Clinical Management of High Risk Lesions: What a Medical Oncologist Needs from Pathology

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Clinical Management of High Risk Breast Lesions

- Identification and categorization of the lesion
  - Pathology, imaging
- Treatment of the current lesion
  - Biopsy/Excision
  - Surgery, radiation, systemic therapy (DCIS)
- Reduction in risk of future development of breast cancer
  - Primary prevention (lifestyle modifications, chemoprevention, prophylactic surgery)
  - Secondary prevention (MRI and mammography)
What a Medical Oncologist Needs from Pathology in DCIS:
Prognostic and Predictive Factors

- Margins
- Size
- Grade
- Estrogen receptor status
- ?HER-2 expression
- ?”DCIS Score”
Estrogen Receptor in DCIS

Estrogen Receptor (ER)+
75-80% of DCIS
(from B-24 study)
NSABP B-24: Tamoxifen in DCIS

- **Patients**: 1804 pts with DCIS
  - s/p lumpectomy and RT
  - Allowed positive or unknown margins (23% of patients)

- **Treatment**: Randomized to tamoxifen vs placebo x 5 years

- **Primary Endpoint**:
  - Reduction in breast cancer events (ipsilateral, contralateral, metastatic) at 5 years with addition of tamoxifen
**Results**

- Overall 37% reduction in all breast cancer events at 5 years with addition of tamoxifen.
- Benefit seen only in ER+ DCIS.
- No survival difference.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tamoxifen</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>13.4%</td>
<td>8.2%</td>
<td>0.009</td>
</tr>
<tr>
<td>Ipsilateral invasive</td>
<td>9.3%</td>
<td>6.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Ipsilateral non-invasive</td>
<td>5.1%</td>
<td>3.9%</td>
<td></td>
</tr>
<tr>
<td>Contralateral invasive</td>
<td>3.4%</td>
<td>2.0%</td>
<td>0.01</td>
</tr>
<tr>
<td>Contralateral non-invasive</td>
<td>1.1%</td>
<td>0.2%</td>
<td></td>
</tr>
</tbody>
</table>
NSABP B-24: Tamoxifen in DCIS
Allred DC et al, SABCS 2002 and J Clin Oncol 2012
epub ahead of print

• Results
  – Retrospective evaluation of ER, PR on 732 patients (41% of study population)
  – Data at 9 years of follow-up

<table>
<thead>
<tr>
<th></th>
<th>ER- DCIS</th>
<th>ER+ DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>placebo</td>
<td>tamoxifen</td>
</tr>
<tr>
<td>All events</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>Contralateral</td>
<td>6%</td>
<td>5%</td>
</tr>
</tbody>
</table>

p=0.51        p=0.002
CLOSED: NSABP B-35
Anastrozole vs. Tamoxifen in Postmenopausal Patients Undergoing Lumpectomy for DCIS

Lumpectomy + XRT for DCIS (ER+)

Anastrozole → Tamoxifen

Closed to accrual - Not yet reported

N = 3000
HER-2 Overexpression in DCIS

HER-2 overexpression most common in high grade, comedo DCIS
ONGOING NSABP B-43: Phase III Trial of Radiation +/- Trastuzumab in HER-2+ DCIS
PI: M Cobleigh

- Patients: n=2,000
  - DCIS, HER2 overexpressed
  - s/p lumpectomy with negative margins

- Study:
  - Radiation alone vs concurrent radiation + trastuzumab
  - Standard whole breast radiation over 5-6 weeks
  - Trastuzumab given IV weeks 1 + 4
ONGOING NSABP B-43: Phase III Trial of Radiation +/- Trastuzumab in HER-2+ DCIS
PI: M Cobleigh

• Primary endpoint:
  – Time from randomization to ipsilateral invasive breast cancer, ipsilateral skin cancer recurrence, or ipsilateral DCIS

• Correlative endpoints:
  – Correlation of cMYC-amplification status with trastuzumab in addition to radiotherapy
  – Correlation of PI3K gene mutation status with trastuzumab in addition to radiotherapy
Who Needs Radiation Following Breast Conserving Surgery for DCIS:

Can Genomic Profiling Help?
Meta-Analysis of Breast Conserving Surgery (BCS) +/- Radiation (RT) in DCIS

A Goodwin et al, Cochrane Database Syst Rev (3), 2009

- 4 trials of BCS +/- RT in DCIS (1986-1999)
  - 3,900 women, median age at diagnosis 50
  - Median follow-up: 4.4 to 10.5 years
- Pooled analysis:
  - Recurrence of ipsilateral DCIS or invasive breast cancer: 10.9% with BCS + RT vs 22.9% with BCS alone (HR 0.49)
  - OS > 90% in both groups
  - No evidence of excess deaths due to radiation
- Conclusion: "This result confirms the benefit of radiotherapy following BCS for DCIS and supports its use for all women"
DCIS Score: A Quantitative Multigene RT-PCR Assay For Predicting Recurrence Risk After Surgical Excision without Radiation

Solin L et al, SABCS 2011

- DCIS Score algorithm developed based on prior studies
- Selected a subset of genes from 21-gene Recurrence Score Assay (Oncotype Dx) that were prognostic in tamoxifen treated and untreated patients
  - Proliferation gene group not predictive in DCIS (proliferation much lower in DCIS compared to invasive breast cancer)
DCIS Score

- DCIS Score (0 – 100) evaluated 2 ways
  - Continuous variable
  - 3 prespecified risk groups:
    - Low < 39
    - Intermediate 39 – 54
    - High ≥ 55

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

**Hormone Receptor Group**
- PR
- GSTM1

**Reference Group**
- ACTB (β-actin)
- GAPDH
- RPLPO
- GUS
- TFRC
DCIS Score:  
ECOG E5194 (Parent Study) 

Prospective multicenter study 1997-2000 (n = 670)  
Cohort 1 (83%): Low/int grade DCIS, ≤ 2.5 cm  
Cohort 2 (17%): High grade DCIS, ≤ 1 cm 

Study treatment  
- Surgical excision with ≥ 3 mm negative margins  
- No radiation  
- Tamoxifen option beginning May 2000 

Reported outcomes at 5 and 7 years (Hughes, JCO, 2009)  
- Currently 10-year outcomes
DCIS Score: Validation Study using E5494 Samples

• Tissue available on 49% of participants (327 patients)
  – Median age: 61 years
  – Median Tumor size: 7 mm
  – Tamoxifen use: 29%
  – ER positive: 97%

• Recurrence Score (RS) assay performed
  – Central pathology review
  – Calculated DCIS Score and 21-gene RS

• Study endpoints: Ipsilateral breast events (IBE)
  – 1º Endpoint: Any IBE (DCIS or invasive)
  – 2º Endpoints: Invasive IBE, DCIS IBE
DCIS Score: 10-year Ipsilateral Breast Events (IBE) By Risk Group

ANY IBE

<table>
<thead>
<tr>
<th>DCIS Score Group</th>
<th>N</th>
<th>10 Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>36</td>
<td>27.3% (15.2%, 45.9%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45</td>
<td>24.5% (13.8%, 41.1%)</td>
</tr>
<tr>
<td>Low</td>
<td>246</td>
<td>12.0% ( 8.1%, 17.6%)</td>
</tr>
</tbody>
</table>

Log rank P = 0.02

INVASIVE IBE

<table>
<thead>
<tr>
<th>DCIS Score Group</th>
<th>N</th>
<th>10 Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>36</td>
<td>19.1% (9.0%, 37.7%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45</td>
<td>8.9% (2.9%, 25.8%)</td>
</tr>
<tr>
<td>Low</td>
<td>246</td>
<td>5.1% (2.8%,  9.5%)</td>
</tr>
</tbody>
</table>

Log rank P = 0.01
### Multivariable Models Of Risk For IBE

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excluding the DCIS Score</strong></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.54 (1.14, 2.02)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>0.49 (0.27, 0.90)</td>
</tr>
<tr>
<td><strong>Including the DCIS Score</strong></td>
<td></td>
</tr>
<tr>
<td>DCIS Score</td>
<td>2.41 (1.15, 4.89)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.52 (1.11, 2.01)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>0.49 (0.27, 0.90)</td>
</tr>
</tbody>
</table>

For study cohort, surgical margins, grade, comedo necrosis, and DCIS pattern, all p > 0.46. For tamoxifen, p = 0.09.
Summary: DCIS Score

• Provides independent information on 10-year ipsilateral breast event risk beyond classic clinical and pathologic variables, including tamoxifen, grade, and negative margin width.

• Study Conclusion: “DCIS Score provides a new clinical tool to guide treatment selection for patients with newly diagnosed DCIS.”

• Low score group: 12% 10-year risk of an ipsilateral breast event (5% for invasive disease)
  • Is this low enough to omit radiation therapy?
  • Can we use to decide who should get tamoxifen?

• Cost: Approx $3500 (will insurance cover?)
From a Medical Oncology perspective, it’s mostly about reducing risk of future breast cancer occurrence.
Breast Cancer Prevention and Risk Reduction

• Primary Prevention
  – Lifestyle
  – Chemoprevention
  – Prophylactic surgery

• Secondary Prevention
  – Screening and early detection
Breast Cancer Chemoprevention Agents

• FDA approved for breast cancer chemoprevention:
  – Tamoxifen (Nolvadex)
  – Raloxifene (Evista)

• Both drugs are synthetic, non-steroidal, Selective Estrogen Receptor Modulators (SERMs)
  – Mixed anti-estrogenic and weak estrogenic effects depending on the tissue
NSABP P-01 Tamoxifen Breast Cancer Prevention Trial

• 13,400 women at high risk for breast cancer

• Randomized to placebo vs. tamoxifen for 5 years

• Study stopped at mean 3.5 years of follow-up
NSABP P-01: Invasive Breast Cancer by ER Status

No reduction in ER negative breast cancer incidence
NSABP P-01: Effect in Patients with Previous High Risk Pathology

Breast cancer risk reduced 56% in subset of 826 women with prior history of LCIS

- LCIS: Placebo 18, Tamoxifen 8
- ADH: Placebo 23, Tamoxifen 3
Why Shouldn’t all High Risk Patients Take Tamoxifen?

5-Year Non-Breast Cancer Events on Tamoxifen (10,000 Women)

Gail M et al, JNCI 1999

<table>
<thead>
<tr>
<th>Event</th>
<th>35-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>-1</td>
<td>-1</td>
<td>-22</td>
<td>-52</td>
<td>-151</td>
</tr>
<tr>
<td>Endometrial CA</td>
<td>+2</td>
<td>+16</td>
<td>+120</td>
<td>+206</td>
<td>+223</td>
</tr>
<tr>
<td>CVA</td>
<td>+2</td>
<td>+13</td>
<td>+32</td>
<td>+91</td>
<td>+196</td>
</tr>
<tr>
<td>PE</td>
<td>+7</td>
<td>+15</td>
<td>+49</td>
<td>+85</td>
<td>+177</td>
</tr>
<tr>
<td>DVT</td>
<td>+13</td>
<td>+15</td>
<td>+16</td>
<td>+28</td>
<td>+44</td>
</tr>
<tr>
<td>Colle’s/Spine Fx</td>
<td>-13</td>
<td>-13</td>
<td>-42</td>
<td>-71</td>
<td>-115</td>
</tr>
<tr>
<td>Cataracts</td>
<td>+35</td>
<td>+35</td>
<td>+101</td>
<td>+269</td>
<td>+384</td>
</tr>
</tbody>
</table>

Quality of life (hot flashes, vaginal discharge) must be factored in as well
NSABP P-02 STAR Chemoprevention Trial (Study of Tamoxifen and Raloxifene)

Vogel V et al, JAMA 295, 2006

• N = 19,747 postmenopausal women at mod-high risk for breast cancer

• Randomized to tamoxifen vs raloxifene for 5 years

• 47 month median follow-up

• Concern about implications of difference in DCIS
ASCO Guideline: Pharmacologic Interventions for Breast Cancer Risk Reduction
Visvanathan K et al, J Clin Oncol 2009

- Premenopausal:
  - 5 years of tamoxifen reduces breast cancer incidence for at least 10 years, especially ER+ invasive
  - Women < 50 experience fewer side effects

- Postmenopausal:
  - Tamoxifen and raloxifene reduce risk of ER+ invasive breast cancer equally
  - Raloxifene associated with reduced thromboembolic risk, benign uterine conditions, cataracts

- No evidence that risk reduction from either agent translates into mortality reduction

- Use of other agents not recommended outside of a clinical trial
Breast Cancer Chemoprevention: Other Agents Under Study

- Aromatase inhibitors
- Other SERMS
- Ovarian suppression
- Cox II inhibitors
- Retinoids
- Statins
- Vitamin D
Aromatase Inhibitors

Adrenal Hormones

Cortisol

Androstenedione

Aldosterone

Estrone

Testosterone

Estradiol

Aromatase inhibitors block postmenopausal estrogen production

- Letrozole
- Anastrozole
- Exemestane
NCIC MAP.3 Exemestane Breast Cancer Prevention Trial (EXCEL)  

• 4,500 postmenopausal women at high risk for breast cancer  
  – 49% > age 60  
  – 40% 5-year risk of breast cancer (Gail risk score) >1.66%  
  – 11% prior ADH, ALH, LCIS, or DCIS treated with mastectomy

• Randomized to placebo vs. exemestane for 5 years

• Reported at 35 month follow-up
NCIC MAP.3 Exemestane Breast Cancer Prevention Trial (EXCEL)

- Discontinuation 25% both arms
- To date, no increase in fractures, osteoporosis, CVD
ONGOING S0812: Phase II Biomarker Modulation Study of Vitamin D in Premenopausal Women at High Risk for Breast Cancer
PI: K Crew

High-Risk Premenopausal Women (Age 18-50 years)
- 5-yr Gail risk ≥1.67% or lifetime risk ≥20%
- LCIS/DCIS
- BRCA1/2 mutation

(N = 200)

Randomize

Baseline data collection:
Mammogram
Optional breast biopsy
Blood

Follow-up data collection:
Mammogram
Optional breast biopsy
Blood

Cholecalciferol (Vit D3)
20,000 IU weekly x 1yr

Vitamin D3 600 IU qd in both arms

Matching placebo x 1yr

Primary Endpoint: Change in mammographic density
Secondary Endpoints: Serum and tissue-based biomarkers, toxicity
NIH State-of the-Science Conference on the Diagnosis and Management of DCIS
September 2009

- Diagnosis and management of DCIS highly complex: many unanswered questions, including natural history of untreated disease
- Strong consideration to remove anxiety-producing term “carcinoma” from description
- Primary question for future research: accurate identification of DCIS subsets, including those that could be managed with less therapeutic intervention without sacrificing excellent outcomes
- Development/validation of accurate risk stratification methods based on understanding clinical, radiological, pathological, and biological factors essential