THE DCIS DILEMMA
IS IT REALLY BREAST CANCER?

Gale England, M.D.
Breast Surgeon
Advocate Medical Group, Advocate Good Samaritan Hospital
What is DCIS?

- Ductal Carcinoma In Situ
- Cancer cells that replace the normal epithelial cells of the breast duct
• Most breast cancers, including DCIS arise in the ducts
• 60,290 new breast cancer cases in 2015, 20% were DCIS (American Cancer Society 2015)
• Incidence has increased
• DCIS tumors are diverse
• Categorized by grade and architecture
• Impacts likelihood of progression to invasive cancer
• The cancer cells are similar to those of invasive cancer, but they have not invaded past the basement membrane into surrounding tissue.
DIAGNOSIS

- Asymptomatic
- Most common presentation is mammographic calcifications
- Core needle biopsy
TREATMENT OF DCIS

- Current standard is surgical
- Sentinel node biopsy not routine
- Radiation
- Antiestrogen therapy
- Goal is to prevent progression to invasive cancer
WHAT IS CANCER?

From the American Cancer Society

“Cancer is a group of diseases characterized by uncontrolled growth of abnormal cells. If the spread is not controlled, it can result in death.”
FEATURES OF INVASIVE CANCER

- Evasion of immune system
- Stimulate own growth
- Resist inhibitory signals to stop their growth
- Resist apoptosis
- Abnormal metabolic pathways
- Metastasis
- Continuous endless replication
- Angiogenesis

Tumor Cell
IS DCIS CANCER??
NATURAL HISTORY OF DCIS

- Untreated DCIS
- Autopsy studies
## UNTREATED DCIS

<table>
<thead>
<tr>
<th>Study</th>
<th># benign biopsy</th>
<th># of DCIS</th>
<th># Invasive</th>
<th>Histology</th>
<th>Follow up (yrs)</th>
<th>% Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eusebi et al</td>
<td>9520</td>
<td>80</td>
<td>11</td>
<td>Mixed</td>
<td>1-14</td>
<td>14</td>
</tr>
<tr>
<td>Page et al</td>
<td>11,760</td>
<td>28</td>
<td>9</td>
<td>Non-comedo</td>
<td>3-31</td>
<td>32</td>
</tr>
<tr>
<td>Rosen et al</td>
<td>&gt;8000</td>
<td>15</td>
<td>8</td>
<td>Micro-papillary</td>
<td>1-24</td>
<td>53</td>
</tr>
<tr>
<td>Collins et al</td>
<td>1877</td>
<td>13</td>
<td>6</td>
<td>Mixed</td>
<td>4-18</td>
<td>46</td>
</tr>
</tbody>
</table>

Table adapted from Erbas et al, Breast Cancer Research and Treatment, 2006
### Table 2. Effect of Surgery on BCSS According to Nuclear Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cancer-Directed Surgery</th>
<th>Weighted BCSS, %</th>
<th>Analysis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 Year</td>
<td>10 Year</td>
<td>Univariate</td>
</tr>
<tr>
<td>1</td>
<td>Performed</td>
<td>99.5</td>
<td>98.8</td>
<td>1.05 (0.26-4.23)</td>
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<tr>
<td></td>
<td>Not performed</td>
<td>98.8</td>
<td>98.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Performed</td>
<td>99.6</td>
<td>98.6</td>
<td>0.23 (0.14-0.39)</td>
</tr>
<tr>
<td></td>
<td>Not performed</td>
<td>90.8</td>
<td>94.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Performed</td>
<td>99.5</td>
<td>98.4</td>
<td>0.15 (0.10-0.22)</td>
</tr>
<tr>
<td></td>
<td>Not performed</td>
<td>94.8</td>
<td>90.5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: BCSS, breast cancer-specific survival.
<sup>a</sup> Weighted by inverse propensity score.

### Table 3. Effect of Surgery on OS According to Nuclear Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cancer-Directed Surgery</th>
<th>Weighted OS, %</th>
<th>Analysis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 Year</td>
<td>10 Year</td>
<td>Univariate</td>
</tr>
<tr>
<td>1</td>
<td>Performed</td>
<td>95.8</td>
<td>87.9</td>
<td>1.14 (0.70-1.86)</td>
</tr>
<tr>
<td></td>
<td>Not performed</td>
<td>95.6</td>
<td>91.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Performed</td>
<td>96.4</td>
<td>89.3</td>
<td>0.68 (0.50-0.91)</td>
</tr>
<tr>
<td></td>
<td>Not performed</td>
<td>96.7</td>
<td>84.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Performed</td>
<td>96.6</td>
<td>90.0</td>
<td>0.45 (0.35-0.57)</td>
</tr>
<tr>
<td></td>
<td>Not performed</td>
<td>89.4</td>
<td>79.1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: OS, overall survival.
<sup>a</sup> Weighted by inverse propensity score.

- No survival benefit with surgery for low grade DCIS
- Golshan et al, JAMA Surg. 2015
INDOLENT DCIS

- Prevalence of DCIS in autopsy studies – 8.9%
  
  (Welch et al, 1997)
IS INVASIVE CANCER THE EVIL TWIN TO DCIS?

- Often found together
- Similar biology
- DCIS can recur
DCIS AND INVASIVE CANCER ARE OFTEN FOUND TOGETHER

• 9-33% of patients undergoing mastectomy for DCIS had invasive cancer
  (Pilewske et al, Dominguez et al, Schneider et al, Tan et al)
• Higher risk if palpable mass, high grade, large size
• 43% of invasive cancers will have a DCIS component
  (Cedolini et al, Doebar et al, Lee et al)
SIMILAR BIOLOGY

Breast cancer cell

- Estrogen Receptor
- HER-2 Receptor
- Progesterone Receptor
- Epidermal growth factor
- p53
- MMP-2
- VEGF
- Cyclin D1
Most studies demonstrate similar genetic changes

Using genomic hybridization, Buerger et al found 5/6 of the invasive cancers had changes identical to the DCIS component

DNA microarray found no differences in the gene profiles between DCIS and invasive just different patterns for different grades (Ma et al)
MODELS OF PROGRESSION
### Table 1: Summary of randomized trials for DCIS comparing lumpectomy alone to lumpectomy plus adjacent radiation

<table>
<thead>
<tr>
<th>Author/country</th>
<th>n</th>
<th>Follow up months</th>
<th>Ipsilateral DCIS or invasive recurrence rate, LR group</th>
<th>Ipsilateral DCIS or invasive recurrence rate, L group</th>
<th>Outcomes (relative risk reduction with LR vs. L; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormick et al, 2015, USA, LR vs. L</td>
<td>686</td>
<td>85 (median)</td>
<td>0.9%</td>
<td>6.7%</td>
<td>0.10 (0.02, 0.41)</td>
</tr>
<tr>
<td>Holmberg, 2008, Sweden, LR vs. L</td>
<td>1,046</td>
<td>101 (mean)</td>
<td>12.2%</td>
<td>27.1%</td>
<td>0.45 (0.34, 0.59)</td>
</tr>
<tr>
<td>Bijik, 2005, Europe, LR vs. L</td>
<td>1,070</td>
<td>126 (median)</td>
<td>14.8%</td>
<td>26.2%</td>
<td>0.56 (0.44, 0.73)</td>
</tr>
<tr>
<td>Houghton, 2003, UK, Australia, New Zealand, LR or LR-Tam vs. L or L-Tam</td>
<td>1,894</td>
<td>52.5 (median)</td>
<td>4.6%</td>
<td>13.2%</td>
<td>0.36 (0.25, 0.56)</td>
</tr>
<tr>
<td>Fisher, 1998, USA, LR vs. L</td>
<td>818</td>
<td>43 (mean)</td>
<td>13.3%</td>
<td>31.0%</td>
<td>0.43 (0.31, 0.59)</td>
</tr>
</tbody>
</table>

*1. LR, lumpectomy and radiation; L, lumpectomy only. **, invasive cancer only. DCIS, ductal carcinoma in situ.

Hwang et al June 2016

**DCIS RECURRENCE**

- With radiation the recurrence ranges from 6.7-31%
- Tamoxifen lowers further
- Half of recurrences are invasive
PREDICTORS OF RECURRENCE

• Young age
• High grade tumor
• Comedo necrosis
• Large size
• Close/positive margins
MODERN METHODS OF PREDICTION

• Van Nuys Prognostic Index
• MSKCC Nomogram
• DCIS Oncotype
• 12-panel gene test that categorizes 10 year local recurrence with lumpectomy
• Low, intermediate, or high risk
• Low risk groups could eliminate radiation
• Validated in grade 1-2, < 2.5cm or grade 3 <1cm; >3mm margins
CURRENT STUDIES

• LORIS trial
• COMET trial
• Phase 3 trial comparing surgery to active monitoring for low risk DCIS
• Accrual began April 2014
• Low risk – low or intermediate grade, age >45
• Monitoring with yearly mammogram for 10 years
THE COMET TRIAL

• Randomized trial comparing surgery +/- RT to endocrine therapy for low risk DCIS
• Criteria age >40, low or intermediate grade ER+ and or PR+, HER 2 negative
• Recruiting 2016
DCIS HAS MANY FACES
NOT ONE SIZE FITS ALL
SUMMARY

- DCIS is technically not cancer
- Some will never cause a problem
- Some will become invasive
- Ongoing studies will help better predict which ones to treat aggressively
- Molecular markers hold the most promise