The pathologist is central to the team approach needed to manage the patient with breast cancer

- Basic pathology
- Evolving issues in LCIS
In 2013, what do we need to know to treat the patient?

- **Stage:**
  - Tumor size
  - Nodal status
  - Metastasis
TNM staging

T1

T1a: >1-5 mm
T1b: >5-10 mm
T1c: >10-20 mm

T2

>20-50 mm

T3

>50 mm

T4a

Direct extension to chest wall not including pectoralis muscle.

AJCC 7th edition
TNM staging

AJCC 7th edition
TNM staging

pN1mi
>0.2-2 mm or more than 200 cells

pN1a: 1-3 nodes
(at least one tumor deposit >2.0 mm)

pN2a: 4-9 nodes
(at least one tumor deposit >2.0 mm)

pN3a: ≥10 nodes
(at least one tumor deposit >2.0 mm)

AJCC 7th edition
<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
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<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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5-Year Survival Rate of Female Breast Cancer Diagnosed in 2003-2004
Weill Cornell vs National Cancer Database Average

<table>
<thead>
<tr>
<th>Stage</th>
<th>WC</th>
<th>NCDB</th>
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<tr>
<td>Stg 0</td>
<td>99.5</td>
<td>95.6</td>
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<tr>
<td>Stg 1</td>
<td>95.6</td>
<td>92.1</td>
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<tr>
<td>Stg 2</td>
<td>90.1</td>
<td>85.2</td>
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<tr>
<td>Stg 3</td>
<td>82.1</td>
<td>66</td>
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<tr>
<td>Stg 4</td>
<td>25</td>
<td>21.9</td>
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In 2013, what do we need to know to treat the patient?

- **Stage**
- **Biomarkers:**
  - ER, PR, HER2
  - Ki 67
In 2013, what do we need to know to treat the patient?

- Stage
- **Biomarkers:** ER, PR, HER2
  - Ki 67
- **Surgical margins**
- **Grade, Lymphovascular invasion**
Specimen types

- Needle core biopsy
- Excisional surgical biopsy
- Mastectomy
Needle core biopsy
Excisional biopsy
Assessing margins
Breast cancer:

Negative Margins:

Positive Margins:

breastcancer.org
Duct ca *in situ* <1 mm of margin

Invasive carcinoma at margin
Routine stain

Hematoxylin-eosin, 
H&E

Immunostain

ER
Basic pathology
Histopathology of the breast

Normal  Hyperplasia  Atypical  In Situ Ca  Invasive Ca
Types of *in situ* carcinoma

- **Ductal carcinoma *in situ***
  - Architecture: solid, cribriform, micropapillary
  - Nuclear grade
  - Luminal necrosis

- **Lobular carcinoma *in situ***
  - Classical & Pleomorphic
Determining size of tumor
Survival by size
2468 cases

Tabar Cancer 1999;86:449
Determination of size is problematic in a multifocal or multicentric tumor.
Relation between histologic grade and breast cancer-specific survival

Rakha, J Clin Oncol; 26:3158, 2008
The most common grading system of invasive duct ca is based on Bloom-Richardson’s system

- Tubule formation: 1 2 3
- Nuclear grade: 1 2 3
- Mitotic activity: 1 2 3

- Score: 1-3 for each feature: range 3-9

- Grade I: 3-5
- Grade II: 6-7
- Grade III: 8-9
Well-differentiated tubular, grade I (1+1+1) tumor: good tubule formation, low nuclear grade, low mitotic activity
Poorly-differentiated, grade III (3+3+3) tumor  no tubule formation, high nuclear grade, high mitotic activity
Mucinous carcinoma
Typical Triple-Negative Carcinoma

CT

PET

Histology

Gross
Survival by lymphovascular invasion: 374 breast cancer cases

$p < 0.005$, log-rank test

Lymphovascular invasion
In 2013, what do we need to know to treat the patient?

- Stage
- Biomarkers: ER, PR, HER2
  - Ki 67
- Surgical margins, Grade, Lymphovascular invasion
- Molecular profile of the tumor
Hierarchical clustering of breast-cancer samples on basis of gene array RNA expression data
How do we define these intrinsic subtypes using the pathologic tools that we have?
INTRINSIC SUBTYPES

- **Luminal A**
  
  ER and/or PR positive, HER2 negative, Ki67 low
INTRINSIC SUBTYPES

- **Luminal A**
  ER and/or PR positive, HER2 negative, Ki67 low
- **Luminal B**
  ER and/or PR pos, HER2 negative, Ki67 high
  (Some allow HER2 positive in this group)
INTRINSIC SUBTYPES

- **Luminal A**
  ER and/or PR positive, HER2 negative, Ki67 low

- **Luminal B**
  ER and/or PR positive, HER2 negative, Ki67 high

- **HER2 enriched**
  ER and PR negative, HER2 positive
INTRINSIC SUBTYPES

- **Luminal A**
  ER and/or PR positive, HER2 negative, Ki67 low

- **Luminal B**
  ER and/or PR positive, HER2 negative, Ki67 high

- **HER2 enriched**
  ER and PR negative, HER2 positive

- **Triple negative**
  ER, PR, and HER2 negative
Correspondence between Molecular Class and Clinicopathological Features of Breast Cancer

<table>
<thead>
<tr>
<th>Pathological Variables</th>
<th>Basal-like (%)</th>
<th>Luminal A (%)</th>
<th>Luminal B (%)</th>
<th>HER2-like (%)</th>
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<tbody>
<tr>
<td>HER2-positive (IHC)</td>
<td>10</td>
<td>12</td>
<td>20</td>
<td>100</td>
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<tr>
<td>ER-positive (IHC)</td>
<td>12</td>
<td>96</td>
<td>97</td>
<td>46</td>
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<tr>
<td>Grade III</td>
<td>84</td>
<td>19</td>
<td>53</td>
<td>74</td>
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<tr>
<td>Tumor size &gt;2 cm</td>
<td>75</td>
<td>53</td>
<td>69</td>
<td>74</td>
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<tr>
<td>Node-positive</td>
<td>40</td>
<td>52</td>
<td>65</td>
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</table>
Intrinsic Subtype Prognosis for Relapse-Free Survival (RFS)

710 node-negative patients, no systemic adjuvant therapy

Parker J S et al. JCO 2009;27:1160-1167
Evolving concepts of Lobular Carcinoma *In Situ*

Winn, JNCCN ’06:4:431  Anderson, JNCCN:’06: 511
Normal duct & lobule  Lobular carcinoma *in situ*
Lobular Carcinoma *In Situ*

>50% of 1 lobule is involved
Atypical Lobular Hyperplasia
<50% of 1 lobule is involved

ALH vs LCIS:
difference is quantitative not qualitative
“Classical” LCIS

- *In situ* ca in lobules
- Microscopic disease
- Multicentric, ~85%
- Bilateral, ~40%
- No palpable mass
- No x-ray abnormality
<table>
<thead>
<tr>
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<th>“Classical”</th>
<th>“Pleomorphic”</th>
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<tbody>
<tr>
<td>Cells</td>
<td>small</td>
<td>large</td>
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<tr>
<td>Nuclei</td>
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<td>pleomorphic</td>
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<tr>
<td>Nucleoli</td>
<td>-</td>
<td>+</td>
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<tr>
<td>X-ray</td>
<td>negative</td>
<td>abnormal</td>
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<tr>
<td>Necrosis</td>
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<td>+/-</td>
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</table>
Summary: Pleomorphic LCIS

- may have greater tendency for invasion
- should be managed similar to DCIS with complete excision
- long-term follow-up studies needed

Georgian-Smith AJR ‘01;176:1255. Eusebi Hum Pathol ’92;23:655
E-cadherin is a marker for lobular ca

- Duct cells are held together by a complex of molecules, chiefly: E-cadherin- a glycoprotein
- E-cadherin is (+) in ductal ca & (-) in all lobular ca, including “pleomorphic” LCIS

De Leeuw J Pathol 1997:183;404
LCIS versus DCIS

H&E stain

E-cadherin stain

DCIS

LCIS
Lobular neoplasia: risk indicator & a precursor of invasive ca

- if ALH/LCIS is a precursor, subsequent cancers should be in the same breast

- 252 women with lobular neoplasia: 50 developed invasive cancer, 68% in the ipsilateral breast, 4% bilateral

Page  Lancet 2003;361:125
If ALH/LCIS is a risk factor, risk of invasive breast cancer should be the same in both breasts.

- Risk of developing invasive breast cancer after LCIS is 7.1% at 10 years with equal predisposition in either breast.
- Lobular type of invasive cancer is more common in women with prior LCIS than in women with no prior LCIS.
How do we manage a patient with LCIS?

- Do all patients with LCIS on core biopsy require further excision?
  - Generally, yes. If the core biopsy is large and the radiologic abnormality is concordant with pathology, close follow up may be reasonable.
How do we manage a patient with LCIS? 
Surveillance

NCCN guidelines for follow-up:
- Physical exam every 6 to 12 months for 5 years and then annually
- Annual diagnostic mammography

ACS guidelines re MRI screening:
- Insufficient evidence to recommend for or against MRI screening

NCCN v.3.2010, Porter ‘07 Ann Surg Oncol 14:1051, Saslow CA ‘07 57:75
How do we manage a patient with LCIS? 

Medication

NSABP-P1 (Women >35):
Tamoxifen reduced risk of developing breast cancer by 56% in women with LCIS

NSABP-P2 (POSTmenopausal women):
Raloxifene was almost as good as tamoxifen to reduce the risk of breast cancer in women with LCIS with less side effects

Primary Dx: Extensive lymphovascular invasion by lobular carcinoma

2nd Opinion Dx: LCIS with artefact simulating lymphovascular invasion
Pathology 2nd Opinions are Crucial Before Initiation of Treatment; Some Common Misconceptions Need to be Dispelled

- **Initial pathology diagnosis is always correct**: False, up to 4% of initial diagnosis is incorrect

- **2nd opinion is not necessary for simple cases**: False, simple diagnosis may be incorrect, e.g. sclerosing adenosis may be mistaken for carcinoma
Pathology 2nd Opinions: Some Common Misconceptions

- Pathology 2nd Opinions Delay Treatment: False, No Delay Occurs, At Most 2-3 Days

- Cost of 2nd Opinion is Prohibitive: False, The Cost is Minimal, and is Covered by Insurance; and its Value is Immense