DCIS Biology and Treatment

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Which in situ breast epithelial lesions are:

Hyperplastic

Neoplastic

Benign      - “adenoma”

Malignant   - “carcinoma in situ”
Which in situ breast epithelial lesions are:

Hyperplastic
  Usual Hyperplasia

Neoplastic

“Benign” - adenoma / microfocal neoplasia / low grade
  ? ADH / microfocal low grade DCIS
  ? Lob Neoplasia
  ? Columnar alteration

“Malignant” - carcinoma in situ
  ? “established” DCIS
  ? some forms of LCIS
Neoplastic insitu breast epithelial lesions

Challenges:

Understanding molecular genetic pathogenesis
Identification of clinical relevance
Effective strategies for management
Development of reproducible criteria for routine classification
Risk and Epithelial Prolif.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florid UEH</td>
<td>1.5 - 2 Minimal risk</td>
</tr>
<tr>
<td>ALH</td>
<td>4x</td>
</tr>
<tr>
<td>ALH + family history</td>
<td>8 - 10x</td>
</tr>
<tr>
<td>ADH</td>
<td>4x</td>
</tr>
<tr>
<td>LCIS</td>
<td>10x</td>
</tr>
<tr>
<td>LCIS + family history</td>
<td>10x</td>
</tr>
<tr>
<td>DCIS low grade</td>
<td>10x</td>
</tr>
</tbody>
</table>

Lobular neoplasia risk most relevant in 5th decade
Slight preponderance of cancer in the ipsilateral breast for LN
Which in situ breast epithelial lesions are:

Hyperplastic = heterogeneous

Neoplastic = homogeneous / clonal

Benign - “adenoma”
Malignant - “carcinoma in situ”
Genetic alterations

LOH Studies

UDH  approx 10% (0-30%) usually one locus only

ADH  approx 50%
      similar loci to low grade DCIS and similar alterations
      found in subsequent inv ca of same breast

DCIS  50 - 80% numerous sites (similar to inv ca)
“..................it is very questionable whether ADH represents a true histopathological entity”

Marc van de Vijver. Biological variables and prognosis of DCIS. The Breast 2005;14; 509-19
### Grade of Invasive Cancers Developing Within DCIS

<table>
<thead>
<tr>
<th>DCIS</th>
<th>I (Low grade</th>
<th>II</th>
<th>III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>13 (81%)</td>
<td>3</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Intermed g</td>
<td>22 (24%)</td>
<td>63 (70%)</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>High grade</td>
<td>3 (1%)</td>
<td>90 (42%)</td>
<td>119</td>
<td>212</td>
</tr>
</tbody>
</table>

Total       | 318          |

DCIS

Relationship to invasive carcinoma

Summary
Morphological and molecular similarities
Clonal process
Analogous to epithelial in situ lesions elsewhere
High frequency of progression to invasive carcinoma if incompletely excised
### Risk of invasive cancer after biopsy alone

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>All</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis</td>
<td>1938</td>
<td>1938</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>Farrow</td>
<td>1970</td>
<td>1970</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Haagensen</td>
<td>1971</td>
<td>1971</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>Millis</td>
<td>1975</td>
<td>1975</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Rosen</td>
<td>1980</td>
<td>1980</td>
<td>8</td>
<td>53</td>
</tr>
<tr>
<td>Eusebi</td>
<td>1994</td>
<td>1994</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Page</td>
<td>1995</td>
<td>1995</td>
<td>9</td>
<td>32</td>
</tr>
</tbody>
</table>

**Mean = 28%**
Natural history of low grade DCIS

- 28 patients with low grade identified from 1950-1968
- 30 yrs follow up
- 11 (39%) invasive cancer
- 5 (18%) breast cancer deaths
- 4 of the 5 breast cancer deaths occurred within 15 years

M Sanders D Page et al Cancer 2005
Natural history of low grade DCIS

D Page et al 2002

• Studies around this time where the DCIS was recognised found that the lesion was completely excised in 40% when mastectomy was performed

• If this was the case in this series, 17 would have had residual DCIS
Natural history of low grade DCIS

D Page et al 2002

• Revised invasive risk 61%
• Revised breast cancer death rate 29%
• 24% breast cancer death rate within 15 years
• Probably still a conservative estimate as residual lesions had been debulked
## Mastectomy for DCIS - Results

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Recurrence</th>
<th>Follow-up (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farrow et al '70</td>
<td>181</td>
<td>1</td>
<td>5 – 20</td>
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<tr>
<td>Ashikari et al '77</td>
<td>74</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Sunshine et al '85</td>
<td>68</td>
<td>3</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Schuh et al '86</td>
<td>52</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>Fisher et al '86</td>
<td>28</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>Kinne et al '89</td>
<td>101</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Arneson et al '89</td>
<td>28</td>
<td>0</td>
<td>6.4</td>
</tr>
<tr>
<td>Silverstein et al '95</td>
<td>167</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>Location</td>
<td>N</td>
<td>All</td>
<td>Invasive</td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>NSABP</td>
<td>403</td>
<td>4.7</td>
<td>2.4</td>
</tr>
<tr>
<td>EORTC</td>
<td>500</td>
<td>4.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Milan</td>
<td>74</td>
<td>4.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Florence</td>
<td>106</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Manchester</td>
<td>127</td>
<td>4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>67</td>
<td>3.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Nottingham</td>
<td>97</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>233</td>
<td>4.4</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>3.9</strong></td>
<td></td>
<td><strong>1.7</strong></td>
</tr>
</tbody>
</table>
Recurrence in remote quadrants
- 5% (2/43)

Adesson Fisher Zafrani
DCIS

Definitions

Unicentric
(1 duct system)
- Focal continuous
- Multifocal discontinuous

Multicentric
(>1 duct system)

Holland
DCIS

81 cases - 1 duct system

1 case - multiple ducts systems

Unicentric process

Holland Lancet 335, 519, 1990
## DCIS Grade and Recurrence

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Nuclear grade</th>
<th>Necrosis</th>
<th>Architecture</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Comedo</td>
<td>High</td>
<td>+++</td>
<td>Solid</td>
<td>7/31</td>
<td>(23)</td>
</tr>
<tr>
<td>II Crib/pap with necrosis</td>
<td>High</td>
<td>+++</td>
<td>Crib/pap</td>
<td>2/5</td>
<td>(40)</td>
</tr>
<tr>
<td>Sub total</td>
<td></td>
<td></td>
<td></td>
<td>9/36</td>
<td>(25)</td>
</tr>
<tr>
<td>III Cribriform/intermediate</td>
<td>Intermediate</td>
<td>+/-</td>
<td>Crib</td>
<td>1/10</td>
<td>(10)</td>
</tr>
<tr>
<td>IV Micropapillary/non necrotic</td>
<td>Low</td>
<td>0</td>
<td>Micropap/crib</td>
<td>0/33</td>
<td>(0)</td>
</tr>
</tbody>
</table>

*Lagios Surg Clin North Am 70, 853, 1990*
## Van Nuys Prognostic Index

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;16mm</td>
<td>16 – 40mm</td>
<td>&gt;40mm</td>
</tr>
<tr>
<td>Margin width</td>
<td>&gt;9mm</td>
<td>1 – 9mm</td>
<td>&lt;1mm</td>
</tr>
<tr>
<td>Pathology</td>
<td>Not high</td>
<td>Not high</td>
<td>High</td>
</tr>
<tr>
<td>Pathology</td>
<td>No necrosis</td>
<td>+/- Necrosis</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;60yr</td>
<td>40 – 60yr</td>
<td>&lt;40yr</td>
</tr>
</tbody>
</table>

### Van Nuys Score
- 4 - 6
- 7 - 9
- 10 - 12

### 10-year act LR free
- 96%
- 73%
- 37%
<table>
<thead>
<tr>
<th>Margin</th>
<th>N</th>
<th>Mean size</th>
<th>High grade</th>
<th>Comedo</th>
<th>LR at 8 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mm</td>
<td>93</td>
<td>9mm</td>
<td>46%</td>
<td>23%</td>
<td>2.2%</td>
</tr>
<tr>
<td>1 – 10mm</td>
<td>124</td>
<td>8mm</td>
<td>32%</td>
<td>32%</td>
<td>18.9%</td>
</tr>
<tr>
<td>&lt; 1mm</td>
<td>39</td>
<td>19mm</td>
<td>67%</td>
<td>74%</td>
<td>33.3%</td>
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</table>
Factors Predicting Local Recurrence after WLE alone

Close / incomplete margins

High grade / Comedo necrosis

Young age

(Size)
## Univariate analysis for ipsilateral recurrence

<table>
<thead>
<tr>
<th>Grading System</th>
<th>n</th>
<th>N of events</th>
<th>H.R.</th>
<th>95 % C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear Grade</td>
<td>86</td>
<td>6 (7.0%)</td>
<td>0.51</td>
<td>0.22 - 1.15</td>
</tr>
<tr>
<td></td>
<td>225</td>
<td>13 (5.8%)</td>
<td>0.41</td>
<td>0.23 - 0.72</td>
</tr>
<tr>
<td></td>
<td>913</td>
<td>135 (14.8%)</td>
<td>1.00*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Nuys Grade</td>
<td>99</td>
<td>5</td>
<td>0.39</td>
<td>0.16 - 0.94</td>
</tr>
<tr>
<td></td>
<td>212</td>
<td>14</td>
<td>0.45</td>
<td>0.26 - 0.78</td>
</tr>
<tr>
<td></td>
<td>913</td>
<td>135</td>
<td>1.00*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td>90</td>
<td>6</td>
<td>0.38</td>
<td>0.22 - 0.66</td>
</tr>
<tr>
<td></td>
<td>248</td>
<td>14</td>
<td>0.47</td>
<td>0.21 - 1.07</td>
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<tr>
<td></td>
<td>886</td>
<td>134</td>
<td>1.00*</td>
<td></td>
</tr>
</tbody>
</table>
Classification of DCIS

- Low Nuclear Grade
- Intermediate Grade
- High Nuclear Grade
- Mixed Type
- Other (Rare) Variants

- RCPath, NHS BSP and EU Pathology Reporting Guidelines 2005
DCIS

Allelic imbalance analysis suggests that low grade & high grade carcinomas follow different genetic pathways

Common Precursor

E Cadherin → Lobular Carcinoma

LOH 16q → Low Grade Carcinoma

C-erbB-2 & p53 → High Grade Carcinoma

Other candidates: BRCA 1 17q, BRCA 2 13q, 1q 3p 11q 13q 17q

Medullary, Tub & Lob, Tubular
?Common Precursor

E Cadherin

16q

LOH 16q

C-erbB-2 & p53

17q

Lobular Carcinoma

Low Grade Carcinoma

High Grade Carcinoma
Class 1

?Common Precursor → E Cadherin

16q → LOH 16q

LOH 16q → Low Grade Carcinoma

E Cadherin → Lobular Carcinoma

Class 2

C-erbB-2 & p53

17q

C-erbB-2 & p53 → High Grade Carcinoma
Expression Arrays

Classification of breast cancer

Distinct subgroups identified

- Basal epithelial
- Luminal epithelial
  - ER positive A & B
  - HER amplified

Prognostic differences

Perou et al., 2000; Sorlie et al., 2001; van 't Veer, 2002
Markers in DCIS

Gene expression patterns in DCIS & invasive & metastatic tumors with serial analysis of gene expression (SAGE) (8 DCIS cases grouped)
16,430 transcripts analyzed
mRNA ISH to examine gene expression (18 tumours) & IHC on TMAs (769 cases)
No universal "in situ" or "invasive" signature

Porter D. Mol Cancer Res. 2003;1:362-75
Translation of cDNA studies

- Distinct sub classes of breast cancer can be identified by expression of proteins of known relevance in breast cancer

- These sub classes are comparable to those identified by cDNA expression array technology

- Molecular classification of breast cancer based on protein expression potentially offers further refinement of traditional methods of classification

- A modern clinically relevant breast cancer classification based on molecular genetic, phenotypic and morphological characteristics appears realistic

Luminal Type A lesions

- Luminal ck
- ER rich
- HER2 neg
- 16q del
• Women (No = 13,388) at increased risk for breast cancer as they
  a) were 60 years or older
  b) were 35-59 with a 5-year predicted risk of at least 1.66%
  c) had a history of LCIS
• Received placebo or 20 mg/day tamoxifen for 5 years
• Tamoxifen reduced the risk of invasive breast cancer by 49%
• Decreased risk occurred in women aged 49 years or younger (44%), 50-59 years (51%) and 60 years or older (55%)
• Risk reduced in women with a history of LCIS (56%) or atypical hyperplasia (86%)
• Tamoxifen reduced the occurrence of ER-positive tumours by 69%, no difference in the occurrence of ER-negative tumours

_Fisher B et al. J NCI. 1998; 90; 1371-1388_
Future classifications systems

• Reflect underlying molecular genetics

• Based on objective morphological and/or protein expression criteria

• Take account of disease extent

• Take account of risk