Why the Term of Low Grade Ductal Carcinoma In Situ Should be Changed to Borderline Breast Disease: Diagnostic Issues and Clinical Implications

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The Plan

- Summarize the current challenges associated with the diagnosis of low grade ductal carcinoma in situ versus atypical ductal hyperplasia
- Define a rationale to abandon the term of low grade ductal carcinoma in situ and use the term borderline breast disease
- Discuss different strategies for clinical management and long term follow up of patients diagnosed with borderline breast disease
Why the Emphasis on Low Grade Ductal Carcinoma In Situ?
Low Grade Ductal Carcinoma In Situ

- Common: screening mammography has resulted in increased number of image detected biopsies and the diagnosis of this disease.
- The distinction from atypical ductal hyperplasia has remained a diagnostic challenge.
- There are more chances of over diagnosis and overtreatment:
  - More expense
  - More patients anxiety
Neoplastic Progression

- Normal
- Hyperplasia
- Atypical Hyperplasia
- Carcinoma In Situ
- Invasive Cancer

Biomarker changes
Cellular changes

Radiologic changes
Anatomic changes
<table>
<thead>
<tr>
<th>Condition</th>
<th>Er</th>
<th>Ki-67</th>
<th>Prog.</th>
<th>Apopt.</th>
<th>RR</th>
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<tbody>
<tr>
<td>Non-Proliferative</td>
<td>10-30%</td>
<td>≤1%</td>
<td>Balanced</td>
<td></td>
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<tr>
<td>Hyperplasia</td>
<td>60%</td>
<td>~3%</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Atypia</td>
<td>90%</td>
<td>~5%</td>
<td></td>
<td></td>
<td>5</td>
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<tr>
<td>In Situ</td>
<td>50%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td>10-20</td>
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IntraEpithelial Neoplasia

ER: Estrogen Receptor
Ki-67: Ki-67 Index
Proliferation and apoptosis balanced
RR: Risk Ratio
Ductal Carcinoma In Situ

“DCIS is a heterogeneous disease characterized by neoplastic proliferation of ductal epithelial cells with no evidence of stromal invasion”
Ductal Carcinoma In Situ

Determinants of tumor behavior

- Morphologic features
  - Nuclear grade
  - Presence or absence of necrosis
  - Growth patterns

- Multicentricity/multifocality
Molecular Biology of DCIS

- High grade lesions are often associated with unfavorable biological markers.
- Genetic alterations and loss of heterozygosity at various chromosomal loci differ according to DCIS pattern and grade.
- Low grade lesions are associated with the “Low Nuclear Grade Breast Neoplasia Family”
Columnar Cell Change

- Columnar Cell Lesions (CCL)
- Columnar Alteration with Prominent Apocrine Snouts and Secretions (CAPSS)
- Atypical Cystic Lobule
- Clinging Carcinoma
- Flat Epithelial Atypia
Columnar Cell Lesions/Flat Epithelial Atypia: Outcome Studies

- Eusebi et al. 1994
  - Long-term follow up of over 19 years of 25 cases: No evidence of subsequent cancer

- Bijker et al. 2001
  - 5.4 year follow up of 50 cases with atypia: No evidence of subsequent cancer event
Columnar Cell Lesions/Flat Epithelial Atypia: Indirect Evidence for Precursor Status

- Association with known atypia, LCIS, DCIS, low grade and tubular carcinoma
- Loss of heterozygosity comparable to adjacent known atypia
- Common biomarkers and oncogenes: ER/PR, Cyclin D, Bcl-2
## Flat Epithelial Atypia

<table>
<thead>
<tr>
<th>Author</th>
<th>Evidence for Follow Up Surgical Excision</th>
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<tbody>
<tr>
<td>Guerra-Wallace MM, et al 2004</td>
<td>13%</td>
</tr>
<tr>
<td>Kunju LP, et al 2007</td>
<td>21%</td>
</tr>
<tr>
<td>Ingegnoli A, et al 2009</td>
<td>20%</td>
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</table>
Ductal Carcinoma In Situ

Precursor Lesion

- May be a direct precursor to invasive cancer
- They are slow in progression and if develop an invasive cancer they are often low grade in nature
- Risk of invasion is limited to ipsilateral breast and generally same quadrant and site
Atypical Ductal Hyperplasia

Morphologic Risk Factor

- Indicates increased risk to both breasts
- It is not a precursor for invasive breast cancer
- Difficult to distinguish from low grade ductal carcinoma in situ
ADH Versus DCIS

“An Entity Which Has Some but Not All The Features of Low Nuclear Grade Ductal Carcinoma In Situ”
Borderline Breast Lesions

Morphologic criteria for low grade DCIS
(Page and Anderson 1987)

- Two ductal spaces completely effaced in a single terminal ductal lobular unit
- Monomorphous population
- Non-polarized epithelium
- Cribriform bridges without attenuation
- Uniform lacunar spaces
Borderline Breast Lesions

Morphologic criteria for low grade DCIS (Tavassoli and Norris 1990)

- Minimum involvement of two duct spaces
- Sums of diameters of duct spaces must be $\geq 2\text{mm}$
Interobserver Variability
Hyperplasia versus low grade ductal carcinoma in situ

No Standardized Criteria: 10 Cases, 5 Pathologists

Number of Pathologists in exact agreement/Percent of Cases:
- 5 of 5 agreed in 0% of cases
- 4 of 5 agreed in 20% of cases
- 3 of 5 agreed in 50% of cases

Interobserver Variability

Hyperplasia versus low grade ductal carcinoma in situ

Standardized Criteria: 24 Cases, 6 Pathologists

Number of Pathologists in exact agreement/Percent of Cases

- 6 of 6 agreed in 58% of cases
- 5 of 6 agreed in 71% of cases
- 4 of 6 agreed in 92% of cases

PATTERN OF EXPRESSION OF VARIOUS BIOMARKERS IN ATYPICAL DUCTAL HYPERPLASIA (ADH) AND DUCTAL CARCINOMA IN SITU (DCIS)
The Issue

“Is it possible that ADH and low grade DCIS are in reality represent the spectrum of the same entity?”
Suggested Terminologies

- “Intraepithelial Mammary Neoplasia”
- “Ductal Intraepithelial Neoplasia”
- “Low Nuclear Grade Breast Neoplasia Family”
Borderline Breast Lesions

ADH vs. DCIS

- There is no consensus presently on the criteria that should be adopted and how they should be applied for the distinction between atypical hyperplasia, and carcinoma in situ

Borderline Breast Lesions

**ADH vs. DCIS**

- Morphological criteria for the diagnosis of “atypia”, implying increased breast cancer risk, and *in situ* carcinoma may be improved when it is possible to relate proliferative lesions to specific genetic or biochemical markers.

Atypical Ductal Hyperplasia vs. Low Grade Ductal Carcinoma In Situ

Diagnostic Challenge

- FNA biopsy
- Core needle biopsy
- Surgical biopsy
The story of a patient
The Story

- A self-referred newly diagnosed breast cancer patient was scheduled to undergo mastectomy and lymph node dissection.

- The patient was 32 years old with no risk factors and discovered the mass when showering.

- The breast mass was sampled by core needle biopsy and was diagnosed as an invasive cancer.

- A palpable lymph node was found and was assumed to represent a lymph node metastasis.

- The patient was advised to have mastectomy and axillary dissection followed by chemotherapy.
Biopsy Original Diagnosis

- Invasive moderately differentiated ductal carcinoma.
- Low grade ductal carcinoma in situ.
Review of the biopsy at our institution

Calponin
Follow-up Excisional Biopsy
Consultant Reviews

- **Diagnosis #1**: Atypical apocrine adenosis with sclerosis and associated florid sclerosing adenosis

- **Diagnosis #2**: Low grade apocrine ductal carcinoma in situ, with focal sclerosis, periductal and radial, involving multiples cores
Prone to Error: Earliest Steps To Find Cancer
Doubt About Pathology Opinions for Early Breast Cancer - NYTimes.com

The New York Times

Well
Tara Parker-Pope on Health

JULY 19, 2010, 9:01 PM

Doubt About Pathology Opinions for Early Breast Cancer

By TARA PARKER-POPE

Advances in imaging technology mean that more and more breast cancers are being detected at the earliest stages — sometimes when the rogue cells are as tiny as a few grains of salt. But now there are new questions about whether many pathologists are able to render reliable opinions on such tiny lesions, according to an extensive New York Times examination of breast cancer cases.

Stephanie Saul of The Times reports that pathology errors put women at risk for unnecessary and disfiguring surgery and potentially harmful radiation treatment.
Discerning the difference between some benign lesions and early stage breast cancer is a particularly challenging area of pathology, according to medical records and interviews with doctors and patients. Diagnosing D.C.I.S. “is a 30-year history of confusion, differences of opinion and under and over treatment,” said Dr. Shahla Masood, the head of pathology at the University of Florida College of Medicine-Jacksonville. “There are studies that show that diagnosing these borderline breast lesions occasionally comes down to the flip of a coin.”

To learn more, read the full report, “Cancer Errors May Increase With Early Test,” then please join Ms. Saul for a discussion below.
The Story of the Patient

The Question

- Whose fault is it?
- Are we overdiagnosing breast cancer?
“The Current Challenges Associated with the Practice of Breast Pathology”
Current Issues In Breast Pathology

- Diversity in tissue handling, processing and reporting
- Insufficient evidence-based correlation between morphology and patient outcome
- Significant interobserver variability in diagnosis and test results
- Communication barriers among physicians involved in breast care
Current Issues In Breast Pathology

- There are no uniform guidelines to measure the rate of diagnostic errors.
- Fear of disclosure and medicolegal issues limits the reporting of diagnostic errors.
- There are many look-alikes in breast pathology that can mimic cancer.
Current Issues in Breast Pathology

- Breast pathology is considered as a component of general surgical pathology
- Breast pathology fellowships are not accredited by ACGME
- Referral of pathology samples to commercial laboratories impairs communication
Suggestions

- To acknowledge the challenges associated with the current practice of breast pathology
- To design studies that can appropriately analyze the problems and quantitate their impact on therapy, patient outcome and health economy
Suggestions

- Establishment of quality assurance programs
  - Internal quality measures
    - Consensus slide conference
    - Mandatory second review of cancer cases
    - Mandatory adherence to established guidelines

- Second opinion
  - The review of outside pathology slides and reports by a local pathologist before the initiation of cancer therapy

- Involvement in external quality assurance programs
Borderline Breast Lesions

The Suggestions

- Abandon the term of “Low Grade Ductal Carcinoma In Situ”
- Use the term of “Borderline Breast Disease”
- Completely remove the entire lesion
- Offer risk assessment/risk reduction options
The Models to Follow

- Offer the options of “wait and watch” for borderline lesions/low grade DCIS similar to low grade prostate cancer

The Impact

- Reduced anxiety to the patient and her family
- Minimizing unnecessary expense
- Restoring patient trust
“ADH vs. Low Grade DCIS”
The Urgent Need

- Better define the morphologic and biologic characteristics of spectrum of high risk proliferative and precursors breast lesions
- Change the concept, terminology, and the pattern of practice

Loss of Tumor Suppressor Genes Linked to DCIS Breast Cancer Progression

Retinoblastoma (RB) status is associated with ductal carcinoma in situ (DCIS) recurrence and invasive progression.

The Significance?

- Over 1.1 million women are diagnosed with breast cancer each year across the globe.
- Estimated diagnostic errors in breast pathology may be about 2%.
- It appears that a significant number of women will receive under/over treatment.
The Message

Raising the Bar:
A plea for standardization and improved quality of breast pathology
