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Breast Cancer Staging: Working With the Sixth Edition of the *AJCC Cancer Staging Manual*

S. Eva Singletary, MD, FACS; James L. Connolly, MD

ABSTRACT The sixth edition of the *AJCC Cancer Staging Manual* contains some of the most extensive and significant revisions that have ever been made in the breast cancer staging system. The principal changes are related to the size, number, location, and method of detection of regional metastases to the lymph nodes. Some changes are related to the growing use of new technology (eg, sentinel lymph node biopsy, immunohistochemical staining, reverse transcriptase-polymerase chain reaction), whereas others are amendments of prior staging criteria, reflecting recent clinical evidence or widespread clinical consensus. Available data did not support the addition of new prognostic indicators such as histologic tumor grade to the tumor-node-metastasis system at this time. Future developments in determining breast cancer prognosis will most likely incorporate new approaches to identifying the genetic fingerprint of individual tumors. (*CA Cancer J Clin* 2006;56:37-47.) © American Cancer Society, Inc., 2006.

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INTRODUCTION

Until fairly recently, breast cancer was treated as a single deadly disease for which the most extreme treatments were justified. Egyptian physicians in 1600 B.C. recorded the use of cauterization to treat breast cancers, and extensive surgeries removing the breast and all the surrounding muscle and bone were used during the Renaissance period. A less extreme but still extensive surgery was later adapted by Halsted as the standard of care in the late 19th century.¹

By the first half of the 20th century, clinicians had become aware that not all breast cancers shared the same prognosis or required the same treatment, and attempts were made to define characteristics that could reliably distinguish those tumors that required aggressive treatment from those that did not. In 1904, the German physician Steintal² proposed the division of breast cancer into three prognostic stages: small tumors that appeared to be localized to the breast (Stage I), larger tumors that involved the axillary lymph nodes (Stage II), and tumors that had clearly invaded tissues around the breast (Stage III). This simple staging system was further refined by Greenough, who based his classifications on microscopic examination of breast cancer specimens.³ The four-stage Columbia Clinical Classification System for breast cancer, with Stages A through C corresponding to Steintal's stages, and Stage D representing disease that had metastasized throughout the body, was introduced in 1956 by Haagensen and Stout.

The tumor-node-metastasis (TNM) system was developed by Pierre Denoix starting in 1942 and represented an attempt to classify cancer based on the major morphological attributes of malignant tumors that were thought to influence disease prognosis: size of the primary tumor (T), presence and extent of regional lymph node involvement (N), and presence of distant metastases (M). The International Union Against Cancer (UICC) presented a clinical classification of breast cancer based on the TNM system in 1958,⁴ and the American Joint Committee on Cancer (AJCC) published a breast cancer staging system based on TNM in their first cancer staging manual in 1977.⁵ Since that time, regular revisions have been issued to reflect major advances in diagnosis and treatment. In the 1987 revision, differences between the AJCC and UICC versions of the TNM system were eliminated.

For the clinician, breast cancer staging is useful because of its ability to estimate prognosis. Figure 1 shows the relationship between cancer stage and 10-year relative survival in breast cancer patients, adapted from a report by Bland and colleagues⁶ that used data from 1.3 million cases (1985 to 1996) in the National Cancer Data Base (NCDB). There are significant differences among stages: only 5% to 12% of Stage I/II patients die in the first 10 years after diagnosis, compared with over 60% of Stage III patients and over 90% of Stage IV patients. Breast cancer staging also provides valuable information about appropriate treatment options for each cancer stage.⁶ Because AJCC/UICC staging is commonly used to select patients and to report outcomes in clinical trials, clinicians can make a reasoned judgment about whether treatment strategies reported in the literature will be appropriate for their patients.

Breast cancer staging provides useful information about the current status of cancer detection and management, and the success of implementing new strategies. For example, data from the NCDB show that the percentage of US patients initially presenting as Stage 0 or Stage I increased from 42.5% in 1985 to 56.2% in 1995, whereas the percentage of patients presenting as Stage III or Stage IV decreased from 18.3% to 11.6% during the same time period.⁶ This changing picture suggests that the increased usage of screening mammography during the same time period was effective in detecting cancer at an earlier stage when it can be more successfully treated.

In developing countries, staging of breast cancer patients can provide revealing epidemiological information about opportunities for improving breast cancer screening and management. In contrast to the NCDB data from US women shown above, studies of women with breast cancer from Tanzania,⁷ Tunisia,⁸ Nigeria,⁹ and South Africa¹⁰ have shown that most are initially seen when their cancers are very advanced (Stage III and IV). Public and private agencies interested in international public health programs can use such information to document need and to optimize their interventions.

In this article, we will review the recent revision of the AJCC staging system for breast cancer,¹¹ detailing the specific changes that were made and providing guidelines for using the system in daily practice. We will then review frequently asked questions about implementation of the revised staging system that have been submitted to the AJCC by clinicians from around the world. Finally, we will discuss the future of TNM staging in a world of rapidly developing new technology.

THE SIXTH EDITION OF THE AJCC CANCER
STAGING MANUAL: NEW STAGING DIRECTIONS
FOR BREAST CANCER

Why a Revision Was Needed

Since the fifth edition of the *AJCC Cancer Staging Manual* was published in 1997,¹² important developments have occurred in breast cancer diagnosis and management:

- Because of the increasing use of screening mammography, the average size of breast tumors when first detected has decreased significantly.¹³ Although many of these small tumors could be treated adequately with surgery alone, a significant percentage of these patients would benefit from adjuvant therapy.
- These smaller tumors are associated with a decreased probability of axillary lymph node metastases.¹⁴ Because of this, clinicians have moved away from the use of axillary lymph node dissection (with its associated morbidities) for assessing lymph nodes and have enthusiastically embraced the new technique of sentinel lymph node biopsy (SLNB). Some issues remain unresolved about the most appropriate candidates and methodology for SLNB.
- The growing use of immunohistochemical (IHC) staining and molecular biology techniques has led to concerns about the clinical significance of the extremely small metastatic lesions that can be detected by these approaches.
- The clinical importance of total number of positive axillary lymph nodes, now widely

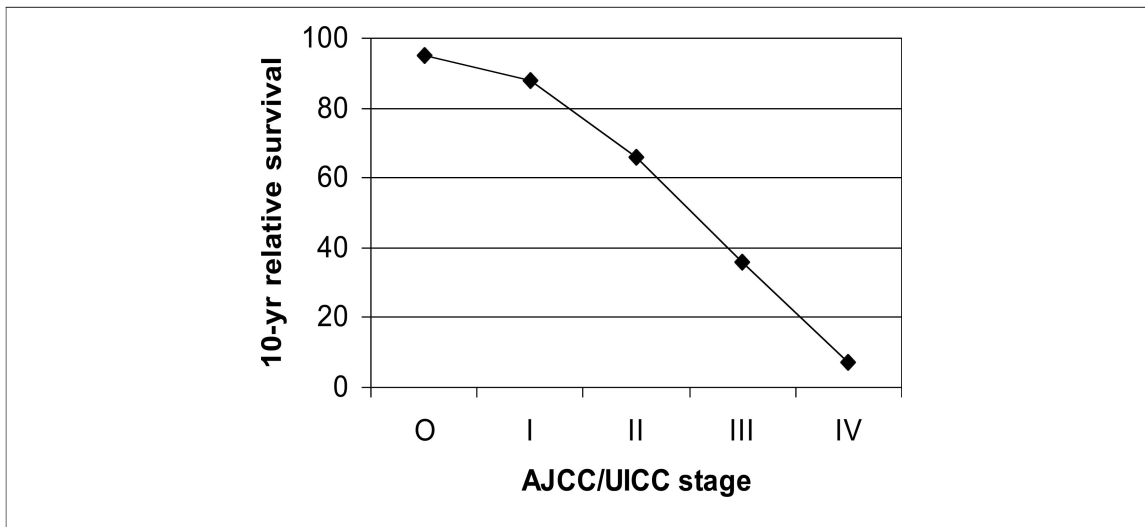


Figure 1 Ten-year Relative Survival Associated with AJCC/UICC (TNM) Breast Cancer Stage. Adapted from a report by Bland, et al.⁶ that used data from 1.3 million cases (1985 to 1996) in the National Cancer Data Base.

recognized by clinicians, has not previously been reflected in breast cancer staging.

- New information about clinical outcomes associated with metastases to supraclavicular, infraclavicular, and internal mammary lymph nodes has led to a reassessment of some classification criteria from the previous edition of the staging manual.

The revision of the breast cancer staging system officially began in January 1998, with the convocation of an AJCC consensus conference to review available data on serum markers or tumor markers as prognostic factors for breast cancer.¹⁵ Conference attendees concluded that there were insufficient data to support the incorporation of any of these markers into the TNM staging system for breast cancer. This conclusion was supported in consensus statements from the College of American Pathologists¹⁶ and the American Society of Clinical Oncology.¹⁷

A Breast Task Force composed of 19 internationally known experts in the field of breast cancer management was appointed by the AJCC to recommend changes in breast cancer staging that would reflect available clinical data and/or widespread clinical consensus about appropriate standards for the management of breast cancer. The newly revised TNM staging system for breast cancer, based on their recommendations, was first presented in print in

2002,^{11,18,19} and was officially adopted for use in tumor registries in January 2003.

General Principles of the TNM Staging System

The TNM staging system includes four classifications: clinical, pathologic, recurrence, and autopsy. Clinical classification (cTNM) is used to make local/regional treatment recommendations. It is based solely on evidence gathered before initial treatment of the primary tumor: physical examination, imaging studies (including mammography and ultrasound), and pathologic examination of the breast or other tissues obtained from biopsy as appropriate to establish the diagnosis of breast cancer. Pathologic classification (pTNM) is used to assess prognosis and to make recommendations for adjuvant treatment. It incorporates the results of clinical staging with evidence obtained from surgery and from detailed pathologic examination of the primary tumor, lymph nodes, and distant metastases (if present). Classification of a recurrent tumor (rTNM) is used when further treatment is needed for a tumor that has recurred after a disease-free interval and includes all information available at the time. Autopsy classification (aTNM) is used for cancers discovered after the death of a patient, when the cancer was not detected before death. Additional descriptors are used for identification

of special cases of cTNM or pTNM classifications, including the “m” prefix in cases with multiple tumors and the “y” prefix in cases where classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both). Thus, ycTNM or ypTNM indicates the extent of tumor actually present at the time of that examination, rather than an estimate of tumor size before initiation of neoadjuvant therapy.

IMPLEMENTING THE REVISED STAGING SYSTEM
FOR BREAST CANCER

Summary of Changes

The principal changes incorporated into the revised staging system for breast cancer (summarized in Table 1) are related to the size, number, location, and method of detection of regional metastases to the lymph nodes. These changes are of two types. Some reflect the growing use of new technology since the publication of the fifth edition, including SLNB, IHC staining, and molecular techniques such as reverse-transcriptase polymerase chain reaction (RT-PCR). Most changes proposed in this category define a nomenclature and coding system that will standardize the collection of important data that may affect treatment in the future. The most significant change in this category was the decision to distinguish between micrometastases and isolated tumor cells on the basis of size. Other changes are amendments of prior staging criteria, reflecting a recognition of the importance of absolute number of affected axillary nodes, and a reassessment of clinical outcomes associated with metastases to the infra- and supraclavicular nodes and internal mammary nodes. These amendments were made in cases where clinical evidence or widespread clinical consensus no longer supported a previous criterion.

TNM Classification of Breast Cancer

The TNM definitions for breast cancer from the sixth edition of the *AJCC Cancer Staging Manual* are shown in Table 2. In addition to the

detailed definitions given in Table 2, the additional guidelines outlined below should be noted.

For Assessment of Tumor Size (T)

- The clinical measurement used for classifying the primary tumor (T) is the one judged to be most accurate for that particular case (ie, physical examination or imaging such as mammography or ultrasound).
- The pathologic tumor size for classification is a measurement of only the invasive component.
- The size of the primary tumor is measured for T classification before any tissue is removed for special studies, such as for hormone receptors or HER2/*neu* status.
- In patients who have received multiple core biopsies, the original tumor size should be reconstructed based on a combination of imaging and all histologic findings.
- Carcinoma in situ with no evidence of an invasive component is classified as Tis, with a subclassification indicating type (ductal [DCIS] or lobular [LCIS]). Cases of ductal carcinoma in situ and cases with both ductal carcinoma in situ and lobular carcinoma in situ are classified Tis (DCIS).
- When there are multiple foci of microinvasion (extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus greater than 1 mm in greatest dimension), the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all the individual foci.)
- In classifying multiple simultaneous ipsilateral primary carcinomas (infiltrating, macroscopically measurable), the largest primary carcinoma is used to designate T classification. Separate T classifications are *not* assigned to the smaller tumors, and the tumors are *not* added together to arrive at a T classification. Most conservatively, tumors are defined as arising independently only if they occur in different quadrants of the breast. The record should reflect that this is a case of multiple simultaneous ipsilateral primary

TABLE 1 Summary of Major Changes in the Sixth Edition of the *AJCC Cancer Staging Manual* for Breast Cancer

	Fifth Edition	Sixth Edition
Size of regional lymph-node metastases	Micrometastases were defined as tumor deposits not larger than 2.0 mm and classified as pN1a. No quantitative distinction was made between micrometastases and isolated tumor cells.	Micrometastases are distinguished from isolated tumor cells on the basis of size. Micrometastases are defined as tumor deposits larger than 0.2 mm but not larger than 2.0 mm and classified as pN1mi. Isolated tumor cells are defined as tumor deposits not larger than 0.2 mm identified by either standard histology or by immunohistochemical staining. They are classified as pN0(i+).
Number of regional lymph-node metastases	The number of affected axillary lymph nodes was considered only in subcategories of pN1.	Major classifications of lymph-node status are defined by the number of affected axillary lymph nodes.
Location of regional lymph-node metastases	Metastases in infraclavicular lymph nodes (axillary level III) were considered equivalent to metastases in other axillary lymph nodes. Metastases to the internal mammary nodes were classified as N3/pN3.	Metastases in the infraclavicular lymph nodes are classified as N3, because of their association with extremely poor prognosis. Metastases to the internal mammary nodes are classified as N1, N2, or N3, based on the size of the lesion and the presence or absence of concurrent axillary nodal involvement.
The use of descriptors to indicate size and method of detection of nodal metastases	Metastases to the supraclavicular lymph nodes were classified as M1. No descriptors were used.	Metastases to the supraclavicular lymph nodes are classified as N3. The descriptor (i+) is used to indicate the presence of isolated tumor cells no larger than 0.2 mm by either standard histology or by immunohistochemical staining. The descriptor (i-) means no detectable tumor cells by either histology or immunohistochemical staining. The descriptor (sn) is used to indicate that the staging classification was based solely on sentinel lymph node dissection. The descriptor (mol+)/(mol-) is used to designate cases that are negative by standard histologic staining for regional lymph node metastasis and in which reverse transcriptase-polymerase chain reaction was used to assess the node for tumor cells.

carcinomas. In the case of simultaneous bilateral breast carcinoma, each carcinoma is staged as a separate primary carcinoma.

- Dimpling of the skin, nipple retraction, or any other skin change except those described under T4b and T4 may occur in T1, T2, or T3 without changing the classification.

For Assessment of Regional Lymph Nodes (N)

- A case in which the classification is based only on SLNB is given the additional designation (sn) for "sentinel node," such as pN1 (sn). For a case in which an initial classification is based on SLNB but a standard axillary lymph node dissection is subsequently performed, the classification is

based on the total results of the axillary lymph node dissection (ie, including the sentinel node).

- Isolated tumor cells (ITCs) are distinguished from micrometastases primarily on the basis of size. They may be identified using standard hematoxylin and eosin (H&E) staining, IHC staining, or both.
 - ITCs are defined as single cells or small clusters of cells not greater than 0.2 mm in largest dimension, usually with no histologic evidence of malignant activity (eg, proliferation or stromal reaction).
 - Per a clarification of the AJCC staging system published in 2003,²⁰ the identifier (i) is used to indicate ITCs. All metastatic

TABLE 2 TNM Classification for Breast Cancer from the AJCC Cancer Staging Manual, 6th Edition

Classification	Definition
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget disease of the nipple with no tumor (Paget disease associated with a tumor is classified according to the size of the tumor.)
T1	Tumor ≤ 2 cm in greatest dimension
T1mic	Microinvasion ≤ 0.1 cm in greatest dimension
T1a	Tumor >0.1 cm but ≤ 0.5 cm in greatest dimension
T1b	Tumor >0.5 cm but ≤ 1 cm in greatest dimension
T1c	Tumor >1 cm but ≤ 2 cm in greatest dimension
T2	Tumor >2 cm but ≤ 5 cm in greatest dimension
T3	Tumor >5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin, 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
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis in movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph-node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph-node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph-node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph-node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)
Regional lymph nodes (pN)†	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells‡
pN0(i-)	No regional lymph node metastasis histologically, negative immunohistochemical staining
pN0(i+)	Isolated tumor cells identified histologically or by positive immunohistochemical staining, no cluster >0.2 mm§
pN0(mol-)	No regional lymph-node metastasis histologically, negative molecular findings (RT-PCR)¶
pN0(mol+)	No regional lymph-node metastasis histologically, positive molecular findings (RT-PCR)¶
pN1	Metastasis in one to three axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*
pN1mi	Micrometastasis (>0.2 mm, none >2.0 mm)
pN1a	Metastasis in one to three axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph-node dissection but not clinically apparent*
pN1c	Metastasis in one to three axillary lymph nodes** and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph-node dissection but not clinically apparent*
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph-node metastasis

Adapted from Greene, et al.,¹¹ with permission from Springer-Verlag.

(cont)

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

†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 lymph node dissection is designated (sn) for "sentinel node," such as pN0(i+)(sn).

‡Isolated tumor cells are defined as single tumor cells or small cell clusters ≤ 0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin stains. Isolated tumor cells do not usually show evidence of metastatic activity (eg, proliferation or stromal reaction).

§Definition of (i+) was adapted in 2003 in order to be consistent with the updated International Union Against Cancer (UICC) classification.²⁰

¶RT-PCR: reverse transcriptase/polymerase chain reaction.

**If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.

TABLE 2 TNM Classification for Breast Cancer from the *AJCC Cancer Staging Manual*, 6th Edition (cont)

Classification	Definition
pN2a	Metastasis in four to nine axillary lymph nodes (at least one tumor deposit >2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the absence 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 lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit >2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three 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
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

lesions not greater than 0.2 mm, whether detected by H&E staining or by IHC staining, are classified as pN0(i+). A classification of pN0(i-) is used to indicate no detectable tumor cells by either staining method. (Note: In the original sixth edition of the *AJCC Cancer Staging Manual*, the designation (i) was used to indicate whether IHC staining had been used. The amendment described above was made to ensure that the AJCC system was consistent with the current UICC system.)

- Micrometastases are defined as tumor deposits greater than 0.2 mm but not greater than 2.0 mm in largest dimension. Cases in which only micrometastases are detected (ie, none greater than 2 mm) are classified pN1mi.
- Metastatic lesions identified only through the use of RT-PCR are currently classified as pN0, because there are as yet insufficient data to determine whether such lesions are clinically significant.
- In cases where there are multiple metastatic lesions in a lymph node and deeper cuts of the node do not show a junction between two or more foci, classification is made according to the size of the largest lesion. If there is doubt, the lower category should be chosen.

For Assessment of Distant Metastasis (M)

- Cases where distant metastasis cannot be assessed are designated MX, cases in which

there is no distant metastasis are designated M0, and cases in which one or more distant metastases are identified are designated M1.

- A negative clinical history and examination are sufficient to designate a case as M0; extensive imaging or other testing is not required. Although some physicians are hesitant to assign a classification of M0, feeling that there is always a remote possibility that occult metastatic disease may exist, this is not appropriate under current staging guidelines.²¹ When the "X" classification is used, patients usually cannot have a stage assigned to their disease, making them ineligible for inclusion in cancer registries or as subjects for clinical trials.

CHALLENGES IN IMPLEMENTING THE SIXTH EDITION

The sixth edition of the *AJCC Cancer Staging Manual* contains some of the most extensive and significant revisions that have ever been made to the breast cancer staging system. Since the new guidelines were first published in September 2002, the AJCC has received many queries from clinicians about correct implementation of the revised system. We reviewed the submitted questions and identified some common themes, illustrated by the questions and answers below. (Note that some of these questions have to

do with topics that were left unchanged from the fifth edition.)

Identification and Measurement of ITCs and Micrometastases

Our pathologist does H&E staining on all his specimens and uses IHC staining only if nothing is found by H&E staining. Can IHC staining be used to identify micrometastases in lymph nodes?

The distinction between micrometastases and ITCs is now based on size alone. Metastatic cell deposits seen with IHC staining alone are considered to be equivalent to those seen on standard H&E staining.

In defining pN1 vs. pN0(i+), is it appropriate to measure size of the IHC micrometastasis to determine whether it exceeds 0.2 mm in any dimension? A case had negative H&E of a sentinel node and positive IHC with subsequent H&E verification. The maximum size was 0.19 mm on H&E and 0.71 mm on IHC.

This would be staged as pN1mi because we stage by greatest dimension regardless of the method of detection.

A sentinel node had a 1-mm metastatic lesion visible by H&E staining. IHC staining showed three additional small foci in the same lymph node, less than or just about equal to 1 mm. What is the pN designation?

If deeper cuts of the node do not show a contiguous process but confirm four separate foci, the classification would be pN1mi, reflecting the size of the largest lesion.

A sentinel node biopsy showed a single cluster of malignant cells with H&E staining measuring 0.18 mm. Results of IHC staining were unknown. Is this staged as pN1 because the malignant cells were detected by H&E?

The classification would be pN0(i+) because the cluster was less than 0.2 mm. It does not matter that the cells were detected by H&E staining.

If a breast carcinoma has one node with a micrometastasis and four nodes with ITCs, all found with IHC, is it staged pN1mi or do the other four ITC nodes upstage it?

ITCs defined as 0.2 mm or less would not upstage the patient.

Examination of the sentinel node in a patient with a primary tumor diagnosis of invasive lobular carcinoma revealed a large number of isolated tumor cells (<0.2 mm in diameter) dispersed throughout the nodal parenchyma in a diffuse pattern. How is this classified?

This is a common metastatic pattern for infiltrating lobular carcinoma. Although these are truly isolated tumor cells, most pathologists would classify this as pN1a based on the number of tumor cells.

Estimating the Size of the Primary Tumor

An invasive breast cancer was removed on stereotactic biopsy so no size was available clinically or pathologically. We classified this tumor as cTX/pTX. Is this correct?

Try to obtain a clinical size from the physician's notation of a palpable size and/or from mammographic or ultrasound imaging of the breast. In addition, because the small invasive tumor was removed entirely by stereotactic biopsy, it must have been less than 2 cm in size, so a classification of T1 would be appropriate.

If there was residual disease found in a re-lumpectomy or mastectomy specimen, does the patient need to be restaged to include the residual tumor?

If the relumpectomy or mastectomy was considered the definitive operation, then staging needs to be updated to include the findings of both the initial and the subsequent definitive breast cancer surgery.

When multiple tumors are present in the same breast, only the largest is measured to determine the T stage. How far apart do the tumors have to be to be considered separate?

Although various studies have suggested ways to make this determination quantitatively, it remains a judgment call. When the foci appear very close microscopically, a review of imaging studies may be useful in determining whether multiple lesions are present.

Classifying Tumors with Dermal Involvement

If there are tumor cells in the dermis without skin ulceration, peau d'orange, edema, or satellite nodules, what is the stage?

Direct skin invasion by AJCC criteria is defined as full-thickness involvement including the epidermis. If the epidermis is intact with only focal dermal involvement, this is not considered T4 but classified by the size of the primary tumor.

Pathology from a lumpectomy revealed a 2 × 1.5-cm mass extending into the skin up to the superficial dermis, without invasion of the epidermis. Is it a T1c or a T4?

This would be classified as T1c. As described above, if the epidermis is intact with only focal dermal involvement, classification is based on the size of the primary tumor.

A patient had breast cancer clinically described as a destructive lesion measuring 4 × 5 cm with obliteration of most of the nipple areolar complex. Biopsy revealed skin and subcutaneous (sc) tissue with infiltrating ductal carcinoma involving dermis and sc subareolar fibrous and muscular tissue. Would this be staged T4b?

Because pathology did not reveal epidermal involvement, this case would be classified as T2 because the greatest dimension of the primary tumor was not more than 5 cm. A tumor with clinically apparent involvement of the nipple areolar complex is classified as T4 if one or more of the following are present: full thickness direct invasive of the epidermis, satellite skin nodules in the same breast, and/or peau d'orange with invasion of the dermal lymphatics. Paget disease, which may involve obliteration of the nipple with no underlying invasive component, is classified as Tis (Paget).

Classification of Lymph Nodes in Unusual Locations

Is a positive intramammary node with negative axillary nodes classified as N1?

A positive intramammary node is considered as an axillary node in staging and thus would be N1 (provided that it is greater than 0.2 mm), even though the axillary nodes are negative.

If there is a nodule in the pectoral muscle not connected to a primary breast tumor, how is it coded?

If the nodule appears to represent involvement of the lymphatics associated with the pectoralis major muscle, it can be considered in the same

category as intramammary lymph node metastases or tumor deposits found in axillary fat without an associated lymph node, and classified as another positive axillary lymph node. However, if the nodule is within breast tissue and only adjacent to the fascia then it would be considered a satellite lesion and the T stage would be based on the index primary lesion.

Pathology reported one clearly identified lymph node negative for metastases, and 10 nodules of tumor ranging in size from 0.2 cm to 0.7 cm in the axillary fat. How is this coded?

Metastatic deposits within axillary fat are considered to be positive nodes. With 11 nodes examined and 10 positive, the classification would be pN3a (10 or more positive nodes).

THE FUTURE OF BREAST CANCER PROGNOSIS

The TNM system for cancer staging is not perfect, but it represents our current best effort to provide a method that is clinically useful and reflective of the available data. Refinements and amendments of the TNM system have been aimed at improving its ability to estimate prognosis. An important aspect of the new staging system is the definition of a nomenclature and coding system that will standardize the collection of important data that may affect treatment in the future. The most significant change in this category is the decision to distinguish between micrometastases and isolated tumor cells on the basis of size. Micrometastases, defined as lesions not greater than 2 mm in diameter, were recognized as clinically significant in the fifth edition of the *AJCC Cancer Staging Manual*,¹² but it seems likely that there is size limit below which this clinical significance would disappear. Lacking sufficient data to define this size limit, many clinicians are erring on the side of caution by aggressively treating *all* metastatic lesions, regardless of size. Since the publication of the sixth edition, a growing number of studies are using the AJCC criteria to evaluate outcome differences based on size in these minute lesions.

Although the sixth edition has given consideration to the relative importance of isolated tumor cells and micrometastases presenting as nodal

metastases, many researchers are now considering the possible prognostic significance of microscopic tumor-cell deposits that may appear in the bone marrow or peripheral blood. A recent pooled analysis by Braun, et al.²² (4,703 patients from nine studies) showed that bone marrow micrometastasis was a significant predictor of poor outcome in a multivariate analysis that included tumor size, lymph-node metastasis, tumor grade, and hormone-receptor expression as covariates. Although tumor-cell deposits in peripheral blood have recently been shown to be predictive of outcome in patients with metastatic breast cancer,²³ the small number of such cells in patients with early-stage breast cancer has hindered the accrual of similar data in these patients. New advances in identifying and collecting these cells should allow definitive studies to address this issue.

During the framing of the sixth edition of the *AJCC Cancer Staging Manual*, the Breast Task Force carefully considered whether the addition of histologic tumor grade or one of the molecular and biochemical markers associated with breast tumorigenesis could offer a significant improvement to the TNM system. It was enticing to think that the one or more of these markers could bring us closer to something that TNM currently does not provide—precise prognosis for the individual cancer patient. At that point in time, however, it was decided that the addition of any of these factors was not yet supported by sufficient data. The reasoning behind this decision has been extensively discussed elsewhere.^{11,19} For histologic grade, the data were sparse and too variable to allow a decision about how best to incorporate grade into the existing TNM system. Although some of the molecular and biochemical markers showed great promise for the future, lack of standardization in measurement techniques for many of them (for example, Ki-67, cathepsin D, HER2/*neu*, and p53) limit their current usefulness.

Although it is likely that tumor grade and selected other markers will again be seriously considered for incorporation into breast cancer staging for the seventh edition of the *AJCC Cancer Staging Manual*, more attention

is now turning to technological approaches that are able to chart the activity of hundreds or even thousands of genes simultaneously.

Over the last 35 years, research has convincingly demonstrated that literally hundreds of genetic and biochemical markers are associated with breast tumorigenesis. Researchers are now using molecular approaches to create a genetic fingerprint of the tumor based on the identification of genes that are actively expressed in tumor cells. For example, Van't Veer, et al. have used RNA-based microarrays to identify a 70-gene expression profile that was a more powerful predictor of 10-year survival rates for young patients with breast cancer than standard prognostic indicators based on clinical and histologic criteria.^{24,25} Soonmyung Paik from the National Surgical Adjuvant Breast and Bowel Project's pathology division recently presented a validation study for another system based on a panel of 16 cancer-related genes.²⁶ In this system, RNA is extracted from paraffin-embedded tumor sections and quantified using RT-PCR. He reported that this system is useful in determining prognosis in newly diagnosed breast cancer patients with Stage I/II, estrogen receptor-positive, node-negative disease who would normally receive tamoxifen as adjuvant therapy.

Such approaches to fingerprinting represent a powerful step forward in characterizing individual breast tumors, but they have yet to address the true complexity of the tumorigenic process. A microarray plate presents a static picture of gene activity associated with the malignant process, but this is somewhat misleading. It appears likely that hundreds of genes are turned on or off sequentially during a developmental process that is thought to involve a linear evolution from hyperplasia to carcinoma in situ to invasive carcinoma.²⁷ Another layer of complexity relates to the heterogeneity of malignant behavior among the cells of a breast tumor. Al-Hajj, et al.²⁸ suggest that most cells in a tumor permanently lack the capacity to proliferate to any significant degree; only a very small and phenotypically distinct subgroup of cells has this ability. They propose that this subpopulation of cells may derive from breast stem cells, retaining the ability for self-renewal and differentiation that is typical of normal

stem cells. If only a small population of phenotypically distinct cells is driving the tumorigenic process, then we may be forced to

rethink our strategies for fingerprinting tumor cells and for designing optimal treatment approaches.

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