Ductal Carcinoma in Situ: Current Issues and Differential Diagnosis

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Definition of DCIS
A proliferation of neoplastic epithelial cells confined to mammary ducts and lobules without light microscopic evidence of invasion through the basement membrane into the surrounding stroma

Incidence of DCIS
Ernster, JNCI, 2002
DCIS now accounts for 20% of mammographically-detected breast cancers
DCIS detected in ~1 per 1300 screening mammograms
Ductal Carcinoma in Situ (DCIS)

- Natural history poorly defined
- Biologic behavior of screen-detected DCIS unclear
- Optimal treatment controversial

Factors determining which DCIS will recur/progress to IBC

Risk Factors for Local Recurrence

**Clinical factors**
- Young age

**Treatment factors**
- Extent of excision
- Use of RT
- Use of Tamoxifen

**Tumor factors**
- Size/extent of lesion
- Nuclear grade
- Comedo necrosis
- Architectural pattern
- Volume of DCIS near margin
- Margins
Young Age and Local Recurrence

- Young age has been shown to be a risk factor for LR in several studies.
- But questionable as to whether this is due to other pathology and surgery related factors such as higher grade, greater residual burden and smaller surgical excisions.
- Others have shown no difference in LR for younger age.

Young Age and Local Recurrence

<table>
<thead>
<tr>
<th>Women treated with WE alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes, JCO, 2009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low Information Rate</th>
<th>High Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>No.</td>
<td>% 5 year LR (%)</td>
</tr>
<tr>
<td>&lt; 45</td>
<td>46</td>
<td>4.5</td>
</tr>
<tr>
<td>&gt; 45</td>
<td>46</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Wapnir, JNCI, 2011

<table>
<thead>
<tr>
<th>NSABP B17 and B24 Women treated with tamoxifen and or exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes, JCO, 2009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
<td>.031</td>
</tr>
<tr>
<td>50-51</td>
<td>1.01 (1.00 to 1.20)</td>
<td>.040</td>
</tr>
<tr>
<td>55-94</td>
<td>1.37 (1.15 to 1.65)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Turaka, J Surg Oncol, 2009

Young Age and Local Recurrence

- Fig. 3: Women per year of local recurrence by age.
Young Age and Pathologic Features of DCIS

• As to whether differences in LR among young women are attributable to pathologic features

<table>
<thead>
<tr>
<th>Pathologic Feature (n=657)</th>
<th>&lt;45 yrs (n=111)</th>
<th>45-54 yrs (n=191)</th>
<th>55-64 yrs (n=160)</th>
<th>65+ yrs (n=195)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS nuclear grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7%</td>
<td>11%</td>
<td>13%</td>
<td>9%</td>
<td>0.48</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36%</td>
<td>39%</td>
<td>38%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>59%</td>
<td>50%</td>
<td>49%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Comedo necrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
<td>55%</td>
<td>0.27</td>
</tr>
<tr>
<td>Present</td>
<td>36%</td>
<td>45%</td>
<td>38%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Extent of DCIS (mean number of low power fields)</td>
<td>18.6</td>
<td>14.2</td>
<td>10.8</td>
<td>11.3</td>
<td>&lt;0.0006</td>
</tr>
<tr>
<td>Cancerization of lobules</td>
<td>77%</td>
<td>73%</td>
<td>66%</td>
<td>50%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Inv-IBTR Rates in NSABP B17 and B24 Trials
Wapnir, JNCI, 2011

BCS and Local Recurrence
Radiation therapy following breast-conserving surgery is now the standard treatment for most women with DCIS

However, the identification of patients who can be spared RT and be adequately treated by BCS alone is an important clinical goal
E5194 EXCISION ALONE WITHOUT RADIATION (+/-TAMOXIFEN): ELIGIBILITY
Hughes, JCO, 2009

- DCIS, locally excised
- Two arms:
  - Low or intermediate grade ≤2.5 cm
  - High grade ≤1cm (NG 3 + necrosis)
- Minimum margin width ≥3mm
- Specimen sequentially sectioned and completely embedded to determine grade, size, and margins
- Post excision mag mammo negative for microcalcifications

ECOG E5194: EXCISION WITHOUT RADIATION (+/-TAM)
Ipsilateral events
- High grade
- Low or intermediate grade

A new pathological system for grading DCIS with improved prediction of local recurrence: results from the UKCCR/ANZ DCIS trial
Pinder, 2010, BrJCancer
Risk Factors for Local Recurrence

**Clinical factors**
- Young age

**Treatment factors**
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**Tumor factors**
- Size/extent of lesion
- Nuclear grade
- Comedo necrosis
- Architectural pattern
- Volume of DCIS near margin
- Margins

### BCT and Local Recurrence

Cancer Research Network

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=225)</th>
<th>Controls (n=384)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic presentation</td>
<td>78</td>
<td>-</td>
<td>1.5</td>
<td>1.1-1.9</td>
</tr>
<tr>
<td>Predominant nuclear grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>20</td>
<td>41</td>
<td>1.5</td>
<td>Ref</td>
</tr>
<tr>
<td>Intermediate</td>
<td>122</td>
<td>210</td>
<td>1.2</td>
<td>0.6-2.5</td>
</tr>
<tr>
<td>High</td>
<td>82</td>
<td>143</td>
<td>1.0</td>
<td>0.4-2.5</td>
</tr>
<tr>
<td>Necrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>51</td>
<td>111</td>
<td>1.0</td>
<td>Ref</td>
</tr>
<tr>
<td>Punctate</td>
<td>34</td>
<td>49</td>
<td>1.3</td>
<td>0.7-2.5</td>
</tr>
<tr>
<td>Comedo</td>
<td>139</td>
<td>234</td>
<td>1.4</td>
<td>0.8-2.5</td>
</tr>
<tr>
<td># of LPFs with DCIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>71</td>
<td>1.0</td>
<td>Ref</td>
</tr>
<tr>
<td>2-5</td>
<td>52</td>
<td>102</td>
<td>1.5</td>
<td>0.9-3.0</td>
</tr>
<tr>
<td>6-9</td>
<td>33</td>
<td>64</td>
<td>1.7</td>
<td>0.9-2.8</td>
</tr>
<tr>
<td>10-19</td>
<td>26</td>
<td>28</td>
<td>3.3</td>
<td>1.4-6.0</td>
</tr>
<tr>
<td>20+</td>
<td>55</td>
<td>77</td>
<td>2.1</td>
<td>1.0-4.4</td>
</tr>
<tr>
<td>Margins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>62</td>
<td>151</td>
<td>1.0</td>
<td>Ref</td>
</tr>
<tr>
<td>Close (&lt;1mm)</td>
<td>80</td>
<td>106</td>
<td>2.6</td>
<td>1.6-4.1</td>
</tr>
<tr>
<td>Positive</td>
<td>31</td>
<td>36</td>
<td>3.3</td>
<td>1.7-6.3</td>
</tr>
</tbody>
</table>

### Nomogram for Predicting the Risk of Local Recurrence After Breast-Conserving Surgery for Ductal Carcinoma In Situ

*JCO, 2010*
Application of MSK Nomogram
Cancer Research Network

- Women with DCIS treated with breast conserving therapy
- 190 cases, 305 controls

Genetic and molecular alterations underlying the various pathologic types of DCIS are emerging

An understanding of these alterations will provide important information regarding the biology of DCIS and will likely have an impact on pathologic classification and clinical management

Differential Diagnosis
In most cases the diagnosis of DCIS is straightforward.

But, there is a great deal of pathologic heterogeneity.

- Invasive Cribriform Carcinoma
- Pleomorphic Lobular Carcinoma in situ
- Collagenous Spherulosis
- Lymphovascular Invasion
The diagnosis of DCIS is not always straightforward.

How Often is the Diagnosis of DCIS a Problem?
### Pathologist Agreement:
Local vs. Central Dx

**Summary**

<table>
<thead>
<tr>
<th>Study</th>
<th>#</th>
<th>% Not DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17</td>
<td>818</td>
<td>6.2%</td>
</tr>
<tr>
<td>RDOG 5</td>
<td>123</td>
<td>7.0%</td>
</tr>
<tr>
<td>CRN DCIS</td>
<td>708</td>
<td>9.9%</td>
</tr>
<tr>
<td>ECOG</td>
<td>662</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

Problems with both under-diagnosis and over-diagnosis
Distinction between ADH and DCIS

- ADH is composed of the same population of atypical epithelial cells as LG DCIS
- Incompletely filling the space
- Some features of UDH
- Comprises 2 spaces or less or 2mm or less

Problems in the Diagnosis of DCIS

Other Intraductal Proliferative Lesions that May Mimic DCIS

- Usual ductal hyperplasia
  - Necrosis
  - UDH vs intermediate nuclear grade DCIS
- Gynecomastoid hyperplasia
- Collagenous spherulosis
Other Intraductal Proliferative Lesions that May Mimic DCIS

- Usual ductal hyperplasia
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  - UDH vs intermediate nuclear grade DCIS
- Gynecomastoid hyperplasia
- Collagenous spherulosis
Other Intraductal Proliferative Lesions that May Mimic DCIS

- Usual ductal hyperplasia
  - Necrosis
  - UDH vs. intermediate nuclear grade DCIS
- Gynecomastoid hyperplasia
- Collagenous spherulosis
• HMW-CK immunostains may be particularly helpful in distinguishing UDH from intermediate nuclear grade DCIS in problematic cases.

Caveats

• Not helpful in distinguishing ADH from LG-DCIS or IG-DCIS (all generally negative for HMW-CK)
• Some HG-DCIS are HMW-CK-positive
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- Usual ductal hyperplasia
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  - UDH vs intermediate nuclear grade DCIS
- Gynecomastoid hyperplasia
- Collagenous spherulosis
Problems in the Diagnosis of DCIS

- LVI
- ADH
- DCIS
- LCIS
- Microinvasive carcinoma
- Invasive carcinoma
- Other intraductal lesions
Problems in the Diagnosis of DCIS

Features of DCIS Associated with Microinvasion

High grade/comedo histology
but, may also be seen in association with other grades/types of DCIS and with LCIS

Extent (size, number of involved ducts)

Periductal lymphoid infiltrates
Problems in Distinguishing “Pure” DCIS from DCIS with Microinvasion

- Over-diagnosis
- DCIS may have areas that mimic invasion
  - Duct branching
  - Involvement of lobules
  - Involvement of benign sclerosing lesions
  - Distortion of involved spaces
  - Tangential sectioning
  - Crush artifact
  - Cautery effect
  - Artifactual displacement of DCIS cells
- Defensive pathology
Distinction Between Mimics of Invasion and Real Invasion

Not always possible on H and E sections, even with multiple levels

Immunostains for myoepithelial cells
Problems in Distinguishing “Pure” DCIS from DCIS with Microinvasion

- **Over-diagnosis**
  - DCIS may have areas that mimic invasion
    - Duct branching
    - Involvement of lobules
    - Involvement of benign sclerosing lesions
    - Distortion of involved spaces
    - Tangential sectioning
    - Crush artifact
    - Cautery effect
    - Artifactual displacement of DCIS cells
  - Defensive pathology

- **Under-diagnosis**
  - Microinvasive foci may be overlooked
  - Microinvasive foci may not be sampled
Practical Implications

Patients with large areas of DCIS with and without microinvasion should probably be managed similarly

?SLN biopsy

Problems in the Diagnosis of DCIS

Invasive Cancers that May Mimic DCIS

Invasive cribriform carcinoma

Adenoid cystic carcinoma

Invasive carcinomas in rounded nests
  – Papillary carcinomas (esp, solid papillary carcinoma)
  – Invasive ductal
Invasive Cribriform Carcinoma

Problems in the Diagnosis of DCIS

- LVI
- ADH
- Other intraductal lesions
- DCIS
- Microinvasive carcinoma
- Invasive carcinoma
- LCIS
LVI Mimicking DCIS

Helpful clue: Pattern of cell nests conforms to location of normal lymphovascular spaces rather than structure of ductal-lobular system

» Vascular bundles
» Periductal
» Interlobular stroma
» Try to assess relationship of worrisome nests to identifiable ducts and lobules
Conclusions

Current issues with management

Diagnosis of DCIS straightforward in most cases

Problems with both under-diagnosis and over-diagnosis

With careful attention to histologic cues and judicious use of appropriate immunostains, correct diagnosis should be possible in virtually all cases

Genetic and molecular alterations underlying the various pathologic types of DCIS beginning to emerge

An understanding of these alterations will provide information regarding the biology of DCIS and have an important impact on classification and management