Conditional Analysis		
Recurrence Score	0.70 (0.15, 2.65)	0.62

*Hazard ratio is for a 30 point difference

Solin et al. JNCI, May 2013



- ### Summary DCIS-1
- DCIS -biologically different processes with different frequencies for occult invasion and axillary metastasis
 - UNICENTRIC in 3-D, usually confined to single segment or quadrant
 - Majority of recurrences local
 - Can evolve to invasion without complete excision in ~ 50% of cases
 - LG recurrence less likely to be life threatening.

- ### DCIS Summary-2
- Majority of DCIS limited in extent and not associated with either occult invasion or axillary metastasis.
 - For limited DCIS attempts at adequate local excision appear appropriate.
 - Risk of local recurrence after a breast conserving procedure without irradiation can be estimated on the basis of the histologic subtype of DCIS, the extent of disease and the adequacy of the resection margins

Thank you!