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
DCIS is UNICENTRIC
Mastectomy Specimens

Serial Sectioning
3-D Reconstruction

Extent
Distribution

Mammographic/Histologic Correlates

Holland et al. Lancet 1990; 335: 618-622

Spread of DCIS within a Mammary Segment
Segmental Duct System

Major Treatment Shift
1980 DCIS  Mastectomy
1990 DCIS  Breast conservation

NSABP B-17 (90 mo F/U)

814 cases DCIS
Lumpectomy Only
N = 403
26.8% LR
51 IMC
104 DCIS

Lumpectomy + XRT
N = 411
12.1% LR
30 IMC
47 DCIS
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
Protocol for Examination of Specimens from Patients (DCIS) of the Breast

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  * ___ Micropapillary
  * ___ Papillary
  * ___ Solid
  * ___ Other (specify: ______ )

*optional

Pure micropapillary DCIS

• May be extensive

• May have positive margins, after several re-excision attempts

• May require total mastectomy

Natural History of DCIS

### Micropapillary = Diffuse Disease

<table>
<thead>
<tr>
<th></th>
<th># Cases</th>
<th>Multi-Quadrant Disease/Total</th>
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</thead>
<tbody>
<tr>
<td>Micropapillary</td>
<td>10/14</td>
<td></td>
</tr>
<tr>
<td>Comedo</td>
<td>2/26</td>
<td></td>
</tr>
<tr>
<td>Solid, cribriform</td>
<td>6/49</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Avg # Involved</th>
<th>Acini or Ducts/Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micropapillary</td>
<td>289</td>
<td></td>
</tr>
<tr>
<td>Comedo</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Solid, cribriform</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

Patchesky et al. *Cancer* 1998; 63:731-741
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

**Incidence of IBC after DCIS: Bx only**

- 45 LG DCIS
- 16 subsequent IBC (35%)
- 3 subsequent DCIS (7%)
- 7 breast cancer deaths (x)

*Nashville Breast Cohort*

**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

Influence of Margin Width on Local Control of DCIS

<table>
<thead>
<tr>
<th>Margin Width</th>
<th>BCT Only</th>
<th>BCT + XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>38 (14%)</td>
<td>213</td>
</tr>
<tr>
<td>No Recurrence</td>
<td>222 (86%)</td>
<td>169</td>
</tr>
</tbody>
</table>

IMC 16  (42%)
DCIS 22 (58%)

72 mo Ave F/U

Silverstein et al, New Eng J Med, 1999

Influence of Margin Width on Local Control of DCIS

- 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)

Silverstein et al, New Eng J Med, 1999

Probability of Freedom from Recurrence

- No benefit from addition of radiation therapy (P=0.92)
- No benefit from addition of radiation therapy (P=0.24)

Silverstein et al, New Eng J Med, 1999

- Significant benefit from addition of radiation therapy (P=0.01)

Silverstein et al, New Eng J Med, 1999

- 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

Silverstein et al, New Eng J Med, 1999
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

Local Excision Alone for DCIS of the Breast: A Trial of the Eastern Cooperative Oncology Group (Hughes et al, J Clin Oncol, 2009)

5 Year Ipsilateral Breast Event Rates

<table>
<thead>
<tr>
<th>Margin size</th>
<th>Low/Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mm</td>
<td>284 5.6%</td>
<td>48 14.8%</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>274 6.7%</td>
<td>55 15.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion size</th>
<th>Low/Intermediate Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mm</td>
<td>426 5.5%</td>
<td>90 12.7%</td>
</tr>
<tr>
<td>10 mm</td>
<td>132 8.1%</td>
<td>13 32.9%</td>
</tr>
</tbody>
</table>

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 XRT may still be necessary

2 Prospective Randomized Trials Breast-Conserving Therapy for DCIS

NSABP B-17 Trial

EORTC Trial 10853
Design: Evaluate efficacy of XRT only
NSABP B-17 (90 mo F/U)

- 814 cases DCIS
- Lumpectomy Only
  - N = 403
  - 26.8% LR
  - 51 IMC
  - 104 DCIS
- Lumpectomy + XRT
  - N = 411
  - 12.1% LR
  - 30 IMC
  - 47 DCIS

EORTC 10853

- 775 cases DCIS
- Lumpectomy Only
  - N = 380
  - 20% LR
  - 37 IMC
  - 39 DCIS
- Lumpectomy + XRT
  - N = 395
  - 12% LR
  - 23 IMC
  - 40 DCIS

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 of 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

<table>
<thead>
<tr>
<th>Proliferation</th>
<th>Hormone Receptor Group</th>
<th>Reference</th>
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<tbody>
<tr>
<td>KI-67</td>
<td>PR</td>
<td>Beta-actin</td>
</tr>
<tr>
<td>Survivin</td>
<td></td>
<td>GAPDH</td>
</tr>
<tr>
<td>Cyclin B1</td>
<td></td>
<td>RPLPO</td>
</tr>
<tr>
<td>MYBL2</td>
<td></td>
<td>GUS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TFRC</td>
</tr>
</tbody>
</table>

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

DCIS Score™ Pre-specified for Validation

- 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

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

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)

1st Endpoint: Any IBE (DCIS or invasive carcinoma)

2nd Endpoint: Invasive IBE

DCIS IBE

Solin et al., JNCI, May 2013
PATIENT AND TUMOR CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
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<tbody>
<tr>
<td>Patient age</td>
<td>61 years (Median)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>248 (76%)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>7 mm (Median)</td>
</tr>
<tr>
<td>Tumor size &lt; 10 mm</td>
<td>260 (80%)</td>
</tr>
<tr>
<td>Negative margins &gt; 3 mm</td>
<td>214 (65%)</td>
</tr>
<tr>
<td>Tamoxifen use</td>
<td>96 (29%)</td>
</tr>
<tr>
<td>ER positive (RT-PCR)</td>
<td>318 (97%)</td>
</tr>
</tbody>
</table>

Study cohorts:
- 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)

<table>
<thead>
<tr>
<th>Hazard Ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Analysis</td>
<td></td>
</tr>
<tr>
<td>DCIS Score</td>
<td>2.34 (1.15, 4.59)</td>
</tr>
<tr>
<td>Tamoxifen use</td>
<td>0.56 (0.24, 1.15)</td>
</tr>
<tr>
<td>Conditional Analysis</td>
<td></td>
</tr>
<tr>
<td>Recurrence Score</td>
<td>0.79 (0.15, 3.80)</td>
</tr>
</tbody>
</table>

*Hazard ratio is for a 50 point difference

Solin et al. JNCI, May 2013

LOCAL EXCISION ALONE FOR DCIS OF THE BREAST: A TRIAL OF THE EASTERN COOPERATIVE ONCOLOGY GROUP

Hughes et al., J Clin Oncol, 2009

BCT (n=670)
- LG or IG ≤ 2.5 cm
- HG < 1.0 cm
- Margins > 3 mm

- IMC 26 (35%)
- DCIS 23 (34%) F/U 6.2 years (median)

- IBE 49 (8.7%)
- DCIS Score 10.6% low

- IMC 6 (35%)
- F/U 6.7 years (median)

- IBE 17 (16%)
- DCIS Score 25.9% hi

Central Pathologic Review Serial Sequential Section

Low/Intermediate (n=565)

High (n=105)

F/U 10 yr

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

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.

Thank you!