Case based workshop on handling breast pathology specimens: Test yourself!

Goals and Objectives

• Be able to critically approach individual breast cases when determining sampling strategies
• Incorporate imaging findings into breast tissue grossing strategies
• Review approaches for challenging cases

Which case meets the CAP cold ischemic time for breast specimens tested for ER/PR/HER2?

A. Time received: 8 am   Time in formalin: 8:30 am
B. Time removed: 10 am   Time in formalin: 10:45 am
C. Time accessioned: 3:30 pm   Time grossed: 4pm
D. Time sliced: 3:30 pm   Time in formalin: 4 pm
Which specimen is most critical to have a short cold ischemic time on?

A. Mastectomy for a 2.0 cm invasive ER positive, HER2 negative breast cancer
B. Mastectomy for 8 cm area of MRI enhancement with a prior core biopsy diagnosis of high grade DCIS
C. Lumpectomy for a 1.0 cm HER2 positive invasive breast cancer
D. Sentinel lymph node sample from a mastectomy for invasive cancer

What’s wrong with this grossing technique?

What can you tell from the way this mastectomy was sampled?
Which of the following is NOT necessary to know prior to sampling a breast surgical case?

A. The total number of lesions expected
B. The expected size of the lesion(s)
C. If the patient has received neoadjuvant chemotherapy
D. The ER/PR/HER2 status of the invasive cancer

Example of information to be collected from imaging/clinical records before grossing a surgical breast case:

<table>
<thead>
<tr>
<th>Targeted lesions expected:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of lesions expected:</td>
</tr>
<tr>
<td>Post-neoadjuvant chemotherapy?:</td>
</tr>
<tr>
<td>For each expected lesion determine the following:</td>
</tr>
</tbody>
</table>

| Label of lesion used in imaging reports: [ex. L1, R1] |
| Targeted imaging finding: [mass, asymmetry, calcifications, MRI enhancement] |
| Expected location: [relative location in a lumpectomy, distance and location relative to other lesions, in a mastectomy the quadrant, o'clock and distance from nipple or margins.] |
| Expected size/extent: [for post-neoadjuvant cases, need to know pre-treatment size] |
| Expected clip biopsy: [prior biopsy documented with clip placement/prior biopsy documented without clip placement/no prior biopsy or clip placement documented] |

Need for accurate imaging summaries; Required part of gross template.
We require this information be gathered by the resident covering frozen.

Which imaging report is most relevant to read prior to grossing a breast surgical case?

A. Mammogram
B. Ultrasound
C. MRI
D. All of the above
Imaging Findings:

**Mammography:** Detects calcifications, many masses, architectural distortions, asymmetries.

**Ultrasound:** Can be used for screening but not as sensitive or specific. Usually used to perform a biopsy of a mass-lesion or other finding initially seen on mammography or MRI (easier).

**MRI:** Usually performed only in high risk pt or to evaluate extent of disease. Detects enhancement of "active" areas (ex. Invasion, DCIS, LCIS, proliferative lesions). Often larger area than initially detected on mammo.

For sampling purposes: Use largest abnormal area.

Case Study:

- Imaging and clinical reports:
  - Mammography: R1 = 1.5 cm area of pleomorphic calcifications and mass at 5:00, 3 CFN
  - Ultrasound: 1.2 cm mass correlating with R1 → biopsied and ribbon clip placed
    - Core biopsy = Invasive ductal carcinoma
  - MRI: 1.3 cm mass (R1) with 6.6 x 4.5 x 3.5 cm of surrounding enhancement (R2) from 4-7:00 → not biopsied

Expected findings summary for gross template:

**Targeted lesions expected:**
- Total number of lesions expected: 2 (R1 and R2)
- Post-neoadjuvant chemotherapy: No

For each expected lesion determine the following:

**Lesion 1:**
- Label of lesion used in imaging reports: R1
- Targeted imaging finding: Mass with associated calcifications
- Expected location: 5:00, 3 CFN
- Expected size/extent: 1.5 cm
- Expected clip/biopsy: prior biopsy documented with ribbon clip placement

**Lesion 2:**
- Label of lesion used in imaging reports: R2
- Targeted imaging finding: MR Enhancement
- Expected location: 4-7:00 surrounding R1
- Expected size/extent: 6.6 cm AP x 4.5 cm ML x 3.5 cm SI
- Expected clip/biopsy: No prior biopsy
Diagram of expected findings

Lesion 1:
- Label of lesion used in imaging reports: R1
- Targeted imaging finding: Mass with associated calcifications
- Expected location: 5:00, 3 CFN
- Expected size/extent: 1.5 cm
- Expected clip/biopsy: prior biopsy documented with ribbon clip placement

Lesion 2:
- Label of lesion used in imaging reports: R2
- Targeted imaging finding: MR Enhancement
- Expected location: 4-7:00 surrounding R1
- Expected size/extent: 6.6 cm x 4.5 cm x 3.5 cm
- Expected clip/biopsy: No prior biopsy

Where are R1 and R2?

Where are R1 and R2 expected?

Does the number of wires correlate with the number of lesions?
How much tissue should be sampled from this lumpectomy?

Staging Cases with Multiple foci of invasion

- 40 year old female presented for screening mammography
- Work up revealed 3 irregular masses in the upper outer quadrant by mammography and ultrasound
- MRI with surrounding enhancement over 6 cm
3 grossly visible masses, spanning 6.0 cm
Sizes: 2.2 cm, 2.0 cm, and 0.9 cm
No invasion in samples between masses
DCIS present in surrounding tissue spanning 6.0 cm

How should she be staged?

A. > 5.0 cm = pT3
B. > 5.0 cm with multiple primaries = pT3(m)
C. 2.1-5.0 cm = pT2
D. 2.1-5.0 cm with multiple primaries = pT2(m)
E. 1.0-2.0 cm = pT1c(m)

Answer:

D. 2.1-5.0 cm with multiple primaries = pT2(m)
If could have documented contiguous extent between the closest masses would have staged as largest contiguous extent
Need to sample tissue between masses!!
Multiple invasive carcinomas

- Macroscopically distinct cancers should be assigned a pT stage based on single largest focus
- Use “m” qualifier to indicated multiple
- Samples between masses to exclude contiguous
- Use judgment, imaging correlation, sections between masses to evaluate continuity

Some cases are challenging and may require correlation with imaging and other histological findings.

6 categories of cancers with “multiple foci”

1. Extensive carcinoma in situ with multiple foci of invasion
2. Invasive carcinoma with smaller satellite foci of invasion (often satellites are irregular extensions, e.g., lobular)

6 categories of cancers with “multiple foci”

3. Invasive carcinoma with extensive lymph-vascular invasion
4. Biologically distinct invasive carcinomas (widely separated, grade, IHC different)
6 categories of cancers with “multiple foci”

5. Post-neoadjuvant foci in tumor bed
6. Transected invasive cancer in more than one specimen (difficult to tell if one lesion, correlate with imaging)

How should this case be sampled?

How should this case be sampled?
Clip Migration

- Blue arrows: Targeted calcifications
- White arrows: Clip
- Be aware that clip may not always be at lesion of interest!
Estimating Size Based on Gross and Microscopic Information:

“Representative sections of the biopsy site area and surrounding fibrous tissue are submitted sequentially in cassettes A1-15 and additional representative sections of non-fibrous tissue are submitted in cassettes A16-20”

Invasive cancer is present in slides A2, A3, A5, A7, A8 and A10

*How big is the invasive cancer?*

Estimating size based on gross and microscopic information

4 consecutive 0.4 cm thick slices involved = 1.6 cm
Size in largest composite span: 1.2 cm
Size on single slide: 0.9 cm

Consistent and accurate slice thickness can make big size differences!

Is this case well-sampled/mapped?

Targeted finding: Single 2.5 cm site of invasion
Is this case well-sampled(mapped?)

Prior biopsies: DCIS at 3:00 biopsy site (clipped) and at 11:00 biopsy site (clipped)

Left breast
outer 1/3

Lateral → medial

Sampling DCIS goals:
- Microscopic examination of the entire region of the targeted lesion(s) to identify possible invasion
- Margins

For specimens with a known diagnosis of DCIS (e.g., by prior core needle biopsy) it is highly recommended that the entire specimen is examined using standard whole slide sampling to exclude the possibility of invasion. To completely evaluate the margins, and to aid in determining extent, if an entire excisional specimen or grossly evident lesion is not examined microscopically, it is helpful to note the approximate percentage of the specimen or lesion that has been examined.

Carcinomas present in excisions removed for lesions seen by MRI studies are generally not grossly evident and not seen on specimen radiography.
Special Clinical Scenarios

• Single lesion: Invasion
  – Document size in 3 dimensions for \( T \) stage
  – Watch out for invasive lobular cases being larger than expected!

• Extensive DCIS
  – Per CAP: submit all if possible! \textit{Need to rule out invasion}

• Invasion but not grossly obvious

• Multiple lesions:
  – Document size of each and if they connect
  – Post-neoadjuvant chemotherapy:
    – Sample entire tumor bed to \textit{quantify extent of residual disease}

Always sample closest margins!

How to sample post-lumpectomy?

Small invasive carcinomas with prior core needle biopsy

• Do not add dimensions from different procedures!

• Do not include large areas of biopsy site

• Use size in needle core, excision and imaging to determine most appropriate
Locally advanced breast cancers: Document skin involvement

Reporting Extent:

- CAP checklist required elements:
  - If skin, nipple or skeletal muscle present
- If skeletal muscle involved:
  - Chest wall invasion requires invasion beyond pectoralis muscle to be T4a
- If skin involved:
  - Note if satellite skin nodules (T4b)
  - Note if involving skin with or without ulceration (T4b)
  - Carcinoma in dermal lymphatic spaces is not considered inflammatory carcinoma unless clinically involving > 1/3 of the breast (AJCC 7th ed)

Inflammatory Breast Cancer

- Carcinoma plugging dermal lymphatics
- A CLINICAL diagnosis

Not all breast cancers present as a lump
Evaluation and staging Post-neoadjuvant

Untreated, grossly obvious invasive cancer

Post neoadjuvant treatment scar

pCR Predicts Survival in Aggressive Subtypes of Breast Cancer

- In Triple negative and HER2 positive
- ER positive less clear

Aggressive types that don’t achieve pCR may get additional therapies
Case: Post-neoadjuvant

- 35 year old female with locally advanced invasive breast cancer
- Pre-therapy: 6.5 cm with at least one biopsy confirmed positive lymph node (T3N1M0)
- Now status post neoadjuvant chemotherapy with good imaging response

Gross evaluation

- Pre-treatment imaging size: 6.5 x 5 x 4.5 cm area
- Gross finding: Scar and fibrosis over 7 cm area
- Some more firm areas but difficult to tell extent of any residual disease, if present
- Sections are submitted to map out potential largest extent

Post Neoadjuvant Chemotherapy: How to sample?
Microscopically many slides contain just scar.

But residual microscopic foci are identified as scattered clusters.

And two more cellular mass-like areas are identified.
Extensive residual DCIS is present throughout the scar as well.

Map of residual disease

What is the appropriate pT stage?

A. 5.5 cm of residual invasive cancer = ypT3
B. Multiple foci of residual invasive cancer over 5.5 cm = ypT3(m)
C. Single largest focus of 2.0 cm = ypT1c
D. Multiple foci of residual invasive cancer, largest focus 2.0 cm = ypT1c(m)

Establishing pT post-therapy

- Use "y" prefix!
- Same criteria as pre-therapy, but will more frequently have to use (m) modifier
- Stage based on largest single contiguous area
- Use (m) modifier if more that one discontinuous area of residual cancer (does not have to be "separate primary" in this setting)
- Accuracy requires mapping out residual areas of invasion
Staging lymph nodes post-neoadjuvant: 
Same as pre!
But cases with *any* residual metastatic disease are not considered to have a pCR

**CAP guidelines on Neoadjuvant Reporting**

- Classification of degree of response to therapy is optional in checklist
- Clinical utility =
  - Useful for prognosis (correlates with amount of residual invasive disease)
  - May qualify for additional therapy in a trial based on extent of residual disease

**Systems of reporting response to therapy:**

- AJCC Residual Tumor (R)
- NSABP B-18 system
- Miller-Payne
- Chevallier
- Sataloff
- Residual Cancer Burden (MD Anderson)
  - Clinicians request this
  - We report these elements at Stanford
MD Anderson RCB Calculator

RCB: Calculating Cellularity

http://www.mdanderson.org/breastcancer_RCB
What is the gross differential of these lesions?

How to assign pN stage?

2 LNs with micro-metastatic deposits, 2 LNs with ITCs:
A. pN1a (1-3 axillary nodes positive)
B. pN2a (4-9 axillary nodes positive)
C. pN1mi (micrometastatic disease)
D. pN0(i+) (isolated tumor cells)

Per AJCC 7th and 8th ed:
• Need at least one macro-metastatic (> 2.0 mm) deposit to get to pN1a
• Once you do, then count micro-metastatic+ LNs in the total lymph node count
• Don’t count ITC+ LNs in total positive lymph node count
Example continued:

• 2 macro-metastatic deposits
• 2 micro-metastatic deposits
• 2 ITC+ lymph nodes
• What is the pN stage?
  A. pN1a (1-3 axillary nodes positive)
  B. pN2a (4-9 axillary nodes positive)
  C. pN1mi (micrometastatic disease)
  D. pN0(i+) (isolated tumor cells)

CAP guidelines recommend:

• Listing how many sentinel and non-sentinel lymph nodes examined and how many are positive
• Listing all lymph nodes categories and detailing how many are in each category
• Listing the size of the largest metastatic focus

Example:

• Lymph node involvement:
  — Sentinel nodes: 2 of 3 total sentinel nodes with carcinoma
  — Non-sentinel nodes: 0 of 19 non-sentinel nodes with carcinoma
  — Total number of nodes with macrometastases: 0
  — Total number of nodes with micrometastases: 2
  — Total number of nodes with isolated tumor cells: 2
  — Size of largest metastatic deposit: 0.1 cm
  — *Extra-nodal extension: Not identified

*optional per CAP, but can change clinical decision about including axilla in radiation field
Additional pearls from AJCC:

- Use of “sn” modifier has been restricted
  - When 6 or more SLN’s are identified on gross examination, the “sn” modifier should be omitted
- Cancer in axillary fat can count as positive LN (be sure not an axillary primary)
- Intra-mammary LNs can count in the axillary total count

Know what the goals and issues for each case are!

- Get access to clinical information needed
- Talk with your pathologists, attend tumor boards, clinical conferences, updates
- Know the clinical guidelines: