

Breast

Protocol applies to all invasive carcinomas of the breast.

*Protocol revision date: January 2004
Based on AJCC/UICC TNM, 6th edition*

Procedures

- **Cytology** (No Accompanying Checklist)
- **Biopsy (Incisional, Core Needle)** (No Accompanying Checklist)
- **Complete Excision Less Than Total Mastectomy (With or Without Axillary Contents)**
- **Mastectomy (Total, Modified Radical, Radical)**

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Surgical Pathology Cancer Case Summary (Checklist)

*Protocol revision date: January 2004
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition*

**BREAST: Excision Less Than Total Mastectomy (Includes
Wire-Guided Localization Excisions), Total Mastectomy,
Modified Radical Mastectomy, Radical Mastectomy**

Patient name:

Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC**Specimen Type**

- Excision
 Mastectomy
 Other (specify): _____
 Not specified

Lymph Node Sampling

- No lymph node sampling
 Sentinel lymph node(s) only
 Sentinel lymph node with axillary dissection
 Axillary dissection

Specimen Size (for excisions less than total mastectomy)

Greatest dimension: ___ cm

*Additional dimensions: ___ x ___ cm

Cannot be determined (see Comment)

Laterality

- Right
 Left
 Not specified

Tumor Site (check all that apply)

- Upper outer quadrant
 Lower outer quadrant
 Upper inner quadrant
 Lower inner quadrant
 Central

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CAP Approved

Breast

___ Not specified

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MICROSCOPIC**Size of Invasive Component**

Greatest dimension: ___ cm

*Additional dimensions: ___ x ___ cm

___ Cannot be determined (see Comment)

Note: The size of the tumor, as measured by gross examination, must be verified by microscopic examination. If there is a discrepancy between gross and microscopic tumor measurement, the microscopic measurement of the invasive component takes precedence and should be used for tumor staging.

Histologic Type (check all that apply)

- ___ Noninvasive carcinoma (NOS)
- ___ Ductal carcinoma in situ
- ___ Lobular carcinoma in situ
- ___ Paget disease without invasive carcinoma
- ___ Invasive carcinoma (NOS)
- ___ Invasive ductal carcinoma
- ___ Invasive ductal carcinoma with an extensive intraductal component
- ___ Invasive ductal carcinoma with Paget disease
- ___ Invasive lobular
- ___ Mucinous
- ___ Medullary
- ___ Papillary
- ___ Tubular
- ___ Adenoid cystic
- ___ Secretory (juvenile)
- ___ Apocrine
- ___ Cribriform
- ___ Carcinoma with squamous metaplasia
- ___ Carcinoma with spindle cell metaplasia
- ___ Carcinoma with cartilaginous/osseous metaplasia
- ___ Carcinoma with metaplasia, mixed type
- ___ Other(s) (specify): _____
- ___ Carcinoma, type cannot be determined

Histologic Grade (any grading system may be used; mitotic count is also required independent of the grading system)Nottingham Histologic Score

(If not used, see Other Grading System below)

Tubule Formation

- Majority of tumor greater than 75% (score = 1)
 Moderate 10% to 75% (score = 2)
 Minimal less than 10% (score = 3)

Nuclear Pleomorphism

- Small regular nuclei (score = 1)
 Moderate increase in size, etc (score = 2)
 Marked variation in size, nucleoli, chromatin clumping, etc (score = 3)

*Mitotic Count (for those using Nottingham system)*For a 25x objective with a field area of 0.274 mm²

- Less than 10 mitoses per 10 HPF (score = 1)
 10 to 20 mitoses per 10 HPF (score = 2)
 Greater than 20 mitoses per 10 HPF (score = 3)

or

For a 40x objective with a field area of 0.152 mm²

- 0 to 5 mitoses per 10 HPF (score = 1)
 6 to 10 mitoses per 10 HPF (score = 2)
 Greater than 10 mitoses per 10 HPF (score = 3)

Total Nottingham Score

- Grade I: 3-5 points
 Grade II: 6-7 points
 Grade III: 8-9 points
 Score cannot be determined

Other Grading System

Specify grading system: _____

- Grade 1
 Grade 2
 Grade 3
 Grade cannot be determined

Mitotic Count (for those using other grading systems)

- Number of mitoses per 10 HPF

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Pathologic Staging (pTNM)Primary Tumor (pT)

- ___ pTX: Cannot be assessed
- ___ pT0: No evidence of primary tumor
- ___ pTis: Ductal carcinoma in situ
- ___ pTis: Lobular carcinoma in situ
- ___ pTis: Paget disease without invasive carcinoma
- pT1: Tumor 2.0 cm or less in greatest dimension
- ___ pT1mic: Microinvasion 0.1 cm or less in greatest dimension
- ___ pT1a: Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
- ___ pT1b: Tumor more than 0.5 cm but not more than 1.0 cm in greatest dimension
- ___ pT1c: Tumor more than 1.0 cm but not more than 2.0 cm in greatest dimension
- ___ pT2: Tumor more than 2.0 cm but not more than 5.0 cm in greatest dimension
- ___ pT3: Tumor more than 5.0 cm in greatest dimension
- pT4: Tumor of any size with direct extension to chest wall or skin, but only as described below.#
- ___ pT4a: Extension to chest wall, not including pectoralis muscle
- ___ pT4b: Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
- ___ pT4c: Both T4a and T4b
- ___ pT4d: Inflammatory carcinoma

Clinical information may be required to designate a tumor as pT4. Dermal invasion alone (without ulceration, satellite nodules, or inflammatory breast cancer) does not alter T category. Such cases are classified as T1, T2, or T3, depending on tumor size.

Regional Lymph Nodes (pN) (choose a category based on data supplied with specimen; immunocytochemistry and molecular studies are not required)

- ___ pNX: Cannot be assessed (previously removed or not removed for pathologic study)
- ___ pN0 No regional lymph node metastasis histologically (ie, none greater than 0.2 mm), no examination for isolated tumor cells (ITCs)
- ___ pN0(i-) No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
- ___ pN0(i+) No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs, no ITC cluster greater than 0.2 mm
- ___ pN0(mol-) No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
- ___ pN0(mol+) No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs
- ___ pN1 Metastasis in 1 to 3 axillary lymph nodes, and/or internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent

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- pN1mi: Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
 pN1a: Metastasis in 1 to 3 axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm)
 pN1b: Metastasis in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
 pN1c: Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
 pN2a: Metastasis in 4 to 9 axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm)
 pN2b: Metastasis in clinically apparent internal mammary lymph nodes in the *absence* of axillary lymph node metastases
 pN3a: Metastasis in 10 or more axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
 pN3b: Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
 pN3c: Metastasis in ipsilateral supraclavicular lymph nodes
 Specify: Number examined: _____
 Number involved: _____

Distant Metastasis (pM)

- pMX: Cannot be assessed
 pM1: Distant metastasis
 *Specify site(s), if known: _____

Margins (check all that apply)

- Margins cannot be assessed
 Margins uninvolved by invasive carcinoma
 Distance from closest margin: _____ mm
 *Specify which margin: _____
 Margins uninvolved by DCIS (if present)
 Distance from closest margin: _____ mm
 *Specify which margin: _____
 Margin(s) involved by invasive carcinoma
 Specify which margin: _____
 Margin(s) involved by DCIS
 Specify which margin: _____

*Extent of Margin Involvement for Invasive Carcinoma

- * Cannot be assessed
 * Unifocal
 * Multifocal
 * Extensive
 * Other (specify): _____

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*Extent of Margin Involvement for DCIS

- * Cannot be assessed
- * Unifocal
- * Multifocal
- * Extensive
- * Other (specify): _____

***Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)**

- * Absent
- * Present
- * Indeterminate

***Microcalcifications (check all that apply)**

- * Not identified
- * Present in DCIS
- * Present in invasive carcinoma
- * Present in non-neoplastic tissue
- * Present in both tumor and non-neoplastic tissue

***Additional Pathologic Findings**

*Specify: _____

***Comment(s)**

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Background Documentation

Protocol revision date: January 2004

I. Cytologic Material

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information (Note A)
 - a. Relevant history
 - b. Physical or mammographic findings
 - c. Procedure (eg, fine-needle aspiration)
 - d. Anatomic site(s) of specimen(s) (eg, right breast, upper outer quadrant, subareolar)
 - e. Type(s) of specimen(s) (eg, nipple discharge, aspirate)

B. Macroscopic Examination

1. Specimen
 - a. Unfixed/fixed (specify fixative)
 - b. Number of slides received, if appropriate
 - c. Quantity and appearance of fluid specimen, if appropriate
 - d. Other (eg, cytologic preparation from tissue)
 - e. Results of intraprocedural consultation
2. Material submitted for microscopic evaluation (eg, smear; cytocentrifuge, touch, or filter preparation; other liquid based cytology preparations; cell block)
3. Special studies (specify)

C. Microscopic Evaluation

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor
 - a. Histologic type, if possible
 - b. Other features (eg, nuclear grade, necrosis)
3. Additional pathologic findings, if present
4. Results/status of special studies (specify)
5. Comments, as appropriate, including correlation with intraprocedural consultation, results of other specimens, and clinical information

II. Biopsy

(Incisional, Core Needle)

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)

3. Date of procedure
4. Other clinical information (Note **A**)
 - a. Relevant history
 - b. Physical or mammographic findings
 - c. Clinical diagnoses, if known
 - d. Procedure(s) (eg, percutaneous core biopsy, image-guided stereotactically guided core biopsy, incisional biopsy)
 - e. Operative findings, as appropriate
 - f. Anatomic site(s) of specimen(s) (eg, right breast, upper outer quadrant, subareolar)

B. Macroscopic Examination

1. Specimen(s)
 - a. Unfixed/fixed (specify fixative)
 - b. Size (3 dimensions, or number and size of cores/fragments)
 - c. Descriptive features (eg, color, consistency)
 - d. Other features (eg, prior biopsy site[s])
 - e. Results of intraoperative consultation
 - f. Single tumor or multiple tumors
2. Tissue submitted for microscopic evaluation
 - a. Submit entire specimen including tissue used for frozen section (unless saved for special studies)
3. Special studies (specify) (Note **B**)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type(s) (Note **C**)
 - b. Histologic grade (Note **D**)
 - c. Mitotic figure count
 - d. Extent of any associated ductal carcinoma in situ (DCIS) (Note **E**)
 - e. Microcalcifications (Note **F**)
 - f. Vascular invasion (Note **G**)
2. Result/status of special studies
 - a. Hormonal receptors
 - b. Other(s) (specify)
3. Additional pathologic findings, if present
4. Comments, as appropriate, including correlation with intraoperative consultation, results of other specimens, and clinical information

**III. Complete Excision of Tumor Less Than Total Mastectomy
(With or Without Axillary Contents;
Includes Wire-Guided [Localization] Excision)****A. Clinical Information**

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information (Note **A**)

- a. Relevant history
- b. Physical or mammographic findings
- c. Clinical diagnosis, if known
- d. Procedure (eg, excisional biopsy, lumpectomy, partial mastectomy, as specified by surgeon)
- e. Operative findings, as appropriate
- f. Anatomic site of specimen (eg, right breast, upper outer quadrant, subareolar)

B. Macroscopic Examination

1. Specimen
 - a. Unfixed/fixed (specify fixative)
 - b. Tissue(s) included
 - c. Received sectioned/unsectioned before receipt (Note **H**)
 - d. Size of specimen (3 dimensions, if removed in 1 piece)
 - e. Dimensions and description of skin, if included
 - f. Orientation, if specified by surgeon; and margin designation (eg, ink) (Note **I**)
 - g. Single tumor or multiple tumors
 - h. Results of intraoperative consultation
2. Tumor
 - a. Size (single greatest dimension) (Note **J**)
 - b. Descriptive features (eg, degree of circumscription, consistency, mucoid appearance)
 - c. Correlation with imaging studies, including specimen radiograph (Note **F**)
 - d. Relation to surgical margins (Note **I**)
3. Regional lymph nodes, if appropriate (Note **K**)
 - a. Number identified, if possible
 - b. Location, if specified by surgeon
 - c. Size of the largest visible nodal metastasis
4. Additional pathologic findings, if present (eg, prior biopsy, prosthetic implant, fibrocystic changes)
5. Tissue(s) submitted for microscopic evaluation (Note **L**)
 - a. Tumor (Notes **F** and **L**)
 - b. Margin(s), as appropriate (Note **I**)
 - c. Other lesion(s)
 - d. Lymph nodes (Note **K**)
 - e. Frozen section tissue fragment(s) (unless saved for special studies)
6. Special studies (specify) (Note **B**)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type(s) (Note **C**)
 - b. Histologic grade (Note **D**)
 - c. Mitotic figure count
 - d. Extent of any associated ductal carcinoma in situ (DCIS) (Notes **E** and **I**)
 - e. Microcalcifications (Note **F**)
 - f. Verification of tumor size (Notes **J** and **M**)
 - g. Extent of invasion (Note **M**)
 - h. Vascular invasion (Note **G**)

- i. Involvement of skin, if possible (Note **M**)
2. Status of surgical margins, as appropriate (Note **I**)
 - a. No tumor (specify distance of tumor and DCIS from nearest margin[s])
 - b. DCIS at margin
 - c. Invasive carcinoma at margin (specify margin) (specify macroscopic or only microscopic)
3. Additional pathologic findings, if present
4. Regional lymph nodes (Note **K**)
 - a. Total number examined (specify location, if indicated by surgeon)
 - b. Number involved by tumor (note extranodal extension, if present)
 - c. Size(s) of the largest nodal metastasis
5. Distant metastasis (specify site[s]) (Note **M**)
6. Results/status of special studies (specify) (Note **B**)
 - a. Hormonal receptors
 - b. Other(s) (specify)
7. Comments, as appropriate, including correlation with intraoperative consultation, results of other specimens, and clinical information

IV. Mastectomy

(Total, Modified Radical, Radical)

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information (Note **A**)
 - a. Relevant history
 - b. Physical or mammographic findings
 - c. Clinical diagnosis, if known
 - d. Procedure (eg, simple mastectomy, modified radical mastectomy)
 - e. Operative findings, as appropriate
 - f. Anatomic site of specimen (eg, right breast)

B. Macroscopic Examination

1. Specimen
 - a. Unfixed/fixed (specify fixative)
 - b. Tissue(s) included
 - c. Size of breast
 - d. Dimensions and description of skin
 - e. Location of biopsy site or tumor (eg, quadrant, relation to deep margin)
 - f. Single tumor or multiple tumors
 - g. Results of intraoperative consultation
2. Tumor
 - a. Size (single greatest dimension) (Note **J**)
 - b. Descriptive features (eg, degree of circumscription, consistency, mucoid appearance)
 - c. Relation to surgical margins (Note **I**)

3. Regional lymph nodes, if appropriate (Note **L**)
 - a. Number identified, if possible
 - b. Location, if specified by surgeon
 - c. Size of the largest visible nodal metastasis
4. Additional pathologic findings, if present (eg, prior biopsy, prosthetic implant, fibrocystic changes)
5. Tissues submitted for microscopic evaluation (Note **L**)
 - a. Tumor (Notes **F** and **L**)
 - b. Biopsy site, needle track, if identified
 - c. Margin(s), as appropriate
 - d. Nipple
 - e. Additional breast tissue (quadrants not involved by tumor)
 - f. Other lesions
 - g. Lymph nodes (Note **K**)
 - h. Frozen section tissue fragment(s) (unless saved for special studies)
6. Special studies (specify) (Note **B**)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type(s) (Note **C**)
 - b. Histologic grade (Note **D**)
 - c. Mitotic figure count
 - d. DCIS, if present (Note **E**)
 - e. Microcalcifications (Note **F**)
 - f. Verification of tumor size (Notes **J** and **M**)
 - g. Extent of invasion (Note **M**)
 - h. Vascular invasion (Note **G**)
 - i. Involvement of other tissues (eg, skin, chest wall) (Note **M**)
2. Regional lymph nodes, if appropriate (Note **K**)
 - a. Total number examined (specify location, if indicated by surgeon)
 - b. Number involved by tumor (note extranodal extension of tumor, if present)
 - c. Size(s) of the largest nodal metastasis
3. Additional pathologic findings, if present (specify)
4. Distant metastasis (specify site[s]) (Note **M**)
5. Results/status of special studies (specify) (Note **B**)
 - a. Hormonal receptors
 - b. Other(s)
6. Comments, as appropriate, including correlation with intraoperative consultation, results of other specimens, and clinical information

Explanatory Notes

A. Clinical Information

Elements of the history that are important for breast cancer include family history, previous therapeutic irradiation to the breast, history of collagen vascular disease, nipple discharge, previous biopsy or other treatment, and, especially, whether the patient is currently pregnant or nursing.¹ In order to ensure that mammographic abnormalities have been sampled and examined microscopically, the pathologist must correlate the histologic features with the physical and mammographic findings, such as

whether the lesion was palpable or detected only by imaging studies, whether suspicious microcalcifications were seen, or whether the tumor is solid or cystic.

B. Special Studies

Fresh tissue should not be used for special studies (eg, hormone receptor analysis by ligand binding assay) unless the neoplasm is of sufficient size such that histologic evaluation will not be compromised. When needed, hormone receptor analysis by immunohistochemistry and many other studies can be performed on routinely fixed, paraffin-embedded tissue. Besides a formal interpretation, each pathology report should specify the fixative used, if other than formalin; the antibody clone and vendor; and the results of control stains. Any deviation from the laboratory's standard staining and antigen retrieval protocol should be mentioned. The percentage of positive cells should also be mentioned when clinically relevant.

C. Histologic Type

This protocol applies to all carcinomas of the breast. The World Health Organization (WHO) classification of breast carcinoma is presented below, although the protocol does not preclude the use of other classifications or histologic types, such as that published in the Armed Forces Institute of Pathology Fascicle on breast tumors.^{2,3}

WHO Classification of Carcinoma of the Breast

Noninvasive carcinoma (NOS)

 Ductal carcinoma in situ

 Lobular carcinoma in situ

Invasive carcinoma (NOS)

 Invasive ductal carcinoma

 Invasive ductal carcinoma with an extensive intraductal component

 Invasive ductal carcinoma with Paget disease

 Invasive lobular[#]

 Mucinous^{##}

 Medullary^{###}

 Papillary[^]

 Tubular

 Adenoid cystic

 Secretory (juvenile)

 Apocrine

 Cribriform

 Carcinoma with metaplasia

 Squamous type

 Spindle cell type

 Cartilaginous and osseous type

 Mixed type

 Inflammatory (largely clinically defined; see Note **M**)

 Other(s) (specify)

[#] Classic invasive lobular carcinoma, which has a better prognosis than invasive carcinoma, NOS, is diagnosed only when the tumor exhibits a single file growth pattern, a monotonous population of small cells with very low grade nuclei, and low cell density. Tumors with a diffuse infiltrative growth pattern, which do not fulfill these criteria, should

be reported by histologic grade with the suffix “with lobular features” (or “lobular variant”). Such tumors are separately identified because this growth pattern has been associated with extensive intramammary growth and distinctive patterns of metastasis.

The diagnosis of pure mucinous carcinoma requires the presence of low-grade nuclei and extracellular mucin in at least 90% of the tumor. Tumors with less extensive mucin production should be classified as invasive ductal carcinoma with the suffix “with mucinous features” and graded.

The diagnosis of medullary carcinoma requires strict adherence to diagnostic criteria: a sharply circumscribed tumor border; high histologic grade with patternless, syncytial sheets of large, undifferentiated tumor cells; a substantial and diffuse lymphoplasmacytic infiltrate between cellular nests; and scant fibrous stroma. Tumors lacking all of these features should be classified as invasive ductal carcinoma and graded.

^ The diagnostic category of papillary carcinoma should always be qualified as to invasive or noninvasive.

D. Histologic Grade

All invasive breast carcinomas, with the exception of medullary carcinoma (as defined in Note E), should be graded. The grading system used must be specified in the report; the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is recommended.⁴⁻⁶ Grading of large core needle biopsies may be done when the quantity of tissue available is sufficient. Within each stage grouping there is a relation between histologic grade and outcome.⁷

The Nottingham combined histologic grade depends on the extent of tubule formation, the extent of nuclear pleomorphism, and the mitotic count. 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 (HPFs) in the most mitotically active part of the tumor. Only clearly identifiable mitotic figures (eg, cells in prophase, metaphase, or anaphase) should be counted; hyperchromatic, karyorrhectic, or apoptotic nuclei are excluded. Because of variations in field size, the high power field size must be determined for each microscope and the appropriate point score determined accordingly. Using a micrometer to measure the field diameter of the microscope is recommended.

The following tabulation⁵ relates to the use of 25x objective with a field diameter of 0.59 mm and a field area of 0.274 mm².

Feature	Score
Tubule formation	
Majority of tumor: greater than 75%	1
Moderate: 10% to 75%	2
Minimal: less than 10%	3
Nuclear pleomorphism	
Small regular nuclei	1
Moderate increase in size, etc	2

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Marked variation in size, nucleoli, chromatin clumping, etc	3
Mitotic count (see also below)	
Less than 10 mitoses per 10 HPF	1
10 to 20 mitoses per 10 HPF	2
Greater than 20 mitoses per 10 HPF	3

For a 40x objective with a field diameter of 0.44 mm (area = 0.152 mm²), the equivalent scoring of mitotic activity is as follows.

Feature	Score
0 to 5 mitoses per 10 HPF	1
6 to 10 mitoses per 10 HPF	2
Greater than 10 mitoses per 10 HPF	3

The total score is then added and the grade assigned as follows.

- Grade I: 3 to 5 points
- Grade II: 6 to 7 points
- Grade III: 8 to 9 points

E. Ductal Carcinoma In Situ

The following histologic features of ductal carcinoma in situ (DCIS) should be included in the pathology report⁸:

Nuclear Grade

- Grade 1: Monotonous nuclei, 1.5 to 2.0 RBC diameters, with finely dispersed chromatin and only occasional nucleoli.
- Grade 2: Neither nuclear grade 1 nor nuclear grade 3.
- Grade 3: Markedly pleomorphic nuclei, usually greater than 2.5 RBC diameters, with coarse chromatin and prominent or multiple nucleoli.

Presence or Absence of Necrosis**Architectural Pattern(s)**

- Comedo
- Cribriform
- Papillary
- Micropapillary
- Solid

Although not required for pT classification and stage assignment, the extent (size) of DCIS is an important factor in patient management. Mammographic assessment of DCIS, usually based on distribution of calcifications, frequently underestimates the size of DCIS.⁹ While precise measurement may be impossible on nonpalpable, grossly inapparent lesions, the pathologist should estimate the size or extent of DCIS and include this in the report. Methods for estimating the extent of DCIS include directly measuring the lesion when confined to a single histologic slide, determining size by submitting the entire specimen in sequence and in sections of uniform thickness, and estimating the percentage of tissue involved in relation to the total specimen.¹⁰

In breast carcinomas with both invasive and in situ components, the pathology report should specify whether an extensive intraductal component (EIC) is present. EIC is identified when DCIS comprises a substantial portion of the main tumor mass (approximately 25%) and extends into the surrounding breast parenchyma. Cases in which the lesion is primarily DCIS with foci of invasion are also classified as EIC.¹¹ This finding is associated with an increased risk of local recurrence when the surgical margins are not evaluated or focally involved.¹² The finding appears to have less significance when DCIS does not extend close to any of the margins following careful histologic evaluation.

F. Microcalcifications

If the biopsy is done for microcalcifications, their presence in the specimen must be confirmed by specimen radiography and microscopy. Ultimately, the pathologist must be satisfied that the lesion responsible for the calcifications is present in the specimen and that it has been examined microscopically. For biopsies showing calcifications, the relationship of the calcifications to the tumor 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 see if calcifications remain in the block(s). If microcalcifications cannot be confirmed by routine microscopic evaluation, polarized light may be helpful, since calcium oxalate crystals are birefringent but unstained in hematoxylin-eosin (H&E) sections. On rare occasions, calcifications do not survive tissue processing.

G. Vascular or Lymphatic Invasion

Peritumoral vascular invasion should be noted because it has been associated with local failure and reduced overall survival.^{13,14} Distinguishing lymphatic channels from blood vessels is unnecessary. While sometimes difficult to identify in skin biopsies, documenting the presence of dermal lymphatic invasion is particularly important because of its strong association with inflammatory breast carcinoma.¹⁵

H. Specimen Examination

It should be noted whether the tumor was sectioned prior to receipt, since this may preclude proper marking of the surgical margins of excision as well as ascertaining the dimensions of the specimen or tumor. Evaluation of margins does not apply to a diagnostic incisional biopsy.

I. Orientation and Identification of Surgical Margins

Whenever feasible, the specimen should be oriented so the pathologist can 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 (eg, superior, inferior, medial, lateral, deep). Identification of surgical margins also allows measurement of the distance between the tumor and specific margins. Data indicate that the most significant predictors of local control after breast conservation treatment with lumpectomy and radiation are the status of the surgical margins and the presence or absence of an extensive intraductal component (EIC).¹⁶ Correlating

mammograms with the pathologic findings and assessing surgical margins are particularly important in patients with EIC.¹⁷

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.

Macroscopic or microscopic involvement of surgical margins by invasive carcinoma or DCIS should be noted in the report. If the specimen is oriented, the specific site(s) of involvement (eg, superior) should also be reported. When possible, the pathologist should report the distance from the tumor to the closest margin. Blocking of tissue should be directed to evaluating the distance from the edge of the tumor to the resection margin, in addition to other sampling.

Specimen radiography with compression of the specimen should be reserved for nonpalpable lesions (eg, microcalcifications). Accurate assessment of the distance of tumor from the surgical margin may be compromised following mechanical compression.

J. Tumor Size

Tumor size is a major predictor of tumor behavior.¹⁸ The tumor should be measured in at least 2 dimensions, and the single greatest dimension of the invasive component used for determining tumor stage.⁶ The size of the tumor, as measured by gross examination, must be verified by microscopic examination. If there is a discrepancy between gross and microscopic tumor measurement, the microscopic measurement of the invasive component takes precedence and should be used for tumor staging. For pT1 lesions or those with an extensive in situ component, measurement of tumor size on the histologic slide is more accurate than gross measurement. For tumors with both invasive and in situ components, only the invasive component is included in the tumor measurement for pT classification and stage assignment (see Note **M**). When 2 or more distinct invasive tumors are present, each is separately measured and reported; they are not combined into a single larger size. Determination of tumor size may not be possible with a core or incisional biopsy.

K. Lymph Nodes

Grossly uninvolved nodes should be submitted in their entirety for histologic examination, while representative sections of grossly positive nodes may be submitted. Small nodes may be submitted intact, but larger nodes should be sectioned for proper fixation and examination.

The pathology report should clearly state the total number of lymph nodes examined, the total number of involved nodes, and the greatest dimension of the largest metastatic focus. A single microscopic section from each lymph node block is considered sufficient for routine evaluation. The presence of extranodal tumor extension should be included in the pathology report since it may be associated with a higher frequency of axillary recurrence.

Isolated tumor cells (ITCs) are defined as single cells or small clusters of cells not larger than 0.2 mm, usually with no histologic evidence of malignant activity (eg, proliferation or stromal reaction). If morphologic techniques (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) are used to detect ITCs, the regional lymph nodes should be designated as pN0(i+) or pN0(i-), as appropriate.¹⁹ If nonmorphologic (molecular) methods (eg, reverse transcriptase polymerase chain reaction [RT-PCR]) are used, the nodes are designated as pN0(mol-) or pN0(mol+), as appropriate.²⁰

Micrometastases are defined as tumor deposits larger than 0.2 mm but not larger than 2.0 mm. Cases in which only micrometastases are detected are classified as pN1mi. While the prognosis for patients with a solitary micrometastasis has been reported to be better than those with larger metastatic deposits, the significance of multiple micrometastases in 1 node or multiple lymph nodes with metastases of that size is unknown. These are still classified as pN1mi. The number of nodes that contain micrometastases should be clearly specified in the pathology report since this may affect treatment.

L. Specimen Sample

The number of sections submitted varies with the size and character of the specimen, the nature of the underlying neoplastic process, and whether the surgical margins need to be assessed. If the biopsy is performed because of a mammographic abnormality, the entire mammographic lesion (not necessarily the entire specimen) should be submitted, when practical. For excisions less than total mastectomy, blocking of tissue includes evaluating the resection margins.

M. TNM and Stage Groupings

The TNM staging system for carcinoma of the breast of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended and shown below.^{21,22} Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If other measurements, such as mammographic or pathologic, are used, the subsets of T1 can be used.

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease and whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) but the highest T and N categories or the M1 category of the tumor can be confirmed

microscopically, then the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Although the pathologist provides information about the individual pTNM categories based on examination of the surgical specimen, the referring physician usually has the responsibility for grouping the TNM categories into a stage of disease.

Primary Tumor (T)

TX	Primary tumor cannot be assessed [#]
T0	No evidence of primary tumor
Tis	Carcinoma in situ: ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), or Paget disease of the nipple with no tumor ^{##}
T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension ^{###}
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin, [^] but only as described below
T4a	Extension to chest wall, not including pectoralis muscle ^{^^}
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma ^{^^^}

[#] If tumor is present at the margin of the resection by macroscopic examination, the case is coded as pTX because the total extent of tumor cannot be assessed.

^{##} Paget disease associated with a tumor is classified according to the size of the tumor.

^{###} Microinvasion is extension of cancer cells beyond the basement membrane into adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion (do not use the sum of all the individual foci). The presence of multiple foci should be noted and/or quantified, as with multiple larger invasive carcinomas.

[^] Dermal invasion alone (without ulceration, satellite nodules, or inflammatory breast cancer) does not alter T category. Such cases are classified as T1, T2, or T3, depending on tumor size.

^{^^} Tumor in pectoral muscle should be measured with the breast tumor for determining tumor size and final T category.

^{^^^} Inflammatory carcinoma of the breast is a clinicopathologic entity characterized by diffuse erythema and edema involving the majority of the skin of the breast, often without an underlying palpable mass. The clinical presentation is due to tumor emboli in

dermal lymphatics, although these may not be seen on skin biopsy. The diagnosis is established by the combination of the clinical findings and a biopsy showing cancer, either within dermal lymphatics or in the breast parenchyma. Involvement of dermal lymphatics alone does not indicate inflammatory carcinoma. If the skin biopsy is negative and there is no localized measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

Regional Lymph Nodes (pN)[#]

pNX:	Cannot be assessed (previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs) ^{##}
pN0(i-)	No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+)	No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs, no ITC cluster greater than 0.2 mm
pN0(mol-)	No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
pN0(mol+)	No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs
pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent ^{###}
pN1mi:	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a:	Metastasis in 1 to 3 axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm)
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent ^{###}
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent. (If associated with more than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
pN2	Metastasis in 4 to 9 axillary lymph nodes <i>or</i> in clinically apparent ^{###} internal mammary nodes in the <i>absence</i> of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least 1 tumor deposit larger than 2.0 mm)
pN2b	Metastasis in clinically apparent ^{###} internal mammary nodes in the <i>absence</i> of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ^{###} ipsilateral internal mammary nodes in the <i>presence</i> of 1 or more positive axillary lymph nodes; <i>or</i> in more than

	3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary nodes or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least 1 tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent ^{###} ipsilateral internal mammary lymph nodes in the <i>presence</i> of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

There are instances when the pathologist cannot make this determination because the complete staging procedure, such as a lymph node dissection, has not been performed or because information about a prior procedure is unavailable. In such situations an “X” is used rather than a number in the TNM designation.

[#] Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary dissection is designated (sn) for “sentinel node,” eg, pN0(i+)(sn).

^{##} Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm. They may be detected by routine histologic examination or by immunohistochemical (IHC) or molecular methods. ITCs do not usually show evidence of malignant activity (eg, proliferation or stromal reaction).

^{###} *Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination. *Not clinically apparent* is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

[^] Micrometastases may show histologic evidence of malignant activity (eg, proliferation or stromal reaction).

Distant Metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1 [#]	N0	M0
Stage IIA	T0	N1	M0
	T1 [#]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1 [#]	N2	M0
	T2	N2	M0
	T3	N1	M0

	T3	N2	M0
Stage IIIB	T4	Any N	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

T1 includes T1mic.

TNM Descriptors

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

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 following 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 prior to 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.

The “a” prefix designates the stage determined at autopsy: aTNM.

Additional Descriptors

Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Vessel Invasion

By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of

a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows:

Lymphatic (Small Vessel) Invasion (L)

LX	Lymphatic vessel invasion cannot be assessed
L0	No lymphatic vessel invasion
L1	Lymphatic vessel invasion

Venous (Large Vessel) Invasion (V)

VX	Venous invasion cannot be assessed
V0	No venous invasion
V1	Microscopic venous invasion
V2	Macroscopic venous invasion

Regional Lymph Nodes (pN0): Isolated Tumor Cells

Isolated tumor cells (ITC) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITC found by either histologic examination, immunohistochemistry, or nonmorphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITC are the only evidence of possible metastatic disease.²⁰

pN0	No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
pN0(i-)	No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+)	No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(mol-)	No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
pN0(mol+)	No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs

Sentinel Lymph Nodes

The sentinel lymph node is the first node to receive drainage from a primary tumor. There may be more than 1 sentinel node for some tumors. If a sentinel node contains metastatic tumor, it indicates that other more distant nodes may also contain metastatic disease. If sentinel nodes are negative, other regional nodes are less likely to contain metastasis. Sentinel lymph nodes that have been examined for ITCs are denoted as follows:

pN0(sn)	No sentinel lymph node metastasis histologically (ie, none greater than 0.2 mm), no additional examination for isolated tumor cells (ITCs)
pN0(i-)(sn)	No sentinel lymph node metastasis histologically (ie, none greater than 0.2 mm), negative morphologic findings for ITCs
pN0(i+)(sn)	No sentinel lymph node metastasis histologically, positive morphologic findings for ITCs

- pN0(mol-)(sn) No sentinel lymph node metastasis histologically, negative nonmorphologic findings for ITCs
- pN0(mol+)(sn) No sentinel lymph node metastasis histologically, positive nonmorphologic findings for ITCs

References

1. Winchester DP, Cox JD, et al. Standards for diagnosis and management of invasive breast carcinoma. *CA Cancer J Clin.* 1998;48:83-107.
2. Rosen PP, Oberman HA. Tumors of the mammary gland. In: *Atlas of Tumor Pathology*. 3rd Series. Fascicle 7. Washington, DC: Armed Forces Institute of Pathology, American Registry of Pathology; 1993.
3. Histological typing of breast tumours. In: *International Classification of Tumours*. 2nd ed. Geneva, Switzerland: World Health Organization; 1981.
4. Bloom HJG, Richardson WW. Histological grading and prognosis in breast carcinoma: a study of 1049 cases of which 359 have been followed for 15 years. *Br J Cancer.* 1957;11:359-377.
5. Elston CW, Ellis JO. Pathological prognostic factors in breast cancer: experience from a long study with long-term follow-up. *Histopathology.* 1991;19:403-410.
6. Fitzgibbons PL, Page DL, Weaver D, et al. Prognostic factors in breast cancer: College of American Pathologists consensus statement, 1999. *Arch Pathol Lab Med.* 2000;124:966-978.
7. Henson DE, Ries L, Freedman LS, Carriaga M. Relationship among outcome, stage of disease, and histologic grade for 22,616 cases of breast cancer. *Cancer.* 1991;68:2142-2149.
8. Schwartz GF, Lagios MD, Carter D, et al. Consensus conference on the classification of ductal carcinoma in situ. *Cancer.* 1997;80:1798-1802.
9. Holland R, Hendriks JHCL, Verbeek ALM, et al. Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. *Lancet.* 1990;335:519-522.
10. Winchester DP, Strom EA, et al. Standards for diagnosis and management of ductal carcinoma in situ (DCIS) of the breast. *CA Cancer J Clin.* 1998;48:108-128.
11. Connolly JL, Boyages J, Nixon AJ, et al. Predictors of breast recurrence after conservative surgery and radiation therapy for invasive breast cancer. *Mod Pathol.* 1998;11:134-139.
12. Gage I, Schnitt SJ, Nixon AJ, et al. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer.* 1996;78:1921-1928.
13. Lee A, DeLellis R, Silverman M, Heatley GJ, Wolfe H. Prognostic significance of peritumoral lymphatic and blood-vessel invasion in node-negative carcinoma of the breast. *J Clin Oncol.* 1990;8:1457-1465.
14. Pinder S, Ellis IO, O'Rourke S, et al. Pathological prognostic factors in breast cancer. Vascular invasion: relationship with recurrence and survival in a large series with long-term followup. *Histopathology.* 1994;24:41-47.
15. Bonnier P, Charpin C, Lejeune C, et al. Inflammatory carcinomas of the breast: a clinical, pathological, or a clinical and pathological definition. *Int J Cancer.* 1995;62:382-385.
16. Smitt MC, Nowels KW, Zdeblick MJ, et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. *Cancer.* 1995;76:259-267.

17. Stomper PC, Connolly JL. Mammographic features predicting an extensive intraductal component in early stage infiltrating ductal carcinoma. *AJR Am J Roentgenol.* 1992;158:269-272.
18. Leitner S, Swern AS, Weinberger D, Duncan LJ, Hutter RVP. Predictors of recurrence for patients with small (one centimeter or less) localized breast cancer (T1a,b N0 M). *Cancer.* 1995;76:2266-2274.
19. 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.
20. Wittekind C, Greene FL, Henson DE, Hutter RVP, Sobin LH, eds. *TNM Supplement. A Commentary on Uniform Use.* 3rd ed. New York: Wiley-Liss; 2003.
21. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002:223-240.
22. Sobin LH, Wittekind C, eds. *UICC TNM Classification of Malignant Tumours.* 6th ed. New York, NY: Wiley-Liss; 2002:131-141.

Bibliography

- Allred DC, Harvey HM, Berardo MD, et al. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol.* 1998;11:155-168.
- Association of Directors of Anatomic and Surgical Pathology. Immediate management of mammographically detected breast lesions. *Hum Pathol.* 1993;24:689-690.
- Baak JPA. Mitosis counting in tumors. *Hum Pathol.* 1990;21:683-685.
- Bellamy COC, McDonald C, Salter DM, Chetty U, Anderson TJ. Noninvasive ductal carcinoma of breast: the relevance of histologic categorization. *Hum Pathol.* 1993;24:16-23.
- Clark GM, Mathieu MC, Owens MA, et al. Prognostic significance of S-phase fraction in good-risk, node-negative breast cancer patients. *J Clin Oncol.* 1992;10:428-432.
- Connolly JL, Schnitt SJ. Evaluation of breast biopsy specimens in patients considered for treatment by conservative surgery and radiation therapy for early breast cancer. *Pathol Annu.* 1988;23(pt 1):1-23.
- Contesso G, Mouriesse H, Friedman S, Genin J, Sarrazin D, Rouesse J. The importance of histologic grade in long-term prognosis of breast cancer: a study of 1,010 patients uniformly treated at the Institute Gustave-Roussy. *J Clin Oncol.* 1987;5:1378-1386.
- Fisher ER, Gregorio RM, Fisher B, Redmond C, Vellios F, Sommers SC. The pathology of invasive breast cancer: a syllabus derived from findings of the National Surgical Adjuvant Breast Project (protocol No. 4). *Cancer.* 1975;36:1-78.
- Lagios MD, Westdahl PR, Margolin FR, Roses MR. Duct carcinoma in situ; Relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. *Cancer.* 1982;50:1309-1314.
- Lennington WJ, Jensen RA, Dalton LW, Page DL. Ductal carcinoma in situ of breast: heterogeneity of individual lesions. *Cancer.* 1994;73:118-124.
- Miller WR. Prognostic factors in breast cancer. *Br J Cancer.* 1992;66:775-776.
- Page DL, Jensen RA, Simpson JF. Routinely available indicators of prognosis in breast cancer. *Br Cancer Res Treat.* 1998;51:195-208.
- Page DL. Prognosis and breast cancer: recognition of lethal and favorable prognostic types. *Am J Surg Pathol.* 1991;15:334-349.

Page DL, Anderson TJ, Sakamoto G. Infiltrating carcinoma: major histological types. In: Page DL, Anderson TJ, eds. *Diagnostic Histology of the Breast*. New York, NY: Churchill Livingstone; 1987:193-235.

Rosen PP, Groshen S. Factors influencing survival and prognosis in early stage breast carcinoma (T1N0M0-T1N1M0): assessment of 644 patients with median follow-up of 18 years. *Surg Clin North Am*. 1990;70:937-962.

Schnitt SJ, Connolly JL. Processing and evaluation of breast excision specimens: a clinically oriented approach. *Am J Clin Pathol*. 1992;98:125-137.

Schnitt SJ, Wang HH. Histologic sampling of grossly benign breast biopsies: how much is enough? *Am J Surg Pathol*. 1989;13:505-512.

Silvestrini R. Proliferation markers in breast cancer. *Eur J Cancer*. 1993;29A:1501-1502.

Veronese SM, Gambacorta M, Gottardi O, Scanzi F, Ferrari M, Lampertico P. Proliferation index as a prognostic marker in breast cancer. *Cancer*. 1993;71:3926-3931.