Management of the Atypical Lesion
New Studies for DCIS

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CASE STUDY

• 42yo female
  – Screening Mammogram
    • New left breast calcifications

• Nov 2008- mammogram
  – Right breast amorphous calcifications
  – Stereotactic core biopsy
    • Atypia
  – Excisional biopsy
    • Multifocal Atypical ductal and lobular hyperplasia with associated microcalcifications
    • No in situ or invasive carcinoma

• Feb 2011- mammogram
  • New right amorphous calcifications

CASE STUDY

• ROS:
  – No clinical changes

• OB Gyn Hx:
  – First Menses: 13yo
    – G1P0

• Fam Hx:
  – Mother: Ovarian Cancer- 38yo, ⊗40yo- metastatic dz
  – No breast cancer hx

NO DISCLOSURES
What was offered to this woman in 2008?

- Continued screening
- No discussion of risk or risk reduction
  - Her family history of ovarian cancer and hispanic origin suggests possible genetic mutation
  - She could reduce her lifetime risk from 50% to 7.5% with tamoxifen

CASE STUDY

- Atypical Hyperplasia
  - 2-7x increase in risk for breast cancer
  - Risk Factors → 50% risk @ 25 yrs
    - Age at Biopsy (<45 yrs)
    - # Foci of Atypia (>3)
    - Family history
  - This young woman has all three factors

Risk Reduction for Tamoxifen Extends Beyond 5-years


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The Current State of Breast Cancer Prevention

- Over $100 million spent worldwide on chemoprevention clinical trials
- Level 1 evidence shows benefit

BUT

- < 5% of eligible women participate if offered
  - Very few are identified and counseled

What are we missing?

- Tools to automate risk assessment and integrate it into the screening process
- Provider workforce educated about breast cancer risk
- Tools to indicate those most at risk for developing breast cancer and most likely to benefit from risk reduction
- Short term indicators of prevention intervention effectiveness

The Gail Model (1.67 Cutoff) Does Not Identify a Truly High Risk Group of Women

Risk Assessment and Patient Preferences Should Drive Prevention Decisions

- Top 10% of the NHS as compared to the lowest 10% had close to a threefold increase in risk.
Athena WISDOM Study

- Introduces automated risk assessment
  - Includes genomic risk (BRCA, BROCA, SNPs)
  - Breast density
  - Family history
  - Hormone exposures
  - Atypia
- Enables learning and refining risk models over time
  - Who is at risk for what kind of breast cancer

What Separates Atypia from Low Grade DCIS?

- The pathologist who is asked to interpret the slides
- The day on which the pathologist reads the slides
- The number of glands involved
  - The distinction is difficult to make because these are essentially the same lesions biologically
- Does it matter if a patient is upgraded to DCIS?

Classification is an Artifact of History

- ATYPIA
  - Flat epithelial Hyperplasia
  - Atypical Ductal hyperplasia
  - Atypical Lobular Hyperplasia
- DCIS
  - Ductal Carcinoma in situ, low/intermediate grade
  - DCIS, high grade (HR+ HER2-)
  - High grade comedo (HER2+ and/or HR-)
- LCIS
  - Lobular carcinoma in situ, classic type
  - Lobular carcinoma in situ, pleiomorphic type
    - Formerly classified at high grade DCIS

Classification According to Biology

- Low Proliferative Hormone Positive Lesions
  - ADH, Non high grade DCIS
  - ALH, LCIS
  - Flat epithelial/atypical hyperplasia: grade creep
- High Grade Hormone Positive Lesions
  - high grade DCIS, HR+
- High Grade Her2+ or HR- DCIS (comedo)
  - ?Pleiomorphic LCIS?
Remarkable Variation in Approach to Management of “Risk”

- Within Breast Cancer
  - BRCA1 patient: 85% risk for invasive breast cancer
    - Surveillance, prophylactic mastectomy
  - DCIS patient: 10-20% risk for invasive breast cancer
    - Surgical excision, radiation, mastectomy
  - Atypia
    - Some will recommend risk reducing endocrine therapy
    - Some will excise,
    - Some recommend both
    - Some do nothing
- Active Surveillance
  - Not recommended for any breast cancer-premalignant (DCIS) or invasive
  - Recommended for Prostate Cancer (Gleason 3+3)

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Atypia and Chemoprevention

- Retrospective review evaluated 2460 patients diagnosed with atypia from 1999 and beyond from Mass General (Hughes et al)
- Atypia included Borderline DCIS, ADH, ALH, LCIS
- Final data set looked at outcomes of 1938 pts
  - 466 patients treated
    - Tamoxifen, Raloxifene, and/or Exemestane
    - Any duration of time
  - 1472 patients not treated

Probability of Cancer After Atypia Diagnosis With and Without Chemoprevention

![Graph showing probability of being cancer-free with and without chemoprevention](image)


DCIS Has Increased 500% Since the Advent of Mammographic Screening

- If the majority of lesions will not be consequential,
- At a minimum, for low grade disease,
- we should not radiate

FIRST DO NO HARM

A QUANTITATIVE MULTIGENE RT-PCR ASSAY FOR PREDICTING RECURRENCE RISK AFTER SURGICAL EXCISION ALONE WITHOUT IRRADIATION FOR DUCTAL CARCINOMA IN SITU (DCIS): A PROSPECTIVE VALIDATION STUDY OF THE DCIS SCORE FROM ECOG E5194


Eastern Cooperative Oncology Group (ECOG)
North Central Cancer Treatment Group (NCCCTG)
Genomic Health, Inc (GHI)

2011 San Antonio Breast Cancer Symposium

In comparison...

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Breast</td>
<td>20%</td>
<td>+18%</td>
</tr>
<tr>
<td>Colon</td>
<td>32%</td>
<td>-17%</td>
</tr>
<tr>
<td>Cervix</td>
<td>55%</td>
<td>-52%</td>
</tr>
</tbody>
</table>

It is likely that we have not found the right precursor—or that only a fraction of the precursors are relevant.
**DCIS SCORE: 10-YEAR IPSILATERAL BREAST EVENTS (IBE) BY RISK GROUP**

**ANY IBE**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Median Year Risk (%)</th>
<th>10-Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>35</td>
<td>(27.3%, 45.0%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45</td>
<td>(30.9%, 41.0%)</td>
</tr>
<tr>
<td>Low</td>
<td>245</td>
<td>(12.0%, 17.0%)</td>
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</table>

Log rank P = 0.02

**INVASIVE IBE**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Median Year Risk (%)</th>
<th>10-Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>21</td>
<td>(18.9%, 24.0%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36</td>
<td>(17.1%, 27.0%)</td>
</tr>
<tr>
<td>Low</td>
<td>46</td>
<td>(2.0%, 5.0%)</td>
</tr>
</tbody>
</table>

Log rank P = 0.01

**Gail Risk 2.5**


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**Timing of Progression Should Determine Focus of Intervention**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next Month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Next Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Next 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Next 5-10 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Next 10-20 years</td>
<td></td>
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</tbody>
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**IT IS UNLIKELY THAT THE MAJORITY OF DCIS DETECTED IS DESTINED FOR SIGNIFICANT CANCERS**

Figure 1. Age-adjusted incidence rates of different histological types of in situ breast carcinoma among women ages ≥30 years, 1980 to 2001. ■, DCIS overall; O, noncomedo DCIS; △, comedo DCIS; ♦, LCIS.
AND YET . . .

Remarkable Variation in Approach to Management of “Risk”

Lessons Learned from Active Surveillance: Invasive Prostate Cancer (Gleason 3+3)

- 1000 men have now been followed in the U.S. Canary/EDRN study
- 99% disease free survival at 5 years
- 97% disease free survival at 10 years

- The question is really - when we find an abnormality, what is the person at risk for?
  - Ultralow risk cancer? High risk Her2+ cancer?
  - Do they need additional surgical excision?
    - More diagnostic material?
  - Additional imaging? MRI?
  - Do they need risk reduction? And what type?

Klotz et al JCO 2010

ATHENA DCIS Registry:

PIs: Alvarado UCSF/Bold UCD

- A prospective registry to track outcomes of women diagnosed with DCIS across the Athena Breast Health Network.
- Incorporation of the Genomic Health Oncotype Dx DCIS Score
- DCIS score will be used to change the terminology for DCIS.
- Initial pilot study: determine distribution of scores and the population of patients for whom the score most likely impacts treatment decisions
- Implementation: All DCIS patients will be profiled with scores and given recommended options based on the Score and new terminology.
- Follows on CALGB 90304-a DCIS neoadjuvant trial of hormonal therapy for 6 months prior to surgery in postmenopausal women

**Treatment Options**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Options</th>
<th>F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active Surveillance (no surgery), Q6 mos F/U</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-add hormone prevention</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Lumpectomy Alone, Q 12 mos F/U</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-add hormone prevention</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Lumpectomy plus Radiation, Q 12 mos F/U</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-add hormone prevention</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Mastectomy</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-add hormone prevention</td>
<td></td>
</tr>
</tbody>
</table>

**Decision Board**

<table>
<thead>
<tr>
<th>DCIS Score</th>
<th>10 yr Invasive Risk</th>
<th>New Terminology (Implement Sept 2014)</th>
<th>Preferred Treatment Options*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 0-40</td>
<td>3.7%</td>
<td>Atypical Ductal Lesion</td>
<td>1 2 3 4 5 6 7 8</td>
</tr>
<tr>
<td>Intermediate 41-54</td>
<td>12.3%</td>
<td>Ductal Neoplasm</td>
<td>1 2 3 4 5 6 7 8</td>
</tr>
<tr>
<td>High &gt;55</td>
<td>19.2%</td>
<td>DCIS</td>
<td>1 2 3 4 5 6 7 8</td>
</tr>
</tbody>
</table>

* Preferred options are “guidelines” only. Physician and patient have all 8 strategies available.

*We are developing immune based neoadjuvant protocols for highest risk DCIS* where risk may be greater than “DCIS” implies.

**Time Can Be Used as the Discriminator of Who Needs Surgical Intervention**

- For those whose DCIS recede or disappear, perhaps no further surgical therapy is needed
- For those who DCIS do not change, close followup may be appropriate
- For those whose DCIS progress, they are declaring the need for more aggressive intervention

DCIS is NOT an emergency, nor a life threatening cancer. We MUST enable an approach that allows us to learn and better inform patients.

**Example of integrating disease dynamics to change classification and treatment**

If we continue on the same clinical path, we cannot hope to see change

**IF WE STUDY AN ALTERNATIVE APPROACH, WE MAY BE SURPRISED AT WHAT WE LEARN**