

## Protocol for the Examination of Specimens from Patients with Invasive Carcinoma of the Breast

**Protocol applies to all invasive carcinomas of the breast of any type with or without ductal carcinoma in situ (DCIS). Includes microinvasion carcinoma and carcinoma with neuroendocrine features.**

### Based on:

AJCC/UICC TNM, 8<sup>th</sup> edition  
CAP Cancer Protocol version: Invasive Breast 4.1.0.0  
CAP Protocol Web Posting Date: January 2018  
AAPA Macroscopic Examination Template Version 2.0  
AAPA Web Posting Date: October 2018

### Revision History:

None

### Summary of Changes:

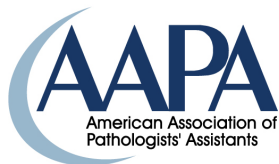
This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol Invasive Breast 4.1.0.0.

### Procedures Covered in this Protocol:

- Biopsies
- Excisions less than total mastectomy with or without axillary contents
  - Localized excision
  - Excisions without localization
- Additional excision performed after the definitive resection (re-excision of surgical margins)
  - Complete
  - Select
- Total mastectomy with or without axillary contents
  - Simple mastectomy
  - Skin-sparing mastectomy
  - Nipple-sparing mastectomy
  - Modified radical mastectomy
  - Radical mastectomy

### Authors:

Moses Bargét, MS, PA(ASCP)<sup>CM\*</sup>  
Department of Pathology, Tarrant Pathology Associates, Fort Worth, TX  
Courtney Hyland, PA(ASCP)  
Mayo Clinic, Rochester, MN  
Monica Kendall, PA(ASCP)<sup>CM</sup>  
Mayo Clinic, Rochester, MN  
Darryl Kinnear, PA(ASCP)<sup>CM</sup>  
Department of Pathology, Baylor College of Medicine, Houston, TX  
Mary Latino, MHS, PA(ASCP)<sup>CM</sup>  
Department of Pathology, Western Connecticut Health Network, Danbury, CT  
John Lehman, PA(ASCP)<sup>CM</sup>  
Mayo Clinic, Rochester, MN  
Stephanie Miller, PA(ASCP)<sup>CM</sup>  
Providence Health & Services, Portland, OR  
Brooke Montgomery, MS, PA(ASCP)<sup>CM\*</sup>  
Department of Pathology, The University of Kansas Hospital, Kansas City, KS



## AAPA Macroscopic Examination Guidelines: Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench

Liam Nolan, MS PA(ASCP)<sup>CM</sup>  
Department of Pathology, Mt Sinai Hospital, Chicago, IL  
Chandra Pettry, PA(ASCP)<sup>CM</sup>  
Mayo Clinic, Rochester, MN  
Tina Rader, PA(ASCP)<sup>CM</sup>  
Drexel University College of Medicine, Philadelphia, PA  
Erica Reed, PA(ASCP)<sup>CM</sup>  
Mayo Clinic, Rochester, MN  
James Romnes, BA/BS, PA(ASCP)<sup>CM</sup>  
Department of Pathology, Incyte Diagnostics, Spokane, WA  
Tia Singleton, MHS, PA(ASCP)<sup>CM</sup>  
Department of Pathology, UPMC East, Monroeville, PA  
Mike Sovocool, MHS, PA(ASCP)<sup>CM</sup>  
Pathology Associates of Syracuse, Syracuse, NY  
Dennis Strenk, PA(ASCP)<sup>CM</sup>  
Wisconsin Diagnostic Laboratories, Milwaukee, WI  
Connie Thorpe, PA(ASCP)<sup>CM</sup>  
Department of Pathology, Saint Louis University, St. Louis, MO  
Jon Wagner, PA(ASCP)<sup>CM</sup>  
Department of Pathology, Sutter Roseville Medical Center, Roseville, CA

\*Denotes primary author. All other contributing authors are listed alphabetically.

### Previous Lead Contributors:

#### Art Director | Illustrator Liaison:

Jesse McCoy, BFA, MHS, PA(ASCP)<sup>CM</sup>  
Hampton Roads Pathology, Chesapeake Regional Medical Center, Chesapeake, VA

Illustrations redrawn/modified, with originals created by James Romnes, PA(ASCP)<sup>CM</sup>.

#### Illustrator:

Tami Tolpa



## **AAPA Macroscopic Examination Guidelines: Utilization of the CAP Cancer Protocols at the Surgical Gross Bench**

### **Copyright:**

**© 2018 American Association of Pathologists' Assistants. All rights reserved.**

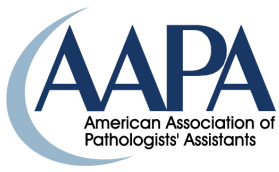
The American Association of Pathologists' Assistants (the "AAPA") hereby authorizes use of The AAPA Macroscopic Examination Guidelines: Utilization of the CAP Cancer Protocols at the Surgical Gross Bench Second Edition (the "Protocols") solely by pathologists' assistants, pathology residents, and/or pathologists (collectively "Laboratory Personnel") within the laboratories in which they work for the purposes of processing of cancer cases and the education of Laboratory Personnel related to the processing of cancer cases (collectively "Permitted Uses"). The modification or creation of derivative works of the Protocols is prohibited. Any reproduction of the Protocols must be of the complete, unmodified Protocols and solely for the Permitted Uses of the Laboratory Personnel within the laboratories in which they work. Reproduction or distribution of: (a) only a portion of the Protocols; (b) all or a portion of these Protocols outside of the laboratories in which the Laboratory Personnel work; or (c) for commercial use of the Protocols beyond the Permitted Uses, is strictly prohibited.

The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

The AAPA cautions that the use of the Protocols in practice may require the use of additional considerations that are beyond the scope of the Protocols. The AAPA does not offer medical advice or diagnoses, or engage in the practice of medicine. The information provided in the Protocols is not intended or implied to be a substitute for the Laboratory Personnel's own training, professional medical opinion, diagnosis, or treatment advice. All content, including text, graphics, images and information contained in the Protocols are for the above stated purposes only. Laboratory Personnel are encouraged to confirm any information provided in these Protocols with other sources. The inclusion of a product name, organization, or service in an AAPA publication, including without limitation the Protocols, should not be construed as an endorsement of such product, organization, or service, nor is failure to include the name of a product, organization or service to be construed as disapproval.

THE AAPA IS NOT RESPONSIBLE NOR LIABLE FOR ANY ADVICE, COURSE OF TREATMENT, DIAGNOSIS OR ANY OTHER INFORMATION, SERVICES OR PRODUCTS THAT LABORATORY PERSONNEL PROVIDE WHETHER OR NOT IN RELATION TO USING THE PROTOCOLS. THE AAPA DOES NOT WARRANT OR MAKE ANY REPRESENTATION REGARDING USE, OR THE RESULT OF USE, OF THE CONTENT OF THE PROTOCOLS IN TERMS OF ACCURACY, RELIABILITY, OR OTHERWISE. THE CONTENT OF THE PROTOCOLS MAY INCLUDE TECHNICAL INACCURACIES OR TYPOGRAPHICAL ERRORS, AND THE AAPA MAY MAKE CHANGES OR IMPROVEMENTS AT ANY TIME. YOUR USE OF THESE PROTOCOLS IS AT YOUR OWN RISK. THE CONTENT IS PROVIDED "AS IS" AND WITHOUT WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THE AAPA DISCLAIMS ALL WARRANTIES, INCLUDING ANY IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, TITLE, OR NON-INFRINGEMENT.

TO THE FULL EXTENT ALLOWED BY THE LAW, THE AAPA, ITS MEMBERS, AFFILIATES, LICENSORS, SERVICE PROVIDERS, CONTENT PROVIDERS, EMPLOYEES, AGENTS, OFFICERS, AND DIRECTORS (THE "AAPA PARTIES") WILL NOT BE LIABLE FOR ANY INCIDENTAL, DIRECT, INDIRECT, PUNITIVE, ACTUAL, CONSEQUENTIAL, SPECIAL, EXEMPLARY, OR OTHER DAMAGES, INCLUDING LOSS OF REVENUE OR INCOME, PAIN AND SUFFERING, EMOTIONAL DISTRESS, OR SIMILAR DAMAGES IN RELATION TO THE PROTOCOLS, EVEN IF THE AAPA PARTIES HAVE BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. IN NO EVENT WILL THE COLLECTIVE LIABILITY OF THE AAPA PARTIES TO ANYONE IN RELATION TO THE PROTOCOLS (REGARDLESS OF THE FORM OF ACTION, WHETHER IN CONTRACT, TORT, OR OTHERWISE) EXCEED THE MINIMUM AMOUNT ALLOWED BY LAW. SOME JURISDICTIONS DO NOT ALLOW THE LIMITATION OR EXCLUSION OF LIABILITY OR



**AAPA Macroscopic Examination Guidelines:  
Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench**

WARRANTIES FOR CERTAIN TYPES OF DAMAGES. AS A RESULT, THE ABOVE LIMITATIONS OR EXCLUSIONS MAY NOT FULLY APPLY TO YOU.

### **Ambiguous Terminology:**

#### **Axillary tail ≠ axillary dissection**

The axillary tail (aka. tail of Spence or axillary process) is an extension of the tissue of the breast that extends into the axilla and is included in all total mastectomies. This would include simple mastectomies which do not include an “axillary dissection” containing lymph nodes as in a modified radical mastectomy. Generally, in a simple mastectomy, the surgeon will mark the axillary tail with a suture for orientation purposes.<sup>1</sup> An axillary dissection (aka. axillary contents) is a surgical procedure that incises the axilla to identify, examine, or remove lymph nodes. Axillary dissection has been the standard technique used in the staging and treatment of the axilla in breast cancer.<sup>2, 3</sup>

#### **Radiographically Identifiable Markers**

There is variation in the use of descriptive terms for markers deployed at the time of a core biopsy procedure (“clips”, “markers”, etc.). We recommend the term “radiographically identifiable marker” or the term “radiographic identified marker”; which may be simplified to “marker” (NCCN guideline uses the term “radiographic identified marker”). Precise description of the marker (e.g., coiled or ribbon) should be dependent on the institution. Be aware of possible marker migration. Ideally, the patient’s imaging should be reviewed and correlated to the surgical specimen.<sup>4,5,6</sup>

#### **Multifocal and Multicentric Disease**

The presence of two or more foci of cancer within the same breast quadrant is defined as multifocal, while the presence of two or more foci of cancer in different quadrants of the same breast is defined as multicentric. Multicentric breast cancers typically exhibit cancer foci > 5cm apart and are frequently associated with extensive intraductal carcinoma (EIC).<sup>7, 8</sup>

#### **Breast Specific Molecular Considerations:**

- ER and PgR levels should have 6 to 72 hours of formalin fixation (fixation time should be documented - a CAP checklist requirement).<sup>11</sup>
- HER2 testing should have 6 to 72 hours of formalin fixation (fixation time should be documented - a CAP checklist requirement).<sup>11</sup>
- The cold ischemic time between breast tissue removal and the initiation of fixation should be documented to be less than or equal to one hour (cold ischemic time should be documented - a CAP checklist requirement).<sup>11</sup>
- Ki67 proliferation index may be useful in predicting prognosis, responsiveness to neoadjuvant therapy, and rate of tumor recurrence.<sup>39</sup>
- Preliminary sectioning may be required to facilitate adequate fixation. If delivery of a resection specimen is delayed (e.g., from a remote site), or the specimen cannot be processed within the one-hour time frame, the tumor should be bisected and immersed into fixative. The identity of the margins needs to be retained or the margins separately submitted.<sup>11</sup>

**AAPA Macroscopic Examination Guidelines:  
Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench**

- Tissue taken for research studies or assays that does not involve the histologic examination of the tissue (e.g., reverse transcriptase polymerase chain reaction [RT-PCR]) should be taken in such a way to be able to evaluate the tissue for areas of invasion. For example, a thin slice of tissue taken for research studies should be matched with an adjacent slice of tissue that will be examined microscopically.

## **PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:**

### ■ **Procedures Covered in this Protocol:**

- Biopsy\*
- Excision (less than total mastectomy)
  - Lumpectomy
  - Quadrantectomy
  - Segmental or Partial Mastectomy; with or without axillary contents
- Total Mastectomy (breast removal with or without axillary contents)
  - Simple mastectomy (without removal of axillary lymph nodes)
  - Skin-sparing mastectomy (with removal of the nipple and only a narrow surrounding rim of skin)
  - Nipple-sparing mastectomy (with no attached skin or nipple)
  - Modified radical mastectomy (with axillary dissection)
  - Radical mastectomy (with an axillary dissection and removal of the pectoralis muscles)
- Lymph Node Sampling
  - Sentinel lymph node(s)
  - Axillary dissection (partial or complete dissection)
  - Lymph nodes present within the breast specimen (i.e., intramammary lymph nodes)
  - Other lymph nodes (e.g., supraclavicular nodes, internal mammary nodes, infraclavicular nodes, or location not identified)

\* Very small incisional biopsies (including core needle biopsies) are included in this protocol for the sole purpose of molecular considerations. These biopsies are otherwise excluded.

### ■ **Specimen Laterality:**

- Specify right or left.

### ■ **Specimen Size and Extent of Resection:**

- Provide specimen weight.
- Provide three dimensions; include anatomic orientation of three planes of dimension if provided (anterior - posterior / medial - lateral / superior - inferior).
- Provide two dimensions of attached skin and include location (anterior, medial, lateral, inferior), if present.
- Document nipple/areola, if present. Document if nipple is inverted, everted, retracted, or ulcerated.
- If unoriented - provide two surface dimensions and thickness.
- Document and measure additional structures/abnormalities, if present.
- Lymph node sampling (Refer to the Lymph Node Section on page 22).

### ■ **Specimen Integrity and Adequacy:**

- For any specimens with a defect or disruption, statements should include, with as much clarity as can be provided, the anatomic location of the defects or disruptions, and should also incorporate statements which assess the relationship of any defects or disruptions to the tumor. If defects or disruptions involve the tumor and serve to hinder assessment of the final

## AAPA Macroscopic Examination Guidelines: Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench

surgical margin this must be stated. Differential application of ink to the margins in areas affected by defects or disruptions can be done to help clarify identifiable true margins from the defect. A gross photograph of any defect may be taken for future documentation.<sup>10</sup> Consultation with the surgeon for clarification should be considered, as this may assist in creating a post-surgery treatment plan.

- Consult the surgeon as necessary / feasible to identify true margins when they are unclear.
  - If the specimen is received sectioned or fragmented, this should be noted.
  - If the specimen is an incisional biopsy, margins do not need to be evaluated. However, one should exercise caution in assuming what constitutes an incisional biopsy and err on the side of applying ink to the surgical margins.
- Maintaining in-vivo orientation:
  - Specimen compression during radiographic imaging should be minimized or avoided (i.e., TranSpec compression device).<sup>12,13</sup>
  - The surgeon should indicate the true orientation of the mastectomy specimen with sutures. If not, clarify orientation with operating surgeon.
  - One should not assume that the skin surfacing an excision specimen represents the anterior surface (the surgical approach may not necessarily originate anteriorly).
  - One should not assume that the skin surfacing a mastectomy specimen always represents a transverse/horizontal incision by the surgeon. The surgical incision can be transverse or oblique (pointing to the axilla) at the discretion of the operating surgeon taking into account the position of the tumor and possible scar encroachment into the cleavage area.<sup>41</sup>

### ■ Specimen Sampling Goals:

- The clinical or radiologic lesion for which the surgery was performed must be examined microscopically.
  - A specimen radiograph or other radiologic imaging study may be necessary to identify a nonpalpable imaging finding.
  - When practical, the entire specimen should be submitted sequentially for microscopic examination or at least the entire region of the targeted lesion.
  - If the specimen consists predominantly of DCIS with microinvasion, submission of the entire specimen, or at a minimum the entire macroscopically involved area is recommended to identify additional areas of invasion and/or lymph-vascular invasion.\*
- Sample all other macroscopically identified lesions.
- Each designated margin must be evaluated for involvement by invasive carcinoma and DCIS.
- State if the specimen is received sectioned or fragmented.
  - Note the approximate percentage of the specimen or lesion that has been examined microscopically if the entire specimen or macroscopically evident lesion has not been examined.

#### **\*Notes:**

The extent of sampling will depend on the radiological size of the lesion. Sampling should include the extremes of the radiographic calcification and adjacent tissue to avoid underestimation of the size of the lesion. This is particularly important as it is recognized that mammographic size may be an underestimate of the true lesion size of DCIS. It is anticipated that

**AAPA Macroscopic Examination Guidelines:  
Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench**

patients undergoing mastectomy for DCIS will in general have larger DCIS lesions with a greater probability of occult invasive cancer being present. It is therefore suggested that a minimum of 1 to 2 conventional blocks per 10 mm of calcification be taken.

■ **Clinical Information:**

The Joint Commission requires that clinical information be provided for pathology specimens. Relevant clinical information is necessary for the accurate evaluation of breast specimens.

## **TUMOR ("T" of TNM)**

### ■ **Tumor Size (size of largest invasive carcinoma):**

- If possible, give three dimensions of palpable tumor in millimeters, with the largest dimension listed first. <sup>11 \*</sup>
- If no discrete mass can be identified, give three dimensions of previous biopsy site or firm/fibrous tissue surrounding the radiographically identifiable marker.
  - If no discrete mass, biopsy site, or marker can be identified, it is recommended the breast tissue located in the general region of the biopsy proven cancer should be submitted in its entirety for microscopic examination. Any firm or fibrous tissue in this area should be measured, with a note stating no biopsy site is macroscopically identifiable.
- If there are multiple tumors, include dimensions for each and the distance from the other tumor(s).
  - If multiple foci of invasion are present, the size listed as the size of largest invasive carcinoma is the size of the largest contiguous area of invasion. The size of multiple invasive carcinomas *should not* be added together.

*\*The single greatest dimension of the largest invasive carcinoma is used to determine T criteria. The most accurate size for AJCC T criteria utilizes information from imaging, macroscopic examination, and microscopic evaluation.*

#### **Notes:**

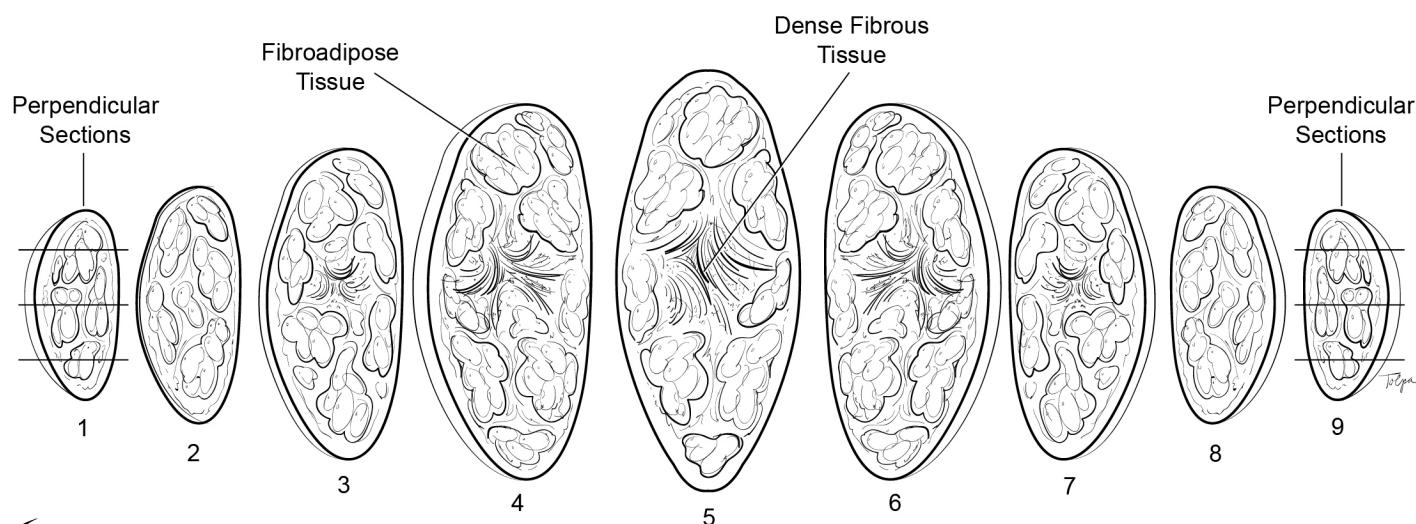
- If necessary, utilize information regarding tumor size from imaging studies.
- If there are multiple biopsy sites, the varying appearance of the markers (if applicable) may also be described in the report. There are multiple marker designs including: ribbon, wing, coil, and cylinder. Be aware that markers do move, sometimes significantly, after placement. <sup>6</sup>

### ■ **Tumor Site: Invasive Carcinoma**

- Specify tumor site
  - Upper outer quadrant
  - Lower outer quadrant
  - Upper inner quadrant
  - Lower inner quadrant
  - Central
  - Nipple
  - Position: \_\_\_\_ o'clock
  - Other (specify)

■ **Specimen Management Including Management of Surgical Margins:**

- **Excisions: (Figures 1 and 2)**
  - Oriented wide local excision:
    - Gross evidence of tumor:
      - ❖ Differentially ink the margins according to your institution's protocol.
      - ❖ Provide measurements of the lesional tissue to the six surgical margins.
      - ❖ Submit sections showing the relationship of the lesional tissue to the closest margin(s). This should be done for all margins where the tumor and margin can be seen on one slide.
      - ❖ Perpendicular sections should be submitted to assess the macroscopically negative margins.
  - No macroscopic evidence of disease - (Typically breast removed after neoadjuvant therapy or all tumor removed at the time of biopsy):
    - Lumpectomy/partial mastectomy:
      - ❖ Apply ink to the specimen according to your institution's protocol.
      - ❖ Identify the area of radiographic concern (area with image detectable marker, area of microcalcifications, or identifiable tumor bed).
      - ❖ If possible, provide the measurement of this area relative to all margins (anterior, posterior, medial, lateral, superior, and inferior).
      - ❖ If feasible, submit the entire specimen using serial sequential sampling (SSS), stating how the specimen was submitted, e.g., "sectioned from medial to lateral".

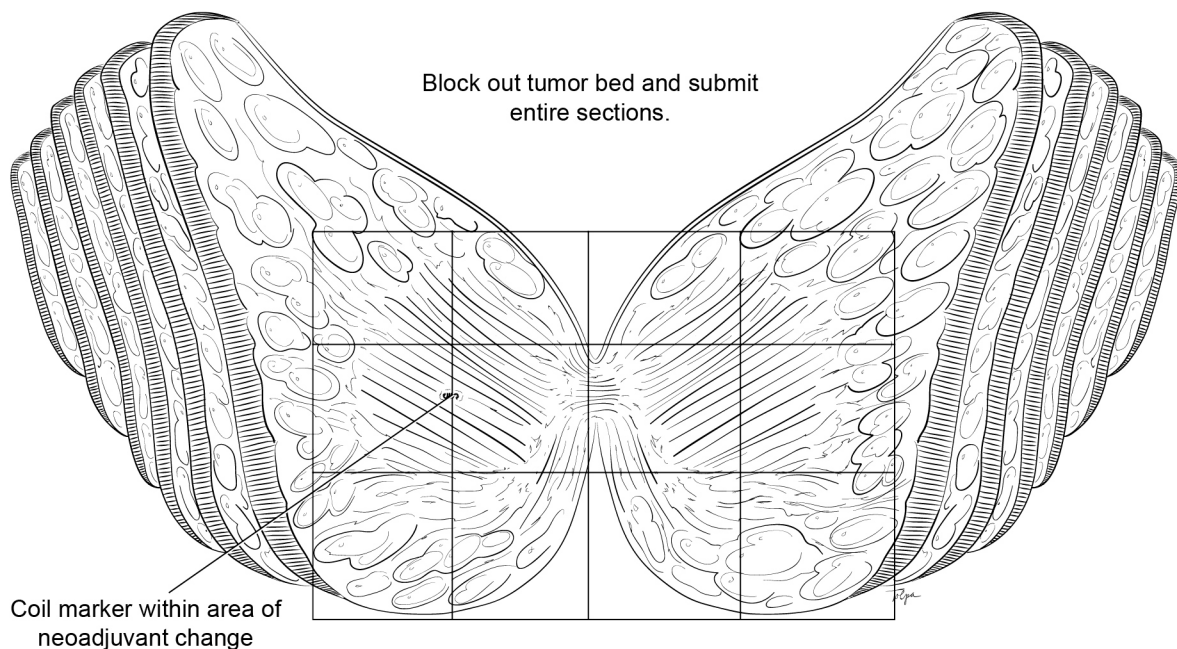


**Figure 1: Excisional Biopsy - Serial Sequential Sectioning with Number Designation**

When serially sectioning an excisional specimen, number each slice and record which slice(s) the tumor, biopsy site, or clip is located.

**AAPA Macroscopic Examination Guidelines:  
Utilization of the CAP Cancer Protocols at the Surgical Gross Bench**

- Large lumpectomy/partial mastectomy:
  - ❖ Apply ink to the specimen according to your institution's protocol.
  - ❖ Where SSS is not possible, the specimen should be sampled to include all areas likely to contain viable tumor, tumor bed, areas with image detectable marker, areas of microcalcifications, and/or breast tissue with other abnormalities.
  - ❖ Sampling of the tumor bed is important to document treatment response from neoadjuvant therapy.
  - ❖ Sections for microscopic examination can be mapped by means of dictation, directly on the radiograph, on a digital or printed image, or other methods deemed appropriate.
- Unoriented wide local excision:
  - ❖ Same as above except the measurement will be to the closest unoriented margin.



**Figure 2: Tumor treated with Neoadjuvant Chemotherapy  
Posterior Portion of Mastectomy**

This illustration demonstrates a method to block out tissue that has undergone a full treatment response to neoadjuvant chemotherapy.

**Notes:**

Multiple techniques have been described to reduce the chance of microscopically positive lumpectomy margins, including, but not limited to (1) radioactive seed localization instead of wire guidance, (2) routine or selective cavity shave excisions, (3) hematoma ultrasound (US)-guided excisions, (4) intraoperative US by surgeon, (5) large-volume oncoplastic lumpectomy or reduction mammoplasty procedures, and (6) immediate intraoperative margin assessment with frozen section (FS) or touch prep analysis (TP).<sup>28-35</sup> There are limitations of FS of fatty tissue, and there is a need for cytopathology expertise if TP are performed. Not all of these techniques are universally available, and they have not been compared to each other for effectiveness.

• **Re-Excisions:**

- Complete re-excision (six margin re-excision - “global”):
  - ❖ Differentially ink the margins according to your institution’s protocol.
  - ❖ Provide a measurement of the cavity in three dimensions, including anatomic planes of orientation.
  - ❖ Provide measurement of margin clearance for each of the six margins.
  - ❖ Submit sequential perpendicular sections (spanning between the biopsy cavity surface and true margin) for any prior margin with clearance of 0.1 cm or less.
  - ❖ Submit non-sequential representative perpendicular sections for previously negative margins, giving preference to fibrous areas or areas of narrow clearance.<sup>14</sup>
- Select re-excision (less than six margin re-excision - “non-global”):
  - ❖ Apply ink (differentially if more than one margin is included and orientation is provided) to the specimen according to your institution's protocol.
  - ❖ Sequentially submit all tissue or, for larger specimens, sequentially submit all areas where thickness is less than 1.0 cm, or biopsy sequelae are less than 1.0 cm from the true margin.
  - ❖ For other thicker areas, non-sequential sections at regular intervals, with preference given to fibrous areas, are acceptable.<sup>14</sup>

• **Total Mastectomy:**

- A total mastectomy encompasses the removal of all breast tissue, thus, while the extent of disease should be documented, the overarching goal of macroscopic examination is to ensure that surgical margins are clear.
  - ❖ The specimen should be oriented per the surgeon.
  - ❖ Document size of any attached skeletal muscle. Apply ink to the specimen according to your institution’s protocol.
  - ❖ Serially section the specimen perpendicular to the medial-lateral axis at 0.5 cm intervals. This is best done from the deep to the superficial surface. If skin is present, keep the skin intact, unless specimen radiography is needed.
  - ❖ Locate, orient by quadrant or o'clock position, and submit all prior biopsy sites/lesions (or representative samples from prior lumpectomy sites) including the closest margin for each. Note distance from closest margin.
  - ❖ If two or more different positive biopsy sites/lesions are present, measure the distance between the two (or more) sites/lesions and submit intervening breast tissue between the sites.
  - ❖ Submit sections from other margins if fibrous tissue spans between the prior biopsy site/tumor and these margins.

**AAPA Macroscopic Examination Guidelines:  
Utilization of the CAP Cancer Protocols at the Surgical Gross Bench**

- ❖ Submit additional sections for any macroscopically evident, non- biopsied lesion(s).
- ❖ Submit additional sections to assess any quadrant which was not previously biopsied, with preference given to fibrous tissue and areas where fibrous tissue approaches the margins.
- ❖ Submit at least one perpendicular section of the nipple unless the nipple is macroscopically abnormal or if there is a clinical history of Paget disease (see page 15 for Paget nipple sampling section).
- ❖ Measure the tumor from nipple (or nipple site, in cases of nipple-sparing mastectomy, which the surgeon may designate with a suture).
- ❖ If the deep margin is not involved by tumor, submit one perpendicular section at the site of the biopsy cavity/lesion. If skeletal muscle is present, this should also be sampled.

■ **Tumor Depth of Invasion and Relationship to Attached Organs / Structures:** <sup>11</sup>

**Pathologic T (pT):**

The pathologic assessment of the primary tumor (pT) is generally based on resection of the primary tumor from a single specimen. Resection of the tumor with several partial removals at the same or separate operations necessitates an effort at reasonable estimates of the size and extension of the tumor to assign the correct or highest pT category. Rarely, the tumor size is obtained from a previous core needle biopsy specimen, as the tumor in the core may be larger than the tumor in the excision specimen.

**AAPA Macroscopic Examination Guidelines:  
Utilization of the CAP Cancer Protocols at the Surgical Gross Bench**

**Definition of Primary Tumor (pT) – Pathological T**

<b>pT Category</b>	<b>pT Criteria</b>
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis (DCIS)*	Ductal carcinoma <i>in situ</i>
pTis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma <i>in situ</i> (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
pT1	Tumor ≤20 mm in greatest dimension
pT1mi	Tumor ≤1 mm in greatest dimension
pT1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement 1.0-1.9 mm to 2 mm).
pT1b	Tumor >5 mm but ≤10 mm in greatest dimension
pT1c	Tumor >10 mm but ≤20 mm in greatest dimension
pT2	Tumor >20 mm but ≤50 mm in greatest dimension
pT3	Tumor >50 mm in greatest dimension
pT4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
pT4a	Extension to chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures (i.e. ribs, intercostal muscles, serratus anterior muscle) does not qualify as T4
pT4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
pT4c	Both T4a and T4b are present
pT4d	Inflammatory carcinoma

\*Note: Lobular carcinoma in situ (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8<sup>th</sup> Edition.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, [www.springer.com](http://www.springer.com).

### **TNM Descriptors:**

*For identification of special cases of pTNM classifications the “m” suffix and “y”, “r”, and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.*

*“m” suffix: indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.*

*“y” prefix: indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy.*

*“r” prefix: indicates a recurrent tumor when staged after a disease-free interval and is identified by the “r” prefix: rTNM.*

*“a” prefix: designates the stage determined after autopsy: aTNM.*

### **Residual Tumor (R) Category**

The absence or presence of residual tumor at the primary tumor site after treatment with surgery and/or with neoadjuvant therapy is denoted by the symbol R. The R categories for the primary tumor site are as follows:

<b>R</b>	<b>R Definition</b>
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, [www.springer.com](http://www.springer.com).

The presence of residual tumor may indicate the effect of therapy, influence further therapy, and be a strong predictor of prognosis. In addition, the presence or absence of disease at the margin of resection may be a predictor of the risk of recurrent cancer.

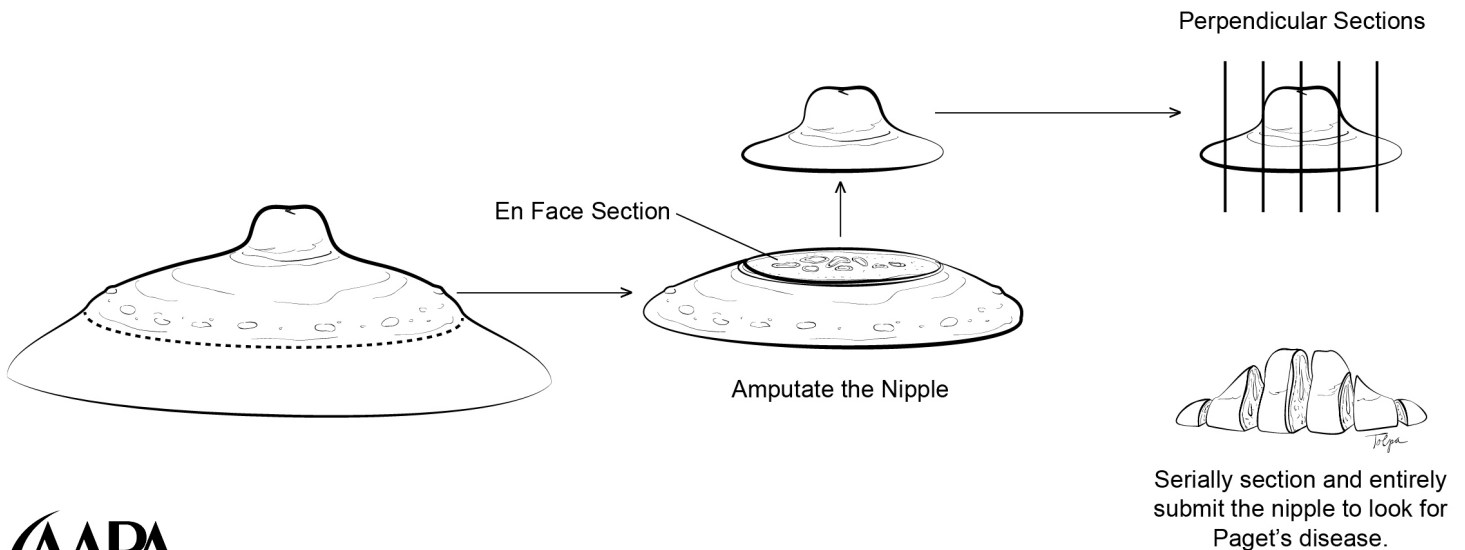
Note: The R category is not incorporated into TNM staging itself. However, the absence or presence of residual tumor and status of the margins may be recorded in the medical record and cancer registry.

■ **Breast Carcinoma and Skin:**

- There are multiple ways breast carcinoma involves the skin:
  - DCIS involving nipple skin (Paget disease of the nipple)
  - Invasive carcinoma invading into dermis or epidermis, without ulceration
  - Invasive carcinoma invading into dermis and epidermis with skin ulceration
  - Ipsilateral satellite skin nodules
  - Dermal lymph-vascular invasion
- Include the presence of skin or muscle and the relationship to the carcinoma in the macroscopic description.

**Sampling Nipple with Paget disease (DCIS involving nipple skin): (Figure 3)**

- The nipple is amputated in a plane parallel to the skin surface.
- A second, deeper section is taken in the same plane. This section will demonstrate all the major ducts as they approach the nipple.
- The more superficial section is serially sectioned perpendicular to the skin surface and all these slices are submitted. This section will demonstrate all of the nipple ducts as they empty onto the skin surface. (Lester 2006) <sup>11</sup>



**Figure 3: Paget's Breast - Nipple Sectioning**

## ■ Margins

All identifiable margins should be evaluated for involvement by tumor. A positive margin requires ink on tumor. There are a variety of opinions on the adequacy of margin width that constitutes a margin that need not be re-excised. The current NCCN guidelines state that: If all margins are ink negative and  $>$  than or  $=$  to 1 mm, no further surgery is needed. If re-excision is or is not performed, the reason is to be documented by the surgeon.

If margins are “close” ( $<1$  mm) or focally involved margin, re-excision is not mandatory. The surgeon must consider on case-by-case basis and document reasoning. If there are “Ink positive margin(s)”, surgeons must perform re-excision or document reason why not performed. <sup>15-27</sup>

### **Invasive Carcinoma:**

- Specify if margins are uninvolved by invasive carcinoma.
  - Specify the distance from the closest margin in mm.
  - Specify the margin.
- Specify if margins are involved by invasive carcinoma.
  - Specify the margin.
- For positive margins, specify extent (focal, minimal / moderate / extensive): anterior, posterior, superior, inferior, medial, lateral, other.

### **DCIS (required only if DCIS is present in the specimen):**

- Specify if margins are uninvolved by DCIS.
  - Specify the distance from the closest margin in mm.
- Specify if margin(s) are positive for DCIS.
  - Specify the margin.
- For positive margins, specify extent (focal, minimal / moderate / extensive): anterior, posterior, superior, inferior, medial, lateral, other.

### **Deep margin:**

The likelihood of breast tissue beyond the muscle fascia is very small and unlikely to have clinical significance in the setting of DCIS. However, invasive carcinoma at the deep margin, especially if associated with muscle invasion, of an indication for postmastectomy radiation.

- Report if there is tumor invasion in the skeletal muscle (typically the pectoralis muscle) as this finding may be used as an indication for postmastectomy radiation therapy.
- Invasion into the pectoralis muscle is not included in T4a. Invasion must extend through this muscle into the chest wall (ribs, intercostal muscles, serratus anterior muscle) in order to be classified as T4a.

### **Superficial margin (generally anterior):**

This margin may be immediately below the skin, and there may not be additional breast tissue beyond this margin. However, breast tissue can be left in skin flaps, and the likelihood of residual breast tissue is related to the thickness of the flap.

**Notes:**

Margins can be identified in a variety of ways including:

- The use of multiple colored inks
- By submitting the margins in specific cassettes
- By the surgeon submitting each margin as a separately excised specimen

Report the extent of margin involvement:

- Focal: one focal area of carcinoma at the margin, <4 mm
- Multifocal: two or more foci of carcinoma at the margin
- Extensive: carcinoma present at the margin over a broad front (>5 mm)
- Stating the location of the positive margin in detail (allowing one to pinpoint the involved location) can assist the post-surgical treatment plan.

Specimen Management: Radiographic considerations:

- Specimen radiography is important to assess the adequacy of excision.
- Compression of the specimen should be minimized, as it can compromise the ability to assess the distance of the DCIS from the surgical margin.
- Mechanical compression devices can provide assistance to radiologists and should be reserved for nonpalpable lesions that require this technique for imaging (e.g., microcalcifications).
- The relationship of the radiographic calcifications to the invasive carcinoma and the DCIS should be indicated.

**LYMPH NODES ("N" of TNM)**

**Definition of Regional Lymph Nodes – Pathological (pN)**

<b>pN Category</b>	<b>pN Criteria</b>
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathologic study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0 (i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0 (mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1 to 3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1 to 3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4 to 9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (Level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes; or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

## AAPA Macroscopic Examination Guidelines: Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, [www.springer.com](http://www.springer.com).

Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

Most patients with invasive carcinoma will have lymph nodes sampled. <sup>11</sup>

- **Regional Lymph Nodes include:**

- Axillary (ipsilateral): interpectoral (Rotter's) nodes and lymph nodes along the axillary vein and its tributaries that may be divided into the following levels:
  - Level I (low-axilla): lymph nodes lateral to the lateral border of the pectoralis minor muscle.
  - Level II (mid-axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes.
  - Level III (apical axilla): lymph nodes medial to the medial margin of the pectoralis minor muscle and inferior to the clavicle. Also known as apical or infraclavicular nodes (removed only if considered suspicious and must be specifically identified).
  - Axillary lymph nodes are removed by en bloc resection of axillary tissue.
- Internal mammary (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia.
- Supraclavicular: lymph nodes in the supraclavicular fossa, a triangle defined by the omohyoid muscle and tendon (lateral and superior border), the internal jugular vein (medial border), and the clavicle and subclavian vein (lower border). Adjacent lymph nodes outside of this triangle are considered lower cervical nodes (M1).
- Intramammary: lymph nodes within the breast; these are considered axillary lymph nodes for purposes of classification and staging. Most commonly found in the upper outer quadrant and may rarely be sentinel lymph nodes. <sup>38</sup>

- **Sentinel lymph nodes:**

- The sentinel node is usually the first involved lymph node. In the unusual situation in which a sentinel node is not involved by metastatic carcinoma, but a nonsentinel node is involved, this information must be included in the pathology report.
- The sentinel node is identified by the surgeon by uptake of radiotracer or dye or both.
- Adjacent palpable nonsentinel nodes may also be removed.

- **Lymph node sampling:**

## AAPA Macroscopic Examination Guidelines: Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench

- Sampling must be adequate to detect all macrometastases, as they are known to have prognostic importance (i.e., all metastatic deposits >2 mm).
- Specify the total number of lymph nodes examined (sentinel and nonsentinel).
- Specify the number of sentinel nodes examined.
- Specify the number of lymph nodes with macroscopic metastases. \*
- Specify the greatest dimension of the largest metastatic focus.
- State if there is or is not macroscopic evidence of extranodal tumor extension. \*\*
- Specify site of lymph nodes identified.
- Measure lymph nodes in three dimensions or provide a range in size of greatest dimension if multiple.

\*An accurate assessment of the number of positive lymph nodes is a critical prognostic indicator.

\*\*The presence of extranodal extension may be associated with a higher frequency of axillary recurrence.

- **Sentinel Nodes:**

- Each node is serially sectioned at 2 mm intervals and, in the absence of macroscopic evidence of metastatic tumor, entirely submitted.

- **For *macroscopically positive* lymph nodes:**

- Describe the cut surface of the identified lymph nodes and the macroscopic appearance of tumor metastasis including the size and location within the node.
- State if the metastatic focus is subcapsular and / or intramedullary.
- Give a precise size of the lymph node and metastatic deposit.
- Representative sampling of these lymph nodes is adequate.
- Sample areas where extranodal tumor extension is seen or cannot be excluded.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- The nodes must be submitted in such a way that every node can be evaluated and counted separately.

- **For small lymph nodes or *macroscopically negative* larger lymph nodes:**

- Submit small lymph nodes (2-3 mm) in toto.
- Thinly section larger lymph nodes at 2 mm intervals and entirely submit.
- Submit the entire capsule of the lymph node for possible extranodal extension.
- If the lymph node is large but macroscopically negative, submit sequentially so that a size calculation can be established.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- The nodes must be submitted in such a way that every node can be evaluated and counted separately.

**Note:**

Cancerous nodules in the axillary fat adjacent to the breast, without histologic evidence of residual lymph node tissue, are classified as regional lymph node metastasis.

**Pathologic N (pN)**

**AAPA Macroscopic Examination Guidelines:  
Utilization of the *CAP Cancer Protocols* at the Surgical Gross Bench**

The pathologic assessment of regional lymph nodes (pN) ideally requires resection of a minimum number of lymph nodes (10) to assure that there is sufficient sampling to identify positive nodes if present. The recommended number generally does not apply in cases where the sentinel node has been accepted as accurate for defining regional node involvement and a sentinel node procedure has been performed. At least one node with presence or absence of tumor documented by pathologic examination is required for pathologic staging N.

Direct extension of primary tumor into a regional node is classified as node positive. A tumor nodule with a smooth contour in a regional node area is classified as a positive node. The size of the metastasis, not the size of the node, is used for the criterion for the N category.

**METASTASIS** ("M" of TNM)

**Definition of Distant Metastasis (pM) (required only if confirmed pathologically)**

<b>pM Category</b>	<b>pM Criteria</b>
M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
pM1	Distant metastases detected by clinical and radiographic means (cM1) and/or histologically proven metastases larger than 0.2 mm (pM1)

\*Note that imaging studies are not required to assign the cM0 category.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, [www.springer.com](http://www.springer.com).

The four major sites of metastasis include the bone, lung, brain, and liver, but tumor cells are also capable of metastasizing to many other sites. <sup>38</sup>

**Pathologic M (pM)**

The pathologic assignment of the presence of metastases (pM1) requires a biopsy positive of cancer at the metastatic site. Pathologic M0 is an undefined concept, and the category "pM0" may not be used. Pathologic classification of the absence of distant metastases can only be made at autopsy.

**REFERENCE REVIEW:**

1. Memon S, Emanuel JC. The axillary tail--an important caveat in prophylactic mastectomy. *Breast J.* 2008;14(3):313–4.
2. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer.* 1989;63(1):181-7.
3. McCready DR, Hortobagyi GN, Kau SW, Smith TL, Buzdar AU, Balch CM. The prognostic significance of lymph node metastases after preoperative chemotherapy for locally advanced breast cancer. *Arch Surg.* 1989;124(1):21-5.
4. Kass R, et al. Clip migration in stereotactic biopsy. *The American Journal of Surgery.* 2002;184: 325-331.
5. Bleiweiss IJ, et al. Breast core biopsy – a pathologic-radiologic correlative approach. Pgs 177-183. Saunders-Elsevier; 2008.
6. Burnside ES, Sohlich RE, Sickles EA. Movement of Biopsy-Site Marker Clip after Completion of Stereotactic Directional Vacuum-assisted Breast Biopsy: Case Report. *Radiology.* 2001;221:504-7.
7. Oh JL. Multifocal or Multicentric Breast Cancer: Understanding Its Impact on Management and Treatment Outcomes. In M.H. Editor (Ed.) *Methods of Cancer Diagnosis, Therapy and Prognosis* Volume 1, pp 583-587 Netherlands: Springer; 2008.
8. Holland R, Veiling SH, Mraunac M, and Hendriks JH. Histologic multifocality of Tis T<sub>1-2</sub> breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer.* 1985;56:979–990.
9. Teixeira MR, Pandis N, Bardi G, Andersen JA, Bohler PJ, Qvist H, and Heim S. Discrimination between multicentric and multifocal breast carcinoma by cytogenetic investigation of macroscopically distinct ipsilateral lesions. *Genes Chromos. Cancer.* 1997;18:170–174.
10. Renshaw AA, Kish R, Gould EW. The value of inking breast cores to reduce specimen mix-up. *Am J ClinPathol.* 2007;127:271-272.
11. Lester SC, Bose S, Chen YY, et al. Protocol for the Examination of Specimens from Patients with Invasive Carcinoma of the Breast. *CAP Protocol* 3.3.0.0. 2016.
12. Clingan R, et al. "Potential Margin Distortion in Breast Tissue by Specimen Mammography." *Archives of Surgical Pathology.* 2003;138:1371-1374.
13. Position statement on breast cancer lumpectomy margins. American College of Breast Surgeons, January 16, 2013.
14. Abraham SC, Fox K, Fraker D, Solin L, Reynolds C. Sampling of grossly benign breast reexcisions: a multidisciplinary approach to assessing adequacy. *Am J Surg Pathol.* 1999;23:316-322.
15. The American Society of Breast Surgeons Position Statement on Breast Cancer Lumpectomy Margins. January 16<sup>th</sup>, 2013.  
[https://www.breastsurgeons.org/statements/PDF\\_Statements/Lumpectomy\\_Margins.pdf](https://www.breastsurgeons.org/statements/PDF_Statements/Lumpectomy_Margins.pdf).

16. Singletary SE. Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg.* 2002;184:383-393.
17. Azu M, Abrahamse P, Katz SJ, Jagsi R, Morrow M. What is an adequate margin for breast-conserving surgery? Surgeon Attitudes and Correlates. *Ann Surg Oncol.* 2010;17:558-563.
18. Blair SL, Thompson K, Rococco J, Malcarne V, Beitsch PD, Ollila DW. Attaining negative margins in breast conservation operations: Is there a consensus among breast surgeons? *J Am Coll Surg.* 2009;209:608-613.
19. McCahill LE, Single RM, Aiello Bowles EJ, et al. Variability in re-excision following breast conservation surgery. *JAMA.* 2012;307:467-475.
20. Taghian A, Mohiuddin M, Jagsi R, Goldberg S, Ceilley E, Powers S. Current perceptions regarding surgical margin status after breast-conserving therapy: results of a survey. *Ann Surg.* 2005;241:629-639.
21. Morrow M, Harris JR, Schnitt S. Surgical margins in lumpectomy for breast cancer—bigger is not better [Sounding Board]. *N Engl J Med.* 2012;367:79-82.
22. Wang SY, Chu H, Shamliyan T, et al. Network meta-analysis of margin threshold for women with ductal carcinoma in situ. *J Natl Cancer Inst.* 2012;104:507-516. Epub 2012 Mar 22. doi:10.1093/jnci/djs142.
23. Lovrics PJ, Gordon M, Cornacchi SD, et al. Practice patterns and perceptions of margin status for breast conserving surgery for breast carcinoma: National Survey of Canadian General Surgeons. *Breast.* 2012;21:730-734. Epub 2012 Aug 16. doi: 10.1016/j.breast.2012.07.017.
24. Jeevan R, Cromwell DA, Trivella M. Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics. *BMJ.* 2012; 345:e4505. E pub 2012 Jul 12. doi: <http://dx.doi.org/10.1136/bmj.e4505>.
25. National Comprehensive Cancer Network Guidelines Version 1.2012 Invasive Breast Cancer: Margin Status in infiltrating carcinoma. 2012; BINV-F. Available [with login] at: [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf).
26. Morrow M, Katz SJ. The challenge of developing quality measures for breast cancer surgery. *JAMA.* 2012;307:509-510.
27. National Comprehensive Cancer Network Guidelines Version 1.2012 DCIS: Margin Status in DCIS. 2012;DCIS-A. Available [with login] at: [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf).
28. McGhan LJ, McKeever SC, Pockaj BA, et al. Radioactive seed localization for nonpalpable breast lesions: review of 1,000 consecutive procedures at a single institution. *Ann Surg Oncol.* 2011;18:3096- 3101. doi: 10.1245/s10434-011-1910-1. Epub 2011 Sep 27.
29. Cabioglu N, Hunt KK, Sahin AA, et al. Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. *Ann Surg Oncol.* 2007;14:1458-1471.

30. Caruso F, Ferrara M, Castiglione G, et al. Therapeutic mammoplasties: full local control of breast cancer in one surgical stage with frozen section. *Eur J Surg Oncol*. 2011;37:871-875. Epub 2011 Aug 24. doi: 10.1016/j.ejso.2011.07.002.
31. Guidroz JA, Larrieux G, Liao J, Sugg SL, Scott-Conner CE, Weigel RJ. Sampling of secondary margins decreases the need for re-excision after partial mastectomy. *Surgery*. 2011;150:802-809. doi: 10.1016/j.surg.2011.07.064.
32. Chakravorty A, Shrestha AK, Sanmugalingam N, et al. How safe is oncoplastic breast conservation? Comparative analysis with standard breast conserving surgery. *Eur J Surg Oncol*. 2012;38:395-398. Epub 2012 Mar 20. doi: 10.1016/j.ejso.2012.02.186.
33. Osborn JB, Keeney GL, Jakub JW, Degnim AC, Boughey JC. Cost-effectiveness analysis of routine frozen-section analysis of breast margins compared with reoperation for positive margins. *Ann Surg Oncol*. 2011;18:3204-3209. Epub 2011 Aug 23. doi: 10.1245/s10434-011-1956-0.
34. Postma EL, Verkooijen HM, van Esser S, et al. Efficacy of 'radioguided occult lesion localisation' (ROLL) versus 'wire-guided localisation' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomised controlled multicentre trial. *Breast Cancer Res Treat*. 2012;136:469-478. Epub 2012 Sep 30. doi: 10.1007/s10549-012-2225-z. Epub 2010 Sep 19. doi: 10.1245/s10434-010-1230-x.
35. Arentz C, Baxter K, Boneti C, et al. Ten-year experience with hematoma-directed ultrasound-guided (HUG) breast lumpectomy. *Ann Surg Oncol*. 2010;17 (suppl 3):378-83. Epub 2010 Sep 19. doi: 10.1245/s10434-010-1230-x.
36. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med*. 2011;364:412-421.
37. Humphrey PA, Dehner LP, & Pfeifer JD. *The Washington manual of surgical pathology*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
38. Amin MB, Edge SB, Greene FL, Byrd DR, et al. (Eds.) *AJCC Cancer Staging Manual*, 8<sup>th</sup> ed. New York, NY: Springer; 2017.
39. Dowsette M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst*. 2011;103(22): 1656-1664. doi: 10.1093/jnci/djr393.
40. Fitzgibbons PL, Bose S, Chen YY, et al. Protocol for the Examination of Specimens from Patients with Invasive Carcinoma of the Breast. *CAP Cancer Protocol Invasive Breast 4.1.0.0*. 2018.
41. Wyld L, Markopoulos C, Leidenius M, Senkus-Konefka, et al (Eds.) *Breast Cancer Management for Surgeons*. Basel, Switzerland: Springer International Publishing, 2018. Print.
42. Ellis IO, Carder P, Hales S, et al. Pathology Reporting of breast disease in surgical excision specimens incorporating the dataset for histologic reporting of breast cancer. *The Royal College of Pathologists*. June 2016.