Surgical Pathology Issues of Practical Importance

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

Received fresh, the specimen consists of a mass of firm tissue measuring 3 x 2.5 x 2 cm. in greatest dimensions. There is surrounding adipose tissue. The specimen measures 6 x 4.5 x 3 cm. in greatest dimension in its entirety. Representative sections are submitted. Summary of sections: Frozen section control-FSC-1 biopsy-BX-1.

MICROSCOPIC REPORT:

1. INFILTRATING DUCT CARCINOMA OF BREAST, BIOPSY.
In 2014, what do we need to know to treat the patient?

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

T1

>1–5 mm = T1a

>5–10 mm = T1b

>10–20 mm = T1c

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
## AJCC Breast Cancer Staging System

### TNM

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5 Year Survival Female Breast Cancer
Diagnosed 2003 – 2006 NYPWC

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<td>Stg 3</td>
<td>86%</td>
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<td>Stg 4</td>
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5 Year Survival Female Breast Cancer
Diagnosed 2003 – 2006 NYPWC vs NCDB

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<td>98%</td>
<td>96%</td>
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<tr>
<td>Stg 1</td>
<td>96%</td>
<td>92%</td>
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<td>Stg 2</td>
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<td>85%</td>
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<tr>
<td>Stg 3</td>
<td>86%</td>
<td>67%</td>
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<td>Stg 4</td>
<td>28%</td>
<td>21%</td>
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In 2014, what do we need to know to treat the patient?

- **Stage**
- **Biomarkers:**
  - ER, PR, HER2
  - Ki 67
In 2014, 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
Duct ca *in situ* <1 mm of margin

Invasive carcinoma at margin
Routine stain

Hematoxylin-eosin, H&E

Immunostain
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.
Stereotactic Core US-guided Core Stereotactic Core
How would you stage this tumor?

- 1.3 cm invasive lobular carcinoma reported on needle core biopsy
- The lumpectomy showed 0.9 cm invasive lobular carcinoma
- Final ‘T’ Stage: T1c or T1b?
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
Secretory ca
Metaplastic ca
Other Triple-Negative Carcinoma
Medullary ca
Adenoid cystic ca
Survival by lymphovascular invasion: 374 breast cancer cases

\[ p < 0.005, \text{ log-rank test} \]

Lymphovascular invasion
In 2014, 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 (often PR negative), 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

- **Basal-like**
  ER, PR, and HER2 negative
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
Circulating tumor cells—Can they guide us for treatment decisions?
Circulating tumor cells in women with metastatic breast cancer

- CellSearch epithelial cell kit by Veridex
- 7.5 cc EDTA whole blood sample
- Identifies cells expressing epithelial cell adhesion molecule and cytokeratin, and lacking CD45=CTC

Cristofanilli et al, NEJM 351: 781, 2004
Circulating Tumor Cells in women with metastatic breast cancer: An independent predictor of survival in 185 untreated stage IV patients

Cancer 113:2422, Nov 1, 2008
Elevated CTC’s after treatment predicted shorter progression-free survival

CTC’s: A marker of progression of metastatic breast cancer

Does this mean that a clinically stable Stage IV patient should change treatment if CTC’s are elevated early in course of treatment?
SWOG 0500 asked that question
Changing therapy at 21 days based on persistent elevation of CTC’s did not effect PFS or OS.

Smerage J B et al. JCO 2014;32:3483-3489
Evolving concepts of Lobular Carcinoma *In Situ*
## LCIS

**“Classical”** | **“Pleomorphic”**
---|---
Cells | small | large
Nuclei | regular | pleomorphic
Nucleoli | - | +
X-ray | negative | abnormal
Necrosis | - | +/-
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
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
- Annual diagnostic mammography

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

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

How do we manage a patient with LCIS?

Medication

NCCN includes exemestane and anastrazole in the choice of risk-reduction agents

(MAP-3 and IBIS-II placebo controlled trials)

However, aromatase inhibitors are not currently FDA approved for breast cancer risk reduction
Primary Dx: Extensive lymphovascular invasion by lobular carcinoma

2nd Opinion Dx: LCIS with artifact 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