The Continuing Dilemma of Ductal Carcinoma in Situ

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Boston, MA
Disclosures

• None
Precursor lesion

Detected incidentally:
- Treat similar to the corresponding cancer
  - Active Surveillance

Detected by screening:
- Treat, but less aggressively than corresponding cancer
  - Ignore
DCIS

- Heterogeneous group of lesions
- Natural history poorly defined (especially for small, mammographically-detected lesions)
- Optimal treatment controversial
Heterogeneity of DCIS

- Presentation
- Distribution in breast
- Pathologic features
- Genetic/molecular alterations
- Clinical behavior
Epidemiology

• Most cases today detected because of microcalcifications on screening mammogram
• Accounts for ~20% of breast “cancers”
• ~61,000 new cases in 2016
Increased Detection of DCIS Due To Mammographic Screening

Age-adjusted incidence of DCIS (red) and invasive breast cancer (blue) relative to number of diagnoses in 1977 (SEER)

Punglia, 2013
How much of this represents “over-diagnosis”?
Reservoir of DCIS in General Population

- Autopsy studies
  - DCIS found in up to 14.7% of women dying of other causes (median 8.9%)

- Reduction mammoplasty studies
  - DCIS found in up to 3% of patients
Reservoir of DCIS in General Population

- These studies undoubtedly underestimate prevalence due to limited sampling
- True prevalence unknown
# Natural History of DCIS

<table>
<thead>
<tr>
<th></th>
<th># Benign Bxs Examined</th>
<th># with DCIS (# with follow-up)</th>
<th>Age (yrs)</th>
<th>Histology</th>
<th>Follow-up</th>
<th>Subsequent Invasive ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eusebi, 1994</td>
<td>9,520</td>
<td>55 (55)</td>
<td>27-44</td>
<td>Comedo and non-comedo</td>
<td>1-14 yrs</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Sanders, 2015</td>
<td>11,760</td>
<td>45 (45)</td>
<td>33-74</td>
<td>Low grade</td>
<td>3-42 yrs</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>Rosen, 1980</td>
<td>&gt;8,000</td>
<td>30 (15)</td>
<td>Not stated</td>
<td>Non-comedo</td>
<td>1-24 yrs</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Collins, 2005</td>
<td>1,877</td>
<td>13 (13)</td>
<td>41-63</td>
<td>Low, int. and high grades</td>
<td>4-18 yrs</td>
<td>OR 13.5</td>
</tr>
</tbody>
</table>

**Caveats:**
- Biopsies initially interpreted as benign
- Extent of lesion and adequacy of excision unknown
Natural History of DCIS

• Not all DCIS will progress to invasive cancer
• Non-obligate precursor
Classification of DCIS

In current practice, most often classified as low, intermediate or high grade (based on nuclear grade)
Classification of DCIS

• Low grade and high grade DCIS are genetically distinct disorders
  • Low:
    • 16q loss
  • High:
    • 11q, 14q, 8p, 13q losses
    • 17q, 8q, 5p gains
• Low grade DCIS more closely related genetically to LCIS than to high grade DCIS
Classification of DCIS

- Molecular subtypes identified in invasive cancers also observed in DCIS
## Molecular Subtypes in DCIS

**Using Surrogate IHC Markers**

<table>
<thead>
<tr>
<th>_subtype</th>
<th>NHS (N=263)</th>
<th>UNC (N=229)</th>
<th>CRN (N=371)</th>
<th>Manchester (N=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>64.4%</td>
<td>65.1%</td>
<td>74.7%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>13.6%</td>
<td>10.0%</td>
<td>10.8%</td>
<td>28.0%</td>
</tr>
<tr>
<td>HER2-E</td>
<td>14.0%</td>
<td>16.6%</td>
<td>10.0%</td>
<td>16.2%</td>
</tr>
<tr>
<td>Basal-like/TN</td>
<td>8.0%</td>
<td>8.3%</td>
<td>4.6%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

*Not all studies used same markers*
Treatment of DCIS

Goals

• Local eradication to prevent the development of invasive breast cancer (prophylactic)
• Ensure sufficient treatment in women at high risk for recurrence/progression
• Avoid over-treatment in women at very low risk for recurrence/progression
Treatment Options

• Mastectomy
• Breast conserving surgery + radiation therapy
• Breast conserving surgery alone
• Endocrine therapy

None offers a survival advantage over the others
Treatment Options

• Confusing to patients
• Treatments offered similar to those for invasive breast cancer, but really not “cancer”
• Clinicians views of DCIS vary
• Patients overestimate their risk
  – >25% think they have at least a moderate chance of DCIS spreading to other parts of the body (Partridge, 2008)
Mastectomy

- Cure rates approach 100%
- Appropriate for patients with extensive disease or those who want to reduce their risk of recurrence to as close to zero as possible
- Does not offer a survival advantage over more conservative treatment
- Over-treatment for most patients encountered in current clinical practice
Breast Conserving Treatment

• Addition of RT to breast conserving surgery reduces risk of local recurrence by ~50% (4 randomized clinical trials)
Breast Conserving Treatment

- Addition of RT to breast conserving surgery reduces risk of local recurrence by ~50% (4 randomized clinical trials)
- ~50% of recurrences are invasive
Breast Conserving Treatment
Role of Endocrine Therapy

• Addition of tamoxifen to breast conserving surgery and RT reduces risk of local recurrence by ~30% (NSABP B-24)
  – Tam benefit limited to women with ER+ DCIS (Allred, 2012)

• Anastrazole
  – Superior to tamoxifen, primarily in women <60 years of age (NSABP B-35)
  – No difference from tamoxifen (IBIS-II DCIS)
Breast Conserving Treatment

- But, the addition of RT and even endocrine therapy is likely over-treatment for some patients
The Continuing DCIS Dilemma

• Only some patients with DCIS will progress to invasive breast cancer

• After decades of research, we still cannot reproducibly identify which patients are unlikely to progress and, in turn, which patients can be safely managed with excision alone or perhaps even no treatment beyond the diagnostic biopsy
### Risk Factors for Local Recurrence

**Clinical factors**
- Young age

**Tumor factors**
- Larger size/extent
- High nuclear grade
- Comedo necrosis
- Volume of DCIS near margin
- Molecular subtype
- Positive/close margins

**Treatment factors**
- Treatment period
- Extent of excision
- Use of RT
- Use of Endocrine therapy
• Combinations of factors likely of greater value than individual factors
Combining Prognostic Factors to Assess Risk

- Informally
- USC/Van Nuys Prognostic Index
- MSKCC Nomogram
- DCIS risk score
The USC/Van Nuys Prognostic Index
Silverstein, 2003

<table>
<thead>
<tr>
<th>SCORE</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (mm)</td>
<td>≤15</td>
<td>16-40</td>
<td>≥41</td>
</tr>
<tr>
<td>Margin (mm)</td>
<td>≥10</td>
<td>1-9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Grade</td>
<td>Non-high, no necrosis</td>
<td>Non-high, necrosis</td>
<td>High</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;60</td>
<td>40-60</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>
The USC/Van Nuys Prognostic Index
Silverstein, 2003

LR rates:
1% at 5yrs
3% at 10yrs
The USC/Van Nuys Prognostic Index

Limitations

- Retrospective study; arbitrary cut points
- Total sequential embedding required to adequately assess size and margins
- Interactions and relative importance of factors unknown
- In practice, can only be applied in minority of cases (largely because of limitations in assessing size)
Nomogram for Predicting the Risk of Local Recurrence After Breast-Conserving Surgery for Ductal Carcinoma In Situ

Udo Rudloff, Lindsay M. Jacks, Jessica I. Goldberg, Christine A. Wynveen, Edi Brogi, Sujata Patil, and Kimberly J. Van Zee

JCO, 2010
Observed vs. Nomogram Predicted 10-Year Probability of Local Recurrence in Community-Based Population

- DCIS pts treated with BCT 1990-2001
- 190 cases, 305 controls

DCIS Risk Score
Punglia, BCRT (in press)

• Data from 2762 women with DCIS in NCCN database treated with breast conserving surgery with negative margins used to develop risk score
  – ER status
  – Comedo necrosis
  – Patient age

• Validated in 301 women with DCIS in KPNC database

• C-statistic 0.67 in validation set
Can patients with “low risk” DCIS be safely treated with surgical excision alone?

Prospective Studies
Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS)

Julia S. Wong · Yu-Hui Chen · Michele A. Gadd · Rebecca Gelman · Susan C. Lester · Stuart J. Schnitt · Dennis C. Sgroi · Barbara J. Silver · Barbara L. Smith · Susan L. Trojan · Jay R. Harris

- 158 pts (1995-2002); median F/U 11 yrs
- DCIS ≤2.5 cm, predominant nuclear grade low or intermediate (median size: 8mm)
- Margin width ≥1cm or re-excision without residual DCIS (negative re-excisions in 78%)
- Accrual closed early due to high LR rate
- 10-year estimated cumulative LR rate 15.6%
• Observational study with two arms:
  – Low or intermediate grade, ≤2.5 cm (n=565)
  – High grade (NG3 + necrosis), ≤1cm (n=105)
• Minimum margin width 3mm
• Specimen totally, sequentially embedded
• Post-excision magnification mammogram negative for microcalcifications
• Tamoxifen allowed (~30% in each group)
<table>
<thead>
<tr>
<th>Cohort</th>
<th>5 yrs</th>
<th>10 yrs</th>
<th>12 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Intermediate grade</td>
<td>6%</td>
<td>12.5%</td>
<td>14.4%</td>
</tr>
<tr>
<td>High grade</td>
<td>15%</td>
<td>24.6%</td>
<td>24.6%</td>
</tr>
</tbody>
</table>

ECOG E5194
Local Recurrence at 5, 10 and 12 years
## ECOG E5194

Local Recurrence at 5, 10 and 12 years

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<tr>
<td>High grade</td>
<td>15%</td>
<td>24.6%</td>
<td>24.6%</td>
</tr>
</tbody>
</table>

**Median size: 6mm**

**Negative margin width >5mm: 70%**
• Same entry criteria as low/intermediate grade arm of ECOG trial
• Randomized to conservative surgery alone or with radiation
• Whole breast irradiation without boost
• Tamoxifen in 62%
RTOG 9804: A Prospective Randomized Trial for Good-Risk Ductal Carcinoma In Situ Comparing Radiotherapy With Observation


A

Failed Total
Observation 19 298
RT 2 287

Gray’s test P < .001
HR = 0.11 (0.03 to 0.47)

Local Failure (%) 30%
25%
20%
15%
10%
5%
0%

Time Since Random Allocation (years)
No. at risk
Observation 298 287 272 270 257 240 225 218 182 126
RT 287 278 265 250 235 211 174 128

6.7%
3.5%
0.4%
0.9%
RTOG 9804
Two Possible Conclusions

• Even among patients with “low risk” DCIS, breast irradiation significantly reduces the risk of local recurrence

• Among patients with “low risk” DCIS, the 7-yr rate of local recurrence is low, even without radiation (~1%/year)
# Local Recurrence Rates in Prospective Studies of “Low Risk” DCIS Treated by Excision Alone

<table>
<thead>
<tr>
<th>Study</th>
<th>Local Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard</td>
<td>15.6% (10 yrs)</td>
</tr>
<tr>
<td>ECOG 5194</td>
<td>14.4% (12 yrs)</td>
</tr>
<tr>
<td>RTOG 9804</td>
<td>6.7% (7 yrs)</td>
</tr>
<tr>
<td></td>
<td>(~10% at 10 yrs, est)</td>
</tr>
</tbody>
</table>
Can patients with “low risk” DCIS be safely treated with surgical excision alone?

The Bottom Line

- Prospective studies have been unable to identify a subset of patients with “low risk DCIS” treated with surgical excision alone who have local recurrence rates of <10-15\% after long-term follow-up based on conventional clinical-pathologic criteria.
Can patients with “low risk” DCIS be safely treated with surgical excision alone?

The Bottom Line

- Views of what is an acceptably low local recurrence rate vary
  - RTOG 9804: Local recurrence rate in patients treated with excision alone (~1%/year) similar to that for patients with LCIS
Biomarkers and Risk of Local Recurrence

- ER

  • The only biomarker that should be used in clinical practice (outside the setting of a clinical trial)
  • Used as a predictive factor (not as a prognostic factor for local recurrence)
Oncotype DCIS Score

- **ECOG E5194**
  - Selected population (n=327)
  - BCS alone, 1997-2002
  *Solin, 2013*

- **Ontario DCIS cohort**
  - General population-based cohort (n=571)
  - BCS alone, 1994-2003
  *Rakovitch, 2015*

**Proliferation Group**
- Ki67
- STK15
- Survivin
- CCNB1 (cyclin B1)
- MYBL2

**Hormone Receptor Group**
- PR
- GSTM1

**Reference Group**
- ACTB (β-actin)
- GAPDH
- RPLPO
- GUS
- TFRC
Oncotype DCIS Score
Ipsilateral Breast Events

E5194

Ontario DCIS Cohort

Solin, 2013
Rakovitch, 2015
# Integrating DCIS Score (DS) with Clinico-pathologic Factors

Rakovitch, ASCO 2017

Meta-analysis of data from E51994 and Ontario DCIS Cohort (773 pts)

## 10 yr LR rates (%)

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Age</th>
<th>Low Risk DS</th>
<th>Intermediate Risk DS</th>
<th>High Risk DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 cm</td>
<td>≥50</td>
<td>7.2</td>
<td>11.3</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>10.2</td>
<td>15.8</td>
<td>19.6</td>
</tr>
<tr>
<td>1.1-2.5 cm</td>
<td>≥50</td>
<td>10.1</td>
<td>13.9</td>
<td>19.5</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>14.5</td>
<td>18.9</td>
<td>23.2</td>
</tr>
</tbody>
</table>
Other Management Strategies Currently Under Study

Two Ends of the Spectrum

• Trastuzumab for HER2+ DCIS
  – NSABP B-43 (radiation vs radiation plus concurrent trastuzumab [2 doses] after lumpectomy)

• Active surveillance for “low risk” DCIS
## Active Surveillance Trials for DCIS

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>COMET</th>
<th>LORIS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>LORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>≥40</td>
<td>≥46</td>
<td>≥45</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td>Low and intermediate</td>
<td>Low and intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Morphology</td>
<td>Calcifications only</td>
<td>Calcifications only</td>
<td>Calcifications only</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td>ER and/or PR positive, plus HER2 negative if performed</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Biopsy technique</td>
<td>VACB and/or surgical biopsy</td>
<td>At least 12 gauge VACB and/or surgical biopsy</td>
<td>6 samples with 8–9 gauge or 12 samples with 10–11 gauge VACB</td>
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<th>LORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of cancer</td>
<td>Exclude if invasive breast cancer</td>
<td>Exclude if invasive breast cancer or ipsilateral DCIS</td>
<td>Exclude if any cancer except in situ of the cervix or basal carcinoma of the skin</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>Exclude</td>
<td>Exclude</td>
<td>Exclude</td>
</tr>
<tr>
<td>Comedonecrosis</td>
<td>Exclude</td>
<td>Exclude</td>
<td>N/A</td>
</tr>
<tr>
<td>Synchronous invasive cancer</td>
<td>Exclude</td>
<td>Exclude</td>
<td>Exclude</td>
</tr>
<tr>
<td>Bilateral DCIS at presentation</td>
<td>Include</td>
<td>Include</td>
<td>Exclude</td>
</tr>
<tr>
<td>High risk</td>
<td>Include</td>
<td>Exclude if high risk per NICE guidelines&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Exclude if family with BRCA 1/2 mutation</td>
</tr>
<tr>
<td>History of chemoprevention</td>
<td>Exclude</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>23</sup> Grimm, 2017
LORIS Trial

- Prospective randomized non-inferiority trial comparing surgical excision with active surveillance (annual mammograms for 10 years) for women with low risk DCIS
- Planned accrual 932 patients over 6 years
- Primary endpoint: Development of ipsilateral invasive cancer
LORIS Trial

• Eligibility:
  – Age ≥ 46 yrs
  – Mammographically-detected or incidental DCIS
  – Low risk DCIS on 11g vacuum assisted needle biopsy, confirmed by central pathology review
    » Low to intermediate nuclear grade
    » No comedo necrosis
The COMET Trial
(Comparison of Operative vs Medical Endocrine Therapy)
PI: Shelley Hwang

• Prospective randomized non-inferiority trial comparing guideline concordant care with active surveillance for women with low risk DCIS on CNB
  – Age > 40 years
  – Low or intermediate grade DCIS
  – No comedo necrosis
  – ER+ and/or PR+
  – 2 pathologists agree on diagnosis
The COMET Trial
(Comparison of Operative vs Medical Endocrine Therapy)
PI: Shelley Hwang

• Patients in both groups offered option of endocrine therapy
• Planned accrual: 892 pts at 100 sites over 2 years
• Primary endpoint: Development of ipsilateral invasive cancer within 2 years
# Active Surveillance Trials for DCIS

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<td>Age (year)</td>
<td>$\geq 40$</td>
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<td>$\geq 45$</td>
</tr>
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<sup>23</sup> NICE guidelines refer to the National Institute for Health and Care Excellence guidelines.
Variability in Diagnostic Threshold for Comedo Necrosis
Harrison, USCAP 2018

• Eight replicate histologic images of a duct with low nuclear grade, solid pattern DCIS
• To simulate necrosis, superimposed pink circle of various diameters representing 10-80% of duct diameter in 10% increments
• 35 experienced breast pathologists
Which image represents minimum amount of necrosis required for “comedo” necrosis?
Proportion of Duct Diameter With Necrosis Required for a Diagnosis of “Comedo Necrosis” (35 experienced breast pathologists)

No one threshold about which more than 30% of pathologists agreed met the minimal criteria for comedo necrosis
Implications for Active Surveillance Trials

- Low threshold: Exclude potentially suitable candidates
- High threshold: Include patients who may not be appropriate study subjects
- Definition of “comedo necrosis” requires standardization
Upgrade of DCIS to Invasive Cancer

• How often does CNB underestimate invasion in patients with DCIS?
Ductal Carcinoma in Situ at Core-Needle Biopsy: Meta-Analysis of Underestimation and Predictors of Invasive Breast Cancer

- 52 studies
- 7350 cases of DCIS on core biopsy followed by excision
- Pooled underestimation (upgrade) rate: 25.9%
• But, what is the underestimation (upgrade) rate for patients who would be eligible for the trials of active surveillance?
Concordance between vacuum assisted biopsy and postoperative histology: Implications for the proposed Low Risk DCIS Trial (LORIS)

S. Soumian \textsuperscript{a,b,e}, E.T. Verghese \textsuperscript{c,e}, M. Booth \textsuperscript{c}, N. Sharma \textsuperscript{c}, S. Chaudhri \textsuperscript{a}, S. Bradley \textsuperscript{a}, S. Umranikar \textsuperscript{a}, R.A. Millican-Slater \textsuperscript{c}, A.M. Hanby \textsuperscript{c,d}, A. Francis \textsuperscript{a,*}

225 DCIS cases diagnosed by VAB, 2001-2010

<table>
<thead>
<tr>
<th>DCIS</th>
<th>Number ( n (%) )</th>
<th>Upgrade to intermediate grade DCIS ( n (%) )</th>
<th>Upgrade to high grade DCIS ( n (%) )</th>
<th>Upgrade to invasive cancer ( n (%) )</th>
</tr>
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<tbody>
<tr>
<td>LORIS cases</td>
<td>19 (100)</td>
<td>3 (16)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*includes only low grade cases
296 LORIS-eligible patients identified between 2009-2012 (≥46 yo, non-high grade DCIS on vacuum assisted CNB for screen-detected mammographic microcalcs)

- Invasive carcinoma at surgery in 58 (20%)
  » 31% T1b or larger
  » 21% high grade
  » 3% TNBC
  » 9% HER2+
  » 5% node+
  » 90% received RT
  » 18% recommended for chemo
# Surgical Upstaging Rates for Vacuum Assisted Biopsy Proven DCIS: Implications for Active Surveillance Trials

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## TABLE 2 Patient demographics and DCIS characteristics for the entire study population and cases eligible for the COMET, LORIS, and LORD trials (eligibility criteria for each trial are listed in Table 1)

<table>
<thead>
<tr>
<th></th>
<th>Entire population (n = 307) no. (%)</th>
<th>COMET (n = 81) no. (%)</th>
<th>LORIS (n = 74) no. (%)</th>
<th>LORD (n = 10) no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year, mean [range])</strong></td>
<td>60.3 (33.5–86.7)</td>
<td>61.3 (44.1–86.7)</td>
<td>62.5 (44.1–86.7)</td>
<td>63.1 (51.5–80.6)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>198 (64)</td>
<td>54 (67)</td>
<td>52 (70)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Black</td>
<td>96 (31)</td>
<td>27 (33)</td>
<td>22 (30)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>ER-positive</strong></td>
<td>249 (81)</td>
<td>80 (99)</td>
<td>71 (96)</td>
<td>10 (100)</td>
</tr>
<tr>
<td><strong>PR-positive</strong></td>
<td>216 (70)</td>
<td>77 (95)</td>
<td>68 (92)</td>
<td>10 (100)</td>
</tr>
<tr>
<td><strong>Nuclear grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>15 (5)</td>
<td>12 (15)</td>
<td>12 (16)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>95 (31)</td>
<td>69 (85)</td>
<td>62 (84)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>High</td>
<td>197 (64)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Comedonecrosis</td>
<td>157 (51)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Upgrade to high-grade DCIS</strong></td>
<td>10 (3)</td>
<td>6 (7)</td>
<td>5 (7)</td>
<td>1 (10)</td>
</tr>
<tr>
<td><strong>Upstage to invasive disease</strong></td>
<td>53 (17)</td>
<td>5 (6)</td>
<td>5 (7)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>
What drives the progression of DCIS to invasive breast cancer?
Gene Expression and Genomic Alterations in DCIS and Invasive Cancer

• Gene expression
  – Very few genes differentially expressed in DCIS and invasive cancer
  – No clear “DCIS” or “invasive” signature

• Genomic alterations
  – Genomic profiles of DCIS and invasive cancer generally similar for lesions of equivalent grade
  – Low grade DCIS more similar to low grade invasive cancer than to high grade DCIS
Possible Explanations

• Only a very small number of genes associated with the progression of DCIS to invasive breast cancer

• Progression of DCIS to invasive breast cancer strongly dependent upon epigenetic and/or microenvironmental factors (perhaps even more so than on molecular/genetic changes in DCIS cells themselves)
Potential Microenvironmental Factors in DCIS Progression

- Myoepithelial cells
- Stroma
- Immune cells (TILs)
Myoepithelial Cells

- Surround entire ductal lobular system
- Physiologic functions
  - Natural tumor suppressor function
    - Maintenance of basement membrane
    - Physical barrier between benign epithelium/DCIS and stroma
    - Paracrine effects on epithelial cells, stromal cells and endothelial cells
Myoepithelial Cells Associated with DCIS
Polyak Lab, DFCI

• Compared with MEC from reduction mammaplasty specimens, DCIS-associated MEC show:
  – Downregulation of a variety of genes involved in normal functions
    » Oxytocin receptor, laminin, thrombospondin
  – Upregulation of genes for chemokines that enhance epithelial cell proliferation, migration, invasion
    » SDF1/CXCL12 and CXCL14
  – Epigenetic changes
• DCIS-associated MEC often show immunophenotypic alterations when compare with normal MEC
• ?Altered state of differentiation
• ?Altered tumor suppressor capability
• MCF10DCIS.com cells injected into mammary ducts of immunodeficient mice
  – Alterations in DCIS-associated MEC occur before invasion
  – Reduced expression of p63, calponin and SMA
    » p63 > calponin > SMA
• Similar findings in limited number of human DCIS samples
• Co-culture of tumor-associated MEC and MCF10DCIS.com cells
  – Stimulated MEC to secrete TGFβ-1 resulting in activation of TGFβ/Smads pathway in DCIS cells
    » Promoted EMT, basal-like phenotype, stem cell properties, migration and invasiveness of DCIS cells
  – miR-10b-5p downstream mediator of TGFβ signaling

• Xenografts
  – Tumor-associated MEC enhanced DCIS to IDC progression
Is Altered Expression of Myoepithelial Cell Markers Clinically Important?
Low CD10 mRNA Expression Identifies High-Risk Ductal Carcinoma In Situ (DCIS)

Jérôme Toussaint, Virginie Durbecq, Sevilay Altintas, Valérie Doriath, Ghizlane Rouas, Marianne Paesmans, Philippe Bedard, Benjamin Haibe-Kains, Wiebren A. Tjalma, Denis Larsi, Martine Piccart, Christos Sotiriou

PLoS One, 2010

Independent prognostic factor in MVA: HR 2.39 (95% CI, 1.52-3.76)
• Upregulation of αVβ6 integrin in DCIS-associated MEC associated with switch from tumor-suppressor to tumor-promoting activity via TGFβ and MMP9 signaling

• Case-control study nested within UK/ANZ cohort (52 case-control pairs)
  – High MEC expression of αVβ6 integrin by IHC significantly associated with local recurrence and shorter time to recurrence independent of DCIS size, grade and patient age
Summary

• Loss of normal myoepithelial cell function may be a key determinant of progression of DCIS to invasive breast cancer

• Identifying the molecular underpinnings of normal myoepithelial cell differentiation and the aberrations that occur in DCIS may identify predictors of invasion and, possibly, targets for prevention
Microenvironmental Factors in DCIS Progression

- Myoepithelial cells
- Stroma
- Immune cells (TILs)
Stromal Alterations in DCIS

- Stromal alterations characteristic of invasive cancers are already manifested in some DCIS lesions
  - Stromal angiogenesis
  - Increased stromal expression of mRNA for stromal matrix proteins (collagen type I, total fibronectin, ED-A+ fibronectin, versican, decorin, thrombospondin)

- Increased expression of some MMPs

Guidi, JNCI, 1994
Brown, Clin Cancer Res, 1999
Jacobs, Hum Pathol, 2002
Hotary, Genes Dev, 2006
Two distinct gene expression signatures identified in stroma of invasive cancers also seen in stroma of DCIS
- Macrophage (CSF1) response
- Fibroblastic (DTF-like) response

Macrophage response signature associated with high grade, ER/PR negative DCIS

Prognostic significance not yet studied
Injection of MCFDCIS cells into nude mice produces a lesion histologically similar to human DCIS
<table>
<thead>
<tr>
<th>Cells Injected into Nude Mice</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCFDCIS alone</td>
<td>DCIS</td>
</tr>
<tr>
<td>MCFDCIS + Normal MEC</td>
<td>DCIS</td>
</tr>
<tr>
<td>MCFDCIS + activated fibroblasts</td>
<td>Invasive ca</td>
</tr>
<tr>
<td>MCFDCIS + activated fibroblasts + MEC</td>
<td>DCIS</td>
</tr>
</tbody>
</table>
Summary

• In these experimental models, progression to invasive carcinoma and tumor growth
  – promoted by fibroblasts
  – inhibited by MEC
• Results highlight potential importance of microenvironment in breast tumor progression
Microenvironmental Factors in DCIS Progression

- Myoepithelial cells
- Stroma
- Immune cells (TILs)
Immune Microenvironment of DCIS

- Some TILs common (86% of cases in one study; mean 5%)
  - Large numbers of TILs associated with high nuclear grade, ER-, HER2+, TN, TP53 mutations, fraction genome altered, telomeric imbalances

- Some PD-L1+ TILs common (81% of cases in one study)
  - Large numbers of PD-L1+ TILs associated with high nuclear grade, ER-, HER2+

- PD-L1 staining of DCIS cells infrequent (0-11% of cases)
  - associated with high nuclear grade, ER-, HER2+

- No association between periductal TILs and ipsilateral breast events (one study of 1488 cases)

Thompson, Mod Pathol 2016
Hendry, Clin Cancer Res, 2017
Prunerí, Ann Oncol 2017
Miligy, Histopathol, 2017
Immune Escape in Breast Cancer During In Situ to Invasive Carcinoma Transition

Carlos R. Gil Del Alcazar¹,²,³, Sung Jin Huh¹,²,³, Muhammad B. Ekram¹,²,³, Anne Trinh¹,²,³, Lin L. Liu⁴,⁵, Francisco Beca¹,²,³, Xiaoyuan Zi⁶,⁷, Minsuk Kwak⁶, Helga Bergholtz⁸, Ying Su¹,²,³, Lina Ding¹,²,³, Hege G. Russnes⁸, Andrea L. Richardson⁹,¹⁰,¹¹, Kirsten Babski¹², Elizabeth Min Hui Kim¹², Charles H. McDonnell III¹², Jon Wagner¹², Ron Rowberry¹², Gordon J. Freeman¹³, Deborah Dillon¹⁰,¹¹, Therese Sorlie⁸, Lisa M. Coussens¹³, Judy E. Garber¹,²,³, Rong Fan⁶, Kristie Bobolis¹², D. Craig Allred¹⁴, Joon Jeong¹⁵, So Yeon Park¹⁶, Franziska Michor⁴,⁵, and Kornelia Polyak¹,²,³,¹⁷,¹⁸

Cancer Discovery, 2017

Diagram:

- DCIS
  - Activated immune environment
  - Enrichment of cytotoxic T-cell gene sets
  - Many activated CD8⁺ T cells
  - High diversity of TCR clonotypes
  - More TIGIT⁺ T cells

- Microinvasive DCIS
  - Change in immune environment

- IDC
  - Suppressed immune environment
  - Enrichment of Treg gene sets
  - Fewer activated CD8⁺ T cells
  - Less diverse TCR clonotypes
  - Higher PD-L1 expression
Some New Approaches

• Cyclic Immunofluorescence (CyCIF)
  – Multiplexed IF
  – MEC phenotypes
  – Immune microenv.

Courtesy of Dr. Sandro Santagata
Some New Approaches

- Biophysical properties of DCIS stroma using second-harmonic generation (SHG) microscopy
  - Assessment of collagen structure

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Wavy Fibrous
Thin Fibrous
Cloudy/ Dense Thick
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Some New Approaches

• Combined genomic and morphometric analysis (NHS, Rob West)

• Assessment of intra-lesional heterogeneity and clonal selection

• Pre-cancer Atlas (PCA)
Management of DCIS
Two Perspectives

• Arguments for more aggressive treatment
  – Radiation reduces local recurrence risk even in “low risk” DCIS
  – Any local recurrence is psychologically devastating for patients; viewed as treatment failure
  – Half of recurrences after breast conserving treatment are invasive

• Arguments for less aggressive treatment
  – Local recurrence of DCIS is inconsequential
  – Only important clinical endpoint is development of potentially lethal invasive breast cancer
  – Most invasive breast cancers are small, mammographically-detected, N- lesions amenable to treatment
Conclusions

• Although great progress has been made in the treatment of patients with DCIS over the past two decades, much remains to be done.
Conclusions

• In particular, accurate risk stratification remains elusive; communication of risk to patients remains problematic
Conclusions

• A better understanding of the molecular alterations associated with the progression of DCIS to invasive breast cancer will hopefully lead to
  – new methods to distinguish those patients with DCIS who are likely to recur or progress from those who are not
  – identification of new targets for treatment and prevention