Protocol for the Examination of Biopsy Specimens from Patients with Ductal Carcinoma In Situ (DCIS) of the Breast

Version: 1.1.0.0

Protocol Posting Date: June 2026

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

Procedure	Description
Biopsy	Includes specimens designated needle biopsy, fine needle aspiration, and others (for excisional biopsy, see below)
Tumor Type	**Description**
Ductal carcinoma in situ without invasive carcinoma or microinvasion	
Paget disease of the nipple not associated with invasive breast carcinoma	
Encapsulated papillary carcinoma without invasive carcinoma	
Solid papillary carcinoma without invasive carcinoma	

The following should NOT be reported using this protocol:

Procedure
Resection (consider Breast DCIS Resection protocol)
Excisional biopsy (consider Breast DCIS Resection protocol)
Tumor Type
Any tumor with invasive carcinoma (consider the Breast Invasive Carcinoma Biopsy protocol)
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

Version Contributors

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Glossary:

Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.

Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 1.1.0.0

- WHO 6th Edition updates to content and explanatory notes
- Cover page update
- Tumor Site and Architectural Pattern(s) question updates
- Histologic Type and Nuclear Grade questions now multi-select
- Added Extent of DCIS in this Limited Biopsy in Millimeters (mm) question
- Added Additional Lesion(s) question

Reporting Template

Protocol Posting Date: June 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (DCIS OF THE BREAST: Biopsy)
Standard(s):
This template is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure
___ Needle biopsy
___ Fine needle aspiration
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

+Tumor Site
Tumor Site descriptor should specify the location of the invasive cancer based on correlation with radiology designation (e.g., "R1, 3:00, 2 cm from nipple" or "upper outer quadrant").
___ Specify tumor site / location: _____
___ Not specified

Histologic Type (Note A) (select all that apply)
___ Ductal carcinoma in situ (DCIS)
___ Paget disease
___ Encapsulated papillary carcinoma in situ (features)
___ Solid papillary carcinoma in situ (features)
___ Other histologic type not listed (specify): _____

+Extent of DCIS in this Limited Biopsy Sample in Millimeters (mm)
Measure the largest extent based on span in a single core. Do not add up extent in multiple separate cores since this may overestimate size. Note that the span in a core biopsy sample may be used for radiation decisions if there is no residual DCIS in the excision.
___ Exact measurement: _____ mm
___ At least: _____ mm
___ Other (specify): _____
___ Cannot be determined: _____

+Architectural Pattern(s) (Note B) (select all that apply)
___ Comedo
___ Cribriform

___ Micropapillary
___ Papillary
___ Solid
___ Solid papillary carcinoma in situ
___ Encapsulated papillary carcinoma in situ
___ Paget disease (DCIS involving nipple skin)
___ Other (specify): _____

Nuclear Grade (Note C) (select all that apply)
___ Grade I (low)
___ Grade II (intermediate)
___ Grade III (high)
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Nuclear Grade Comment: _____

Necrosis (Note D)
___ Not identified
___ Present, focal (small foci or single cell necrosis)
___ Present, central (expansive "comedo" necrosis)
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Microcalcifications (Note E) (select all that apply)
___ Not identified
___ Present in DCIS
___ Present in non-neoplastic tissue
___ Other (specify): _____

+Additional Lesion(s) (Note F) (select all that apply)
Non-classic / variant subtypes of LCIS include: Pleomorphic LCIS (pleomorphic nuclei greater than 4 times the size of a lymphocyte or equivalent to nuclei of high-grade DCIS) and Florid LCIS (proliferation of cells cytologically similar to those of classic LCIS but expanding the acini of the involved TDLUs so that little to no residual intervening intra-lobular stroma is present, and / or an expanded acinus or duct spans approximately 40–50 cells in diameter). Comedonecrosis in classic LCIS may also be considered non-classic / variant (describe in "Other (specify)).
___ Not identified
___ Lobular carcinoma in situ, classic
___ Lobular carcinoma in situ, pleomorphic
___ Lobular carcinoma in situ (specify): _____
___ Atypical lobular hyperplasia
___ Atypical ductal hyperplasia
___ Flat epithelial atypia
___ Other (specify): _____
+Additional Lesion(s) Comment: _____

SPECIAL STUDIES

For hormone receptor and HER2 reporting, the CAP Breast Biomarker Template should be used. www.cap.org/cancerprotocols

+Breast Biomarker Studies (specify pending studies): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Histologic Type

Multiple forms of DCIS may be present in a given sample including papillary forms and Paget's disease. This protocol applies only to cases of DCIS. The protocol for invasive carcinoma of the breast applies if invasion or microinvasion (less than or equal to 1 mm) is present.

When DCIS involves nipple skin only, without underlying invasive carcinoma or DCIS, the classification is DCIS (i.e., pTis [Paget]). The majority of these cases are strongly positive for HER2.

The WHO criteria for a diagnosis of encapsulated papillary carcinoma (EPC) and solid papillary carcinoma in situ (SPC in situ) should be used in classification.[1] Myoepithelial cells may be absent or attenuated, but the contours of these lesions should be circumscribed to classify them as in situ. These lesions are clinically managed like DCIS. On a limited core biopsy sample, features of encapsulated papillary carcinoma or solid papillary carcinoma in situ may be present but definitive classification may not be possible without examination of the entire lesion in a surgical excision. Therefore, in a core biopsy report these diagnoses are often reported as having features of EPC and SPC if no definitive invasion is present.

References

1. WHO Classification of Tumours Editorial Board. *Breast Tumours.* Lyon (France): International Agency for Research on Cancer; 2026. (WHO classification of tumours series, 6th ed.).

B. Architectural Pattern

The architectural pattern has been reported traditionally for DCIS.[1,2] However, nuclear grade and the presence of necrosis are more predictive of clinical outcome. Paget's, encapsulated papillary carcinoma, and solid papillary carcinoma in situ can also be reported as architectural patterns, but they are also considered distinct histologic types of DCIS.

References

1. Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer.* 1997; 80:1798-1802.
2. Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg.* 2005; 201:586-597.

C. Nuclear Grade

The nuclear grade of DCIS is determined using 6 morphologic features (Table 1).[1,2]

Table 1. Nuclear Grade of Ductal Carcinoma In Situ

Feature	Grade I (Low)	Grade II (Intermediate)	Grade III (High)
Pleomorphism	Monotonous (monomorphic)	Intermediate	Markedly pleomorphic
Size	1.5 to 2 x the size of a normal RBC or a normal duct epithelial cell nucleus	Intermediate	>2.5 x the size of a normal RBC or a normal duct epithelial cell nucleus
Chromatin	Usually diffuse, finely dispersed chromatin	Intermediate	Usually vesicular with irregular chromatin distribution

Nucleoli	Only occasional		Prominent, often multiple
Mitoses	Only occasional	Intermediate	May be frequent
Orientation	Polarized toward luminal spaces	Intermediate	Usually not polarized toward the luminal space

Definition: RBC, red blood cell.

References

1. Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer.* 1997; 80:1798-1802.
2. Bane A.: Ductal Carcinoma In Situ: What the Pathologist Needs to Know and Why. *Int J Breast Cancer* 2013:914053. doi: 10.1155/2013/914053.

D. Necrosis

The presence of necrosis[1,2] is correlated with the finding of mammographic calcifications (i.e., most areas of necrosis will calcify). DCIS that presents as mammographic calcifications often recurs as calcifications. Necrosis can be classified as follows:

- **Central ("comedo"):** The central portion of an involved ductal space is replaced by an area of expansive necrosis that is easily detected at low magnification. Ghost cells and karyorrhectic debris are generally present. Although central necrosis is generally associated with high-grade nuclei (i.e., comedo DCIS), it can also occur with DCIS of low or intermediate nuclear grade. This type of necrosis often correlates with a linear and/or branching pattern of calcifications on mammography.
- **Focal (punctate):** Small foci, indistinct at low magnification, or single cell necrosis (<10%).

Necrosis should be distinguished from secretory material, which can also be associated with calcifications, cytoplasmic blebs, and histiocytes, but does not include nuclear debris.

References

1. Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer.* 1997; 80:1798-1802.
2. Fox SB, Webster F, Chen CJ, et al. Dataset for pathology reporting of ductal carcinoma in situ, variants of lobular carcinoma in situ and low-grade lesions: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Histopathology.* 2022 Oct;81(4):467-476. doi: 10.1111/his.14725. Epub 2022 Aug 8. PMID: 35869801.

E. Microcalcifications

DCIS found in biopsies performed for microcalcifications will almost always be at the site of the calcifications or in close proximity.[1,2,3] The presence of the targeted calcifications in the specimen should be confirmed by specimen radiography. The pathologist must be satisfied that the specimen has been sampled in such a way that the lesion responsible for the calcifications has been examined microscopically. The relationship of the radiologic calcifications to the DCIS should be indicated.

References

1. Owings DV, Hann L, Schnitt SJ, How thoroughly should needle localization breast biopsies be sampled for microscopic examination? A prospective mammographic/pathologic correlative study. *Am J Surg Pathol.* 1990; 14:578-583.
2. Buono M, Schiavone L, Rizzo S, et. al. Imaging Ductal Carcinoma In Situ in the Era of De-Escalation: Role, Limits, and Clinical Implications for Risk-Adapted Management. *Diagnostics* (Basel). 2026 Mar 5;16(5):776. doi: 10.3390/diagnostics16050776.
3. Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg.* 2005; 201:586-597.

F. Additional Lesions

If the biopsy was performed for a benign lesion and the DCIS is an incidental finding, this should be documented. An example would be the finding of DCIS in an excision for a palpable fibroadenoma. In some cases, other pathologic findings, such as risk lesions or non-classic/variant subtypes of LCIS, are important for the clinical management of patients.

COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Resection Specimens from Patients with Ductal Carcinoma In Situ (DCIS) of the Breast

Version: 4.5.0.1
Protocol Posting Date: June 2026

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2027
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Excision less than total mastectomy	Includes specimens designated excision, segmental resection, lumpectomy, quadrantectomy and segmental or partial mastectomy, with or without axillary contents
Total Mastectomy	Includes skin-sparing and nipple-sparing mastectomy, with or without axillary contents
Tumor Type	**Description**
Ductal carcinoma in situ without invasive carcinoma or microinvasion	
Paget disease of the nipple not associated with invasive breast carcinoma	
Encapsulated papillary carcinoma without invasive carcinoma	
Solid papillary carcinoma without invasive carcinoma	

This protocol is NOT required for accreditation purposes for the following:

Procedure
Needle or skin biopsies
Primary resection specimen with no residual cancer
Additional excision performed after the definitive resection (e.g., re-excision of surgical margins)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Any tumor with invasive carcinoma, including DCIS with microinvasion only or neoadjuvantly treated invasive cancer with only residual DCIS (consider Breast Invasive Carcinoma Resection protocol)

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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements
Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).
Full accreditation requirements can be found on the CAP website under Accreditation Checklists.
A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.
**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where can'applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.5.0.1 (June 24, 2026)

- Display item updated in the Regional Lymph Nodes section

v 4.5.0.0 (June 17, 2026)

- WHO 6th Edition updates to content and explanatory notes
- Cover page update
- Tumor Site, Size (Extent) of DCIS, and Architectural Pattern(s) question updates
- Histologic Type and Nuclear Grade questions now multi-select
- Added Additional Lesion(s) question
- MARGIN, REGIONAL LYMPH NODE, SPECIAL STUDIES section updates
- pTMN Classification updates to include Modified Classification, T Suffix, optional pN Category, and addition of N Suffix

Reporting Template
Protocol Posting Date: June 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (DCIS OF THE BREAST: Resection)
Standard(s): AJCC 8

SPECIMEN

Procedure (Note A)
___ Excision (less than total mastectomy, including lumpectomy and partial mastectomy)
___ Total mastectomy (including nipple-sparing and skin-sparing mastectomy)
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

+Tumor Site (Note B)
Tumor Site descriptor should specify the location of the invasive cancer based on correlation with radiology designation and / or gross findings (e.g., "R1, 3:00, 2 cm from nipple" or "upper outer quadrant").
___ Specify tumor site / location: _____
___ Not specified

Histologic Type (Note C) (select all that apply)
___ Ductal carcinoma in situ (DCIS)
___ Paget disease
___ Encapsulated papillary carcinoma in situ
___ Solid papillary carcinoma in situ
___ Other histologic type not listed (specify): _____

Size (Extent) of DCIS (Note D)
The size (extent) of DCIS (greatest dimension using gross and microscopic evaluation) is an estimation of the volume of breast tissue occupied by DCIS.
___ Estimated size (extent) of DCIS is at least in Millimeters (mm): _____ mm
___ Cannot be determined (explain): _____
+Size of DCIS Comment (e.g., clarify aspects of extent / size, such as sizes of in situ papillary components if relevant): _____

+Architectural Pattern(s) (Note E) (select all that apply)
___ Comedo
___ Cribriform
___ Micropapillary
___ Papillary

___ Solid
___ Solid papillary carcinoma in situ
___ Encapsulated papillary carcinoma in situ
___ Paget disease (DCIS involving nipple skin)
___ Other (specify): _____

Nuclear Grade (Note F) (select all that apply)
___ Grade I (low)
___ Grade II (intermediate)
___ Grade III (high)
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Nuclear Grade Comment: _____

Necrosis (Note G)
___ Not identified
___ Present, focal (small foci or single cell necrosis)
___ Present, central (expansive "comedo" necrosis)
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Additional Lesion(s) (Note H) (select all that apply)
Non-classic / variant subtypes of LCIS include: Pleomorphic LCIS (pleomorphic nuclei greater than 4 times the size of a lymphocyte or equivalent to nuclei of high-grade DCIS) and Florid LCIS (proliferation of cells cytologically similar to those of classic LCIS but expanding the acini of the involved TDLUs so that little to no residual intervening intra-lobular stroma is present, and / or an expanded acinus or duct spans approximately 40–50 cells in diameter). Comedonecrosis in classic LCIS may also be considered non-classic / variant (describe in "Other (specify)".
___ Not identified
___ Lobular carcinoma in situ, classic
___ Lobular carcinoma in situ, pleomorphic
___ Lobular carcinoma in situ (specify): _____
___ Atypical lobular hyperplasia
___ Atypical ductal hyperplasia
___ Flat epithelial atypia
___ Other (specify): _____
+Extent of LCIS: _____
+Additional Lesion(s) Comment: _____

+Microcalcifications (Note I) (select all that apply)
___ Not identified
___ Present in DCIS
___ Present in non-neoplastic tissue
___ Other (specify): _____

MARGINS (Note J)

Margin Status#

 # Final margin status should be determined based on findings in any additional separately submitted final margins, as well as margins that are considered final in the primary resection specimen (i.e., a final margin status summary). If the final margin status is not clear based on the specimens received (i.e., additional margins without a clear relationship to initial margins), the distances to each can be stated in the "Other (specify)" reporting section with a recommendation for surgical correlation.

___ Not applicable (no residual DCIS in specimen)
___ All final margins greater than 2 mm from DCIS
___ DCIS present within 0-2 mm of final margins (specify specific margins below)
Margin(s) Involved by DCIS (at ink)
___ None identified
___ Specify involved margins: _____
Margin(s) Less than 1 mm from DCIS (but not at ink)
___ None identified
___ Specify: _____
Margin(s) 1 to 2 mm from DCIS
___ None identified
___ Specify: _____
+Margin(s) Greater than 2 mm from DCIS
___ None identified
___ Specify: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Margin Comment for DCIS (consider using for pleiomorphic or florid LCIS): _____

REGIONAL LYMPH NODES (Note K)

Regional Lymph Node Status

___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Macrometastases (greater than 2 mm)
___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes with Micrometastases (greater than 0.2 mm to 2 mm and / or greater than 200 cells)
___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes with Isolated Tumor Cells (0.2 mm or less OR 200 cells or less) (required only if applicable)#
 # Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of

macrometastasis or micrometastasis in other lymph nodes.

___ Not applicable
___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Total Number of Positive Macroscopic and Microscopic Lymph Nodes Counted Towards pN Category#

 # Add macrometastases and micrometastases for pN total. If only micrometastasis are present, use "Other (specify)" since they do not change the total lymph nodes counted toward the pN stage (staged as pN1mi even if multiple). ITCs also do not count towards the total pN staging (staged as pN0(i+) even if multiple).

___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined: _____

Size of Largest Nodal Metastatic Deposit#

 # The size of a tumor deposit is determined by measuring the largest dimension of any group of cells that are touching one another (confluent or contiguous tumor cells), regardless of whether the deposit is confined to the lymph node, extends outside the node (extranodal extension), is totally present outside the lymph node and invading adipose tissue, or is present within a lymphatic channel adjacent to the node.
Specify in Millimeters (mm)

___ Exact size: _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

Extranodal Extension (ENE)#

 # The measurement of extranodal extent can be performed either perpendicular to the lymph node capsule or in another dimension. As a general principle, the larger measurement can be preferentially used but there is no evidence to support a specific method. It is optional to report the specific measurement of extranodal extension, which may not be feasible when extensive (details of extranodal extension can also be described in the "Regional Lymph Node Comment" or the "Other (specify)" sections).

___ Not identified
___ Present

+Largest Measurement of Extranodal Extension

Specify in Millimeters (mm)

___ Exact measurement: _____ mm
___ Other (specify): _____
___ Cannot be determined: _____

+Number of Lymph Nodes with Extranodal Extension

___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined: _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

Total Number of Lymph Nodes Examined (sentinel and non-sentinel)

___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Non-regional lymph node(s) (specify, if possible): _____
___ Lung: _____
___ Liver: _____
___ Bone: _____
___ Brain: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note L)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
Paget disease with underlying DCIS is classified as Tis (DCIS). Encapsulated and solid papillary carcinomas without conventional invasive carcinoma are classified as pTis (DCIS). If there has been a prior core needle biopsy, the pathologic findings from the core, if available, should be considered when determining the T category. If invasive carcinoma or microinvasion were present on the core, the protocol for invasive carcinomas of the breast should be used and should incorporate this information.
 # Lobular carcinoma in situ (LCIS) is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.
___ pTis (DCIS): Ductal carcinoma in situ
___ pTis (Paget): Paget disease of the nipple NOT associated with invasive carcinoma and / or DCIS in the underlying breast parenchyma#

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category
Choose a category if lymph nodes received with the specimen; immunohistochemistry and / or molecular studies are not required
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
 # Isolated tumor cells (ITCs) are defined as small clusters of cells not larger 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 (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count when determining the N category but should be included in the total number of nodes evaluated.
___ 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
___ pN1mi: Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
Approximately 1000 tumor cells are contained in a 3-dimensional 0.2 mm cluster. Thus, if more than 200 individual tumor cells are identified as single dispersed tumor cells or as a nearly confluent elliptical or spherical focus in a single histologic section of a lymph node, there is a high probability that more than 1000 cells are present in the lymph node. In these situations, the node should be classified as containing a micrometastasis (pN1mi). Cells in different lymph node cross-sections or longitudinal sections or levels of the block are not added together; the 200 cells must be in a single node profile even if the node has been thinly sectioned into multiple slices. It is recognized that there is substantial overlap between the upper limit of the ITC and the lower limit of the micrometastasis categories due to inherent limitations in pathologic nodal evaluation and detection of minimal tumor burden in lymph nodes. Thus, the threshold of 200 cells in a single cross-section is a guideline to help pathologists distinguish between these 2 categories. The pathologist should use judgment regarding whether it is likely that the cluster of cells represents a true micrometastasis or is simply a small group of isolated tumor cells.
___ pN1a: Metastases in 1-3 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
___ pN2a: Metastases in 4-9 axillary lymph nodes, at least one tumor deposit larger than 2.0 mm##
___ pN2b: Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary 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

N Suffix (required only if applicable) (select all that apply)
The (sn) modifier is added to the N category when a sentinel node biopsy is performed (using either dye or tracer) and fewer than six lymph nodes are removed (sentinel and nonsentinel). The (f) modifier is added to the N category to denote confirmation of metastasis by fine needle aspiration / core needle biopsy with NO further resection of nodes.
___ Not applicable
___ (sn): Sentinel node(s) evaluated. If 6 or more nodes (sentinel or nonsentinel) are removed, this modifier should not be used.
___ (f): Nodal metastasis confirmed by fine needle aspiration or core needle biopsy.

pM Category (required only if confirmed pathologically)
The presence of distant metastases in a case of DCIS would be very unusual. Additional sampling to identify invasive carcinoma in the breast or additional history to document a prior or synchronous invasive carcinoma is advised in the evaluation of such cases.
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Histologically proven metastases larger than 0.2 mm
+Specify Case Number (if from a previous procedure): _____

SPECIAL STUDIES
This section is available to include prior breast cancer biomarker results on the DCIS, typically as reported on the initial core biopsy specimen(s). Specify the case number, tumor identifier (if relevant), and the available biomarker results. The CAP Breast Biomarker Template should be used for reporting biomarkers performed on samples from this resection specimen. Pending biomarker studies can be listed in the "Comments" section of this report.

+Biomarker Testing Performed on Prior Case (specify): _____

Specify Tumor Identifier (if multiple tumors are present): _____

+Breast Biomarker Testing Performed on Previous Biopsy (select all that apply)
___ Estrogen Receptor (ER)
Estrogen Receptor (ER) Status
___ Positive (greater than 10% of cells demonstrate nuclear positivity)
+Percentage of Cells with Nuclear Positivity
___ Specify percentage: _____ %
OR
Select range below
___ 11-20%
___ 21-30%
___ 31-40%
___ 41-50%
___ 51-60%
___ 61-70%
___ 71-80%
___ 81-90%
___ 91-100%
___ Low positive (1-10% of cells with nuclear positivity)
___ Negative
___ Cannot be determined (explain): _____
___ Progesterone Receptor (PgR)
Progesterone Receptor (PgR) Status
___ Positive
+Percentage of Cells with Nuclear Positivity
___ Specify percentage: _____ %
OR
Select range below
___ 1-10%
___ 11-20%
___ 21-30%
___ 31-40%
___ 41-50%
___ 51-60%
___ 61-70%
___ 71-80%
___ 81-90%
___ 91-100%
___ Negative
___ Cannot be determined (explain): _____

COMMENTS

Comment(s): _____

Explanatory Notes
A. Breast Specimens and Breast Procedures
Breast Specimens
The following types of breast specimens and procedures may be reported with the case summary:

Excisions. Removal of breast tissue without the intent of removing the entire breast. The nipple is only rarely removed with excisions. Excisions include specimens designated biopsies, partial mastectomies, lumpectomies, and quadrantectomies.

Total Mastectomy. Removal of all breast tissue, including the nipple and areola.

- Simple mastectomy: This procedure consists of a total mastectomy without removal of axillary lymph nodes.
- Skin-sparing mastectomy: This is a total mastectomy with removal of the nipple and only a narrow surrounding rim of skin.
- Modified radical mastectomy: This procedure consists of a total mastectomy and an axillary dissection. In the case summary, the breast and lymph node specimens are documented separately.
- Radical mastectomy: This procedure consists of a total mastectomy, axillary contents, and removal of the pectoralis muscles, and currently is performed only rarely. This type of specimen and procedure can be indicated on the case summary as ‘‘Other.’’

The following types of specimens should not be reported using this protocol:

- Very small incisional biopsies (including core needle biopsies).
- Excisions or mastectomies containing only residual DCIS after a core needle biopsy or other specimen showing invasive carcinoma or DCIS with microinvasion (invasion measuring ≤1 mm). This type of case should be reported by using the protocol for invasive carcinoma of the breast,[1], and the report should incorporate information from the prior needle biopsy.

Specimen Sampling
Specimen sampling for specimens with DCIS has the following goals:[2,3,4,5]

- The clinical or radiologic lesion for which the surgery was performed must be examined microscopically. If the lesion is a nonpalpable imaging finding, the specimen radiograph and/or additional radiologic studies may be necessary to identify the lesion. When practical, the entire specimen should be submitted in a sequential fashion for histologic examination. If this is not possible, at least the entire region of the targeted lesion should be examined microscopically.
- Any additional potentially clinically relevant lesions noted in the specimen must be sampled.
- The margins must be evaluated for involvement by DCIS. If the specimen is received sectioned or fragmented, this should be noted, as this will limit the ability to evaluate the size of the lesion and the status of margins. If the specimen is an incisional biopsy, margins need not be evaluated.

For specimens with a known diagnosis of DCIS (e.g., by prior core needle biopsy), it is recommended that the entire specimen be examined, if practical, using serial sequential sampling to exclude the possibility of invasion, to completely evaluate the margins, and to aid in determining extent.[6,7,8] 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 best by MRI studies are generally not grossly evident and not seen on specimen radiography.

Recording the specimen size in the gross description is important, as the volume of tissue excised has been associated with the likelihood of recurrence.[9]

Tissue may be taken for research studies or assays that do not involve the histologic examination of the tissue (e.g., reverse transcriptase polymerase chain reaction [RT-PCR]) only when taken in such a way to be able to evaluate the tissue for small 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.

References

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B. Tumor Site

The site/location and lesion designation (ex. L1 mass, R2 calcifications, etc.) of DCIS is helpful to document, when provided by the surgeon, breast imaging, or previous pathology report, to correlate with prior studies (e.g., a core needle biopsy) or with future biopsies or cancer events. The site/location can be listed as designated by the surgeon or imaging finding (ex. 9:00, 4 cm from nipple) or less specifically as a quadrant or gross specimen location. In a mastectomy specimen, it is helpful to locate the DCIS with respect to the clinical site or imaging site, when possible and to use similar designations as used in imaging for lesions (ex. L1, R3).

C. Histologic Type

This protocol applies only to cases of DCIS. The protocol for invasive carcinoma of the breast[1] applies if invasion or microinvasion (less than or equal to 1 mm) is present. Pleomorphic lobular carcinoma in situ (LCIS) has overlapping features with DCIS and may be treated similarly, but at present, there is insufficient evidence to establish definitive recommendations for treatment. Thus, pleomorphic LCIS is not currently included in the pTis classification.

When DCIS involves nipple skin only, without underlying invasive carcinoma or DCIS, the classification is DCIS (i.e., Tis [Paget]). The majority of these cases are strongly positive for HER2.

The WHO criteria for a diagnosis of Encapsulated Papillary Carcinoma and Solid Papillary Carcinoma In Situ should be used in classification.[2] Myoepithelial cells may be absent or attenuated, but the contours of these lesions should be circumscribed to classify them as in situ. These lesions are clinically managed like DCIS.

References

1. Krishnamurti, UG, Allison, KH, Fitzgibbons, P, Connolly, JL. Protocol for the Examination of Resection Specimens from Patients with Invasive Carcinoma of the Breast. 2024; www.cap.org/cancerprotocols, accessed March 19, 2026.
2. WHO Classification of Tumours Editorial Board. Breast *tumours.* Lyon (France): International Agency for Research on Cancer; 2026. (WHO classification of tumours series, 6th ed.).

D. Size (Extent) of DCIS

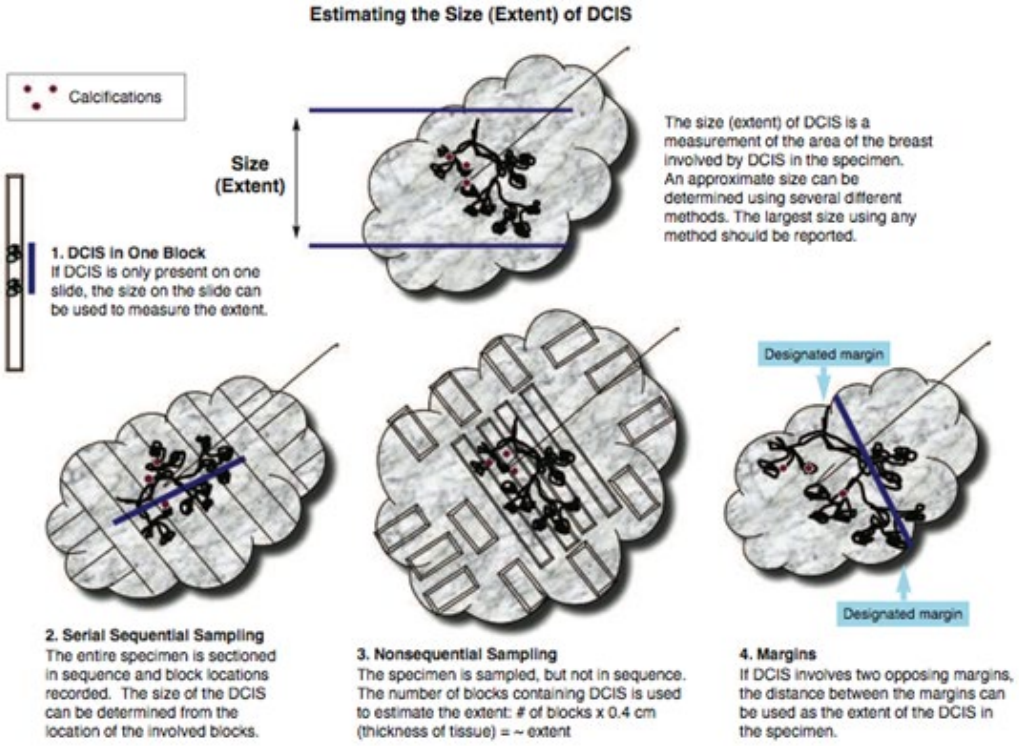
Although not required for pT classification or stage assignment, the size (extent) of DCIS is an important factor in patient management.[1,2] Extent (as determined by a number of different methods) is correlated with the likelihood of residual disease after re-excision,[3,4,5,6] close or positive margins, local recurrence,[7,8,9] and the possibility of missed areas of invasion.[10,11] Extent is not as important for predicting local recurrence when wide margins are obtained.[7,8,12] Extent is an estimation of the volume of breast tissue involved by DCIS. Mammographic assessment of DCIS, usually based on distribution of calcifications, frequently underestimates, and sometimes overestimates, the extent of DCIS.

Although a precise measurement is often not possible, an estimate of the extent of DCIS is clinically important (Table 1).

Table 1. Extent of Ductal Carcinoma In Situ (DCIS) and Clinical Significance

Size	Extent
Up to 20 mm	Breast conservation with wide negative margins can be achieved in most women. Microscopic examination of the entire area involved by DCIS is recommended and should be possible in most cases. This will require complete microscopic examination of smaller biopsies, or sampling of large excisions or mastectomies to include all areas likely to contain DCIS (e.g., tissue with radiologic calcifications or grossly abnormal tissue).
>20-40 mm	Wide negative margins may be difficult to achieve in some women with breast-conserving surgery. Microscopic examination of the entire area involved by DCIS is recommended but may be difficult to achieve in some cases. This will require complete microscopic examination of smaller biopsies or sampling of large excisions or mastectomies to include all areas likely to contain DCIS (e.g., tissue with radiologic calcifications or grossly abnormal tissue).
>40 mm	Breast conservation with wide negative margins may be impossible to achieve in some women. Microscopic examination of the entire area involved by DCIS is recommended but may be impractical in some

	cases. This will require complete microscopic examination of smaller biopsies or selective sampling of large excisions or mastectomies to include areas likely to contain DCIS (e.g., tissue with radiologic calcifications or grossly abnormal tissue). There is a possibility of undetected areas of invasion if the area involved by DCIS is not completely examined. Lymph node sampling may be recommended.



There are multiple methods for estimating the extent of DCIS (see Figure):

- **DCIS in 1 block:** The area involved by DCIS can be measured from a single slide, if DCIS is present in only 1 block. If separate foci are present, the largest distance between foci should be reported. This method will underestimate the extent of DCIS when multiple blocks are involved and should not be used in such cases.[13]
- **Serial sequential sampling:** The entire specimen is blocked out in such a way that the location of each block can be determined. The extent of the DCIS can be calculated by using a diagram of the specimen, the thickness of the slices, and the location of the involved blocks.[13,14,15] This method is recommended for all excisions likely to harbor DCIS or with previously diagnosed DCIS (e.g., by diagnosis on a prior core needle biopsy).
- **Nonsequential sampling:** The number of blocks involved by DCIS is not recommended as the only method of estimating DCIS extent since this is highly dependent on how many sections are

taken from each slice (and therefore can both significantly over and underestimate extent). However, this information can be included in the additional extent descriptors section.

- **Edges of specimens:** If DCIS involves or is close to 2 opposing margins of a surgical excision, the distance between the margins can be used as the extent of the DCIS within the specimen.
- **Gross lesions: In** some cases of high-grade DCIS, there may be a gross lesion that can be measured. Confirmation of the gross size must be confirmed by microscopic evaluation.

The largest estimate obtained using any of these methods should be used to report the estimated size (extent) of the DCIS. Additional extent descriptors might include if multiple separate areas of DCIS are present, or other estimations of extent/volume).

References

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15. Silverstein MJ, Poller D, Craig P, et al. A prognostic index for ductal carcinoma in situ of the breast. *Cancer.* 1996; 77:2267-2274.

E. Architectural Pattern

The architectural pattern has been reported traditionally for DCIS.[1,2] However, nuclear grade and the presence of necrosis are more predictive of clinical outcome. Paget's encapsulated papillary carcinoma and solid papillary carcinoma in situ can also be reported as architectural patterns, but they are also considered distinct histologic types of DCIS.

References

1. Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer.* 1997; 80:1798-1802.
2. Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg.* 2005; 201:586-597.

F. Nuclear Grade

The nuclear grade of DCIS is determined using 6 morphologic features (Table 2).[1,2,3]

Table 2. Nuclear Grade of Ductal Carcinoma In Situ

Feature	Grade I (Low)	Grade II (Intermediate)	Grade III (High)
Pleomorphism	Monotonous (monomorphic)	Intermediate	Markedly pleomorphic
Size	1.5 to 2 x the size of a normal RBC or a normal duct epithelial cell nucleus	Intermediate	>2.5 x the size of a normal RBC or a normal duct epithelial cell nucleus
Chromatin	Usually diffuse, finely dispersed chromatin	Intermediate	Usually vesicular with irregular chromatin distribution
Nucleoli	Only occasional		Prominent, often multiple
Mitoses	Only occasional	Intermediate	May be frequent
Orientation	Polarized toward luminal spaces	Intermediate	Usually not polarized toward the luminal space

Definition: RBC, red blood cell.

References
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G. Necrosis

The presence of necrosis is correlated with the finding of mammographic calcifications (i.e., most areas of necrosis will calcify). DCIS that presents as mammographic calcifications often recurs as calcifications.
Necrosis can be classified as follows:[1,2]

- **Central ("comedo"):** The central portion of an involved ductal space is replaced by an area of expansive necrosis that is easily detected at low magnification. Ghost cells and karyorrhectic debris are generally present. Although central necrosis is generally associated with high-grade nuclei (i.e., comedo DCIS), it can also occur with DCIS of low or intermediate nuclear grade. This type of necrosis often correlates with a linear and/or branching pattern of calcifications on mammography.
- **Focal (punctate):** Small foci, indistinct at low magnification, or single cell necrosis (<10%).

Necrosis should be distinguished from secretory material, which can also be associated with calcifications, cytoplasmic blebs, and histiocytes, but does not include nuclear debris.

References
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H. Additional Lesions

In some cases, other pathologic findings are important for the clinical management of patients, such as risk lesions or non-classic/variant subtypes of lobular carcinoma in situ.

If the biopsy was performed for a benign lesion and the DCIS is an incidental finding, this should be documented. An example would be the finding of DCIS in an excision for a palpable fibroadenoma.

Peritumoral vascular invasion is a very rare finding in association with DCIS alone. Additional sampling should be considered to attempt to identify an area of invasion. If there has been prior surgery or needle biopsy, the possibility of artifactual displacement of epithelial cells into lymphatics should be considered. Lymph node biopsy may be performed in patients with DCIS and lymphovascular invasion.

If there has been a prior core needle biopsy or incisional biopsy, the biopsy site should be sampled and documented in the report. If the intention was to completely re-excise a prior surgical site, the report

should document biopsy changes at the margin that could indicate an incomplete excision. This protocol should only be used for re-excisions that reveal the largest extent of DCIS.

I. Microcalcifications

DCIS found in biopsies performed for microcalcifications will almost always be at the site of the calcifications or in close proximity.[1,2] The presence of the targeted calcifications in the specimen should be confirmed by specimen radiography. The pathologist must be satisfied that the specimen has been sampled in such a way that the lesion responsible for the calcifications has been examined microscopically. The relationship of the radiologic calcifications to the DCIS should be indicated.

References

1. Owings DV, Hann L, Schnitt SJ, How thoroughly should needle localization breast biopsies be sampled for microscopic examination? A prospective mammographic/pathologic correlative study. *Am J Surg Pathol.* 1990; 14:578-583.
2. Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg.* 2005; 201:586-597.

J. Margins

Whenever feasible, the specimen should be oriented in order to identify specific margins.

Margins may be identified by sutures or clips placed on the specimen surface or by other means of communication between surgeon and pathologist, and should be documented in the pathology report. Margins can be identified microscopically in several ways, including the use of multiple colored inks, by submitting the margins in specific cassettes, or by the surgeon submitting each margin as a separately excised specimen. Inks should be applied to the surface of the specimen, taking care to avoid penetration into the specimen.

Margin status is considered Involved if the final margins have DCIS at ink (inclusive of any additional margins removed). If the specimen is oriented, the specific site(s) of involvement should also be reported. Additionally, margins less than 1 mm to DCIS (but not at ink), margins 1-2 mm from DCIS should be specified. Margins greater than 2 mm from DCIS can be specified if considered relevant. For ease of reporting, an option for “all final margins greater than 2 mm” is also available in the protocol. “Other” can be used for complex scenarios (such as description of the margin status of multiple specimens that require surgical correlation) and “Cannot be determined” for other uncommon scenarios with explanation. The Margin comment section can be used to clarify any additional margin details.

The deep margin may be at muscle fascia. If so, the likelihood of additional breast tissue beyond this margin (and therefore possible involvement by DCIS) is extremely small. A deep muscle fascial margin (e.g., on a mastectomy specimen) is unlikely to have clinical significance.

A superficial (generally anterior) margin may be immediately below the skin, and there may not be additional breast tissue beyond this margin. However, some breast tissue can be left in skin flaps, and the likelihood of residual breast tissue is related to the thickness of the flap.[1]

Specimen radiography is important to assess the adequacy of excision. Compression of the specimen should be minimized, as it can severely compromise the ability to assess the distance of the DCIS from the surgical margin.[2] Mechanical compression devices should be used with caution and preferably reserved for nonpalpable lesions that require this technique for imaging (e.g., microcalcifications).

If DCIS is present at the margin, the extent of margin involvement is associated with the likelihood of residual disease:[3,4]

- Focal: DCIS at the margin in a <1 mm area in 1 block
- Minimal/moderate: between focal and extensive
- Extensive: DCIS at the margin in an area ≥15 mm or in 5 or more low-power fields and/or in 8 or more blocks)

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K. Lymph Node Sampling and Reporting

Lymph Node Sampling

Patients with DCIS may have lymph nodes sampled in the following situations:

- Extensive DCIS: Patients with extensive DCIS are more likely to have areas of invasion and it may be difficult or impractical to examine all involved areas of the breast microscopically.[1,2,3] A lymph node with a metastasis would indicate an occult area of invasion.
- Pathologic findings on a prior needle biopsy or excision raising concern for invasion or microinvasion (invasion measuring ≤1 mm in size): If invasion has been documented, the protocol for invasive carcinoma of the breast[4] should be used.
- Imaging findings (e.g., an irregular mass) or clinical findings (e.g., a large palpable mass) that increase the likelihood that stromal invasion is present.[2]
- Planned mastectomy: The additional sampling of low lymph nodes or a sentinel lymph node does not result in increased morbidity. If the node or nodes are negative, and invasive cancer is found, another surgical procedure for node sampling can be avoided.

Most tumor cells in lymph nodes of patients with DCIS would be classified as isolated tumor cells.[5,6] Artifactual displacement of epithelium to a lymph node(s) can occur following a core needle biopsy; this finding should not be considered isolated tumor cells or a micrometastasis.[7,8] If a larger nodal metastasis is found and the breast tissue has not been entirely submitted for microscopic examination, additional sampling should be considered to attempt to identify invasive carcinoma.[1,3]

Grossly uninvolved nodes should be submitted in their entirety for histologic examination, whereas a representative section of a grossly positive node may be submitted. Small nodes (e.g., 2 to 3 mm) may be submitted intact, but larger nodes should be thinly sectioned. An accurate assessment of the number of positive lymph nodes is a critical prognostic indicator.

Sentinel lymph nodes are identified as such by the surgeon, generally by uptake of radiotracer or dye.

Reporting Lymph Nodes

The pathology report should state the total number of lymph nodes examined (including the number of sentinel nodes), the number of nodes with metastases, and the greatest dimension of the largest metastatic focus. If a patient has at least 1 macrometastasis, only nodes with micro and macrometastases are included for the total number of positive nodes for determining the N category.[9] Nodes with isolated tumor cells are not included in this count. At least 1 node with presence or absence of cancer documented by pathologic examination is required for determining the pathologic N category.

The (sn) modifier indicates that nodal categorization is based on less than an axillary dissection. When the combination of sentinel and nonsentinel nodes removed is less than a standard low axillary dissection (fewer than six nodes), the (sn) modifier is used," e.g., pN0(i+)(sn). The (sn) modifier is not used if 6 or more lymph nodes are examined (including sentinel and nonsentinel lymph nodes).

Isolated tumor cells (ITCs) are defined as single tumor cells or small cell clusters not greater than 0.2 mm and numbering less than 200 cells.[4,10,11,12] They may be detected by routine histologic examination or by immunohistochemical (IHC) or molecular methods. ITCs do not usually show evidence of malignant activity (e.g., proliferation or stromal reaction), but micrometastases may show these changes.

Almost all tumor cells present in lymph nodes of patients with DCIS are isolated tumor cells or the cells may be artifactually displaced from a previous procedure.[7,8] Isolated tumor cells detected in cases of DCIS have not been shown to have prognostic importance.[5,6] If a larger metastasis is found, additional tissue sampling and review of slides are helpful to determine if an area of invasion is present.[3]

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L. pTNM Classification

The tumor-node-metastasis (TNM) staging system maintained collaboratively by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.[1,2,3,4,5]

Pathologic Classification

The pathologic classification of a cancer is based on information acquired before treatment supplemented and modified by the additional evidence acquired during and from surgery, particularly from pathologic examination of resected tissues. The pathologic classification provides additional precise and objective data. Reporting of T, N, and M categories by pathologic means is denoted by use of a lower case “p” prefix (pT, pN, pM).

Pathologic T. DCIS is classified as pTis (DCIS) or pTis (Paget).

Pathologic N. At least one node with presence or absence of cancer documented by pathologic examination is required for determining the pathologic N category. A tumor nodule 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.

Specialized pathologic techniques such as immunohistochemistry or molecular techniques may identify limited metastases in lymph nodes that may not have been identified without the use of the special diagnostic techniques. Single tumor cells or small clusters of cells are classified as isolated tumor cells (ITCs). The standard definition for ITC is a cluster of cells not more than 0.2 mm in greatest diameter. Cases with ITC only in lymph nodes are classified as pN0. This rule also generally applies to cases with findings of tumor cells or their components by nonmorphologic techniques such as flow cytometry or DNA analysis.

Pathologic M. The pathologic assignment of the presence of metastases (pM1) requires a biopsy positive for 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. It would be extremely rare to have distant metastasis in examples of DCIS and would surely indicate an unsampled area of invasive carcinoma.

Posttherapy or Postneoadjuvant Therapy Classification (yTNM). Cases where systemic and/or radiation therapy are given before surgery (*neoadjuvant*) or where no surgery is performed may have the extent of disease assessed at the conclusion of the therapy by clinical or pathologic means (if resection performed). This classification is useful to clinicians because the extent of response to therapy may provide important prognostic information to patients and help direct the extent of surgery or subsequent systemic and/or radiation therapy. T and N are classified by using the same categories as for clinical or pathologic staging for the disease type, and the findings are recorded by using the prefix designator y (e.g., ycT; ycN; ypT; ypN). The yc prefix is used for the clinical stage after therapy, and the yp prefix is used for the pathologic stage for those cases that have surgical resection after neoadjuvant therapy. The M component should be classified by the M status defined clinically or pathologically prior to therapy.

Retreatment Classification. The retreatment classification (rTNM) is assigned when further treatment is planned for a cancer that recurs after a disease-free interval. The original stage assigned at the time of initial diagnosis and treatment does not change when the cancer recurs or progresses. The use of this staging for retreatment or recurrence is denoted with the r prefix (rTNM). All information available at the time of retreatment should be used in determining the rTNM stage. Biopsy confirmation of recurrent cancer is important if clinically feasible. However, this may not be appropriate for each component, so clinical evidence for the T, N, or M component by clinical, endoscopic, radiologic, or related methods may be used.

Multiple tumors. If there are multiple simultaneous areas of DCIS in the breast, Tis remains the appropriate choice. For simultaneous bilateral examples of DCIS, each DCIS is classified separately as independent tumors in different organs.

Metachronous primaries. Second or subsequent primary examples of DCIS occurring in the same organ or in different organs are staged as a new DCIS with the TNM system. Second DCIS examples are not staged using the y prefix unless the treatment of the second cancer warrants this use.

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
2. Connolly JL. Changes and problematic areas in interpretation of the AJCC Cancer Staging Manual, 6th Edition, for breast cancer. *Arch Pathol Lab Med.* 2006; 130:287-291.
3. Singletary SE, Connolly JL, Breast cancer staging: working with the sixth edition of the AJCC Cancer Staging Manual. *CA Cancer J Clin.* 2006; 56:37-47.
4. Singletary SE, Greene FL, Sobin LH. Classification of isolated tumor cells: clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. *Cancer.* 2003; 90:2740-2741
5. Brierley JD, Gospodarowicz MK, Wittekind CH, et al, eds. *TNM Classification of Malignant Tumours.* 8th ed. Oxford UK: Wiley; 2016.

Protocol for the Examination of Resection Specimens From Patients with Phyllodes Tumor of the Breast

Version: 1.1.0.1
Protocol Posting Date: September 2022
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.
This protocol may be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes excision, segmental resection, lumpectomy, quadrantectomy, and partial or total mastectomy
Tumor Type	**Description**
Phyllodes tumor	

The following should NOT be reported using this protocol:

Procedure
Biopsy
Cytologic specimens

Important Note
The American Joint Committee on Cancer (AJCC) eighth edition and the World Health Organization (WHO) recommend staging malignant phyllodes tumors according to guidelines established for soft tissue sarcomas – extremity and trunk. T category, N category and stage group assignments do not apply to benign or borderline tumors. An abbreviated stage group table that only applies to malignant phyllodes tumors is included in the Explanatory Notes.

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.

Accreditation Requirements
The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 1.1.0.1

- Added the answers 'Other (specify)' and 'Cannot be determined (explain)' to the Margin Status question

Reporting Template

Protocol Posting Date: September 2022

Select a single response unless otherwise indicated.

CASE SUMMARY: (PHYLLODES OF THE BREAST: Resection)

Standard(s): AJCC-UICC 8

Note: Use of this reporting template is optional and is not required for accreditation purposes. The template can be used for benign and borderline phyllodes tumors, but pathologic stage classification should only be done for those tumors classified as malignant.

SPECIMEN

Procedure

___ Excision (less than total mastectomy)
___ Total mastectomy (including nipple-sparing and skin-sparing mastectomy)
___ Other (specify): _____
___ Not specified

Specimen Laterality

___ Right
___ Left
___ Not specified

TUMOR

+Tumor Site (select all that apply)

___ Upper outer quadrant
___ Lower outer quadrant
___ Upper inner quadrant
___ Lower inner quadrant
___ Central
___ Nipple
___ Clock position

Specify Clock Position (select all that apply)

___ 1 o'clock
___ 2 o'clock
___ 3 o'clock
___ 4 o'clock
___ 5 o'clock
___ 6 o'clock
___ 7 o'clock
___ 8 o'clock
___ 9 o'clock
___ 10 o'clock
___ 11 o'clock
___ 12 o'clock

___ Specify distance from nipple in Centimeters (cm): _____ cm
___ Other (specify): _____

___ Not specified

Tumor Size

___ Greatest dimension in Millimeters (mm): _____ mm

+Additional Dimension in Millimeters (mm): ____ x ____ mm

___ Cannot be determined (explain): _____

Histologic Type (Note A)

A diagnosis of malignant phyllodes tumor requires the presence of all five of the following features: marked stromal cellularity, marked stromal atypia, stromal overgrowth, an infiltrative tumor border and greater than or equal to 10 mitoses per 10 high power fields (HPFs). Tumors should be classified as borderline when some but not all of these changes are present. Malignant phyllodes tumor is also diagnosed when malignant heterologous elements other than pure well differentiated liposarcoma are present, even if not all of the other histologic features of malignancy are observed.

___ Phyllodes tumor, benign

___ Phyllodes tumor, borderline

___ Phyllodes tumor, malignant

Stromal Cellularity (Note B)

___ Mild (stromal nuclei are non-overlapping)

___ Moderate (some overlapping stromal nuclei)

___ Marked (many overlapping stromal nuclei)

Stromal Atypia (Note C)

___ None

___ Mild (minimal variation in nuclear size, even chromatin, and smooth nuclear contours)

___ Moderate (more variation in nuclear size and irregular nuclear membranes)

___ Marked (marked nuclear pleomorphism, hyperchromasia, and irregular nuclear contours)

Stromal Overgrowth (Note D)

Stromal overgrowth is present when there is at least one low-power microscopic field (4x objective and 10x eyepiece or 22.9 mm2) that contains stroma only without epithelial elements.

___ Absent

___ Present

___ Cannot be determined

Mitotic Rate (Note E)

Malignant phyllodes tumors have greater than or equal to 10 mitoses per 10 high-power fields (40x objective and 10x eyepiece) or greater than or equal to 5 mitoses / mm2. Benign phyllodes tumors have less than 5 mitoses per 10 HPFs (less than 2.5 mitoses / mm2).

___ None identified: _____

___ Specify number of mitoses per 10 high power fields: _____ mitoses per 10 High Power Fields (HPFs)

OR

___ Specify number of mitoses per square Millimeter (mm): _____ mitoses per mm2

___ Cannot be determined

Histologic Tumor Border

A circumscribed border is smooth and well-defined or shows a minimally irregular tumor interface with adjacent stroma. Infiltrative (permeative) tumor borders can be focally infiltrative (unequivocal invasion into adjacent stroma in one low power field) or extensively infiltrative (unequivocal invasion in a wide area or in multiple foci along the tumor periphery).

___ Circumscribed (well-defined; pushing)
___ Infiltrative (permeative)
+___ Focal
+___ Extensive
___ Cannot be determined

Malignant Heterologous Elements (Note F)

A phyllodes tumor is regarded as malignant when there are malignant heterologous elements, even when not all of the other histological features of malignancy are present. This rule does not apply if the only heterologous element is well differentiated liposarcoma. In the breast, those tumors usually lack MDM2 and CDK4 amplifications and have a low metastatic risk. A diagnosis of malignant phyllodes tumor should therefore not be based solely on the presence of well-differentiated liposarcoma without all of the other histologic features of malignancy.

___ Not identified
___ Liposarcoma (excluding well-differentiated liposarcoma)
___ Osteosarcoma
___ Chondrosarcoma
___ Other (specify): _____

MARGINS

Margin Status for Phyllodes Tumor

Margin status is listed as positive if there is ink on phyllodes tumor (i.e., the distance is 0 mm)

___ All margins negative for phyllodes tumor

Closest Margin(s) to Phyllodes Tumor (select all that apply)

___ Anterior
___ Posterior
___ Superior
___ Inferior
___ Medial
___ Lateral
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Distance from Phyllodes Tumor to Closest Margin

Specify in Millimeters (mm)

___ Exact distance: _____ mm
___ Less than: _____ mm
___ Greater than: _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Phyllodes tumor present at margin

Margin(s) Involved by Phyllodes Tumor (select all that apply)

___ Anterior
___ Posterior

___ Superior
___ Inferior
___ Medial
___ Lateral
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph nodes
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable
___ Not applicable
___ Other (specify): _____
___ Cannot be determined

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th Edition) (Note G)
Staging applies only to malignant phyllodes tumors. pT and pN categories should not be assigned for benign and borderline tumors.

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (required only if the tumor is malignant)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.
___ Not applicable (tumor is not graded as malignant)

___ Tumor is malignant

The following section applies only if the tumor is malignant. Do not assign pT and pN stage categories for benign or borderline tumors.

TNM Descriptors (select all that apply)

___ Not applicable
___ m (multiple)
___ r (recurrent)
___ y (post treatment)

pT Category

___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pT1: Tumor 5 cm or less in greatest dimension
___ pT2: Tumor more than 5 cm but not more than 10 cm
___ pT3: Tumor more than 10 cm but not more than 15 cm
___ pT4: Tumor more than 15 cm in greatest dimension

pN Category

When no lymph nodes are present, the pathologic 'N' category is not assigned (pNX is not used and should not be reported)

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

pM Category (required only if confirmed pathologically)

___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

ADDITIONAL FINDINGS

+Additional Findings (select all that apply)

___ Fibroepithelial proliferation (coexisting fibroadenoma or fibroadenomatoid change in the tissue surrounding the phyllodes tumor)
___ Atypical ductal hyperplasia
___ Atypical lobular hyperplasia
___ Other (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Histologic Type / Grade

Phyllodes tumors are classified as malignant when all five of the following histological features are present: marked stromal hypercellularity; marked stromal atypia; stromal overgrowth; an infiltrative (permeative) tumor border; and greater than or equal to 10 mitotic figures in 10 high power fields (see Table 1). Tumors should be classified as borderline if some but not all of these changes are present.

There are rare phyllodes tumors that do not have all five histologic features but display malignant behavior. When a tumor lacks one or two features but shows severe abnormalities in others, the pathologist should consider adding a comment that such tumors may exhibit aggressive behavior.

Benign phyllodes tumors have mild stromal hypercellularity, minimal to no stromal atypia, no stromal overgrowth, circumscribed (pushing) tumor borders and less than or equal to 4 mitoses per 10 high-power fields (HPFs).[1]

The distinction between benign and borderline phyllodes tumors is not well-defined and there is no universal agreement which histologic features should be given greater emphasis. When the distinction between a benign and borderline tumor is unclear, it may be helpful to include a comment about this in the pathology report.

A phyllodes tumor is also categorized as malignant if there is a malignant heterologous mesenchymal component (e.g. liposarcoma, chondrosarcoma, osteosarcoma) even if the other histological parameters are not present, or if only some are present. An exception to this rule is if the heterologous element is atypical lipomatous tumor/well-differentiated liposarcoma. Well-differentiated liposarcomas in the breast usually lack MDM2 and CDK4 amplifications and appear to have a low metastatic risk. Hence, a diagnosis of malignant phyllodes tumor should not be based solely on the presence of well-differentiated liposarcoma without the other histologic features that support malignancy.[1]

Table 1. Histologic features of phyllodes tumors (adapted from Tse G, et al[2])

Histologic feature	Benign	Borderline	Malignant
Stromal cellularity	Mild	Moderate	Marked
Stromal atypia	Mild or none	Mild or moderate	Marked
Stromal overgrowth	Absent	Absent or very focal	Present
Mitotic rate	≤4 mitoses per 10 HPFs or <2.5 mitoses per mm^2	5 - 9 mitoses per 10 HPFs or 2.5 - 5 mitoses/mm^2	≥10 mitoses per 10 HPFs or ≥5 mitoses/mm^2
Tumor border	Circumscribed	Usually circumscribed but may be focally infiltrative	Focally or extensively infiltrative (permeative)
Malignant heterologous stromal elements	Absent	Absent	Sometimes present

HPF: High power field (40x objective and 10x eyepiece)

References

1. Tan BY, Apple SK, Badve S, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016;68:5-21.
2. Tse G, Koo JS, Thike AA. Phyllodes tumour. In: WHO Classification of Tumours Editorial Board. Breast Tumours, 5th ed, vol 2. Lyon (France): *International Agency for Research on Cancer*; 2019:172-176.

B. Stromal Cellularity

Mild hypercellularity is characterized by a slight increase in stromal cells as compared with normal perilobular stroma, with evenly spaced nuclei that are not touching or overlapping, while marked stromal cellularity shows confluent areas of densely overlapping nuclei. Moderate stromal cellularity has findings that are intermediate between the two, with some overlapping stromal nuclei.[1,2]

References

1. Tan BY, Apple SK, Badve S, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016;68:5-21.
2. Jara-Lazaro AR, Akhilesh M, Thike AA, et al. Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*. 2010; 57:220–232.

C. Stromal Atypia

Mild stromal atypia is reported when there is little variation in nuclear size and the nuclear contours are smooth. Cases with moderate atypia show some variation in the size of stromal nuclei and some wrinkling of nuclear membranes. Marked stromal atypia is identified when there is marked variation in nuclear size, coarse chromatin and irregular nuclear membranes with discernible nucleoli.[1,2]

References

1. Tan BY, Apple SK, Badve S, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016;68:5-21.
2. Jara-Lazaro AR, Akhilesh M, Thike AA, et al. Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*. 2010; 57:220–232.

D. Stromal Overgrowth

Stromal overgrowth is defined by the absence of epithelial elements in at least one low-power microscopic field containing only stroma. A low-power field can be defined either as a 4x objective and 10x eyepiece or as 22.9 mm^2.[1,2,3]

References

1. Tan BY, Apple SK, Badve S, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016;68:5-21.
2. Jara-Lazaro AR, Akhilesh M, Thike AA, et al. Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*. 2010; 57:220–232.
3. Tan PH, Thike AA, Tan WJ, et al. Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. *J Clin Pathol* 2012;65:69-76.

E. Mitotic Rate

A diagnosis of malignant phyllodes tumor requires at least 10 mitoses per 10 high power fields (40x objective and 10x eyepiece) or at least 5 mitoses/mm^2. Mitotic activity in benign phyllodes tumor is usually low (less than or equal to 4 mitoses per 10 HPFs or less than 2.5 mitoses per mm^2). Borderline phyllodes tumors usually have 5 to 9 mitoses per 10 HPF (2.5 to 5 mitoses/mm^2).[1]

To report the number of mitoses per square millimeter, the area of the high power field must be known, but microscopes vary in field size so the area must be determined for each microscope. The diameter of an HPF can be determined using a micrometer or calculated by using the method below:

Using a clear ruler, measure the diameter of a low-power field. This number can be used to calculate a constant based on the following formula:

Eyepiece Magnification x Objective Magnification x Microscopic Field Diameter = A Constant

Once the value of the constant is known, the diameter of the high power field can be calculated by using the following formula:

High Power Field Diameter = Constant / (Eyepiece Magnification x Objective Magnification)

Half of the field diameter is the radius of the field (r), which can then be used to calculate the area of the HPF:

Area of High Power Field = r^2 x 3.1415

References

1. Tse G, Koo JS, Thike AA. Phyllodes tumour. In: *WHO Classification of Tumours Editorial Board. Breast Tumours, 5th ed*, vol 2. Lyon (France): International Agency for Research on Cancer; 2019:172-176.

F. Malignant Heterologous Elements

Malignant heterologous elements include osteosarcoma, chondrosarcoma, rhabdomyosarcoma, and rarely other types of sarcoma. The presence of well differentiated liposarcoma alone is not used to categorize a phyllodes tumor as malignant.[1,2]

References

1. Tan BY, Apple SK, Badve S, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016;68:5-21.
2. Jara-Lazaro AR, Akhilesh M, Thike AA, et al. Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*. 2010; 57:220–232.

G. Pathologic Stage Classification

The American Joint Committee on Cancer (AJCC) eighth edition[1] and the World Health Organization (WHO)[2] recommend staging malignant phyllodes tumors according to guidelines established for soft tissue sarcomas – extremity and trunk. T category, N category and stage group assignments do not apply to benign or borderline phyllodes tumors and should only be reported if the tumor is malignant.

AJCC Prognostic Stage Groups

T	N	M	Stage group
T1	N0	M0	II
T2	N0	M0	IIIA
T3, T4	N0	M0	IIIB
Any T	N1	M0	IV
Any T	Any N	M1	IV

TNM Descriptors

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

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

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation 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 before multimodality therapy (ie, before initiation of neoadjuvant therapy).

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

T Category Considerations

Only malignant phyllodes tumors are staged according to AJCC staging rules. The pathologic 'T' category (pT) is not assigned for benign and borderline phyllodes tumors.

N Category Considerations

Regional nodal metastasis is uncommon in phyllodes tumor and lymph nodes may not be sampled. When no lymph nodes are resected or present in the specimen, the pathologic ‘N’ category is not assigned; pNX should not be used.

References

1. Maki RG, Folpe AL, Guadagnolo BA, et al. Chapter 45. Soft tissue sarcoma – Unusual histologies and sites. In: Amin MB, ed. *AJCC Cancer Staging Manual. 8th ed.* New York: Springer; 2017:539-544.
2. Tse G, Koo JS, Thike AA. Phyllodes tumour. In: *WHO Classification of Tumours Editorial Board. Breast Tumours, 5th ed, vol 2*. Lyon (France): International Agency for Research on Cancer; 2019:172-176.

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

Version: 1.3.0.0
Protocol Posting Date: June 2026

The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.

This protocol may be used for the following procedures AND tumor types:

Procedure	Description
Biopsy	Includes specimens designated needle biopsy, fine needle aspiration and others (for excisional biopsy, see below)
Tumor Type	**Description**
Invasive breast carcinoma of any type, with or without ductal carcinoma in situ (DCIS)	Includes microinvasive carcinoma and carcinoma with neuroendocrine features

The following should NOT be reported using this protocol:

Procedure
Resection (consider Breast Invasive Carcinoma Resection protocol)
Excisional biopsy (consider Breast Invasive Carcinoma Resection protocol)
Tumor Type
Ductal carcinoma in situ (DCIS) without invasive carcinoma (consider the DCIS Biopsy protocol)
Paget disease of the nipple without invasive carcinoma (consider the DCIS Biopsy protocol)
Encapsulated or solid papillary carcinoma without invasion (consider the Breast DCIS Biopsy protocol)
Phyllodes tumor
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 1.3.0.0

- WHO 6th Edition updates to content and explanatory notes
- Cover page update
- Tumor Site, Histologic Type, Histologic Grade, Nuclear Pleomorphism, Mitotic Rate, and Overall Grade question updates
- Largest Invasive Focus in this Limited Biopsy Sample in Millimeters (mm) question made required (core)
- Ductal Carcinoma In Situ question modifications to include addition of Extent of DCIS (relative to invasion) question and updates to Architectural Pattern question, previously required
- Added Additional Lesion(s) question

Reporting Template

Protocol Posting Date: June 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (INVASIVE CARCINOMA OF THE BREAST: Biopsy)
Standard(s):
This template is recommended for reporting biopsy specimens, but is not required for accreditation purposes.

SPECIMEN

Procedure
___ Needle biopsy
___ Fine needle aspiration
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

+Tumor Site
Tumor Site descriptor should specify the location of the biopsy site as designated by radiology or clinical note (e.g., "R1, 3:00, 2 cm from nipple" or "upper outer quadrant").
___ Specify tumor site / location: _____
___ Not specified

Histologic Type (Note A)
The latest WHO Breast Tumours criteria should be used to classify histologic type. For favorable histologic types that require greater than 90% for the diagnosis of the pure / non-mixed form (such as mucinous, tubular and cribriform), these histologic types should only be used if the material in the biopsy sample would be consistent with this diagnosis if it all looked similar on surgical excision (e.g., not high-grade and not mixed with non-special type cancer histology). Invasive cancers with histology that is considered a "specific morphologic pattern" of invasive breast cancer of no special type / ductal include: invasive carcinoma with neuroendocrine differentiation, medullary pattern, and other rare patterns such as osteoclast-like stromal giant cell rich. For carcinomas with some features of a specific type that are not definitive, or rare tumor types not otherwise listed, use "Other histologic type" and specify / describe. Microinvasion is not considered a histologic type.
___ Invasive carcinoma of no special type (ductal)
___ Invasive carcinoma of no special type (ductal) with specific morphologic pattern (specify, e.g., with neuroendocrine differentiation, with medullary pattern, etc.): _____
___ Invasive lobular carcinoma, classic
___ Invasive lobular carcinoma, variant pattern (specify, e.g., pleomorphic, histiocytoid, etc.): _____
___ Mixed histologic types (specify types and percentages): _____
___ Tubular carcinoma, features of pure type
___ Invasive cribriform carcinoma, features of pure type
___ Mucinous carcinoma, features of pure type
___ Invasive micropapillary carcinoma
___ Invasive apocrine carcinoma
___ Metaplastic carcinoma, spindle cell
___ Metaplastic carcinoma, with heterologous differentiation / matrix production

___ Metaplastic carcinoma, squamous cell
___ Metaplastic carcinoma, mixed (specify types and percentages): _____
___ Metaplastic carcinoma, favorable type, low-grade adenosquamous
___ Metaplastic carcinoma, favorable type, low-grade fibromatosis-like
___ Metaplastic carcinoma, other type (specify): _____
___ Invasive solid papillary carcinoma
___ Adenoid cystic carcinoma, classic
___ Secretory carcinoma
___ Other histologic type not listed (specify): _____
+Histologic Type Comment: _____

Histologic Grade (Nottingham Histologic Score) (required only if applicable) (Note B)
___ Not applicable (no residual carcinoma or microinvasion only)
___ Nottingham Score

Tubule Formation
___ Score 1 (greater than 75% of tumor area forming glandular / tubular structures)
___ Score 2 (10% to 75% of tumor area forming glandular / tubular structures)
___ Score 3 (less than 10% of tumor area forming glandular / tubular structures)
___ Only microinvasion present (not graded)
___ Score cannot be determined (explain): _____

Nuclear Pleomorphism
___ Score 1 (similar / less than 1.5 times the size of benign epithelial cell nuclei, minimal pleomorphism, even chromatin pattern, nucleoli either not visible or very inconspicuous)
___ Score 2 (larger / 1.5–2 times the size of benign epithelial cell nuclei, mild to moderate pleomorphism and visible but small and inconspicuous nucleoli)
___ Score 3 (larger / greater than 2 times the size of benign epithelial cell nuclei, vesicular chromatin, marked variation in size and shape of nuclei, often prominent nucleoli)
___ Only microinvasion present (not graded)
___ Score cannot be determined (explain): _____

Mitotic Rate
See Table 1 in Note B
___ Score 1
___ Score 2
___ Score 3
___ Only microinvasion present (not graded)
___ Score cannot be determined (explain): _____

Overall Grade
___ Grade 1 (scores of 3, 4 or 5)
___ Grade 2 (scores of 6 or 7)
___ Grade 3 (scores of 8 or 9)
___ Only microinvasion present (not graded)
___ Score cannot be determined (explain): _____
+Histologic Grade Comment: _____

Largest Invasive Focus in this Limited Biopsy Sample in Millimeters (mm)
Measure the largest invasive focus based on span in a single core (using judgement to determine if small discontinuous foci are more likely to be separate vs contiguous). Do not add up extent in multiple separate cores since this may overestimate size. Note that the largest invasive focus in a core biopsy sample may be used for future pT stage if invasive cancer is more limited or absent in the final surgical specimen (non-neoadjuvant treatment setting only).

___ Exact measurement: _____ mm
___ At least: _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

Ductal Carcinoma In Situ (DCIS) (Note C)
___ Not identified
___ Present
+Extent of DCIS (relative to invasion)
___ DCIS is more extensive than invasive carcinoma
___ DCIS is similar in extent to invasive carcinoma
___ DCIS is focal or a minor component relative to invasive carcinoma
___ Other (specify): _____
+Architectural Pattern(s) (select all that apply)
___ Comedo
___ Cribriform
___ Micropapillary
___ Papillary
___ Solid
___ Solid papillary carcinoma in situ
___ Encapsulated papillary carcinoma in situ
___ Paget disease (DCIS involving nipple skin)
___ Other (specify): _____
Nuclear Grade
___ Grade I (low)
___ Grade II (intermediate)
___ Grade III (high)
___ Other (specify): _____
___ Cannot be determined (explain): _____
Necrosis
___ Not identified
___ Present, focal (small foci or single cell necrosis)
___ Present, central (expansive "comedo" necrosis)
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Cannot be excluded (explain): _____
+DCIS Comment: _____

+Lymphatic and / or Vascular Invasion
___ Not identified
___ Present
___ Cannot be determined: _____
+Lymphatic and / or Vascular Invasion Comment: _____
+Microcalcifications (Note D) (select all that apply)
___ Not identified
___ Present in DCIS
___ Present in invasive carcinoma
___ Present in non-neoplastic tissue
___ Other (specify): _____

+Additional Lesion(s) (select all that apply)
Non-classic / variant subtypes of LCIS include: Pleomorphic LCIS (pleomorphic nuclei greater than 4 times the size of a lymphocyte or equivalent to nuclei of high-grade DCIS) and Florid LCIS (proliferation of cells cytologically similar to those of classic LCIS but expanding the acini of the involved TDLUs so that little to no residual intervening intra-lobular stroma is present, and / or an expanded acinus or duct spans approximately 40–50 cells in diameter). Comedonecrosis in classic LCIS may also be considered non-classic / variant (describe in "Other (specify)").

___ None identified
___ Lobular carcinoma in situ, classic
___ Lobular carcinoma in situ, pleomorphic
___ Lobular carcinoma in situ (specify): _____
___ Atypical lobular hyperplasia
___ Atypical ductal hyperplasia
___ Flat epithelial atypia
___ Other (specify): _____

+Additional Lesion(s) Comment: _____

ADDITIONAL FINDINGS (Note E)

+Additional Findings (specify): _____

SPECIAL STUDIES
For hormone receptor and HER2 reporting, the CAP Breast Biomarker Template should be used. www.cap.org/cancerprotocols

+Breast Biomarker Studies (specify pending studies): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Histologic Type

This protocol applies to all invasive carcinomas of the breast. The World Health Organization (WHO)[1] classification of breast carcinoma is recommended, although the protocol does not preclude the use of other classifications or histologic types. Carcinomas may be classified based on the H&E appearance without the use of immunohistochemical studies. The most common histologic types are listed. Uncommon types can be added as free text in the "other" category. Carcinomas may be classified based on the H&E appearance without the use of immunohistochemical studies.

Since biopsy samples are usually only a small representative sample of a larger invasive cancer, the histologic type is preliminary and may be modified upon examination of a subsequent surgical specimen. However, since initial treatment decisions are made based on initial biopsy samples, the preliminary histologic type (and other characteristics) should be based on standardized criteria using the findings in the sample.

For favorable histologic types that require > 90% for the diagnosis of the pure/non-mixed form (such as mucinous, tubular and cribriform), these histologic types should only be used if the material in the sample would be consistent with this diagnosis if it all looked similar on surgical excision (e.g., not high grade and not mixed with non-special type cancer histology). For example, if high-grade or mixed features are present in a mucin producing carcinoma, it should NOT be categorized as "Mucinous carcinoma, features of pure type" since this diagnosis would be excluded per the WHO diagnostic criteria. Consider reporting notable features like mucin production, neuroendocrine differentiation or special patterns using the "Invasive carcinoma of no special type (ductal) with specific morphologic pattern" reporting option. Additional comments can also be added in the optional Histologic Type Comment section to clarify details or modify the type with additional findings such as variant features (e.g., Invasive lobular carcinoma with pleomorphic features, etc.).

References

1. WHO Classification of Tumours Editorial Board. *Breast Tumors*. Lyon (France): International Agency for Research on Cancer; 2026. (WHO classification of tumours series, 6th ed).

B. Histologic Grade

All invasive breast carcinomas should be graded.[1,2,3,4] The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) should be used for reporting. Within each stage grouping, there is a relation between histologic grade and outcome.

The Nottingham combined histologic grade evaluates the amount of tubule formation, the extent of nuclear pleomorphism, and the mitotic count (or mitotic rate). Each variable is given a score of 1, 2, or 3, and the scores are added to produce a grade. The mitotic score is determined by the number of mitotic figures found in 10 consecutive high-power fields (HPF) in the most mitotically active part of the tumor. Only clearly identifiable mitotic figures should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei are excluded. Because of variations in field size, the HPF size must be determined for each microscope and the appropriate point score determined accordingly. It is recommended that the size be measured by using a micrometer. However, the diameter of an HPF can also be calculated by using the method below.

Measuring the Size of a High-Power Field (HPF) with a Ruler

Use a clear ruler to measure the diameter of a low-power field. This number can be used to calculate a constant based on the following formula:

Eyepiece Magnification x Objective Magnification x Microscopic Field Diameter = A Constant

When the value of the constant is known, the diameter of an HPF can be calculated for other objectives by using the following formula:
Unknown Field Diameter = Constant/(Eyepiece Magnification x Objective Magnification)

Half of the field diameter is the radius of the field (*r*), which can then be used to calculate the area of the HPF:
3.1415 x r^2= Area of Microscopic Field

If the microscopic field diameter or the area of the field is known, Table 1 can be used to determine the number of mitoses corresponding to different scores.

Table 1. Score Categories According to Field Diameter and Mitotic Count

Scoring Categories of Mitotic Counts				
		Number of mitoses per 10 fields corresponding to:		
Field diameter (mm)	Area (mm^2)	Score 1	Score 2	Score 3
0.40	0.125	≤4	5 to 9	≥10
0.41	0.132	≤4	5 to 9	≥10
0.42	0.139	≤5	6 to 10	≥11
0.43	0.145	≤5	6 to 10	≥11
0.44	0.152	≤5	6 to 11	≥12
0.45	0.159	≤5	6 to 11	≥12
0.46	0.166	≤6	7 to 12	≥13
0.47	0.173	≤6	7 to 12	≥13
0.48	0.181	≤6	7 to 13	≥14
0.49	0.189	≤6	7 to13	≥14
0.50	0.196	≤7	8 to 14	≥15
0.51	0.204	≤7	8 to 14	≥15
0.52	0.212	≤7	8 to 15	≥16
0.53	0.221	≤8	9 to 16	≥17
0.54	0.229	≤8	9 to 16	≥17
0.55	0.238	≤8	9 to 17	≥18
0.56	0.246	≤8	9 to 17	≥18
0.57	0.255	≤9	10 to 18	≥19
0.58	0.264	≤9	10 to 19	≥20
0.59	0.273	≤9	10 to 19	≥20
0.60	0.283	≤10	11 to 20	≥21
0.61	0.292	≤10	11 to 21	≥22
0.62	0.302	≤11	12 to 22	≥23
0.63	0.312	≤11	12 to22	≥23
0.64	0.322	≤11	12 to 23	≥24
0.65	0.332	≤12	13 to 24	≥25
0.66	0.342	≤12	13 to 24	≥25
0.67	0.353	≤12	13 to 25	≥26
0.68	0.363	≤13	14 to 26	≥27
0.69	0.374	≤13	14 to 27	≥ 28

From Pathology Reporting of Breast Disease.[2] *Copyright 2005 National Health Service Cancer Screening Programme and The Royal College of Pathologists. Adapted with permission.*

References

1. Ellis IO, Elston CW. Histologic grade. In: O'Malley FP, Pinder SE, eds. *Breast Pathology.* Philadelphia, PA: Elsevier; 2006:225-233.
2. Ellis I, Webster F, Allison KH et al.: Dataset for reporting of the invasive carcinoma of the breast: recommendations from the International Collaboration on Cancer Reporting (ICCR).(2024) *Histopathology* 85, 418–436. https://doi.org/10.1111/his.15191

3. Schwartz AM, Henson DE, Chen D, Rajamarthandan S: Histologic grade remains a prognostic factor for breast cancer regardless of the number of positive lymph nodes and tumor size: a study of 161 708 cases of breast cancer from the SEER Program. *Arch Pathol Lab Med.* 2014;138(8):1048-52. doi: 10.5858/arpa.2013-0435-OA.
4. Royal College of Pathologists. Dataset for histopathological reporting of breast disease in surgical excision specimens of breast cancer, November 2024 https://www.rcpath.org/static/d255f34c-176a-490d-9b5a7d58ac85f3a6/b4cf9184-33ff-4662-b33990b3701c3d87/G148-Dataset-for-histopathological-reporting-of-breast-disease-in-surgical-excision-specimens-of-breast-cancer.pdf Accessed February 6, 2026.

C. Ductal Carcinoma In Situ
Nuclear Grade of DCIS
The nuclear grade of DCIS is determined using 6 morphologic features (Table 1).[1,2,3,4]

Table 2. Nuclear Grade of Ductal Carcinoma in Situ

Feature	Grade I (Low)	Grade II (Intermediate)	Grade III (High)
Pleomorphism	Monotonous (monomorphic)	Intermediate	Markedly pleomorphic
Size	1.5 to 2 x the size of a normal red blood cell or a normal duct epithelial cell nucleus	Intermediate	>2.5 x the size of a normal red blood cell or a normal duct epithelial cell nucleus
Chromatin	Usually diffuse, finely dispersed chromatin	Intermediate	Usually vesicular with irregular chromatin distribution
Nucleoli	Only occasional	Intermediate	Prominent, often multiple
Mitoses	Only occasional	Intermediate	May be frequent
Orientation	Polarized toward luminal spaces	Intermediate	Usually not polarized toward the luminal space

Necrosis
The presence of necrosis is correlated with the finding of mammographic calcifications (i.e., most areas of necrosis will calcify). Ductal carcinoma in situ that presents as mammographic calcifications often recurs as calcifications. Necrosis can be classified as follows:

- Central ("comedo"): The central portion of an involved ductal space is replaced by an area of expansive necrosis that is easily detected at low magnification. Ghost cells and karyorrhectic debris are generally present. Although central necrosis is generally associated with high-grade nuclei (i.e., comedo DCIS), it can also occur with DCIS of low or intermediate nuclear grade.
- Focal: Small foci, indistinct at low magnification, or single cell necrosis.

Necrosis should be distinguished from secretory material, which can also be associated with calcifications, but does not include nuclear debris.

References
1. Morrow M, Harris JR. Local management of invasive breast cancer (chapter 33). In: Harris JR, Lippman ME, Morrow M, Osborne KE, eds. *Diseases of the Breast*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:522-523.
2. Bane A.: Ductal Carcinoma In Situ: What the Pathologist Needs to Know and Why. *Int J Breast Cancer* 2013:914053. doi: 10.1155/2013/914053.
3. Hanna WM, Parra-Herran C, Lu FI et al. Ductal carcinoma in situ of the breast: an update for the pathologist in the era of individualized risk assessment and tailored therapies. *Mod Pathol.* 2019 32 (7): 896-915.

4. Fitzgibbons PL, Connelly, JL. Protocol for the Examination of Specimens from Patients with Ductal Carcinoma In Situ (DCIS) of the Breast. 2021; www.cap.org/cancerprotocols., accessed March 3, 2026.

D. Microcalcifications

Cancer found in biopsies performed for microcalcifications will almost always be at the site of the calcifications or in close proximity. The presence of the targeted calcifications in the specimen should be confirmed by specimen radiography. The pathologist must be satisfied that the specimen has been sampled in such a way that the lesion responsible for the calcifications has been examined microscopically. The relationship of the radiologic calcifications to the invasive carcinoma and the DCIS should be indicated.

If calcifications can be seen in the specimen radiograph but not in the initial histologic sections, deeper levels should be examined. If needed, radiographs of the paraffin block(s) may be obtained to detect calcifications remaining in the block(s). If microcalcifications cannot be confirmed by routine microscopic evaluation, polarized light may be helpful, since calcium oxalate crystals are refractile and polarizable but usually clear or tinged yellow in H&E sections. On rare occasions, calcifications do not survive tissue processing or prolonged fixation in formalin. Foreign material can sometimes simulate calcifications (e.g., metallic fragments after surgery or trauma).

E. Additional Findings

In some cases, additional pathologic findings are important for the clinical management of patients. If multiple invasive carcinomas are present and differ in histologic type, grade, or the expression of ER, PgR, or HER2, this information should be included as text in this section.

COLLEGE of AMERICAN PATHOLOGISTS

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

Version: 4.11.0.0

Protocol Posting Date: June 2026

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2027

The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Excision less than total mastectomy	Includes specimens designated excision, segmental resection, lumpectomy, quadrantectomy, and segmental or partial mastectomy, with or without axillary contents
Total Mastectomy	Includes skin-sparing and nipple-sparing mastectomy, with or without axillary contents
Tumor Type	**Description**
Invasive breast carcinoma of any type, with or without ductal carcinoma in situ (DCIS)	Includes invasive and microinvasive carcinomas

This protocol is NOT required for accreditation purposes for the following:

Procedure
Needle or skin biopsies
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Additional excision performed after the definitive resection (e.g., re-excision of surgical margins)
Cytologic specimens

The following specimen types should NOT be reported using this protocol:

Specimen
Very small incisional biopsies (including core needle biopsies)
Re-excision of a biopsy site after removal of most of the carcinoma (including completion mastectomy) if there are no additional findings relevant to the original pT, pN stage

The following tumor types should NOT be reported using this protocol:

Tumor Type
Ductal carcinoma in situ (DCIS) without invasive carcinoma (consider the Breast DCIS Resection protocol)
Paget disease of the nipple without invasive carcinoma (consider the Breast DCIS Resection protocol)
Encapsulated or solid papillary carcinoma without invasion (consider the Breast DCIS Resection protocol)
Phyllodes tumor (consider the Phyllodes tumor protocol)
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.
A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.
**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.11.0.0

- WHO 6th Edition updates to content and explanatory notes
- Cover page update
- Tumor Site, Histologic Type, Histologic Grade, Nuclear Pleomorphism, Tumor Size, Tumor Extent, Lymphatic and / or Vascular Invasion, Treatment Effect in Lymph Nodes, and Residual Cancer Burden (RCB) Parameters question updates
- Tumor Focality question updated and made required (core)
- Ductal Carcinoma In Situ question modifications to include updates to Architectural Pattern question
- Added repeating Tumor Characteristic section, Additional Lesion(s), and Extent of LCIS questions
- MARGIN, REGIONAL LYMPH NODE, SPECIAL STUDIES section updates
- Minor pTNM Classification updates to include pT4 staging display item and pM Category Special Case Number(s) with Metastasis question terminology

Reporting Template

Protocol Posting Date: June 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (INVASIVE CARCINOMA OF THE BREAST: Resection)
Standard(s): AJCC 8

SPECIMEN

Procedure (Note A)
___ Excision (less than total mastectomy, including lumpectomy and partial mastectomy)
___ Total mastectomy (including nipple-sparing and skin-sparing mastectomy)
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

Tumor Focality (Note B)
___ Unifocal
___ Multifocal
  ___ Multiple foci of invasive carcinoma with similar features (e.g., satellites or post-treatment foci of the same histologic type, grade, and biomarkers) (complete only one Tumor Characteristics section)
  ___ Multiple foci of invasive carcinoma with different features (complete a separate Tumor Characteristics section for each distinct invasive carcinoma)
  ___ Other (specify): _____
  ___ Cannot be determined (explain): _____
  +Number of Foci
  ___ Specify number: _____
  ___ At least: _____
  ___ Cannot be determined: _____
___ No residual invasive carcinoma
___ Cannot be determined (explain): _____

Tumor Characteristics

Separate invasive cancers in the same breast should be included in a single cancer summary protocol using the option to report multiple separate foci. The American Joint Committee on Cancer (AJCC) pT stage is assigned based on the largest focus (and the "m" modifier is used only if they are also macroscopically distinct). If a patient has bilateral breast carcinomas, the cancers are reported in separate case summaries.

For multifocal tumors with different features, one may choose to repeat the following 4 elements (Tumor Site, Histologic Type, Histologic Grade, and Tumor Size). For this scenario, assign a unique Tumor Identifier to each invasive cancer you want to report the additional features for (e.g., "Lesion 1" or other more specific descriptor). May be repeated up to 5 times for invasive carcinomas.

Tumor Identifier (required only for cases with multiple tumors): _____

+Tumor Site (Note C)

Tumor Site descriptor should specify the location of the invasive cancer based on correlation with radiology designation and / or gross findings (e.g., "R1, 3:00, 2 cm from nipple" or "upper outer quadrant").

___ Specify tumor site / location: _____

___ Not specified

Histologic Type (Note D)

The latest WHO Breast Tumours criteria should be used to classify histologic type. Pure special type favorable carcinomas (e.g., pure tubular, mucinous, and cribriform) should be at least 90% special type histology (or classified as Mixed). Invasive cancers with histology that is considered a "specific morphologic pattern" of invasive breast cancer no special type / ductal include: invasive carcinoma with neuroendocrine differentiation, medullary pattern, and other rare patterns such as osteoclast-like stromal giant cell rich. For carcinomas with some features of a specific type that are not definitive, or rare tumors not otherwise listed, use "Other histologic type" and specify / describe.

___ No residual invasive carcinoma
___ Invasive carcinoma of no special type (ductal)
___ Invasive carcinoma of no special type (ductal) with specific morphologic pattern (specify, e.g., with neuroendocrine differentiation, with medullary pattern, etc.): _____
___ Invasive lobular carcinoma, classic
___ Invasive lobular carcinoma, variant pattern (specify, e.g., pleomorphic, histiocytoid, etc.): _____
___ Mixed histologic types (specify types and percentages): _____
___ Tubular carcinoma, pure or greater than 90%
___ Invasive cribriform carcinoma, pure or greater than 90%
___ Mucinous carcinoma, pure or greater than 90%
___ Invasive micropapillary carcinoma, pure or greater than 90%
___ Invasive apocrine carcinoma
___ Metaplastic carcinoma, spindle cell
___ Metaplastic carcinoma, with heterologous differentiation / matrix production
___ Metaplastic carcinoma, squamous cell
___ Metaplastic carcinoma, mixed (specify types and percentages): _____
___ Metaplastic carcinoma, favorable type, low-grade adenosquamous
___ Metaplastic carcinoma, favorable type, low-grade fibromatosis-like
___ Metaplastic carcinoma, other type (specify): _____
___ Invasive solid papillary carcinoma
___ Adenoid cystic carcinoma, classic
___ Secretory carcinoma
___ Other histologic type not listed (specify): _____

+Histologic Type Comment: _____

Histologic Grade (Nottingham Histologic Score) (required only if applicable) (Note E)

___ Not applicable (no residual carcinoma or microinvasion only)
___ Nottingham Score

Tubule Formation

___ Score 1 (greater than 75% of tumor area forming glandular / tubular structures)
___ Score 2 (10 to 75% of tumor area forming glandular / tubular structures)
___ Score 3 (less than 10% of tumor area forming glandular / tubular structures)
___ Only microinvasion present (not graded)

___ Score cannot be determined (explain): _____

Nuclear Pleomorphism

___ Score 1 (similar / less than 1.5 times the size of benign epithelial cell nuclei, minimal pleomorphism, even chromatin pattern, nucleoli either not visible or very inconspicuous)
___ Score 2 (larger / 1.5-2 times the size of benign epithelial cell nuclei, mild to moderate pleomorphism and visible but small and inconspicuous nucleoli)
___ Score 3 (larger / greater than 2 times the size of benign epithelial cell nuclei, vesicular chromatin, marked variation in size and shape of nuclei, often prominent nucleoli)
___ Only microinvasion present (not graded)
___ Score cannot be determined (explain): _____

Mitotic Rate

See Table 1 in Note E

___ Score 1
___ Score 2
___ Score 3
___ Only microinvasion present (not graded)
___ Score cannot be determined (explain): _____

Overall Grade

___ Grade 1 (scores of 3, 4 or 5)
___ Grade 2 (scores of 6 or 7)
___ Grade 3 (scores of 8 or 9)
___ Only microinvasion present (not graded)
___ Score cannot be determined (explain): _____

+Histologic Grade Comment: _____

Tumor Size (Note F)

The size of the invasive carcinoma should take into consideration the gross and imaging findings correlated with the microscopic examination and be based on the tissue sampling strategy and cassette map. The size does not include adjacent ductal carcinoma in situ (DCIS) or separate satellites of invasion (greater than 5 mm apart). If multifocal, use the largest contiguous focus for pT category.

If there has been a prior core needle biopsy or incisional biopsy showing a larger area of invasion than in the excisional specimen, the largest dimension of the invasive carcinoma in the prior specimen, if known, should be used for determining the T category. This also applies if the entire tumor has been removed by prior biopsy. The size of the largest foci in the two specimens should not be added together.

If there has been prior neoadjuvant treatment and no invasive carcinoma is present, the cancer is classified as ypTis if there is residual DCIS and ypT0 if there is no remaining carcinoma. A cancer protocol is recommended (but not required) in this scenario.

___ No residual invasive carcinoma
___ Microinvasion only (less than or equal to 1 mm)
___ Largest contiguous focus of invasive carcinoma (specify exact measurement in Millimeters (mm)): _____ mm
___ Size of largest invasive focus cannot be determined (explain): _____

+Size(s) and Location(s) of Additional Foci in Millimeters (mm) (if additional invasive foci have similar features)#

 # Values may be recorded on a single line using units (mm) and semicolons (;) as separators

___ Specify size(s) and location(s): _____
___ Cannot be determined: _____

___ Not applicable
+Tumor Size Comment: _____

Ductal Carcinoma In Situ (DCIS) (Note G)

___ Not identified
___ Present

Extent of DCIS (select all that apply)

Extent of DCIS can be reported in a number of ways depending on its relationship to the invasive cancer. This information may be helpful for correlation with the size of imaging findings and describing the relative proportions of invasive disease vs DCIS. Any of the below options can be used (including using multiple options). For example, when DCIS is a minor admixed component of a larger invasive cancer, DCIS extent can be included as a percentage of the entire tumor volume rather than a span in mm. If DCIS extends beyond the invasive cancer, reporting the estimated size of DCIS can be useful for imaging correlation.

___ Admixed with invasive carcinoma
+Specify DCIS as a Percentage of Entire Tumor: _____ %
___ Extends beyond the invasive carcinoma
___ Separate from the invasive carcinoma
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Estimated Size of DCIS

___ Largest dimension of DCIS in Millimeters (mm): _____ mm
___ Other (specify): _____

+Architectural Pattern(s) (select all that apply)

Reporting all architectural patterns present may not always be clinically relevant. The dominant pattern can also be selected. Solid papillary carcinoma in situ and Encapsulated papillary carcinoma patterns ideally should be reported if present in association with invasive cancers. These forms of papillary DCIS / encapsulated carcinoma may lack myoepithelial staining but if they meet criteria otherwise for these diagnoses they are not considered a part of the invasive cancer size (note that invasive forms of solid papillary carcinoma also exist).

___ Comedo
___ Cribriform
___ Micropapillary
___ Papillary
___ Solid
___ Solid papillary carcinoma in situ
___ Encapsulated papillary carcinoma in situ
___ Paget disease (DCIS involving nipple skin)
___ Other (specify): _____

+Nuclear Grade

___ Grade I (low)
___ Grade II (intermediate)
___ Grade III (high)

+Necrosis

___ Not identified
___ Present, focal (small foci or single cell necrosis)
___ Present, central (expansive "comedo" necrosis)

___ Cannot be excluded (explain): _____

+DCIS Comment: _____

+Additional Lesion(s) (select all that apply)

Variant subtypes of LCIS include: Pleomorphic LCIS (pleomorphic nuclei greater than 4 times the size of a lymphocyte or equivalent to nuclei of high-grade DCIS) and Florid LCIS (proliferation of cells cytologically similar to those of classic LCIS but expanding the acini of the involved TDLUs so that little to no residual intervening intra-lobular stroma is present, and / or an expanded acinus or duct spans approximately 40–50 cells in diameter). Comedonecrosis in classic LCIS may also be considered variant (describe in "Other (specify)").

___ Not identified
___ Lobular carcinoma in situ, classic
___ Lobular carcinoma in situ, pleomorphic
___ Lobular carcinoma in situ (specify): _____
___ Atypical lobular hyperplasia
___ Atypical ductal hyperplasia
___ Flat epithelial atypia
___ Other (specify): _____

+Extent of LCIS: _____
+Additional Lesion(s) Comment: _____

Tumor Extent (required only if nipple, skin, or skeletal muscle are present and involved) (Note H)

___ Not applicable (skin, nipple, and skeletal muscle are absent OR are uninvolved and it is not necessary to document their presence)
___ Applicable (nipple, skin or skeletal muscle involved or are uninvolved and want to document their presence)

Nipple Status (select all that apply)

___ Not present in specimen
___ Present and not involved
___ Paget's disease present
___ Involved by invasive carcinoma
___ DCIS in major lactiferous ducts present
___ Other (specify): _____
___ Cannot be determined (explain): _____

Skin Status

___ Not present in specimen
___ Present and not involved
___ Carcinoma directly invades into the dermis or epidermis without macroscopic skin ulceration (this does not change the T classification)
___ Carcinoma directly invades into the dermis or epidermis with macroscopic skin ulceration (classified as T4b)
___ Other (specify): _____
___ Cannot be determined (explain): _____

Macroscopic Skin Satellite Foci

Satellite skin nodules must be separate from the primary tumor and macroscopically identified to assign a category as T4b. Skin nodules identified only on microscopic examination and in the absence of epidermal ulceration or skin edema (clinical peau d'orange) do not qualify as T4b. Such tumors should be categorized based on tumor size.

___ Not identified
___ Present (T4b)
___ Cannot be determined (explain): _____

Skeletal Muscle

Invasion into pectoralis muscle is not considered chest wall invasion, and cancers are not classified as T4a unless

there is invasion deeper than this muscle which typically requires surgical / clinical correlation.
___ Not present in specimen
___ Present and not involved
___ Carcinoma invades skeletal muscle
___ Carcinoma invades into the chest wall deep to pectoralis muscle (classified as T4a)
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Tumor Extent Comment: _____

Lymphatic and / or Vascular Invasion (Note I)
___ Not identified
___ Present, focal (limited to one to two vessels in one block)
___ Present, extensive (greater than two vessels in one block or present in two or more blocks)
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Lymphatic and / or Vascular Invasion Comment: _____

Dermal Lymphatic and / or Vascular Invasion (required only if applicable)
___ Not applicable (no skin present)
___ Not identified
___ Present
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Microcalcifications (Note J) (select all that apply)
___ Not identified
___ Present in DCIS
___ Present in invasive carcinoma
___ Present in non-neoplastic tissue
___ Other (specify): _____

Treatment Effect in Breast (Note K)
The largest contiguous focus of residual tumor, if present, is used to determine ypT category. Treatment-related fibrosis in the tumor bed adjacent to foci of residual invasive carcinoma is not included in determining ypT dimension.
___ No known presurgical therapy
___ No definite response to presurgical therapy in the invasive carcinoma
___ Evidence of response to presurgical therapy in the invasive carcinoma (specify in Treatment Effect in Breast Comment if need to clarify extent of response)
___ No residual invasive carcinoma is present in the breast after presurgical therapy
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Treatment Effect in Breast Comment: _____

Treatment Effect in Lymph Node(s) (required if nodes are submitted and it is known that the patient had presurgical therapy)
The largest contiguous focus of residual tumor in the lymph nodes, if present, is used to determine ypN category. Treatment-related fibrosis adjacent to residual nodal deposits is not included in determining ypN dimension.

___ Not applicable
___ No definite response to presurgical therapy in metastatic carcinoma
___ Metastatic carcinoma present with evidence of response to presurgical therapy (specify in Treatment Effect in Lymph Node(s) Comment if need to clarify extent of response)
___ No lymph node metastases. Fibrous scarring or histiocytic aggregates, possibly related to prior lymph node metastases with pathologic complete response
___ No lymph node metastases and no fibrous scarring or histiocytic aggregates in the nodes
___ Cannot be determined (explain): _____

+Treatment Effect in Lymph Node(s) Comment: _____

Residual Cancer Burden (RCB) Parameters (NCCN recommends reporting RCB parameters in all post-neoadjuvant chemotherapy cases (category 2B) and cancer registries currently collect the RCB Score and Class)# (Note K)

 # The RCB calculator can be found at the MD Anderson website: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Primary Tumor Bed. Note that RCB score and class in the pathology report is the only treatment response parameter that can be collected by most cancer registries (if you report only the individual RCB parameters without calculating and reporting the RCB score and class, the parameters are not used by registries to calculate RCB). If you need to report more than one RCB score (when more than one biologically distinct invasive cancer is / was present), use the "RCB Comment" to describe additional details.

+Greatest Dimension of Primary Tumor Bed Area in Millimeters (mm) (involved by residual invasive carcinoma): _____ mm

+Second Greatest Dimension of Primary Tumor Bed Area in Millimeters (mm): _____ mm

+Percentage of Overall Cancer Cellularity (in the area measured above): _____ %

+Percentage of Cancer that is In Situ Disease: _____ %

Lymph Nodes

+Number of Positive Lymph Nodes: _____

+Diameter of Largest Nodal Metastasis in Millimeters (mm): _____ mm

RCB Calculations

+Residual Cancer Burden Score: _____

+Residual Cancer Burden Class
___ RCB-0 (pCR)
___ RCB-I
___ RCB-II
___ RCB-III

+RCB Comment: _____

MARGINS (Note L)

Final Margin Status for Invasive Carcinoma (required only if residual invasive carcinoma is present in specimen)#

 # Final margin status should be determined based on findings in any additional separately submitted final margins, as well as margins that are considered final in the primary resection specimen (i.e., a final margin status summary). If the final margin status is not clear based on the specimens received (i.e., additional margins without a clear relationship to initial margins), the distances to each can be stated in the "Other (specify)" reporting section with a recommendation for surgical correlation.

___ Not applicable (no residual invasive carcinoma in specimen)
___ All final margins greater than 2 mm from invasive carcinoma
___ Invasive carcinoma present within 0-2 mm of final margins
Margin(s) Involved by Invasive Carcinoma (at ink)
___ None identified
___ Specify involved margins: _____
+Margin(s) Less than 1 mm from Invasive Carcinoma (but not at ink)
___ None identified
___ Specify: _____
+Margin(s) 1 to 2 mm from Invasive Carcinoma
___ None identified
___ Specify: _____
+Margin(s) Greater than 2 mm from Invasive Carcinoma
___ None identified
___ Specify: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Margin Comment for Invasive Carcinoma: _____

Final Margin Status for DCIS (required only if DCIS is present in specimen)#

 # Final margin status should be determined based on findings in any additional separately submitted final margins, as well as margins that are considered final in the primary resection specimen (i.e., a final margin status summary). If the final margin status is not clear based on the specimen(s) received (i.e., additional margins without a clear relationship to initial margins), the distances to each can be stated in the "Other (specify)" reporting section with a recommendation for surgical correlation.

___ Not applicable (no residual DCIS in specimen)
___ All final margins greater than 2 mm from DCIS
___ DCIS present within 0-2 mm of final margins (specify specific margins below)
Margin(s) Involved by DCIS (at ink)
___ None identified
___ Specify involved margins: _____
Margin(s) Less than 1 mm from DCIS (but not at ink)
___ None identified
___ Specify: _____
Margin(s) 1 to 2 mm from DCIS
___ None identified
___ Specify: _____
+Margin(s) Greater than 2 mm from DCIS
___ None identified

___ Specify: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Margin Comment for DCIS (consider using for pleiomorphic or florid LCIS):

_____

REGIONAL LYMPH NODES (Note M)

For multiple separate primary cancers with different features, it may be relevant to describe the histologic features of the lymph node metastases in the "Regional Lymph Node Comment"

Regional Lymph Node Status

___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)

Number of Lymph Nodes with Macrometastases (greater than 2 mm)

___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

Number of Lymph Nodes with Micrometastases (greater than 0.2 mm to 2 mm and / or greater than 200 cells)

___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

Number of Lymph Nodes with Isolated Tumor Cells (0.2 mm or less OR 200 cells or less) (required only if applicable)#

 # Reporting the number of lymph nodes with isolated tumor cells is required only in the absence of macrometastasis or micrometastasis in other lymph nodes.

___ Not applicable
___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Total Number of Positive Macroscopic and Microscopic Lymph Nodes Counted Towards pN Category#

 # If only micrometastasis is present, count them as pN1mi regardless of how many are present

___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined: _____

Size of Largest Nodal Metastatic Deposit#

 # The size of a tumor deposit is determined by measuring the largest dimension of any group of cells that are touching one another (confluent or contiguous tumor cells), regardless of whether the deposit is confined to the lymph node, extends outside the node (extranodal extension), is totally present outside the lymph node and invading adipose tissue, or is present within a lymphatic channel adjacent to the node.
Specify in Millimeters (mm)

___ Exact size: _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

Extranodal Extension (ENE)#

 # The measurement of extranodal extent can be performed either perpendicular to the lymph node capsule or in another dimension. As a general principle, the larger measurement can be preferentially used but there is no evidence to support a specific method. It is optional to report the specific measurement of extranodal extension, which may not be feasible when extensive (details of extranodal extension can also be described in the "Regional Lymph Node Comment" or the "Other (specify)" sections).

___ Not identified
___ Present

+Largest Measurement of Extranodal Extension
Specify in Millimeters (mm)
___ Exact measurement: _____ mm
___ Other (specify): _____
___ Cannot be determined: _____

+Number of Lymph Nodes with Extranodal Extension
___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined: _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

Total Number of Lymph Nodes Examined (sentinel and non-sentinel)
___ Exact number (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Non-regional lymph node(s) (specify, if possible): _____
___ Lung: _____
___ Liver: _____
___ Bone: _____
___ Brain: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note N)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)

___ r (recurrence)

pT Category

 # For the purposes of this checklist, these categories should only be used in the setting of preoperative (neoadjuvant) therapy for which a previously diagnosed invasive carcinoma is no longer present after treatment. Patients with pathological complete response (absence of residual invasive carcinoma in both the breast and lymph nodes) should be categorized as ypT0N0 or ypTisN0, not ypTX.

___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor#
___ pTis (DCIS): Ductal carcinoma in situ#

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.

___ pTis (Paget): Paget disease of the nipple NOT associated with invasive carcinoma and / or carcinoma in situ (DCIS) in the underlying breast parenchyma##

pT1: Tumor less than or equal to 20 mm in greatest dimension

___ pT1mi: Tumor less than or equal to 1 mm in greatest dimension

Round any measurement greater than 1.0-1.9 mm to 2 mm

___ pT1a: Tumor greater than 1 mm but less than or equal to 5 mm in greatest dimension###
___ pT1b: Tumor greater than 5 mm but less than or equal to 10 mm in greatest dimension
___ pT1c: Tumor greater than 10 mm but less than or equal to 20 mm in greatest dimension
___ pT1 (subcategory cannot be determined)
___ pT2: Tumor greater than 20 mm but less than or equal to 50 mm in greatest dimension
___ pT3: Tumor greater than 50 mm in greatest dimension

Invasion of the dermis alone does not qualify as pT4.

pT4: Tumor of any size with direct extension to the chest wall and / or to the skin (ulceration or macroscopic nodules)####

___ pT4a: Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
___ pT4b: Ulceration and / or ipsilateral satellite nodules and / or edema (including peau d'orange) of the skin which do not meet the criteria for inflammatory carcinoma
___ pT4c: Both T4a and T4b are present

Inflammatory carcinoma requires the presence of clinical findings of erythema and edema involving at least one-third or more of the skin of the breast. (Note N)

___ pT4d: Inflammatory carcinoma#####
___ pT4 (subcategory cannot be determined)

T Suffix (required only if applicable)

___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category

Choose a category based on lymph nodes received with the specimen; immunohistochemistry and / or molecular studies are not required.

If internal mammary lymph nodes, infraclavicular nodes, or supraclavicular lymph nodes are included in the specimen, consult the AJCC Cancer Staging Manual for additional lymph node categories.

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)

 # Isolated tumor cells (ITCs) 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 (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count when determining the N category but should be included in the total number of nodes evaluated.

___ 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
___ pN1mi: Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
Approximately 1000 tumor cells are contained in a 3-dimensional 0.2 mm cluster. Thus, if more than 200 individual tumor cells are identified as single dispersed tumor cells or as a nearly confluent elliptical or spherical focus in a single histologic section of a lymph node, there is a high probability that more than 1000 cells are present in the lymph node. In these situations, the node should be classified as containing a micrometastasis (pN1mi). Cells in different lymph node cross-sections or longitudinal sections or levels of the block are not added together; the 200 cells must be in a single node profile even if the node has been thinly sectioned into multiple slices. It is recognized that there is substantial overlap between the upper limit of the ITC and the lower limit of the micrometastasis categories due to inherent limitations in pathologic nodal evaluation and detection of minimal tumor burden in lymph nodes. Thus, the threshold of 200 cells in a single cross-section is a guideline to help pathologists distinguish between these 2 categories. The pathologist should use judgment regarding whether it is likely that the cluster of cells represents a true micrometastasis or is simply a small group of isolated tumor cells.
___ pN1a: Metastases in 1-3 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
___ pN2a: Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)##
___ pN2b: Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary 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

N Suffix (required only if applicable) (select all that apply)
The (sn) modifier is added to the N category when a sentinel node biopsy is performed (using either dye or tracer) and fewer than six lymph nodes are removed (sentinel and nonsentinel). The (f) modifier is added to the N category to denote confirmation of metastasis by fine needle aspiration / core needle biopsy with NO further resection of nodes.
___ Not applicable
___ (sn): Sentinel node(s) evaluated. If 6 or more nodes (sentinel or nonsentinel) are removed, this modifier should not be used
___ (f): Nodal metastasis confirmed by fine needle aspiration or core needle biopsy

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Histologically proven metastases larger than 0.2 mm
+Specify Case Number(s) with Metastasis (if from a previous procedure): _____

ADDITIONAL FINDINGS (Note O)

+Additional Findings (specify): _____

SPECIAL STUDIES

This section is available to include prior breast cancer biomarker results on the invasive cancer in the resection, typically as reported on the initial core biopsy specimen(s). Specify the case number, tumor identifier (if relevant), and the available biomarker results. The CAP Breast Biomarker Template should be used for reporting biomarkers performed on samples from this resection specimen. Pending biomarker studies can be listed in the "Comments" section of this report.
If information from other specimens is included in completing the case summary (e.g., the results of biomarkers from a prior core needle biopsy or relevant diagnoses on prior specimens), then this must be clearly stated in the "Comments" section, and the accession numbers of the other cases should be provided.

+Biomarker Testing Performed on Prior Case (specify): _____

Specify Tumor Identifier (if multiple tumors are present): _____

+Breast Biomarker Testing Performed on Previous Biopsy (select all that apply)
___ Estrogen Receptor (ER)
Estrogen Receptor (ER) Status
___ Positive (greater than 10% of cells demonstrate nuclear positivity)
+Percentage of Cells with Nuclear Positivity for ER
___ Specify percentage: _____ %
OR
Select range below:
___ 11-20%
___ 21-30%
___ 31-40%
___ 41-50%
___ 51-60%
___ 61-70%
___ 71-80%
___ 81-90%
___ 91-100%
___ Low Positive (1-10% of cells with nuclear positivity)
___ Negative
___ Cannot be determined (explain): _____
___ Progesterone Receptor (PgR)
Progesterone Receptor (PgR) Status
___ Positive
+Percentage of Cells with Nuclear Positivity for PgR
___ Specify percentage: _____ %
OR
Select range below:
___ 1-10%
___ 11-20%
___ 21-30%
___ 31-40%
___ 41-50%
___ 51-60%
___ 61-70%

___ 71-80%
___ 81-90%
___ 91-100%
___ Negative
___ Cannot be determined (explain): _____
___ HER2 (by immunohistochemistry)

HER2 Status (by immunohistochemistry)
 # Breast cancers with HER2 IHC scores of 0+, 1+, or 2+ (ISH negative) may be eligible for treatment targeting non-amplified levels of HER2 expression in the metastatic setting. Currently, patients with no membrane staining by IHC (0) are ineligible / excluded.
___ Negative (Score 0): no membrane staining detected (0 / absent membrane staining)#
___ Negative (Score 0+): membrane staining that is incomplete and is faint / barely perceptible and in less than or equal to 10% of tumor cells (0+ / with membrane staining)#
___ Negative (Score 1+)#
___ Equivocal (Score 2+)#
___ Positive (Score 3+)
+HER2 Clustered Heterogeneity
___ Not identified
___ Present
Percentage of Cells with Uniform Intense Complete Membrane Staining
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Not applicable
___ Cannot be determined (explain): _____
___ HER2 (by in situ hybridization)
HER2 Status (by in situ hybridization)
___ Negative (not amplified)
___ Positive (amplified)
___ Cannot be determined (explain): _____
___ Ki-67
Percentage of Ki-67 Positive Nuclei (select all that apply)
___ Specify percentage: _____ %
___ Specify range: _____
___ Cannot be determined (explain): _____
+Specify Prior Biomarkers on Additional Foci of Invasion (if relevant; i.e., if foci differ in histologic type, grade, or biomarker status; specify tumor identifier for each; may repeat up to 10X): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Procedures

The following types of breast specimens and procedures may be reported with the case summary:

Excisions: These procedures resect breast tissue without the intent of removing the entire breast. The nipple is usually not included with excisions. Excisions include specimens designated "partial mastectomies," "lumpectomies," and "quadrantectomies."

Total Mastectomy: Removal of all breast tissue, generally including the nipple and areola.

- Simple mastectomy: This procedure consists of a total mastectomy without removal of axillary lymph nodes.
- Skin-sparing mastectomy: This is a total mastectomy with removal of the nipple and only a narrow surrounding rim of skin.
- Nipple sparing mastectomy: This is a total mastectomy without removal of skin or nipple. The subareolar tissue is examined and the nipple later removed if involved by carcinoma.
- Modified radical mastectomy: This procedure consists of a total mastectomy with an axillary dissection. In the case summary, the breast and lymph node specimens are documented separately. A small portion of pectoralis muscle is sometimes removed.
- Radical mastectomy: This procedure consists of a total mastectomy with removal of the pectoralis major and pectoralis minor muscles as well as axillary contents. This type of specimen and procedure can be indicated on the case summary as "Other."

B. Tumor Focality (Single or Multiple Foci of Invasive Carcinoma)

If a single focus of invasive cancer is present, Unifocal is selected and the specific tumor characteristics are reported in the subsequent sections.

If multiple invasive carcinomas are present in the same breast, Multifocal should be selected and the specific scenario clarified using the reporting options (or other). Foci of invasion can be considered separate if they are at least 5 mm apart (with some judgment involved for exceptions like post-neoadjuvant treatment, microinvasion, etc.). For pT categorization purposes, the "(m)" modifier is used to indicate multiple foci are present that are macroscopically distinct, and the size of the largest focus is used for the pT category (the "(m)" modifier is not used when there are only microscopic satellites). If there are bilateral invasive cancers, separate reporting protocols for each breast are utilized.

If there are multiple foci of invasive carcinoma with similar features (same histologic type, grade and biomarkers) only one Tumour Characteristics section is needed, but the number of foci present can be estimated and reported here, and the in the Tumor Size section the sizes of additional foci can be reported.

When there are multiple foci of invasive carcinoma that are considered separate and biologically distinct, a separate Tumor Characteristics section for each invasive cancer can be reported. A unique **Tumor Identifier** is required (e.g., "L1 invasive lobular carcinoma", "Lesion 2" or "Larger invasive focus", etc.) to distinguish each cancer that will have a separately reported Tumor Site, Histologic Type, Histologic Grade, and Tumor Size.

Breast cancer biomarker status (ER, PR, HER2, and/or Ki67) for different cancers on prior biopsies can be reported in the Special Studies section if relevant. If being performed on the surgical specimen samples,

separate Breast Cancer Biomarker protocols should be used to report on separate invasive cancers with the appropriate Tumor Identifier included for each.

In Figure B1, examples of multiple foci of invasive carcinoma include the following:

- **Extensive carcinoma in situ (CIS) with multiple foci of invasion (Figure B1, A).** Extensive DCIS is sometimes associated with multiple areas of invasion. The invasive carcinomas are usually similar in histologic appearance and immunophenotype, unless the DCIS is heterogeneous.
- **Invasive carcinoma with smaller satellite foci of invasion (Figure B1, B).** A large carcinoma is sometimes surrounded by smaller adjacent foci of invasion. They are usually identical in histologic appearance and immunophenotype to the dominant carcinoma. If foci are more than 5 mm away from the main tumor, they can be considered separate satellites (multifocal, similar histologic features).
- **Invasive carcinoma with extensive lymphovascular invasion (LVI) (Figure B1, C).** Additional foci of invasion may arise from areas of LVI (i.e., an intramammary metastasis). The multiple carcinomas are usually identical in histologic appearance and immunophenotype. The origin of satellite skin nodules classified as T4b is generally due to invasion arising from foci of dermal lymphovascular invasion.
- **#Multiple biologically separate invasive carcinomas is illustrated in Panel D.** Some patients have multiple, synchronous, biologically independent carcinomas. If invasive carcinomas differ in histologic type, grade, or biomarker status, then these details may be reported using separate Tumor Characteristics sections in the same protocol.
- **Invasive carcinomas after neoadjuvant therapy (Figure B1, E).** Cancers with a significant response to chemotherapy typically present as multiple residual foci within a fibrotic tumor bed (see Note K). The foci of invasion are usually identical in appearance and immunophenotype.
- **Transection of a single carcinoma into multiple fragments (Figure B1, F).** If invasive carcinoma is present in multiple fragments of a fragmented specimen, transection of 1 carcinoma should be considered. Correlation with clinical and imaging findings can sometimes be helpful to determine the best size for T classification and to determine whether or not multiple foci were present.

 # Multiple biologically separate invasive carcinomas may now be reported using separate Tumor Characteristics sections in the same protocol.

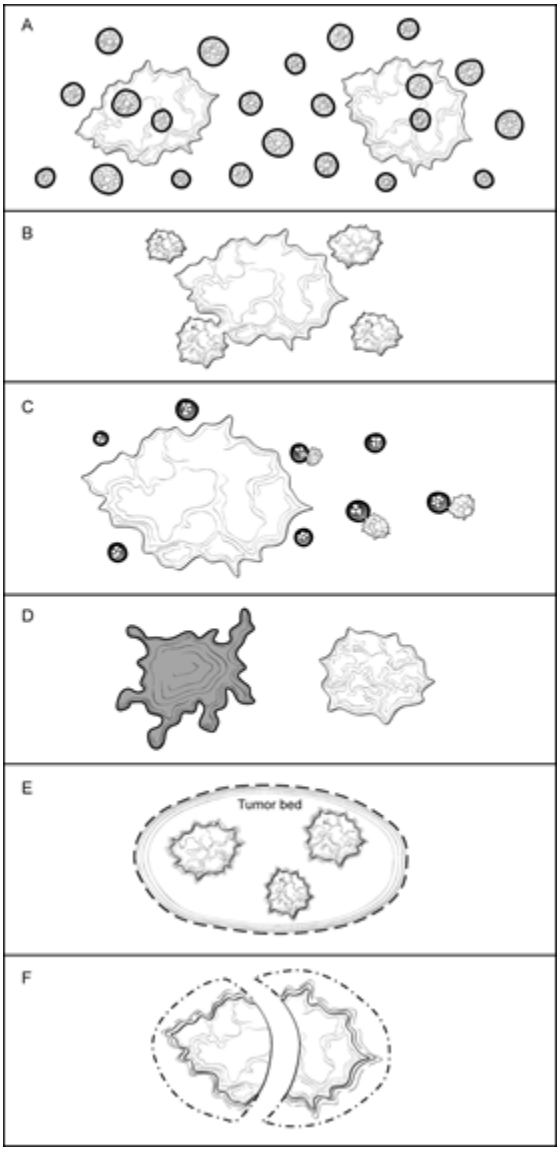

Figure B1. Multiple Invasive Carcinomas. A. Extensive carcinoma in situ with multiple foci of invasion. **B**. Invasive carcinoma with smaller satellite foci. **C**. Invasive carcinoma with extensive lymphovascular invasion. Areas of lymphovascular invasion can give rise to additional foci of invasive carcinoma (i.e., intramammary metastasis). **D.** Multiple biologically separate invasive carcinomas. These carcinomas are usually widely separated and may be histologically and immunophenotypically distinct. **E.** Invasive carcinomas after presurgical (neoadjuvant) therapy. If there is a marked response to treatment, multiple foci of carcinoma may be scattered over a fibrotic tumor bed. **F**. Transection of a single carcinoma into multiple fragments. If a carcinoma is transected during excision, it may be difficult to determine if 1 or multiple carcinomas are present.

C. Tumor Identifier and Tumor Site

A unique Tumor Identifier is required only when reporting Tumor Characteristics for multiple separate ipsilateral invasive cancers. This unique identifier should help distinguish each invasive focus and can be terms used clinically, in the imaging reports, gross exam or as designated by the pathologist (e.g., “R1 focus,” “Lesion 2,” etc.). The site of an invasive carcinoma is also helpful to document, when provided by the surgeon, breast imaging, or previous pathology report, to correlate with prior studies (e.g., a core needle biopsy) or with future biopsies or cancer events. The site is often indicated by a clock position and distance from the nipple or by involved quadrant(s) when large.

The approximate tumor site can be determined in a mastectomy. However, it is sometimes difficult to correlate exactly with the position as determined in vivo because of differences in how the specimen would be positioned on the chest wall (i.e., the skin ellipse may be horizontal or point to the axilla). It is helpful to locate the carcinoma with respect to the clinical site or imaging site, when possible.

If the patient has undergone presurgical (neoadjuvant) therapy and there is no residual invasive carcinoma, the tumor site refers to the location of the prior invasive carcinoma.

D. Histologic Type

This protocol applies to all invasive carcinomas of the breast. The World Health Organization (WHO)[1] classification of breast carcinoma is recommended, although the protocol does not preclude the use of other classifications or histologic types. Carcinomas may be classified based on the H&E appearance without the use of immunohistochemical studies; however, the ER and HER2 status can sometimes help inform histologic type.

Pure special type favorable histologic type carcinomas of luminal/ER positive biology (ex. pure tubular, mucinous and cribriform) should be at least 90% special type histology (or classify as Mixed).

For metaplastic carcinomas, the specific subtype should ideally be reported since these can have very different outcomes. Subtypes of metaplastic carcinoma recognized by the WHO include spindle cell, heterologous differentiation/matrix production, squamous cell and mixed forms as well as two favorable types: low-grade adenosquamous carcinoma and fibromatosis-like.

Invasive cancers with histology that is considered a “specific morphologic pattern” of invasive breast cancer no special type/ductal include: invasive carcinoma with neuroendocrine differentiation, medullary pattern, and other rare patterns such as osteoclast-like stromal giant cell rich.

A modified list is presented in the case summary based on the most frequent types of invasive carcinomas and terminology that is in widespread usage. The modified list is intended to capture the majority of tumors and reduce the frequency of tumors being reported as “other.”

Very rare types, such as invasive papillary carcinoma, neuroendocrine tumor, acinic-cell like, mucoepidermoid carcinoma, mucinous cystadenocarcinoma and tall cell carcinoma with reversed polarity should be indicated by their WHO terminology in the “other” category. For carcinomas with some features of a specific type that are not definitive, the features can be described in the “other” category.

References
1. WHO Classification of Tumours Editorial Board. *Breast tumours.* Lyon (France): International Agency for Research on Cancer; 2026. (WHO classification of tumours series, 6th ed.).

E. Histologic Grade

All invasive breast carcinomas should be graded.[1,2,3,4] The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) should be used for reporting. Within each stage grouping there is a relation between histologic grade and outcome.

The Nottingham combined histologic grade evaluates the amount of tubule formation, the extent of nuclear pleomorphism, and the mitotic count (or mitotic rate). Each variable is given a score of 1, 2, or 3, and the scores are added to produce a grade. The mitotic score is determined by the number of mitotic figures found in 10 consecutive high-power fields (HPF) in the most mitotically active part of the tumor. Only clearly identifiable mitotic figures should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei are excluded. Because of variations in field size, the HPF size must be determined for each microscope and the appropriate point score determined accordingly. It is recommended that the size be measured by using a micrometer or by digital image measurements. However, the diameter of an HPF can also be calculated by using the method below.

Measuring the Size of a High-Power Field (HPF) with a Ruler

Use a clear ruler to measure the diameter of a low-power field. This number can be used to calculate a constant based on the following formula:

Eyepiece Magnification x Objective Magnification x Microscopic Field Diameter = A Constant

When the value of the constant is known, the diameter of an HPF can be calculated for other objectives by using the following formula:

Unknown Field Diameter = Constant / (Eyepiece Magnification x Objective Magnification)

Half of the field diameter is the radius of the field (*r*), which can then be used to calculate the area of the HPF:

$3.1416 \times r^2 =$ Area of Microscopic Field

If the microscopic field diameter or the area of the field is known, Table 1 can be used to determine the number of mitoses corresponding to different scores.

Table 1. Score Categories According to Field Diameter and Mitotic Count

Scoring Categories of Mitotic Counts				
		Number of mitoses per 10 fields corresponding to:		
Field diameter (mm)	Area (mm^2)	Score 1	Score 2	Score 3
0.40	0.125	≤4	5 to 9	≥10
0.41	0.132	≤4	5 to 9	≥10
0.42	0.139	≤5	6 to 10	≥11
0.43	0.145	≤5	6 to 10	≥11
0.44	0.152	≤5	6 to 11	≥12
0.45	0.159	≤5	6 to 11	≥12
0.46	0.166	≤6	7 to 12	≥13

0.47	0.173	≤6	7 to 12	≥13
0.48	0.181	≤6	7 to 13	≥14
0.49	0.189	≤6	7 to13	≥14
0.50	0.196	≤7	8 to 14	≥15
0.51	0.204	≤7	8 to 14	≥15
0.52	0.212	≤7	8 to 15	≥16
0.53	0.221	≤8	9 to 16	≥17
0.54	0.229	≤8	9 to 16	≥17
0.55	0.238	≤8	9 to 17	≥18
0.56	0.246	≤8	9 to 17	≥18
0.57	0.255	≤9	10 to 18	≥19
0.58	0.264	≤9	10 to 19	≥20
0.59	0.273	≤9	10 to 19	≥20
0.60	0.283	≤10	11 to 20	≥21
0.61	0.292	≤10	11 to 21	≥22
0.62	0.302	≤11	12 to 22	≥23
0.63	0.312	≤11	12 to22	≥23
0.64	0.322	≤11	12 to 23	≥24
0.65	0.332	≤12	13 to 24	≥25
0.66	0.342	≤12	13 to 24	≥25
0.67	0.353	≤12	13 to 25	≥26
0.68	0.363	≤13	14 to 26	≥27
0.69	0.374	≤13	14 to 27	≥ 28

From Pathology Reporting of Breast Disease*. Copyright 2005 National Health Service Cancer Screening Programme and The Royal College of Pathologists. Adapted with permission.*

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F. Tumor Size (Size of Invasive Carcinoma)

The size of an invasive carcinoma is an important prognostic factor. The single greatest dimension of the largest invasive carcinoma is used to determine T classification (Figure E1, A through F). The best size for AJCC pT classification should use information from imaging, gross examination, and microscopic evaluation.[1] Sizes should be measured to the nearest millimeter.

The clinical information, gross evaluation and tissue submission strategy are essential to determining an accurate pT category. Knowing the following clinical/radiographic information when deciding the tissue

sampling strategy is helpful: 1. Expected number and size of lesions in the resection (and location for mastectomy specimens). 2. Prior biopsies and/or clips (and specific diagnoses). 3. If patient had neoadjuvant treatment for the current cancer.

Visual determination of size is often unreliable, especially for invasive lobular carcinoma, post-neoadjuvant invasive cancers, and carcinoma in situ. The size by palpation of a hard mass correlates with invasion of tumor cells into stroma when there is a robust desmoplastic response. Frequently, there is not a palpable hard mass or invasion may extend beyond a palpable abnormality. Therefore, it is helpful to use serial sequential sampling, focusing on the area around the biopsy site. A schematic diagram indicating where blocks have been submitted, slice thickness, and the location of blocks involved by invasive carcinoma will aid in determining tumor size. Specimen slices, especially of the peripheral slices submitted should be thinned to 3-4 mm to avoid overestimating tumor size.

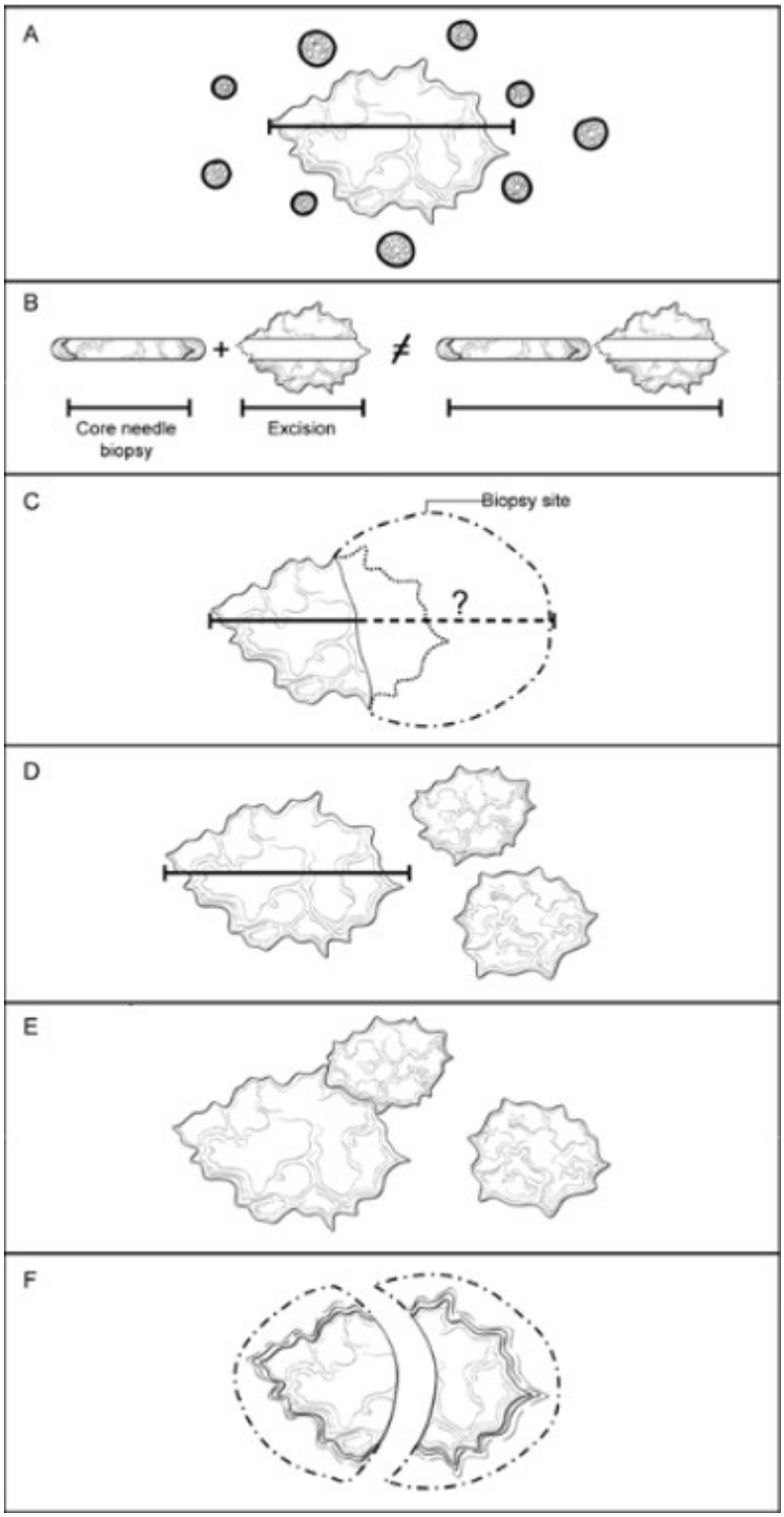
A
B
Core needle biopsy
Excision
C
Biopsy site
?
D
E
F

Figure F1. Determining the size of an invasive carcinoma. A. Invasive carcinoma with surrounding ductal carcinoma in situ (DCIS). The size only includes the area of the invasive carcinoma and does not include the adjacent DCIS. The size should be measured to the closest 1 mm. **B.** Small invasive carcinoma with prior core needle biopsy. The size of the carcinoma in the core needle biopsy should not be added to the size of the carcinoma in the excisional specimen, as this will generally overestimate the true size. The best size for classification must take into consideration the largest dimension of the carcinoma in both specimens as well as the size by imaging before the core needle biopsy. **C.** Small invasive carcinomas with adjacent biopsy site changes. In some excisional specimens, a small carcinoma will be present adjacent to a relatively large area of biopsy site changes. The actual size cannot be determined with certainty. The size in the core needle biopsy, in the excisional specimen, and by imaging should be considered to determine the best size for classification. **D.** Multiple invasive carcinomas. If multiple carcinomas are present, the size of the largest invasive carcinoma is used for pT classification. The modifier "(m)" is used to indicate that multiple invasive carcinomas are present. **E**. Multiple invasive carcinomas in close proximity. It may be difficult to distinguish multiple adjacent carcinomas from one large invasive carcinoma. Careful examination of the specimen with submission of tissue between grossly evident carcinomas is recommended. Correlation with imaging findings can be helpful. Generally, microscopic size confirmation of the largest grossly identified invasive carcinoma is used for pT classification. As a pragmatic approach, if two histologically similar carcinomas are within 5.0 mm of each other, measure from outer edges of the two but if they are 5 mm or more apart they can be considered separate foci. **F**. Invasive carcinomas that have been transected. If an invasive carcinoma has been transected and is present in more than 1 tissue fragment, the sizes in each fragment should not be added together, as this may overestimate the true size. In many cases, correlation with the size on breast imaging will be helpful to choose the best size for classification. In other cases, the pathologist will need to use his or her judgment in assigning an AJCC T category.

Microinvasion: Microinvasion is defined by the AJCC as invasion measuring 1 mm or less in size.[1] Invasive tumors that are larger than 1.0 mm but less than 2.0 mm are rounded up to 2.0 mm and are not considered microinvasive. In some cases, immunoperoxidase studies for myoepithelial cells may be helpful to document areas of invasion and the size of the invasive foci. Microinvasion is not a histologic type.

If more than 1 focus of microinvasion is present, the number of foci present, an estimate of the number, or a note that the number of foci is too numerous to quantify should be reported.

Per the WHO, "if there are multiple foci of microinvasion in close proximity, a pragmatic approach would be to apply the same recommendation used for staging multifocal established invasive carcinomas and regard deposits <5 mm apart as parts of a single invasive tumour deposit. Although there is only limited evidence, this is a practical approach which would classify close proximity multifocal microinvasion (<5mm apart) as an established invasive carcinoma, base the invasive tumour size measurement on the maximum dimension of the region with 2 or more microinvasive foci, and stage accordingly. There should be caution in applying this rule if there is very minimal infiltration and examination of further deeper sections should be considered".[2]

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G. Ductal Carcinoma In Situ

Ductal carcinoma in situ[1,2,3,4] associated with invasive carcinoma increases the risk of local recurrence for women undergoing breast-conserving surgery. It is more important to report the features of DCIS when in situ disease is predominant (e.g., cases of DCIS with microinvasion or extensive DCIS associated with T1a carcinoma). If DCIS is a minimal component of the invasive carcinoma, the features of the DCIS have less clinical relevance. The extent of DCIS and its relative proportions to the invasive cancer can be useful for imaging correlation, to justify the indications for the extent of the surgery and to reflect the risk of possible occult invasion or margin involvement when very extensive.

The pathology report should include an estimate of the extent of the DCIS present. It can be reported in multiple ways depending on its relationship to the invasive cancer present: 1. As an estimated percentage of the entire tumor when admixed intimately with invasion. 2. As an estimated size or span of DCIS by correlation of gross sampling and microscopic involvement (this is useful to report when the DCIS is larger than the invasion). The College of American Pathologists (CAP) DCIS protocol provides additional information on determining the extent of DCIS.

Architectural Pattern of DCIS

The architectural pattern has traditionally been reported for DCIS but reporting all patterns present may not always be clinically relevant. The dominant pattern can also be selected. Solid papillary carcinoma in situ and Encapsulated papillary carcinoma patterns ideally should be reported if present in association with invasive cancers. These forms of papillary DCIS/encapsulated carcinoma may lack myoepithelial staining but if they meet criteria otherwise for these diagnoses, they are not considered a part of the invasive cancer size (note that invasive forms of solid papillary carcinoma also exist).

Nuclear grade and the presence of necrosis are more predictive of clinical outcome than architectural pattern.

Nuclear Grade of DCIS

The nuclear grade of DCIS is determined using 6 morphologic features (Table 2).

Table 2. Nuclear Grade of Ductal Carcinoma in Situ

Feature	Grade I (Low)	Grade II (Intermediate)	Grade III (High)
Pleomorphism	Monotonous (monomorphic)	Intermediate	Markedly pleomorphic
Size	1.5 to 2 x the size of a normal red blood cell or a normal duct epithelial cell nucleus	Intermediate	>2.5 x the size of a normal red blood cell or a normal duct epithelial cell nucleus
Chromatin	Usually diffuse, finely dispersed chromatin	Intermediate	Usually vesicular with irregular chromatin distribution
Nucleoli	Only occasional	Intermediate	Prominent, often multiple
Mitoses	Only occasional	Intermediate	May be frequent
Orientation	Polarized toward luminal spaces	Intermediate	Usually not polarized toward the luminal space

Necrosis
The presence of necrosis is correlated with the finding of mammographic calcifications (i.e., most areas of necrosis will calcify). Ductal carcinoma in situ that presents as mammographic calcifications often recurs as calcifications. Necrosis can be classified as follows:

- Central ("comedo"): The central portion of an involved ductal space is replaced by an area of expansive necrosis that is easily detected at low magnification. Ghost cells and karyorrhectic debris are generally present. Although central necrosis is generally associated with high-grade nuclei (i.e., comedo DCIS), it can also occur with DCIS of low or intermediate nuclear grade.
- Focal: Small foci, indistinct at low magnification, or single cell necrosis.

Necrosis should be distinguished from secretory material, which can also be associated with calcifications, but does not include nuclear debris.

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H. Macroscopic and Microscopic Extent of Tumor
The extent of an invasive breast cancer involving local structures such as the skin and chest wall can alter the AJCC pT stage. If skin or muscle are part of a specimen, their presence should always be included in the gross description and the relationship of these structures to the carcinoma reported in the final diagnosis. The gross extent of skin involvement if present should be clearly documented since macroscopic skin ulceration or macroscopic skin satellites are required for a change in pT category (microscopic findings can support this but without gross findings there is no change in pT category).

If a surgical specimen includes the nipple this can be documented and specified whether it is not involved, contains Paget's disease (extension of cancer into the nipple epidermis), DCIS in the major lactiferous ducts or stromal involvement by invasive carcinoma. While nipple involvement may be relevant to surgical planning or local recurrence risk, it does not change the overall pT stage.

Figure H1 illustrates multiple ways that breast carcinoma can involve the skin:

- DCIS involving nipple epidermis (Paget disease of the nipple) (Figure H1, A): DCIS can extend from the lactiferous sinuses into the contiguous skin without crossing the basement membrane. This finding does not change the T classification of the invasive carcinoma.

- Invasive carcinoma invading into dermis or epidermis, without ulceration (Figure H1, B): Skin invasion correlates with the clinical finding of a carcinoma fixed to the skin and may be associated with skin or nipple retraction. This finding does not change the T classification.
- Invasive carcinoma invading into dermis and epidermis with gross skin ulceration (Figure H1, C): In the past, skin ulceration was associated with very large, locally advanced carcinomas. However, skin ulceration can also be associated with superficially located small carcinomas. It is unknown if skin involvement confers a worse prognosis as compared to carcinomas of similar size without skin invasion. Carcinomas with grossly evident skin ulceration are classified as T4b.
- Ipsilateral satellite skin nodules (Figure H1, D): An area of invasive carcinoma within the dermis, separate from the main carcinoma, is usually associated with lymphovascular invasion. The satellite nodules should be macroscopically evident and confirmed microscopically. This finding is classified as T4b. The clinical significance of incidental microscopic satellite nodules in the dermis has not been investigated.
- Dermal lymphovascular invasion (Figure H1, E): Carcinoma present within lymphatic spaces in the dermis is often correlated with the clinical features of inflammatory carcinoma (diffuse erythema and edema involving one-third or more of the breast), and such cases would be classified as T4d. In the absence of the clinical features of inflammatory carcinoma, this finding remains a poor prognostic factor but is insufficient to classify a cancer as T4d. This finding is separately documented under “Dermal Lymphovascular Invasion.”

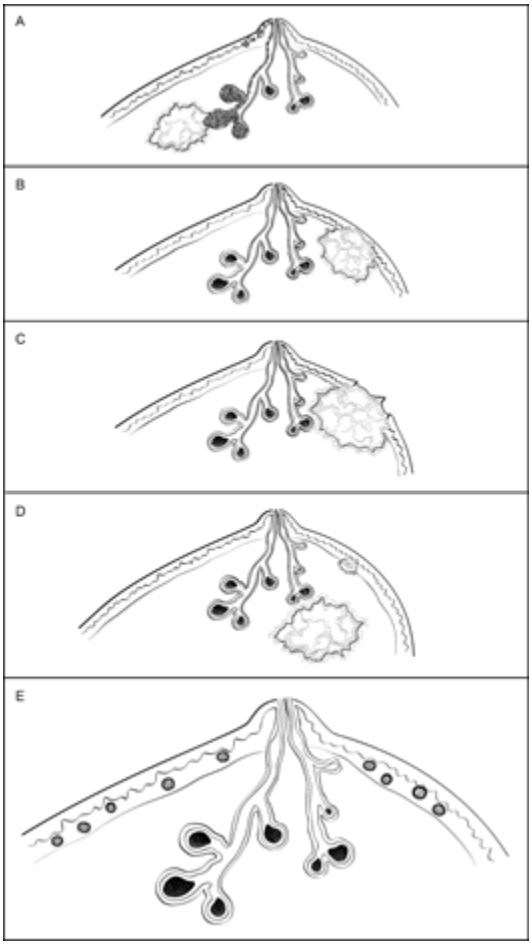

Figure H1. Invasive Carcinoma: Skin Involvement. A. Ductal carcinoma in situ (DCIS) involving nipple epidermis (Paget disease of the nipple) associated with an invasive carcinoma. DCIS can traverse the lactiferous sinuses into the epidermis without crossing a basement membrane. This finding does not change the T classification of an underlying invasive carcinoma. **B**. Invasive carcinoma invading into dermis or epidermis, without ulceration. This finding does not change the T classification of the invasive carcinoma. **C**. Invasive carcinoma invading into dermis and epidermis with gross skin ulceration. This carcinoma would be classified as T4b, unless additional features warrant classification as T4c (chest wall invasion) or T4d (inflammatory carcinoma). **D.** Ipsilateral satellite skin nodules. An area of invasive carcinoma in the skin, separate from the main carcinoma, is usually associated with lymphovascular invasion. This finding is classified as T4b if the skin nodules are grossly/clinically apparent, unless additional features warrant classification as T4c (chest wall invasion) or T4d (inflammatory carcinoma). **E.** Dermal lymphovascular invasion. If carcinoma within lymphatic spaces in the dermis is correlated with the clinical features of inflammatory carcinoma (diffuse erythema and edema involving one-third or more of the breast), the carcinoma is classified as T4d. If clinical signs are not present, this finding does not change the T classification, but is an indicator of a poor prognosis.

Muscle
Skeletal muscle may be present at the deep/posterior margin. The presence of muscle documents that the excision has extended to the deep fascia. Invasion into skeletal muscle should be reported, as this finding may be used as an indication for postmastectomy radiation therapy.

The skeletal muscle present is generally pectoralis muscle. Invasion into this muscle is not included as T4a. Invasion must extend through this muscle into the chest wall (intercostal muscles or deeper) in order to be classified as T4a. However, chest wall muscles are rarely removed in mastectomy specimens. The T4a classification is generally established with imaging of locally advanced carcinomas.

I. Lymphatic and/or Vascular Invasion
Lymphatic and/or vascular invasion (LVI) is associated with local recurrence and reduced survival.[1,2,3] Distinguishing lymphatic channels from blood vessels is unnecessary. Documenting the presence of dermal lymphatic and/or vascular invasion is particularly important because of its strong association with the clinical findings of inflammatory breast carcinoma. Reporting the LVI status for stage IIA and IIB patients who have an axillary lymph node dissection (ALND) may influence the use of radiotherapy.[4]

Strict criteria have been proposed for the diagnosis of LVI (Table 3).[5] Lymphatic and/or vascular invasion may be seen in stroma between uninvolved lobules and can sometimes be mistaken for DCIS if the cells completely fill the lymphatic space.

Guidelines issued by the St. Gallen International Expert Consensus Conference[6] include recommendations based on the presence of “extensive” LVI but do not define the term “extensive”. There are conflicting results on the significance of the number of foci of LVI.[2,3] There is no agreed definition of extensive LVI and sub categorization of LVI as extensive or focal is subjective. Pathologists may report the number of foci and/or the number of blocks with LVI as a measure of extent. 1-2 vessels involved in one block maybe considered focal and more than 2 vessels involved in two or more blocks may be considered extensive.

Table 3. Criteria for Lymphatic and/or Vascular Invasion (LVI)

1.	LVI must be diagnosed outside the border of the invasive carcinoma. The most common area to find LVI is within 1 mm of the edge of the carcinoma.
2.	The tumor emboli usually do not conform exactly to the contours of the space in which they are found. In contrast, invasive carcinoma with retraction artifact mimicking LVI will have exactly the same shape.
3.	Endothelial cell nuclei should be seen in the cells lining the space.
4.	Lymphatics are often found adjacent to blood vessels and often partially encircle a blood vessel.

Data derived from Rosen.[5]

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J. Microcalcifications

Cancer found in biopsies performed for microcalcifications will almost always be at the site of the calcifications or in close proximity. The presence of the targeted calcifications in the specimen should be confirmed by specimen radiography. The pathologist must be satisfied that the specimen has been sampled in such a way that the lesion responsible for the calcifications has been examined microscopically. The relationship of the radiologic calcifications to the invasive carcinoma and the DCIS should be indicated.

If calcifications can be seen in the specimen radiograph but not in the initial histologic sections, deeper levels should be examined. If needed, radiographs of the paraffin block(s) may be obtained to detect calcifications remaining in the block(s). If microcalcifications cannot be confirmed by routine microscopic evaluation, polarized light may be helpful, since calcium oxalate crystals are refractile and polarizable but usually clear or tinged yellow in H&E sections. On rare occasions, calcifications do not survive tissue processing or prolonged fixation in formalin. Foreign material can sometimes simulate calcifications (e.g., metallic fragments after surgery or trauma, ink from margin evaluation, and hemosiderin).

K. Treatment Effect

Patients may be treated with endocrine therapy or chemotherapy before surgical excision (neoadjuvant therapy). A y prefix is added when assigning AJCC T and N categories after neoadjuvant treatment (ypT and ypN). The y prefix does apply to neoadjuvant endocrine therapy if it was a formal, planned course of neoadjuvant systemic treatment done for several months. The y prefix should not be reported if endocrine treatment was just a short course (a few days or weeks). The response of the invasive carcinoma to neoadjuvant therapy is a strong predictor of disease-free and overall survival. Special attention to finding the tumor bed grossly so it can be sampled and examined microscopically is necessary for these specimens.[1,2,3,4,5,6]

The NCCN recommends that post neoadjuvant chemotherapy treatment response be included in breast pathology reports using the Residual Cancer Burden (RCB) system (category 2B recommendation). The RCB protocol instructions and calculator can be found at the MD Anderson website: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3. This site also includes materials and guides that explain the system. Pathologists should be aware that, while the individual RCB parameters as well as the RCB Score and Class are each optional reporting elements, cancer registries can only collect the RCB Score and Class from the pathology report.

The RCB was not validated or designed for neoadjuvant endocrine treatment and an RCB Score and Class should not be reported. However, individual RCB parameters such as cellularity might be helpful in describing residual disease burden; reporting these parameters may be of interest but is optional.

RCB Assessment of Primary Tumor Bed

The size (area) of the primary tumor bed with residual viable invasive carcinoma and the cellularity of residual carcinoma in the tumor bed provide a reproducible estimate of the volume of residual invasive carcinoma. The "tumor bed" size for RCB parameters of a treated cancer is measured as the span of residual invasive carcinoma (contiguous or discontiguous foci) in two dimensions, which requires gross tissue sampling methods that can provide this information (see RCB website for protocol). See figure below for an example of the tumor bed parameter measurements.

The residual invasive carcinoma cellularity is estimated by determining the overall cancer cellularity (invasive and in situ) and the percentage of residual in situ carcinoma. The RCB calculation subtracts the amount of in situ disease to obtain the estimate of residual invasive carcinoma cellularity used to determine the RCB. If only LVI remains after therapy, the area with LVI is used as the primary tumor bed area and the cellularity of the LVI is used as the residual cancer cellularity.

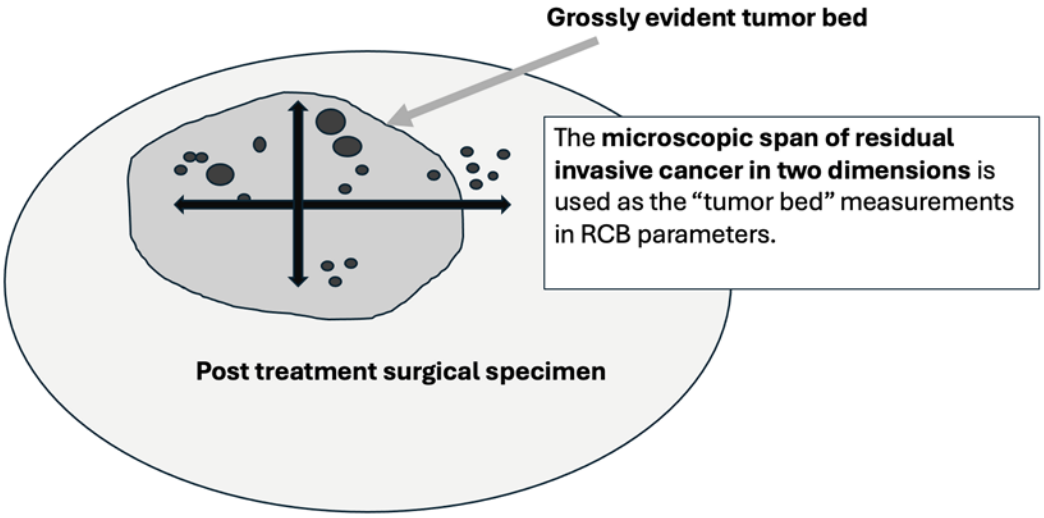

Figure K1. Tumor bed measurements for RCB parameters

If reporting RCB parameters, the "tumor bed" dimensions should be the largest two-dimensional span of residual invasive carcinoma confirmed on microscopic examination. The gross fibrous tumor bed (shown as grey area) is not always the same measurements as the span of residual invasion (shown as multiple smaller solid circles in this example). The two-dimensional span of residual invasion may include foci that are not contiguous and present across multiple slices/sections. Only the largest span of invasion (not DCIS) is included in the overall tumor bed measurements.

RCB Assessment of Regional Lymph Nodes

According to the AJCC 8th edition staging system, the size of the largest contiguous focus of residual metastatic carcinoma present in the lymph nodes is used to assign the pN category; intervening therapy-

related fibrosis is not included in this measurement. However, when measuring the diameter of the largest lymph node metastasis for the RCB calculation, foci of residual metastatic carcinoma with intervening therapy-related fibrosis and any extracapsular extension are included in the measurement.

Lymph nodes containing only isolated tumor cells (ITCs) are not included in the number of positive lymph nodes when determining the AJCC pN category, but nodes containing only ITCs detected by routine stains are included in the RCB calculation. A size smaller than 0.2 mm (e.g., 0.05 mm) can be entered in the RCB calculator.

If there are separate metastases within the node with intervening normal nodal tissue, then these should be considered as separate foci and the largest single focus is used as the size of the largest metastatic deposit for both AJCC Staging and RCB calculation.

Post Neoadjuvant Treatment Staging, Grading and Biomarkers

Invasive carcinomas with a minor response may show little or no change in size. With greater degrees of response, the carcinoma shows decreased cellularity and may be present as multiple foci of invasion scattered over a larger tumor bed. The post-neoadjuvant therapy pathologic T-category (ypT) is based on the largest single focus of residual tumor, if present. Treatment-related fibrosis adjacent to residual invasive carcinoma is not included in the ypT maximum dimension. The “m” modifier is used to indicate that multiple foci of invasive carcinoma are present. The inclusion of additional information, such as the distance over which invasive carcinoma is present, the number of foci of invasive carcinoma, or the number of slides or blocks with invasive carcinoma, may be helpful in estimating the extent of residual disease. If no residual invasive carcinoma is present in the breast, the case summary can be used to report residual DCIS and/or metastatic carcinoma in lymph nodes. If there is no residual carcinoma in the breast or in the lymph nodes, then a CAP protocol case summary need not be used for reporting. Cases with no residual invasive carcinoma after neoadjuvant therapy are categorized as ypTis if there is residual DCIS or ypT0 if there is no residual cancer (not ypTX). It can be categorized as ypTx if there is only LVI in the breast resection specimen. Cases categorized as M1 before neoadjuvant therapy stay that way (i.e., they remain Stage IV even if there is complete pathologic response).

Most carcinomas are of the same grade after treatment. In a few cases, the grade will be higher because of marked nuclear pleomorphism. In very rare cases, the carcinoma will be of lower grade. The prognostic significance of a change in grade after treatment has not been determined.

If negative prior to treatment, it is recommended that ER, PgR, and HER2 be repeated on invasive carcinomas after treatment, as significant changes may occur in a subset of carcinomas, sometimes due to tumor heterogeneity and limited sampling prior to treatment.

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L. Margins

Whenever feasible, the specimen should be oriented in order for the pathologist to identify specific margins. This is particularly important for excisions less than total mastectomy, where it may be necessary for the surgeon to excise residual tumor at a specific margin (e.g., superior, inferior, medial, lateral, anterior, or deep). Identification of surgical margins also allows measurement of the distance between the carcinoma and specific margins. All identifiable margins should be evaluated for involvement by carcinoma both grossly and microscopically. Final margin status should be based on additional separately submitted margins as well as those that are considered final in the main resection specimen.[1]

Orientation may be done by sutures or clips placed on the specimen surface or by other means of communication between surgeon and pathologist and should be documented in the pathology report. Margins can be identified in several ways, including the use of multiple-colored inks, by submitting the margins in specific cassettes, or by the surgeon submitting each margin as a separately excised specimen. Inks should be applied carefully to avoid penetration deep into the specimen.

The final margin status should be reported for both invasive carcinoma and the DCIS when present (cancer in angiolymphatic spaces is not included in the final margin status). Margin status is considered Involved if the final margins have invasive cancer or DCIS at ink (inclusive of any additional margins removed). If the specimen is oriented, the specific site(s) of involvement should also be reported. Additionally, margins less than 1 mm to cancer (but not at ink), margins 1-2 mm from cancer and margins greater than 2 mm from cancer can be specified if considered relevant. For ease of reporting, an option for “all final margins greater than 2 mm” is also available in the protocol. “Other” can be used for complex scenarios (such as description of the margin status of multiple specimens that require surgical correlation) and “Cannot be determined” for other uncommon scenarios with explanation. The Margin comment section can be used to clarify any additional margin details.

The deep margin may be at muscle fascia. If so, the likelihood of additional breast tissue beyond this margin (and therefore possible involvement by DCIS) is extremely small. A deep muscle fascial margin (e.g., on a mastectomy specimen) positive for DCIS is unlikely to have clinical significance. However, invasive carcinoma at the deep margin, especially if associated with muscle invasion, is often an indication for postmastectomy radiation.

A superficial (generally anterior) margin may be immediately below the skin, and there may not be additional breast tissue beyond this margin. However, some breast tissue can be left in skin flaps, and the likelihood of residual breast tissue is related to the thickness of the flap.[2]

Specimen radiography is important to assess the adequacy of excision. Compression of the specimen should be minimized, as it can severely compromise the ability to assess the distance of the DCIS from the surgical margin. Mechanical compression devices should be used with caution and preferably reserved for nonpalpable lesions that require this technique for imaging (e.g., microcalcifications).

It is helpful to report the approximate extent of margin involvement (e.g. linear extent of invasion at margin and/or number of foci/blocks involved).

References

1. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *Pract Radiat Oncol.* 2016;6(5):287-295.
2. Torresan RZ, dos Santos CC, Okamura H, Alvarenga M. Evaluation of residual glandular tissue after skin-sparing mastectomies. *Ann Surg Oncol.* 2005;12(12):1037-1044.

M. Lymph Node Sampling and Reporting

Most patients with invasive carcinoma will have lymph nodes sampled.

Types of lymph nodes:

- **Sentinel lymph nodes** are identified by the surgeon by uptake of radiotracer or dye or both. They are considered sentinel lymph nodes if less than six nodes are removed. Adjacent palpable non-sentinel nodes may also be removed.
- **Axillary lymph nodes** are removed by en bloc resection of axillary tissue. The nodes are divided into levels: I (low-axilla: lateral to the lateral border of the pectoralis minor muscle); II (mid-axilla: between the medial and lateral borders of the pectoralis minor muscle and the interpectoral [Rotter's] lymph nodes); and III (apical axilla or infraclavicular nodes: medial to the medial margin of the pectoralis minor muscle and inferior to the clavicle). A surgeon may choose to remove 1 or more of these levels. Levels I and II are typically removed in the axillary dissection, with level III nodes only removed if considered suspicious by the surgeon intraoperatively. Level III nodes must be specifically identified, as there are additional AJCC N categories for these nodes.
- **Intramammary nodes** are present within breast tissue and are most commonly found in the upper outer quadrant. Intramammary nodes may rarely be sentinel lymph nodes. These nodes are included with axillary nodes for AJCC N classification.
- **Internal mammary nodes, supraclavicular nodes, and infraclavicular nodes** are rarely removed for breast cancer staging. If metastases are present in these nodes, there are specific AJCC N categories (see *AJCC Cancer Staging Manual*).[1]

Lymph node sampling:

- **Grossly positive nodes:** The size of grossly positive nodes should be recorded. One section to include any areas suggestive of extranodal invasion is sufficient. Cancerous nodules in the axillary

fat adjacent to the breast, without histologic evidence of residual lymph node tissue or surrounding breast tissue or ductal carcinoma in situ, are classified as regional lymph node metastasis.

- **Grossly negative nodes:** Sampling must be adequate to detect all macrometastases, as they are known to have prognostic importance (i.e., all metastatic deposits >2 mm). Thus, each node should be thinly sliced along the long axis of the node at 2 mm, and all slices should be submitted for microscopic examination. At least 1 representative hematoxylin-and-eosin (H&E) level must be examined. Additional methods of sampling, such as additional H&E levels or immunohistochemical studies, may detect isolated tumor cells or micrometastases. However, the clinical impact on outcome of these small metastases is minimal.[2]

The nodes must be submitted in such a way that every node can be evaluated and counted separately.
Reverse transcriptase polymerase chain reaction has been developed as an alternative method for examining lymph nodes.[3,4] The tissue used for this assay cannot be examined microscopically. All macrometastases must be identified histologically. Therefore, nodal tissue can only be used for other assays if all macrometastases can be identified by H&E examination. False-positive and false-negative results can occur with RT-PCR. The significance of a positive RT-PCR result for a histologically negative lymph node is unknown.

Reporting lymph nodes:

- **Number of nodes examined:** The total number of nodes includes sentinel nodes, nonsentinel nodes, nodes from axillary dissections, and intramammary nodes. When the number of sentinel and nonsentinel nodes removed is less than 6 nodes, the AJCC “sn” modifier is used.
- **Size of metastases:** The size of a tumor deposit is determined by measuring the largest dimension of any group of cells that are touching one another (confluent or contiguous tumor cells), regardless of whether the deposit is confined to the lymph node, extends outside the node (extranodal extension), is totally present outside the lymph node and invading adipose tissue, or is present within a lymphatic channel adjacent to the node or in the capsule.
- Metastases are classified into 3 groups:
    - Isolated tumor cell clusters (ITCs) are defined as small clusters of cells not larger than 0.2 mm, or single cells, or fewer than 200 cells in a single cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are not included in the total number of positive nodes when determining the N category.
    - Micrometastases measure more than 0.2 mm, but not more than 2 mm, and/or comprise more than 200 cells in a single cross-section. If only micrometastases are present, the N category is pN1mi. If at least 1 macrometastasis is present, nodes with micrometastases are included in the total number of positive nodes when determining the N category.
    - Macrometastases measure more than 2 mm.

In most cases, if metastases are present, the sentinel node will be involved. In rare cases, only nonsentinel nodes contain metastases. These cases can occur if the true sentinel node is completely replaced by tumor (and therefore is not detected by radioactive tracer or dye), if there is unusual lymphatic drainage, or if there is failure of the technique to identify the node. This finding should be included in the report.

Details of Lymph node metastases from one or more biologically distinct tumors may be added in the comment section of the Regional Lymph node section.

In some cases, the best N category can be difficult to determine (Figure M1).

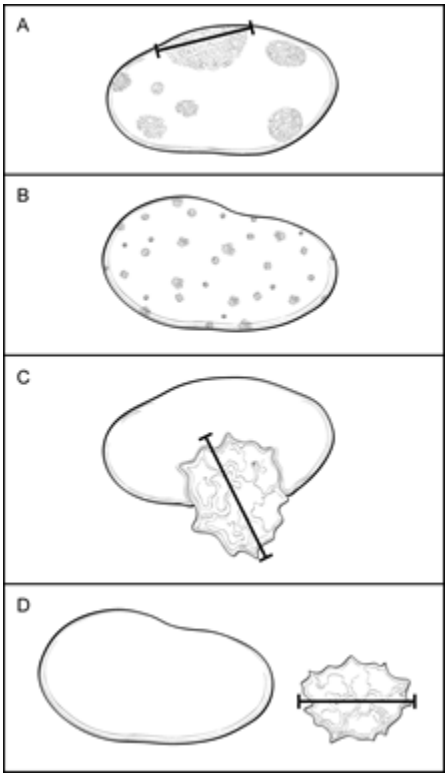

Figure M1. Classification of Lymph Node Metastases. A. Multiple clusters of tumor cells. Classification is based on the size of the largest contiguous cluster of tumor cells. The distance between clusters should not be included in the size measurement. However, if the overall volume of tumor is similar to the next highest nodal category, it is recommended that the pathologist use his or her judgment to assign the best N category and to include the reasoning in a note. **B**. Dispersed pattern of lymph node metastasis. Some carcinomas, in particular lobular carcinomas, metastasize as single cells and do not form cohesive clusters. In such cases, the "size" of the metastasis is difficult to determine. If more than 200 tumor cells are present in 1 cross-section of the node, then the category of isolated tumor cells should not be used. If there is difficulty in assigning the N category, it is recommended that the reason be provided in a note. **C**. Extranodal invasion. The area of invasion outside the lymph node capsule is included in the overall size of the lymph node metastasis. The size of the metastasis includes the tumor cells and the desmoplastic response (i.e., the cells do not need to be contiguous, but the cells plus fibrosis should be contiguous). The finding of extranodal invasion is also reported. **D.** Cancerous nodules in axillary fat. Areas of carcinoma invading into the stroma in axillary adipose tissue, without residual nodal tissue, are considered to be positive lymph nodes. However, if there is surrounding breast tissue or ductal carcinoma in situ, then the invasive carcinoma should be classified as an invasive carcinoma and not as a lymph node metastasis.

- **Nodes after neoadjuvant therapy:** The response of metastatic carcinoma in lymph nodes after treatment is an important prognostic factor. In addition to the information described above, evidence of treatment response (e.g., small tumor deposits within an area of fibrosis) should also be reported (see Note K). Only the largest contiguous focus of residual tumor in the node evaluation is used for classification; any treatment-associated fibrosis is not included.

References
1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
2. 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.
3. Viale G, Dell'Orto P, Biasi MO, et al, Comparative evaluation of an extensive histopathologic examination and a real-time reverse-transcription-polymerase chain reaction assay for mammaglobin and cytokeratin 19 on axillary sentinel lymph nodes of breast carcinoma patients. *Ann Surg.* 2008; 247:136-142.
4. Julian TB, Blumencranz P, Deck K, et al. Novel intraoperative molecular test for sentinel lymph node metastases in patients with early-stage breast cancer. *J Clin Oncol.* 2008; 26:3338-3345.

N. pTNM Classification

The tumor-node-metastasis (TNM) staging system maintained collaboratively by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.[1] Assignment of Pathologic Prognostic Stage Group is the responsibility of the managing physician and not the pathologist.[1]

Pathologic Classification

The pathologic classification of a cancer is based on information acquired before treatment supplemented and modified by the additional evidence acquired during and from surgery, particularly from pathologic examination of resected tissues. The pathologic classification provides additional precise and objective data. Classification of T, N, and M by pathologic means is denoted by use of a lower case "p" prefix (pT, pN, pM).

Pathologic T (pT): The pathologic assessment of the primary tumor (pT) generally is based on resection of the primary tumor generally 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. In this situation, imaging findings can be used for determination of the pathologic size (pT). On rare occasions, 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.

AJCC/UICC definition of inflammatory carcinoma (T4d): Inflammatory carcinoma is a clinical-pathologic entity characterized by diffuse erythema and edema (peau d'orange) involving one-third or more of the skin of the breast. The skin changes are due to lymphedema caused by tumor emboli within dermal lymphatics, which may or may not be obvious in a small skin biopsy. However, a tissue diagnosis is still necessary to demonstrate an invasive carcinoma in the underlying breast parenchyma or at least in the dermal lymphatics, as well as to determine biological markers, such as ER, PgR, and HER2 status. Tumor emboli in dermal lymphatics without the clinical skin changes described above do not qualify as inflammatory carcinoma. Locally advanced breast cancers directly invading the dermis or ulcerating the skin without the clinical skin changes also do not qualify as inflammatory carcinoma. Thus, the term inflammatory carcinoma should not be applied to neglected locally advanced cancer of the breast presenting late in the course of a patient's disease. The rare case that exhibits all the features of inflammatory carcinoma, but in which skin

changes involve less than one-third of the skin, should be classified by the size and extent of the underlying carcinoma.

Pathologic N (pN): The pathologic assessment of regional lymph nodes (pN) ideally requires resection of a minimum number of lymph nodes to assure that there is sufficient sampling to identify positive nodes if present. The recommended number generally does not apply in cases where sentinel node has been accepted as accurate for defining regional node involvement and a sentinel node procedure has been performed. At least 1 node with *presence or absence* of cancer documented by pathologic examination is required for pathologic N classification.

Direct extension of primary tumor into a regional node is classified as node positive. A tumor nodule 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.

Specialized pathologic techniques such as immunohistochemistry or molecular techniques may identify limited metastases in lymph nodes that may not have been identified without the use of the special diagnostic techniques. Single tumor cells or small clusters of cells are classified as isolated tumor cells (ITCs). The standard definition for ITCs is a cluster of cells not more than 0.2 mm in greatest diameter. Cases with ITCs only in lymph nodes are classified as pN0. This rule also generally applies to cases with findings of tumor cells or their components by nonmorphologic techniques such as flow cytometry or DNA analysis.

AJCC/UICC definition of isolated tumor cells: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm or single tumor cells, or fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) 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.

Approximately 1000 tumor cells are contained in a 3-dimensional 0.2-mm cluster. Thus, if more than 200 individual tumor cells are identified as single dispersed tumor cells or as a nearly confluent elliptical or spherical focus in a single histologic section of a lymph node, there is a high probability that more than 1000 cells are present in the lymph node. In these situations, the node should be classified as containing a micrometastasis (pN1mi). Cells in different lymph node cross-sections or longitudinal sections or levels of the block are not added together; the 200 cells must be in a single node profile even if the node has been thinly sectioned into multiple slices. It is recognized that there is substantial overlap between the upper limit of the ITC and the lower limit of the micrometastasis categories due to inherent limitations in pathologic nodal evaluation and detection of minimal tumor burden in lymph nodes. Thus, the threshold of 200 cells in a single cross-section is a guideline to help pathologists distinguish between these 2 categories. The pathologist should use judgment regarding whether it is likely that the cluster of cells represents a true micrometastasis or is simply a small group of isolated tumor cells.

Pathologic M (pM): The pathologic assignment of the presence of metastases (pM1) requires histologic confirmation of cancer at the metastatic site. The designation MX has been eliminated from the AJCC/UICC TNM system. 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. Cases with a biopsy of a possible metastatic site that shows ITCs such as circulating tumor cells (CTCs) or disseminated tumor cells

(DTCs), or bone marrow micrometastases detected by IHC or molecular techniques, are classified as M0(i+) to denote the uncertain prognostic significance of these findings, and to classify the stage group according to the T and N and M0.

Posttherapy or post-neoadjuvant therapy classification (yTNM): Cases for which systemic and/or radiation therapy are given before surgery ("neoadjuvant") or for which no surgery is performed may have the extent of disease assessed at the conclusion of the therapy by clinical or pathologic means (if resection performed). This classification is useful to clinicians because the extent of response to therapy may provide important prognostic information to patients and help direct the extent of surgery or subsequent systemic and/or radiation therapy. T and N are classified by using the same categories as for clinical or pathologic staging for the disease type, and the findings are recorded by using the prefix designator "y" (e.g., ycT; ycN; ypT; ypN). The "yc" prefix is used for the clinical stage after therapy, and the "yp" prefix is used for the pathologic stage for those cases that have surgical resection after neoadjuvant therapy. The M component should be classified by the M status defined pathologically prior to therapy.

Recurrence classification (rTNM): This classification is assigned when further treatment is planned for a cancer that recurs after a disease-free interval. Second or subsequent primary cancers detected outside the staging window (generally 4 months) are known as metachronous primary tumors and are not staged with the 'y' prefix. The original stage assigned at the time of initial diagnosis and treatment does not change when the cancer recurs or progresses. The use of this staging for retreatment or recurrence is denoted with the 'r' prefix (rTNM). All information available at the time of retreatment should be used in determining the rTNM stage.

Multiple tumors: For patients with multiple ipsilateral invasive carcinomas, the T category assignment is based on the largest tumor. The "(m)" modifier is used to distinguish these cases from those with only a single invasive focus. For patients with simultaneous bilateral invasive carcinomas, each carcinoma is staged as a separate primary tumor, with independent determination of T and N categories and biomarker status.

Metachronous primaries: Second or subsequent primary cancers occurring in the same organ or in different organs are staged as a new cancer with the TNM system. Second cancers are not staged using the "y" prefix unless the treatment of the second cancer warrants this use.

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.

O. Additional Findings

In some cases, additional pathologic findings are important for the clinical management of patients.

If the biopsy was performed for a benign lesion and the invasive carcinoma is an incidental finding, this should be documented. An example would be the finding of DCIS with microinvasion in an excision for a large palpable fibroadenoma.

If there has been a prior core needle biopsy or excisional biopsy, the biopsy site should be sampled and documented in the report. If the intention was to completely re-excise a prior surgical site, the report should

document biopsy changes at the margin that could indicate an incomplete excision. This protocol should not be used if the main area of carcinoma has been previously removed and the current specimen is a re-excision of the margins.

Special Studies/Biomarker[1,2,3]
Reporting the results of biomarkers previously performed on a biopsy is helpful for a complete cancer summary. If there are multiple separate primary cancers, indicate which you are reporting the biomarkers on using the unique Tumor Identifier used in the protocol for each tumor to distinguish them. The Biomarker comment section can be used to report the profiles of the additional foci.

It may be useful to perform the breast cancer biomarkers on the invasive cancer(s) in the surgical specimen in some scenarios. If biomarkers are being performed or repeated, they can be reported separately using the Breast Cancer Biomarkers protocol.[1]

References

1. Allison K, Krishnamurti, U. Template for Reporting Results of Biomarker Testing of Specimens from Patients with Carcinoma of the Breast. 2025; www.cap.org/cancerprotocols., accessed March 3, 2026.
2. Allison KH, Hammond EH, Dowsett M: Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol* 2020; 38 (12): 1346-66; DOI: 10.1200/JCO.19.02309.
3. Wolff AC, Somerfield MR, Dowsett M: Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update. *J Clin Oncol* 2023: 41 (22): 3867-3872; DOI: 10.1200/JCO.22.02864.

Template for Reporting Results of Biomarker Testing of Specimens from Patients with Carcinoma of the Breast

Version: 1.6.1.0
Protocol Posting Date: June 2025

This biomarker template is not required for accreditation purposes but may be used to facilitate compliance with CAP Accreditation Program Requirements.

Version Contributors
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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements
Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (e.g., a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient's medical record and thus readily available to the treating clinical team. This template is not required for accreditation purposes.

Summary of Changes

v 1.6.1.0

- Updated ER, PgR, and HER2 IHC Testing Methodology to conditionally reported

Reporting Template

Protocol Posting Date: June 2025

Select a single response unless otherwise indicated.

CASE SUMMARY: (Breast Biomarker Reporting Template)

Includes interpretative content from the ASCO / CAP HER2 Guidelines (2018)

Completion of the template is the responsibility of the laboratory performing the biomarker testing and / or providing the interpretation. When both testing and interpretation are performed elsewhere (e.g., a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient's medical record and thus readily available to the treating clinical team.

Core data elements in this template comply with the CAP Accreditation requirements for HER2 and hormone receptor testing. Core data elements should be reported only for tests performed. If some studies were performed on different specimen(s), the specimen number(s) should be provided.

TEST(S) PERFORMED

Testing Performed on Specimen / Block Number(s) (specify, add lesion / site if applicable):

_____

Test(s) Performed (Note A) (select all that apply)

___ Estrogen Receptor (ER) Status

Estrogen Receptor (ER) Status (Note B)

 # Percentage of cells with nuclear positivity for ER may be reported as a specific number or a range if more than 10%.

___ Positive (greater than 10% of cells demonstrate nuclear positivity)#

Percentage of Cells with Nuclear Positivity

___ Specify percentage: _____ %

--OR--

Select range below:

___ 11-20%
___ 21-30%
___ 31-40%
___ 41-50%
___ 51-60%
___ 61-70%
___ 71-80%
___ 81-90%
___ 91-100%

Average Intensity of Staining

___ Weak (1+)
___ Moderate (2+)
___ Strong (3+)

Include standardized reporting comment for Low Positive results (see ER Comments section below)

___ Low Positive (1-10% of cells with nuclear positivity)##

+Specify Percentage of Cells with Nuclear Positivity: _____ %

Average Intensity of Staining

___ Weak (1+)
___ Moderate (2+)

___ Strong (3+)
___ Negative (less than 1%)
___ Cannot be determined (explain): _____
Status of Internal Controls (required only if low positive or negative)
___ Not applicable
___ Internal control present and stains as expected
___ Internal control absent; external controls stain as expected
___ Other (specify): _____
+Alternative Scoring System Scores
___ Allred
+Proportion Score: _____
+Intensity Score: _____
+Total Allred Score: _____
___ Other scoring system
+Specify System: _____
+Specify Score Result: _____
+Comment(s) on ER Result
___ See standardized ER comment(s) below
___ Other (specify): _____

___ Progesterone Receptor (PgR) Status
Progesterone Receptor (PgR) Status (Note B)
 # Percentage of cells with nuclear positivity may be reported as a specific number or a range if more than 10%.
___ Positive#
Percentage of Cells with Nuclear Positivity
___ Specify percentage: _____ %
--OR--
Select range below:
___ 1-10% (specify): _____ %
___ 11-20%
___ 21-30%
___ 31-40%
___ 41-50%
___ 51-60%
___ 61-70%
___ 71-80%
___ 81-90%
___ 91-100%
Average Intensity of Staining
___ Weak (1+)
___ Moderate (2+)
___ Strong (3+)
___ Negative (less than 1%)
___ Cannot be determined (explain): _____
Status of Internal Controls (required only if negative)
___ Not applicable

___ Internal control present and stains as expected
___ Internal control absent; external controls stain as expected
___ Other (specify): _____

+Alternative Scoring System Scores
___ Allred
+Proportion Score: _____
+Intensity Score: _____
+Total Allred Score: _____
___ Other scoring system
+Specify System: _____
+Specify Score Result: _____
+Comment(s) on PgR Results: _____

___ HER2 by Immunohistochemistry (IHC) Status

HER2 by Immunohistochemistry (IHC) Status (Note C)
 # Breast cancers with HER2 IHC scores of 0+, 1+, or 2+ (ISH negative) may be eligible for treatment targeting non-amplified levels of HER2 expression in the metastatic setting. Currently, patients with no membrane staining by IHC (0) are ineligible / excluded. Consider using the optional standardized HER2 IHC report comment to explain the clinical relevance of lower levels of HER2 IHC staining in the metastatic setting and definitions of "ultralow and low" HER2 used in clinical trials. See Note C.

___ Negative (Score 0)#
___ No membrane staining detected (0 / absent membrane staining)
___ Membrane staining that is incomplete and is faint / barely perceptible and in less than or equal to 10% of tumor cells (0+ / with membrane staining)
___ Other (specify): _____
___ Negative (Score 1+)#
___ Incomplete membrane staining that is faint / barely perceptible and in greater than 10% of tumor cells
___ Other (specify): _____
Most often, equivocal staining has the first staining pattern defined below, but other less common staining patterns are also included as reporting options. If other artifacts preclude evaluation of membrane stain intensity (crush, etc.), describe in the "Other (specify)" category.
___ Equivocal (Score 2+)#,##
___ Weak to moderate complete membrane staining observed in greater than 10% of tumor cells
 # This pattern can be seen in some micropapillary cancers that are HER2 gene amplified
___ Moderate to intense but incomplete membrane staining (basolateral)#
There should be a clearly clustered pattern of heterogeneity
___ Less than or equal to 10% of the cancer has circumferential staining that is complete and intense (3+) (heterogeneous, but very limited in extent; consider results of additional samples)##
___ Abundant cytoplasmic staining present, obscuring evaluation of membrane stain intensity
___ Other (specify): _____
___ Positive (Score 3+)
 # Readily appreciated using a low-power objective and observed within a homogeneous and contiguous population
___ Circumferential membrane staining that is complete, intense, and in greater than 10% of tumor

cells#
___ Other (specify): _____
Clustered Heterogeneity (required only if clustered heterogeneity is present as discrete, separate populations, one of which has 3+ staining)
___ Not applicable
___ Not identified (3+ staining is homogeneous throughout sample)
___ Present (distinct 3+ as well as non-3+ staining populations)
Specify Percentage of Cancer with 3+ Staining (must be greater than 10%): _____ %
Staining Score in Non-3+ Areas
___ 0
___ 1+
___ 2+
___ Other (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
+Comment(s) on HER2 IHC
___ See standardized HER2 IHC comment(s) below
___ Other (specify): _____

___ HER2 by In Situ Hybridization (ISH) Status
HER2 by In Situ Hybridization (ISH) Status (Note C)
 # See Note C for more detailed definitions and recommendations for ISH Groups 1-5. Use standardized or free text comments for Groups 2-4 which can be selected from the COMMENTS section below.

For quick reference:
Ratio greater than or equal to 2.0 and greater than or equal to 4.0 HER2 signals / cell = Group 1 (amplified)
Ratio greater than or equal to 2.0 and less than 4.0 HER2 signals / cell = Group 2
Ratio less than 2.0 and greater than or equal to 6.0 HER2 signals / cell = Group 3
Ratio less than 2.0 and greater than or equal to 4.0 and less than 6.0 HER2 signals / cell = Group 4
Ratio less than 2.0 and less than 4.0 HER2 signals / cell = Group 5 (not amplified)
___ Not performed
___ Pending
___ Negative (not amplified, Group 5 result)
___ Negative, based on IHC and ISH results#
___ Group 2 ISH result (with IHC 0-2+)
___ Group 3 ISH result (with IHC 0-1+)
___ Group 4 ISH result (with IHC 0-2+)
___ Positive (amplified, Group 1 result in greater than 10% of cell population)
___ Positive based on IHC and ISH results#
___ Group 2 ISH result (with IHC 3+)
___ Group 3 ISH result (with IHC 2-3+)
___ Group 4 ISH result (with IHC 3+)
___ Other (specify): _____
___ Cannot be determined (explain): _____
HER2 ISH Testing Signal Counts and Ratio

Average Number of HER2 Signals per Cell (required only if applicable): _____

Average Number of CEP17 Signals per Cell (required only if applicable): _____

HER2 / CEP17 Ratio (required only if applicable): _____

Number of Observers (required only if applicable): _____

Number of Invasive Tumor Cells Counted (required only if applicable): _____ cells
+Heterogeneity (distinct clustered populations with different scores)
___ Not identified
___ Present
+Specify Percentage of Cell Population HER2 Amplified by ISH: _____ %
+IHC Score in this Amplified Population
___ 0
___ 1+
___ 2+
___ 3+
___ Not known
+Description of Heterogeneity Present: _____
___ Other (specify): _____
+Comment(s) on HER2 ISH Result
___ See standardized HER2 ISH comment(s) below
___ Other (specify): _____

___ Ki-67 Proliferative Index
Ki-67 Proliferative Index (Note D)
___ Specify percentage of positive nuclei: _____ %
--OR--
Select range below:
___ 0-5%
___ 6-10%
___ 11-15%
___ 16-20%
___ 21-30%
___ 31-40%
___ 41-50%
___ 51-60%
___ 61-70%
___ 71-80%
___ 81-90%
___ 91-100%
+Comment(s) on Ki-67 Results: _____

Test(s) Performed Standardized Comments

+Comment(s) on ER Results (select all that apply)

___ The cancer in this sample has a low level (1-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with low level (1-10%) ER expression, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER negative cancers.
___ No internal controls are present, but external controls are appropriately positive. If needed, testing another specimen that contains internal controls may be warranted for confirmation of ER status.
___ Other (specify): _____

+Comment(s) on HER2 IHC Results# (select all that apply)

 # Breast cancers with HER2 IHC scores of 0+, 1+, or 2+ (ISH negative) may be eligible for treatment targeting non-amplified levels of HER2 expression in the metastatic setting. Currently, patients with no membrane staining by IHC (0) are ineligible / excluded. Consider using the optional standardized HER2 IHC report comment to explain the clinical relevance of lower levels of HER2 IHC staining in the metastatic setting and definitions of "ultralow and low" HER2 used in clinical trials.

___ In the DESTINY-Breast 04 and 06 trials, "HER2 low" was considered IHC Score 1+ or 2+ / ISH negative, and "HER2 ultralow" was HER2 IHC Score of 0 (pattern 0+) with membrane staining that is incomplete and faint / barely perceptible in less than or equal to 10% of tumor cells. Breast cancers with these staining patterns may be eligible for treatment with trastuzumab-deruxtecan in the metastatic setting (but those with no staining, IHC 0, are currently excluded).
___ Other (specify): _____

+Comment(s) on HER2 ISH Results# (Note C) (select all that apply)

 # Use appropriate comment when reporting ISH Groups 2-4 (or similar free text comment). See Note C for details.

___ This sample has a Group 2 HER2 ISH result (ratio greater than or equal to 2.0; less than 4.0 HER2 signals / cell). Evidence is limited on the efficacy of HER2-targeted therapy in the small subset of cases with HER2 / CEP17 ratio greater than or equal to 2.0 and an average HER2 copy number less than 4.0 / cell. In the first generation of adjuvant trastuzumab trials, patients in this subgroup who were randomized to the trastuzumab arm did not appear to derive an improvement in disease free or overall survival, but there were too few such cases to draw definitive conclusions. IHC expression for HER2 should be used to complement ISH and define HER2 status. If IHC result is not 3+ positive, it is recommended that the specimen be considered HER2 negative because of the low HER2 copy number by ISH and lack of protein overexpression.
___ This sample has a Group 3 HER2 ISH result (ratio less than 2.0; greater than or equal to 6.0 HER2 signals / cell). There are insufficient data on the efficacy of HER2-targeted therapy in cases with HER2 ratio less than 2.0 in the absence of protein overexpression because such patients were not eligible for the first generation of adjuvant trastuzumab clinical trials. When concurrent IHC results are negative (0 or 1+), it is recommended that the specimen be considered HER2 negative.
___ This sample has a Group 4 result (ratio less than 2.0; greater than or equal to 4.0 and less than 6.0 HER2 signals / cell). It is uncertain whether patients with greater than or equal to 4.0 and less than 6.0 average HER2 signals / cell and HER2 / CEP17 ratio less than 2.0 benefit from HER2 targeted therapy in the absence of protein overexpression (IHC 3+). If the specimen test result is close to the ISH ratio threshold for positive, there is a high likelihood that repeat testing will result in different results by chance alone. Therefore, when IHC results are not 3+ positive, it is recommended that the sample be considered HER2 negative without additional testing on the same specimen.
___ Other (specify): _____

METHODS

Cold Ischemia and Fixation Times
___ Meet requirements specified in latest version of the ASCO / CAP Guidelines
___ Do not meet requirements specified in latest version of the ASCO / CAP Guidelines (explain):
_____
___ Cannot be determined (explain): _____

+Cold Ischemia Time (Minutes)
___ Less than 60 minutes
___ Specify: _____ minutes
___ Other (specify): _____
___ Not known

+Fixation Time (Hours): _____ hours

+Fixative (select all that apply)
___ Formalin
___ Decalcification
___ Other (specify): _____

+Comment(s) on Fixation (select all that apply)
___ This assay has not been validated on decalcified tissues. Results should be interpreted with caution given the possibility of false negative results on decalcified specimens.
___ Other (specify): _____

ER Testing Methodology

ER Test Type (required only if applicable)
___ Not applicable
___ Food and Drug Administration (FDA) cleared (specify test / vendor): _____
___ Laboratory-developed test
+___ Non-U.S.-based health systems
+___ Health Canada Approved (specify test / vendor): _____
+___ Other (specify): _____

ER Primary Antibody (required only if applicable)
___ Not applicable
___ SP1
___ 6F11
___ 1D5
___ Other (specify): _____

PgR Testing Methodology

PgR Test Type (required only if applicable)

___ Not applicable
___ Food and Drug Administration (FDA) cleared (specify test / vendor): _____
___ Laboratory-developed test
+___ Non-U.S.-based health systems
+___ Health Canada Approved (specify test / vendor): _____
+___ Other (specify): _____

PgR Primary Antibody (required only if applicable)
___ Not applicable
___ 1E2
___ 636
___ 16
___ 1A6
___ 1294
___ 312
___ Other (specify): _____

HER2 IHC Testing Methodology

HER2 IHC Test Type (required only if applicable)
___ Not applicable
___ Food and Drug Administration (FDA) cleared (specify test / vendor): _____
___ Laboratory-developed test
+___ Non-U.S.-based health systems
+___ Health Canada Approved (specify test / vendor): _____
+___ Other (specify): _____

HER2 IHC Primary Antibody (required only if applicable)
___ Not applicable
___ 4B5
___ HercepTest
___ A0485
___ SP3
___ CB11
___ Other (specify): _____

HER2 ISH Testing Methodology

HER2 ISH Test Type (required only if applicable)
___ Not applicable
___ Food and Drug Administration (FDA) cleared (specify test / vendor): _____
___ Laboratory-developed test
+___ Non-U.S.-based health systems
+___ Health Canada Approved (specify test / vendor): _____
+___ Other (specify): _____

Ki-67 Primary Antibody (required only if applicable)
___ Not applicable (not performed)
___ MIB1
___ SP6
___ MM1
___ 30-9
___ IR / IS626
___ Other (specify): _____

+Image Analysis
___ Not performed
___ Performed
+Specify Method: _____
+Biomarkers Scored by Image Analysis (select all that apply)
___ ER
___ PgR
___ HER2 by IHC
___ HER2 by ISH
___ Ki-67
___ Other (specify): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Biomarker Testing on Breast Cancer Samples: General Principles

It is recommended that standardized hormone receptor and HER2 testing be done on all primary invasive breast carcinomas and on recurrent or metastatic tumors to determine overall treatment pathways and specific therapy options (see notes B and C). Ki-67 testing of invasive carcinoma is optional but is included in the reporting template (see note D).

For ductal carcinoma in situ (DCIS) samples (including encapsulated papillary carcinoma and solid papillary carcinoma in situ) without invasion, ER testing is recommended to determine potential benefit of endocrine therapies for local recurrence risk reduction. PgR testing of DCIS is considered optional and HER2 testing is not currently recommended (other than when used for diagnostic purposes).

Core needle biopsy samples are preferred for breast cancer biomarker testing at primary diagnosis for initial treatment planning. If hormone receptors and HER2 are negative on a core biopsy or initial results need confirmation, repeat testing on a subsequent specimen can be considered, particularly when the initial results are close to a threshold, unusual or discordant with the histopathologic findings (such as an ER negative or HER2 positive result on a grade 1 invasive carcinoma; **See Table 1 below**). When multiple invasive foci are present, the largest invasive focus should be tested. Testing smaller invasive carcinomas is also recommended if they are of different histologic type or higher grade.

Biomarker testing can be performed on cytology specimens if there is certainty the sample represents invasive breast cancer, such as a positive lymph node or other metastatic site, or rarely when a primary core biopsy is clinically contraindicated. Cell blocks fixed in formalin are preferred. Biomarker results on cytology samples may need confirmation on a subsequent histology sample if there are concerns about the sample adequacy or quality of results.

Fresh tissue should not be used up on other special studies (e.g., RNA expression profiling or investigational studies) unless the invasive carcinoma is of sufficient size that histologic evaluation and ER, PgR, and HER2 assessment will not be compromised or will not be needed.

The specimen/block tested should be indicated when reporting results. If more than one cancer is present, this section should also specify what lesion was tested (e.g., “Block D5, R1 invasive ductal carcinoma”). Multiple breast cancer biomarker reporting templates may be used on one case to report results on different lesions. When there is both invasive cancer and DCIS, the hormone receptor status of the invasive cancer is priority to report but if negative, the clinical team may be interested in the ER status of the DCIS. The specific lesion being reported (DCIS vs invasion, etc.) should be clear.

The College of American Pathologists (CAP) and American Society of Clinical Oncology (ASCO) hormone receptor and HER2 testing in breast cancer guideline recommendations should be followed (see references below). These guidelines note that specific pre-analytic and analytic variables can affect test results and should be recorded so they are available to determine if they may have negatively affected test results. Such variables include cold ischemia time (time between tissue removal and initiation of fixation) and time of fixation. Alternatively, laboratories may record the time the specimen was removed from the patient and the time the specimen was placed in formalin. Both the time the tissue is removed from the patient and the time it is placed in fixative should be communicated to the processing laboratory.

These times are used to determine if the specimen meets requirements specified in latest version of the ASCO/CAP guidelines for cold ischemia time and fixation time. Reporting these times in the pathology report is optional.

If fixatives other than buffered formalin, decalcification, or any other treatment of the tissue that could potentially alter immunoreactivity are used, this should also be reported with information on whether the testing was validated in this setting. A standardized comment on decalcification is available in the fixative section the methods in the reporting template as well a free text option to report on any validation that has occurred.

Additional factors that may affect evaluation such as the specimen adequacy, status of controls (internal and external) and methodology such as primary antibody clone and regulatory status (FDA cleared versus laboratory-developed test) should also be included as relevant.

Information regarding assay validation or verification should be available in the laboratory. Any deviation(s) from the laboratory's validated methods should be recorded. Appropriate positive and negative controls should be used and evaluated.

Table 1: Correlation of ER and HER2 status with specific histologic features:

Histology	Expected staining	Considered unusual/possibly discordant
Low-grade invasive ductal or lobular carcinomas	Uniform ER staining HER2 negative for over-expression/amplification	Low or negative ER staining HER2 positive results
Pure mucinous, tubular, or cribriform carcinomas		
Low-grade forms of DCIS including encapsulated papillary carcinoma and solid papillary carcinoma in situ		
Adenoid cystic carcinomas and other salivary gland-like carcinomas of the breast Secretory carcinoma	Negative (or low) ER staining HER2 negative for over-expression/amplification	High percentages of ER staining HER2 positive results

Note: If a result is considered unusual and possibly discordant, additional steps should be taken to check the accuracy of the histologic type or grade as well as pre-analytic and analytic testing factors. Considering repeat testing and second reviews may be appropriate. If results appear valid, a report comment should note the findings are unusual and that future samples may be informative for additional testing to confirm results.

References for Note A are as follows:[1,2,3,4,5,6,7,8,9]

References

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology, Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Accessed Jan 22, 2025.
2. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *Arch Pathol Lab Med.* 2020 May;144(5):545-563.

3. Wolff AC, Hammond MEH, Allison KH, et al. HER2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *Arch Pathol Lab Med.* 2018;142(11):1364-1382.
4. Wolff AC, Somerfield MR, Dowsett M, Hammond MEH, Hayes DF, McShane LM, Saphner TJ, Spears PA, Allison KH. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Arch Pathol Lab Med.* 2023 Sep 1;147(9):993-1000. doi: 10.5858/arpa.2023-0950-SA. PMID: 37303228.
5. Goldsmith JD, Troxell ML, Roy-Chowdhuri S, et al. Principles of analytic validation of immunohistochemical assays: guideline update. *Arch Pathol Lab Med.* Published online.
6. Yildiz-Aktas IZ, Dabbs DJ, Bhargava R. The effect of cold ischemic time on the immunohistochemical evaluation of estrogen receptor, progesterone receptor, and HER2 expression in invasive breast carcinoma. *Mod Pathol.* 2012;25(8):1098-1105.
7. Arber JM, Arber DA, Jenkins KA, Battifora H. Effect of decalcification and fixation in paraffin-section immunohistochemistry. *Appl Immunohistochem.* 1996; 4:241-248.
8. Gorman BK, Kosarac O, Chakraborty S, et al. Comparison of breast carcinoma prognostic/predictive biomarkers on cell blocks obtained by various methods: Cellient, formalin and thrombin. *Acta Cytol* 2012;56(3):289-96.
9. Kumar SK, Gupta N, Rajwanshi A, Joshi K, Singh G. Immunochemistry for oestrogen receptor, progesterone receptor and HER2 on cell blocks in primary breast carcinoma. *Cytopathology* 2012 Jun;23(3):181-6. PMID: 21375607.

B. Estrogen Receptor and Progesterone Receptor Testing

Scientific rationale: Normal breast epithelial cells have receptors for estrogen and progesterone and proliferate under their influence. Luminal-type breast carcinomas have increased levels of these receptors and may be stimulated to grow by these hormones. Removal of endogenous hormones by oophorectomy or blocking hormonal action pharmaceutically (e.g., with tamoxifen or aromatase inhibitors) can slow or prevent tumor growth and prolong survival in cancers with hormone receptor expression.

Clinical rationale: Estrogen receptor status is determined both to predict which invasive breast cancer patients may benefit from hormonal therapy as well as to determine overall treatment pathways and risk reduction strategies. About 75% to 80% of invasive breast cancers are positive for ER (depending on the population tested), including almost all grade 1 cancers and most grade 2 cancers (see Table 1 expected vs usual ER results based on histology). Studies have shown a substantial survival benefit using endocrine therapies in patients with ER-positive cancers (and a lack of benefit in ER-negative cancers).

PgR expression is more variable than ER and may help stratify prognosis in ER positive invasive cancers (most of which are uniformly ER positive). PgR expression may also serve as an informal control for samples that test ER negative but PgR positive (raising consideration for false negative ER testing). Although controversial as a result category, confirmed ER-negative/PgR-positive samples may be a rare biologic phenotype that may be offered endocrine therapies, although due to the rarity of this result group, there are limited data to support this.

For DCIS without invasion, ER testing is used to determine potential benefit from endocrine therapies for local recurrence risk reduction. PgR testing of DCIS is considered optional.

Method: Hormone receptor status should be determined in formalin-fixed, paraffin-embedded tissue sections by immunohistochemistry (IHC). Only nuclear staining is considered positive. Use of single-gene expression assays are not recommended for the purpose of determining hormone receptor status.

Quality assurance: There are many tissue and technical variables that can affect test results, and the assays must be validated to ensure their accuracy. External proficiency testing surveys for ER and PgR are valuable tools to help ensure that assays perform as expected, and they are available from the CAP and other organizations.

Confirmation of ER negative or Low Positive (1-10%) results*:* False negative or lower than expected results may occur if specimen handling was inadequate, if artifacts (crush or edge artifacts) make interpretation difficult, or if the analytic testing failed. When considering negative or Low Positive results, guidelines recommend a standard operating procedure be established to confirm the result. This should include evaluation of appropriate internal and external controls to ensure the assay is not “false negative” or falsely low.
If the internal controls are also negative, the test should not be reported as negative but should be considered indeterminate (“Cannot be determined”). The test should be repeated on another block or specimen.

When a cancer is negative or Low Positive (1-10%) but no internal control cells are present in the test section, the pathologist must exercise judgment as to whether the assay can be interpreted as a true negative or Low Positive result. This should include consideration of histologic type and grade, cold ischemia and fixation times, and the status of external controls. Second reviews by another pathologist may be helpful to establish consensus.

Standardized reporting comments for ER can be used (as well as free text ones) to describe the specific scenario and communicate the certainty of the results.

Potential reasons for false-negative results include the following:

- Exposure of tumor cells to heat (e.g., carcinomas transected by using cautery during surgery)
- Prolonged cold ischemic time, which may result in antigenic degradation. One hour or less is preferable.
- Under or overfixation; fixation for at least 6 hours in buffered formalin is recommended, and prolonged fixation can also diminish immunoreactivity.
- Type of fixative: ER is degraded in acidic fixatives such as Bouin’s and B-5; formalin should be buffered to ensure pH range between 7.0 and 7.4
- Decalcification, which may result in loss of immunoreactivity
- Nonoptimized antigen retrieval
- Type of antibody
- Dark hematoxylin counterstain obscuring faintly positive diaminobenzidine (DAB) staining

False-positive results: False-positive results occur less frequently. Rare reasons would be the use of an impure antibody that cross-reacts with another antigen or misinterpretation of entrapped normal cells or an in situ component as invasive carcinoma. False-positive tests can also be generated by image analysis devices that mistakenly count overstained nuclei. It has been suggested that highly sensitive assays may detect very low levels of ER in cancers that will not respond to hormonal therapy, but that has not been proven by a clinical trial. A false positive PgR assay is also a consideration in the setting of confirmed ER negative results.

False-negative and false-positive results can be reduced by paying attention to the following:

- Staining of normal breast epithelial cells. Normal epithelial cells serve as a positive internal control and should always be assessed. If the normal cells are negative, repeat studies on the same specimen or on a different specimen should be considered. If normal cells are not present (e.g., core biopsy) and the test results are negative, testing may be repeated on another block or subsequent specimen.
- External controls (must stain as expected). These controls help ensure that the reagents have been appropriately dispensed onto the slide with the clinical sample. Ideally, external ER controls should include negative and positive samples as well as samples with lower percentages of ER expression (such as tonsil). On-slide external controls are recommended when feasible.
- Correlation with histologic type and grade of the cancer. The study should be repeated if the results are discordant (e.g., ER-negative low-grade carcinoma). See **Table 1** above.

Reporting guidelines: CAP/ASCO have issued recommendations for reporting the results of immunohistochemical assays for ER and PgR. Carcinomas with <1% positive cells are considered negative for ER and PgR since there is no evidence of endocrine therapy benefit in this group. However, ER expression as low as 1% positive staining has been associated with clinical response to endocrine treatment. As a result, the guidelines recommend considering all cases with at least 1% ER positive cells as eligible for endocrine treatment. However, cancers with only 1-10% ER expression may behave in other ways more similar to ER negative cancers (e.g., high-grade, basal like gene expression profiles and better response to neoadjuvant chemotherapy).

The ER reporting categories are detailed in **Table 2** below. Cancers with ≥ 10% ER nuclear staining are reported as Positive and the percent and intensity of staining is included in the report. Cases with low ER expression in the 1-10% range should be reported as ER Low Positive with a recommended report comment about the limitations of the data in this group. This reporting comment is available in the reporting template to add in standardized form in the “Comments on ER Results” section. The Low Positive result reporting category applies only to invasive carcinoma and is not required for PgR or DCIS reporting and should only represent a small minority of invasive breast cancers (< 5-10%). Cancers with < 1 % cells staining are reported as Negative.

The status of controls should also be reported for ER Low Positive and negative results. If internal controls are not present but external controls are appropriate, a reporting comment about possible future confirmatory testing is recommended. These reporting comments are available in the reporting template to add in standardized form in the “Comments on ER Results” section.

Table 2. Reporting Results of Estrogen Receptor (ER) Testing

ER Result Category	Criteria	Comments
Positive	≥10% of tumor cell nuclei immunoreactive	Include in report the overall percent cancer cells staining as a range or specific number. Intensity of staining is reported semi-quantitatively as an average (1+, 2+ or 3+).
Low Positive	1-10% of tumor cell nuclei are immunoreactive	The following report comment is recommended and is available to add in standardized form in the "Comments on ER Results" section: "The cancer in this sample has a low level (1-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with low level (1-10%) ER expression, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER negative cancers." The Low Positive designation applies only to invasive carcinoma and is not required for Progesterone receptor or DCIS. Include the status of internal controls in report. If internal controls are absent but external controls stain appropriately, include recommended comment: "No internal controls are present, but external controls are appropriately positive. If needed, testing another specimen that contains internal controls may be warranted for confirmation of ER status. "
Negative	<1% of tumor cell nuclei immunoreactive	Include the status of internal controls in report. If internal controls are absent but external controls stain appropriately, include recommended comment: "No internal controls are present, but external controls are appropriately positive. If needed, testing another specimen that contains internal controls may be warranted for confirmation of ER status. "

Quantification of ER and PgR: There is a wide range of receptor levels in cancers as shown by the biochemical ligand binding assay and as observed with IHC. Patients whose carcinomas have higher levels have improved survival when treated with hormonal therapy.

While there are different quantification systems such as Allred Scores and H-scores that may be included in reports (under Alternative Scoring System Scores) these are optional, and all reports should include the percentage of positive cells and semi-quantitative intensity score per CAP/ASCO guidelines.

- Percentage of positive cells: The number of positive cells can be reported as a specific percentage or within discrete percentage categories (**Figure 1** below).
- Intensity: Refers to degree of nuclear positivity (i.e., pale to dark) and is scored in a semi-quantitative manner such that weak is 1+, moderate is 2+ and strong is 3+. The average intensity is included in the report. The intensity can be affected by the amount of

protein present, as well as the antibody used and the antigen retrieval system, therefore, only the overall percentage is used to determine the result category.

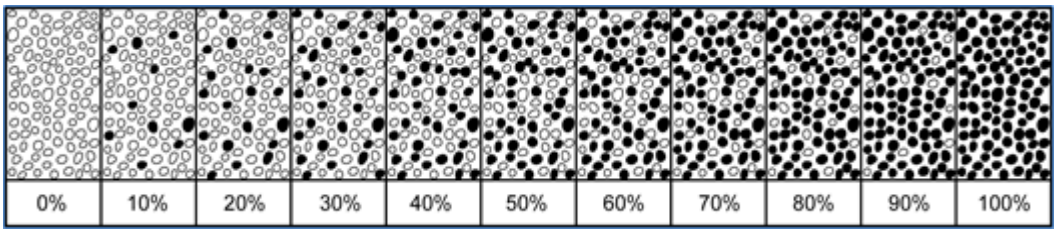

Figure 1. Quantification of Immunohistochemical Findings. The percentage of positive cells can be visually estimated.

References for Note B are as follows:[1,2,3,4,5]

References

1. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *Arch Pathol Lab Med.* 2020 May;144(5):545-563.
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C. HER2 (ERBB2) Testing

Scientific rationale: A subset of breast carcinomas overexpress human epidermal growth factor receptor 2 (HER2; HUGO nomenclature *ERBB2*) due to gene amplification (ranging from 10-20% depending on the population tested). This subset of breast cancers are considered a distinct subtype with aggressive behavior and biology, and are oncologically driven by their HER2 over-expression/amplification. Rarely, HER2 protein overexpression may occur by different mechanisms such as an activating gene mutation.

Clinical rationale: HER2 status is both a prognostic and predictive biomarker in breast cancer. Clinical guidelines such as NCCN utilize HER2 status both to determine overall treatment pathways because of its prognostic relevance and use it predictively to determine patient eligibility for approved anti-HER2 therapies.

Most anti-HER2 therapies, such as monoclonal antibodies and antibody-drug-conjugates are approved only in HER2 positive breast cancers, as defined by 3+ protein over-expression/gene amplification. Therefore, accurate testing to discriminate HER2 positive verses negative breast cancers is essential for primary and metastatic breast cancers and is the main focus of HER2 testing guidelines and proficiency testing.

However, more recently one HER2 antibody-drug-conjugate (trastuzumab-deruxtecan) was approved for treating metastatic breast cancers that have non-overexpressed levels of HER2 by IHC. Although not yet considered a predictive test in this setting, in the DESTINY-Breast04 trial, HER2 IHC results of IHC 1+ or IHC 2+/ISH negative (termed “HER2 Low” in the trial) were used for clinical trial eligibility and are now approved to determine which metastatic patients may be eligible for this treatment. DESTINTY-Breast06 has also been published with similar results that include metastatic breast cancers with IHC Score 0 but with “membrane staining that is incomplete and is faint/barely perceptible and in less than or equal to 10% of tumor cells” (termed “HER2 ultralow” in the trial). In order to identify these results in CAP Breast Cancer Biomarker reporting, the HER2 IHC Score 0 category is further detailed as either “no staining (0/absent membrane staining)” or “membrane staining that is incomplete and faint/barely perceptible and in less than or equal to 10% of tumor cells” (0+/with membrane staining). These are the same two staining pattern definitions used for the IHC Score 0 in the CAP/ASCO HER2 testing in breast cancer 2018 and 2023 guidelines updates.

Methods: HER2 status can be determined in formalin-fixed paraffin-embedded tissue by assessing protein expression on the membrane of cancer cells using IHC or by assessing the number of HER2 gene copies using in situ hybridization (ISH). When both IHC and ISH are performed on the same tumor, the results should be correlated. The most likely reason for a discrepancy is that one of the assays is incorrect, but in a small number of cases there may be protein overexpression without amplification, amplification without protein overexpression, or intratumoral heterogeneity. In addition, ISH results close to a threshold for positive are more likely to be discrepant with IHC.

HER2 (ERBB2) Testing by Immunohistochemistry
Factors altering the detection of HER2 (ERBB2) by IHC have not been studied as well as for ER and PgR. It is recommended that tissue be fixed in buffered 10% formalin for at least 6 hours unless another fixative has been validated. External proficiency testing surveys for HER2 are available from the CAP and other organizations. These surveys are invaluable tools to ensure that the laboratory assays are working as expected.

False-positive IHC results for HER2 may be due to:

- Edge artifact. This is usually seen in core biopsies, where cells near the edges of the tissue stain stronger than in the center, possibly because antibody pools at the sides. Specimens with stronger staining at the edge of the tissue should be interpreted with caution.
- Cytoplasmic positivity, which can obscure membrane staining and make interpretation difficult.
- Overstaining (strong membrane staining of normal cells). May be due to improper antibody titration (concentration too high).
- Misinterpretation of ductal carcinoma in situ (DCIS). High-grade DCIS is often HER2 positive. In cases with extensive DCIS relative to invasive carcinoma (particularly

microinvasive carcinoma), HER2 scoring may mistakenly be done on the DCIS component. Care must be taken to score only the invasive component.

False-negative IHC results for HER2 may be due to:

1. Prolonged cold ischemia time.
2. Tumor heterogeneity. When a negative result is found, but only a small biopsy sample was tested, repeat testing on a subsequent specimen with a larger area of carcinoma should be considered, particularly if the tumor has characteristics associated with HER2 positivity (i.e., tumor grade 2 or 3, weak or negative PgR expression, increased proliferation index).
3. Improper antibody titration (concentration too low)

False-negative and false-positive results can be reduced by paying attention to the following:

- Tissue controls. External controls must stain as expected. There are no normal internal controls for HER2 protein assessment by IHC.
- Correlation with histologic and other biomarker results. See Table 1 above.

Reporting guidelines: CAP and ASCO have issued recommendations for reporting the results of HER2 testing by IHC (**Table 4**). The definitions of staining patterns in each score category are now included in the reporting templates as well as some less common staining patterns that guidelines specify should be classified as IHC equivocal (2+) or heterogeneous.

An optional standardized HER2 IHC reporting comment can be used to indicate to clinical teams the specific HER2 IHC result categories that were defined as “HER2 Low“ and “HER2 ultralow” in the DESTINY-Breast 04 and 06 trials (see Comment on HER2 IHC section of template).

Table 4. Reporting Results of HER2 Testing by Immunohistochemistry (IHC)

Result Category	Criteria
Negative (Score 0 or 0+)#	No staining observed (0/absent membrane staining) *or* Membrane stating that is incomplete and is faint/barely perceptible and within ≤10% of tumor cells (0+/with membrane staining)
Negative (Score 1+)#	Incomplete membrane staining that is faint/barely perceptible and within >10% of tumor cells
Equivocal (Score 2+)#†	Weak to moderate complete membrane staining in >10% of tumor cells *or* Complete membrane staining that is intense but within ≤10% of tumor cells*
Positive (Score 3+)	Complete membrane staining that is intense and >10% of tumor cells*

* Readily appreciated using a low-power objective and observed within a homogeneous and contiguous population of invasive tumor cells.

† Additional less common staining patterns such as moderate to intense but incomplete membrane staining (basolateral) are also categorized as Score 2+. Equivocal 2+ results should reflex to testing to determine final HER2 status (same specimen using ISH) or order a new test (new specimen if available, using IHC or ISH).

An optional standardized reporting comment for HER2 0, 0+, 1+ or 2+ IHC results can be included as follows: “In the DESTINY-Breast 04 and 06 trials, “HER2 low” was considered IHC Score 1+ or 2+/ISH negative, and “HER2 ultralow” was HER2 IHC Score of 0 (pattern 0+) with membrane staining that is incomplete and faint/barely perceptible in less than or equal to 10% of tumor cells. Breast cancers with these staining patterns may be eligible for treatment with trastuzumab-deruxtecan in the metastatic setting (but those with no staining, IHC 0, are currently excluded).”

Heterogeneity for HER2 over-expression is rare in breast cancers. When 3+ over-expression is not uniform but present as distinct clustered separate populations in a non-over-expressed background, the case is reported as Positive (3+) if the population is > 10% and the Clustered Heterogeneity section of the reporting template is used to clarify the percentage of the invasive cancer in the sample with over-expression. The IHC Score of the Non-3+ areas is also reported. If ISH testing will be performed, it should be scored in the area with 3+ IHC staining, with a separate count in the IHC negative or equivocal areas rather than averaged over both. In the even more uncommon scenario of less than or equal to 10% 3+ staining in a clustered pattern, the result is interpreted as HER2 equivocal (2+) with indication of this specific staining pattern and consideration for testing additional samples. Other uncommon staining scenarios may exist, and the Other (specify) category and/or Comments section can be used to describe these.

HER2 Testing by In Situ Hybridization
Fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), and silver-enhanced in situ hybridization (SISH) studies for *HER2* determine the presence or absence of gene amplification. The average of HER2 gene signals as well as the central chromosome enumeration probe (CEP17 or other) and the ratio of HER2 signals to copies of chromosome 17 are used to determine result categories. Single probe testing is no longer recommended.
Failure to obtain results with ISH may be due to the following:

- Prolonged fixation in formalin (>1 week)
- Fixation in non-formalin fixatives
- Procedures or fixation involving acid (e.g., decalcification) may degrade DNA
- Insufficient protease treatment of tissue

External proficiency testing surveys for HER2 by ISH are available from CAP and other organizations. These surveys are invaluable tools to ensure that the laboratory assays are working as expected.

Reporting guidelines: ASCO and CAP have issued recommendations for reporting the results of HER2 testing by ISH (**Table 5**).

Dual Probe ISH Group Definitions:
Group 1 = HER2/CEP17 ratio ≥2.0; ≥4.0 HER2 signals/cell

Group 2 = HER2/CEP17 ratio ≥2.0; <4.0 HER2 signals/cell

Group 3 = HER2/CEP17 ratio <2.0; ≥6.0 HER2 signals/cell

Group 4 = HER2/CEP17 ratio <2.0; ≥4.0 and <6.0 HER2 signals/cell

Group 5 = HER2/CEP17 ratio <2.0; <4.0 HER2 signals/cell

Table 5. Reporting Results of *HER2* Testing by In Situ Hybridization (dual-probe assay)

Result	Criteria (dual-probe assay)
Negative	· Group 5
Negative based on IHC and ISH results* (see comment)	· Group 2 and concurrent IHC 0-1+ or 2+ · Group 3 and concurrent IHC 0-1+ · Group 4 and concurrent IHC 0-1+ or 2+
Positive based on concurrent IHC and ISH results* (see comment)	· Group 2 and concurrent IHC 3+ · Group 3 and concurrent IHC 2+ or 3+ · Group 4 and concurrent IHC 3+
Positive	· Group 1

*For Groups 2-4 final ISH results are based on concurrent review of IHC, with recounting of the ISH test by a second reviewer if IHC is 2+ (per 2018 CAP/ASCO Update recommendations).

Standardized guidelines comments for the Group 2-4 ISH results are available to add to reports in the Comments on HER2 ISH Results section and are as follows:

Comment for Group 2 result: *This sample has a Group 2 HER2 ISH result (ratio greater than or equal to 2.0; less than 4.0 HER2 signals / cell) Evidence is limited on the efficacy of HER2-targeted therapy in the small subset of cases with HER2/CEP17 ratio ≥2.0 and an average HER2 copy number <4.0/cell. In the first generation of adjuvant trastuzumab trials, patients in this subgroup who were randomized to the trastuzumab arm did not appear to derive an improvement in disease free or overall survival, but there were too few such cases to draw definitive conclusions. IHC expression for HER2 should be used to complement ISH and define HER2 status. If IHC result is not 3+ positive, it is recommended that the specimen be considered HER2 negative because of the low HER2 copy number by ISH and lack of protein overexpression.*

Comment for Group 3 result: *This sample has a Group 3 HER2 ISH result (ratio less than 2.0; greater than or equal to 6.0 HER2 signals / cell). There are insufficient data on the efficacy of HER2-targeted therapy in cases with HER2 ratio <2.0 in the absence of protein overexpression because such patients were not eligible for the first generation of adjuvant trastuzumab clinical trials. When concurrent IHC results are negative (0-1+), it is recommended that the specimen be considered HER2 negative.*

Comment for Group 4 result: *This sample has a Group 4 result (ratio less than 2.0; greater than or equal to 4.0 and less than 6.0 HER2 signals / cell). It is uncertain whether patients with ≥4.0 and <6.0 average HER2 signals/cell and HER2/CEP17 ratio <2.0 benefit from HER2 targeted therapy in the absence of protein overexpression (IHC 3+). If the specimen test result is close to the ISH ratio threshold for positive, there is a high likelihood that repeat testing will result in different results by chance alone. Therefore, when IHC results are not 3+ positive, it is recommended that the sample be considered HER2 negative without additional testing on the same specimen.*

Important issues in interpreting ISH are the following:

- Identification of invasive carcinoma: A pathologist should identify on the hematoxylin and eosin (H&E) or HER2 IHC slide the area of invasive carcinoma to be evaluated by ISH.
- Identification of associated DCIS: In some cases, DCIS will show gene amplification, whereas the associated invasive carcinoma will not. ISH analysis must be performed on the invasive carcinoma.
- Use of HER2 IHC to guide areas to score in heterogeneous cases.

Distinct clustered areas of HER2 amplification typically match areas of increased IHC expression and are considered heterogenous. This is rare, but when identified can be reported as a percentage of the cell population HER2 amplified by ISH with the concurrent IHC results. Complex cases can be described in report sections for descriptions of the heterogeneity present.

References for Note C are as follows:[1,2,3,4,5]

References

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology, Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Accessed Jan 22, 2025.
2. Wolff AC, Hammond MEH, Allison KH, et al. HER2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *Arch Pathol Lab Med.* 2018;142(11):1364-1382.
3. Wolff AC, Somerfield MR, Dowsett M, Hammond MEH, Hayes DF, McShane LM, Saphner TJ, Spears PA, Allison KH. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Arch Pathol Lab Med.* 2023 Sep 1;147(9):993-1000.
4. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med* 2022;387(1):9–20.
5. Bardia A, Hu X, Dent R, et al. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. *N Engl J Med.* 2024 Dec 5;391(22):2110-2122.

D. Ki-67 Testing

Ki-67 is a nuclear protein found in all phases of the cell cycle and is a marker of cell proliferation. The monoclonal antibody MIB-1 is the most commonly used antibody for assessing Ki-67 in formalin-fixed paraffin-embedded tissue sections. The percentage of Ki-67 positive cancer cells determined by IHC is used to provide additional data on the proliferation rate of the cancer and as a correlate with the overall grade. It is incorporated into some prognostic scoring schemes and sometimes used in neoadjuvant treatment trials to determine if proliferation decreases with treatment. However, Ki-67 proliferative rates have not been validated as a predictive biomarker. Currently, routine testing of breast cancers for Ki-67 expression is not standard by either ASCO or the National Comprehensive Cancer Network (NCCN). However, it may be reported as an additional data element in breast cancer characterization and reporting. Using a standardized approach to scoring, such as that recommended by the International Ki-67 in Breast Cancer Working Group, can be useful. The Ki-67 proliferation index can be reported either as a discrete numerical percentage or as a range.

References for Note D are as follows:[1,2]
References

1. Dowsett 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.
2. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in Breast Cancer: Updated Recommendations from the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst.* 2021 Jul 1;113(7):808-819. doi: 10.1093/jnci/djaa201. PMID: 33369635; PMCID: PMC8487652.