LOBULAR CARCINOMA IN SITU: WHAT DOES IT MEAN? THE SURGEON’S PERSPECTIVE
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LOBULAR NEOPLASIA Diagnosis and Treatment
• Historical background
• Role of hormones
• Implications for diagnosis
• Implications for management

LOBULAR CARCINOMA IN SITU Historical Perspective
• 1919: Ewing published microphotographs of LCIS
• 1932: Broders described “in situ carcinoma”
• 1941: Foote and Stewart named “LCIS”
• 1952: LCIS -> invasive lobular ca (case report)
• 1978: Haagensen’s 211 cases of “lobular neoplasia”
• 1978: Rosen’s 99 cases treated with excision alone

LOBULAR CARCINOMA IN SITU Multicentricity and Bilaterality
  • 50 mastectomy specimens
  • LCIS in multiple quadrants in 24/50 cases (48%)
  • 104 cases of LCIS. 82 had contralateral sampling
  • LCIS bilateral in 41/82 cases (50%)
LOBULAR CARCINOMA IN SITU
Natural History of Disease

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Mean Follow-Up</th>
<th>Ipsilateral Cancer</th>
<th>Contralateral Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haagensen, 1981</td>
<td>14.7 yrs</td>
<td>27/257 (11%)</td>
<td>27/258 (10%)</td>
</tr>
<tr>
<td>Anderson, 1974</td>
<td>15 yrs</td>
<td>9/46 (20%)</td>
<td>9/52 (17%)</td>
</tr>
<tr>
<td>Wheeler, 1974</td>
<td>15.7 yrs</td>
<td>1/25 (4%)</td>
<td>5/34 (15%)</td>
</tr>
<tr>
<td>Page, 1991</td>
<td>19 yrs</td>
<td>6/39 (15%)</td>
<td>4/39 (10%)</td>
</tr>
<tr>
<td>Rosen, 1978</td>
<td>24 yrs</td>
<td>18/83 (22%)</td>
<td>17/83 (20%)</td>
</tr>
</tbody>
</table>

LOBULAR NEOPLASIA
Diagnosis and Treatment

- Historical background
- Role of hormones
- Implications for diagnosis
- Implications for management

BIOLOGICAL QUESTION:
Is the incidence of lobular disease affected by the increasing use of hormone replacement?

Percent change in the incidence of invasive breast cancers from 1987-89 to 1993-95

Li et al., Cancer 88:2561, 2000
Risk of lobular and ductal cancer associated
with use of hormone replacement therapy*

<table>
<thead>
<tr>
<th>Type of HRT</th>
<th>Lobular R=29</th>
<th>Ductal = 254</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen only</td>
<td>1.8 (0.9-3.8)</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>Estrogen &amp; Progestin</td>
<td>2.4 (1.1-5.2)</td>
<td>0.7 (0.4-1.0)</td>
</tr>
</tbody>
</table>

*Li C, Weiss NS, Stanford JL, Daling JR.

Estimated number of dispensed Rx of oral and transdermal menopause estrogens and medroxyprogesterone from 1982-92 in USA

Ever use of Estrogen and Combination HRT by histology

LOBULAR CARCINOMA IN SITU

LCIS AND CHRT ASSOCIATION

Hypotheses

- **PROMOTION:** CHRT may permit LCIS to persist in postmenopausal women and become ILC in selected cases
- **DETECTION:** CHRT may facilitate detection of occult ILC on mammograms or clinical examination
- **DIFFERENTIATION:** CHRT may allow preexisting invasive ductal carcinoma to develop lobular features and present as mixed IDC/ILC or pure ILC
**BREAST CANCER INCIDENCE**

Mammographic Screened Population

- Between 2000-3, annual rates of invasive cancer declined by 5% ($P_{\text{trend}} = 0.003$)
- Between 2001-3, annual rates of ER-positive invasive cancer declined by 13% ($P_{\text{trend}} = 0.02$)
- DCIS rates stable

**LOBULAR NEOPLASIA**

Diagnosis and Treatment

- Historical background
- Role of hormones
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- Implications for management

ALH: Proliferation of cytologically bland, discohesive cells filling the individual acinar units but not distending them
**LOBULAR CARCINOMA IN SITU**

Lobular Carcinoma In Situ (LCIS)

- LCIS: Proliferation of cytologically bland, discohesive cells filling and distending at least half of the acinar units of a lobule.

**LOBULAR CARCINOMA IN SITU**

Pleomorphic LCIS

- Pleomorphic LCIS: Neoplastic proliferation of discohesive cells growing in a "lobular" growth pattern but containing cells with greater nuclear pleomorphism, nucleoli, and often central necrosis.

**DIAGNOSIS QUESTION:**

When ALH or LCIS is seen on needle sampling, should it be surgically excised?

**LCIS ON NEEDLE SAMPLING:**

Upgrade potential

**Table 1. Summary of Overall Findings in All Patients**

<table>
<thead>
<tr>
<th>Diagnosis on CNB</th>
<th>Number of Cases</th>
<th>Number of Patients with Excision</th>
<th>Number of Patients with Cancer on Excision</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCIS</td>
<td>14</td>
<td>9</td>
<td>2*</td>
</tr>
<tr>
<td>ALH</td>
<td>17</td>
<td>6</td>
<td>4*</td>
</tr>
<tr>
<td>LN</td>
<td>4</td>
<td>2</td>
<td>0*</td>
</tr>
<tr>
<td>TOTAL</td>
<td>35</td>
<td>17</td>
<td>6*</td>
</tr>
</tbody>
</table>

LCIS = lobular carcinoma in situ; ALH = atypical lobular hyperplasia; LN = lobular neoplasia; CNB = core needle biopsy.

* Associated with mastectomy


**LOBULAR NEOPLASIA**

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LOBULAR NEOPLASIA
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MANAGEMENT QUESTION:
To what degree will tamoxifen or raloxifen reduce risk among patients with LCIS?

ELIGIBLE PARTICIPANTS
RANDOMIZATION
(n=13,388)

TAMOXIFEN
5 YEARS
(n= 6681)

PLACEBO
5 YEARS
(n = 6707)

BCPT SCHEMA

Invasive Breast Cancer

<table>
<thead>
<tr>
<th>Events</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>175</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>89</td>
</tr>
</tbody>
</table>

P < 0.00001

Noninvasive Breast Cancer

<table>
<thead>
<tr>
<th>Events</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>69</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>35</td>
</tr>
</tbody>
</table>

P < 0.002

BCPT SCHEMA

- LCIS as indication for entry into BCPT:
  - Placebo arm: 411 LCIS cases
  - Tamoxifen arm: 415 LCIS cases
- Breast cancers among patients in BCPT:
  - Placebo arm: 18 cases of invasive breast cancer
  - Tamoxifen arm: 8 cases of invasive breast cancer
- 44% reduction of invasive cancer
**NSABP STAR Schema**

- Risk-Eligible Postmenopausal Women
- **STRATIFICATION**
  - Age
  - Gail Model Risk
  - Race
  - History of LCIS

- **TAMOXIFEN**
  - 20 mg/day x 5 years

- **RALOXIFENE**
  - 60 mg/day x 5 years

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**STAR Summary of Screening, Accrual and Follow-Up Information**

- Women screened for breast cancer risk: 184,460
- Women who were breast cancer risk eligible: 96,368
- Women randomly assigned treatment: 19,747
- LCIS: 1,789 (9.2%)
- Total person-years of follow-up: 76,828
- Average follow-up (months): 47.3

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**P-2 STAR**

**Cumulative Incidence of Invasive Breast Cancer**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>9726</td>
<td>509</td>
<td>163</td>
<td>25.1</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745</td>
<td>613</td>
<td>168</td>
<td>24.8</td>
</tr>
</tbody>
</table>

**Average Annual Rate and Number of Invasive Breast Cancers**

- Gail Model Projection: 312* (TAM: 163, Raloxifene: 168)

**Relative risk = 1.40**

95% Confidence Interval: 0.98 to 2.00

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**P-2 STAR**

**Cumulative Incidence of Non-Invasive Breast Cancer**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>9726</td>
<td>505</td>
<td>57</td>
<td>8.1</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745</td>
<td>612</td>
<td>80</td>
<td>11.6</td>
</tr>
</tbody>
</table>

**Average Annual Rate and Number of Non-invasive (In Situ) Cancers**

- TAM: 57*
- Raloxifene: 80*

**Relative risk = 1.40**

95% Confidence Interval: 0.98 to 2.00

* # of events
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* Raloxifene appears to have a similar risk reduction benefit for invasive breast carcinoma as does tamoxifen among high risk women (category 1), but does not appear to reduce the risk of developing non-invasive cancer.

LOBULAR CARCINOMA IN SITU

BIOLOGICAL QUESTION:

Is there a subset of patients with LCIS who are at increased risk for malignant progression of their lobular neoplasia?

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• Vos et al., Brit J Cancer 76:1131, 1997
  • E-cadherin gene truncating mutation analysis:
  • Same comparing LCIS and adjacent ILC

• Buerger et al., Mol Pathol 53:118, 2000
  • Comparative genomic hybridization (CGH):
  • Similar comparing LCIS and well diff. DCIS

• Lakhani et al, J Clin Path 1995;48: M74 – M78
  • Loss of heterozygosity (LOH) at chromosomes 17P, 17Q, & 16Q (E-cadherin)
    in ILC, mixed ILC/LCIS and pure LCIS

• Page et al., Hum Pathol 22:1232, 1991
  • LOH of chromosomal markers similar high frequency in invasive carcinoma and LCIS

• 12 pts with pleomorphic ILC
  • 7 had coexisting pleomorphic LCIS
  • 11 had long term clinical follow-up
  • 9 developed fatal metastatic disease
  • Median survival 2.1 years

Findings suggest that:
  • Pleomorphic ILC is as aggressive as IDC
  • Pleomorphic LCIS may indicate aggressive potential

• 39 patients with only LCIS in biopsy
  – followed average 19 years

• 9 patients developed invasive cancer
  – 7 of 9 were lobular cancer
  – 3 of 7 died of breast cancer
  – ALL 3 associated with PLEOMORPHIC
    INVASIVE LOBULAR CANCER


Page et al., Hum Pathol 22:1232, 1991
LOBULAR CARCINOMA IN SITU
Excision of Pleomorphic LCIS?

- Data on behavior of pleomorphic LCIS remains anecdotal
- Incidence of invasive cancer at site of previously biopsied pleomorphic LCIS has not been reported
- Responsiveness of pleomorphic LCIS to tamoxifen is unknown

LOBULAR NEOPLASIA
Summary 1

- LCIS may be a direct precursor lesion to invasive cancer in uncommon circumstances
- Progestin-containing HRT regimens has been associated with lobular neoplasia and ILC
- Pleomorphic forms of LCIS and ILC may be more aggressive variants with worsened prognosis

LOBULAR NEOPLASIA
Summary 2

- ALH or LCIS seen on needle sampling should be excised for definitive diagnosis
- Tamoxifen should be considered for selected LCIS patients; raloxifene may be considered for risk reduction in LCIS patients, although it has not been shown to decrease likelihood of a subsequent non-invasive cancer diagnosis

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