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After reading the article "Breast Cancer–Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual," the learner should be able to:

1. Summarize major changes in the guidelines for the staging of breast cancer.
2. Describe clinical implications for treatment decision making based on the eighth edition of the American Joint Committee on Cancer guidelines.

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Breast Cancer—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

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ABSTRACT: The revision of the eighth edition of the primary tumor, lymph node, and metastasis (TNM) classification of the American Joint Commission of Cancer (AJCC) for breast cancer was determined by a multidisciplinary team of breast cancer experts. The panel recognized the need to incorporate biologic factors, such as tumor grade, proliferation rate, estrogen and progesterone receptor expression, human epidermal growth factor 2 (HER2) expression, and gene expression prognostic panels into the staging system. AJCC levels of evidence and guidelines for all tumor types were followed as much as possible. The panel felt that, to maintain worldwide value, the tumor staging system should remain based on TNM anatomic factors. However, the recognition of the prognostic influence of grade, hormone receptor expression, and HER2 amplification mandated their inclusion into the staging system. The value of commercially available, gene-based assays was acknowledged and prognostic input added. Tumor biomarkers and low Oncotype DX recurrence scores can alter prognosis and stage. These updates are expected to provide additional precision and flexibility to the staging system and were based on the extent of published information and analysis of large, as yet unpublished databases. The eighth edition of the AJCC TNM staging system, thus, provides a flexible platform for prognostic classification based on traditional anatomic factors, which can be modified and enhanced using patient biomarkers and multifactorial prognostic panel data. The eighth edition remains the worldwide basis for breast cancer staging and will incorporate future online updates to remain timely and relevant. **CA Cancer J Clin 2017;000:000–000.**

Keywords: biomarkers, distant metastases, ductal carcinoma in situ, estrogen receptor, human epidermal growth receptor 1 (HER2), infiltrating ductal carcinoma, infiltrating lobular carcinoma, lobular carcinoma in situ, lymph node metastases, neoadjuvant chemotherapy

Practical Implications for Continuing Education

- **Immunohistochemically detected tumor markers that are known to have great practical treatment importance are now incorporated into the staging system to refine prognosis.**
- **The eighth edition of the staging system also uses genomic assays when available to downstage some estrogen receptor-positive, lymph node-negative tumors.**
- **Lobular carcinoma in situ is removed from the staging system because it is not a malignancy but a risk factor. It is no longer considered Tis.**

Introduction

The TNM (primary tumor [T], regional lymph nodes [N], distant metastases [M]) staging system began in 1959 as a product of the American Joint Committee for Cancer (AJCC) staging end results reporting.[1] Changes for the eighth edition were based on evidence available from peer-reviewed literature and on findings from large, as yet unpublished databases and were carefully reviewed by a panel of breast cancer experts and AJCC representatives.

The expert panel that formulated the prior (seventh) edition of the staging manual carefully considered the introduction of biomarkers to identify groups with different molecular characteristics and different prognoses. That panel decided that evidence in the literature then available could not support the addition of biomarkers to the TNM staging classification. For the eighth edition, the expert panel concluded that the ensuing advances in clinical and laboratory science and translational research seriously challenged the relevance of the purely anatomic TNM staging for breast cancer. A better understanding of biologic markers, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), and their respective impact on prognosis, selection of therapy, and response to therapy warranted modification of the TNM staging system for breast cancer.

The panel acknowledged that the clinical utility of biologic factors such as grade, hormone receptor expression, HER2 overexpression and/or amplification, and genomic panels has become at least as important as the anatomic extent of disease to predict survival. These factors enable accurate determination of prognosis and selection of systemic therapy and increasingly are affecting locoregional management. The widespread use of immunohistochemical evaluation of these markers to permit reproducible identification of their presence in tumors has greatly altered breast cancer therapy. Although a careful review of the literature did not always result in level I evidence to support the impact of these biologic factors on prognosis, the expert panel felt that, despite the limitations of available evidence, it was essential to incorporate these factors into the revision of the AJCC staging system to remain relevant to contemporary practice.

The panel also recognized that much of the world does not have access to reliable analysis of these factors. The anatomic basis of the TNM staging classification is relevant worldwide, but staging based solely on anatomic factors remains especially relevant where biological markers are not routinely available. In addition, continuing the use of anatomic TNM staging provides continuity with the past and enables breast cancer investigators to compare groups of patients who were treated during different times over the last one-half century. TNM staging also permits current investigators to communicate with each other around the world using a standardized language that reflects tumor burden.

To ensure that the cancer care community has the necessary infrastructure in place for documenting eighth edition stage, the AJCC Executive Committee—in dialogue with the National Cancer Institute-Surveillance, Epidemiology, and End Results program; the Centers for Disease Control and Prevention; the College of American Pathologists; the National Comprehensive Cancer Network (NCCN); the National Cancer Data Base; and the Commission on Cancer—made the decision to delay implementation of the eighth edition cancer staging system to January 1, 2018. Clinicians will continue to use the latest information for patient care, including scientific content of the eighth edition manual. All newly diagnosed cases through December 31, 2017 should be staged with the seventh edition. The time extension will allow all partners to develop and update protocols and guidelines and for software vendors to develop, test, and deploy their products in time for the data collection and implementation of the eighth edition in 2018.

Innovations and Changes to Traditional Anatomic TNM

The anatomic TNM system for reporting extent of disease continues to provide quantitative classification categories for the primary tumor (T), regional lymph nodes (N), and distant metastases (M), which are combined to determine an overall stage group. Historically, the TNM anatomic stage groups have been associated with outcome measures, including overall survival (OS) and disease-free survival. When applied to groups of patients, TNM staging provides an accurate prediction of outcome. However, outcome predictions derived from groups of patients within stage groups and subgroups are more problematic when applied to individual patients who have different biologic subtypes of cancers that express different biomarkers. Thus, while anatomic TNM classifications remain the basis for the eighth edition stage groups, tumor grade, hormone receptor status, and HER2 status are important additional determinants of outcome and are now incorporated into parallel prognostic stage groups that recognize intrinsic tumor biology. Despite the predictive power of intrinsic breast cancer phenotypes, such as luminal, basal, and HER2,[2] extent of disease also offers predictive synergy. The anatomic TNM classification provides a common language for communicating disease burden. Over time, the definitions for classification have required modification, particularly to accommodate additional subclasses of earlier stage breast cancers that are diagnosed with increasing frequency among women who undergo mammographic screening. The eighth edition of the staging manual has continued this evolution and further refined and clarified the definitions for T, N, and M. Table 1 summarizes the significant changes to the TNM classification.

Lobular carcinoma in situ (LCIS) has been removed from the staging classification system and is no longer included in the pathologic tumor in situ (pTis) category. LCIS is treated as a benign entity with an associated risk for developing carcinoma in the future but not as a malignancy capable of metastases. There is a small subset of LCIS that has high-grade nuclear features and may exhibit central necrosis. This subset has been referred to as pleomorphic LCIS and has

TABLE 1. Summary of Changes in the Eighth Edition

CHANGE	DETAILS OF CHANGE	LEVEL OF EVIDENCE
AJCC anatomic and prognostic stage groups	There are 2 stage group tables presented in this chapter:	II
	1. The anatomic stage group table is based solely on anatomic extent of cancer as defined by the T, N, and M categories.	
	2. The prognostic stage group table is based on populations of persons with breast cancer that have been offered—and mostly treated with—appropriate endocrine and/or systemic chemotherapy, which includes anatomic T, N, and M plus tumor grade and the status of the biomarkers human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR).	
Selecting the appropriate stage group table	The prognostic stage group table is preferred for patient care and is to be used for reporting of all cancer patients in the United States.	
	The anatomic stage group table is provided so that stage can be assigned in regions of the world where the biomarkers cannot be routinely obtained.	N/A
Definition of primary tumor (T)	Lobular carcinoma in situ (LCIS) is removed as a pathologic tumor in situ (pTis) category for T categorization. LCIS is a benign entity and is removed from TNM staging.	I
Definition of primary tumor (T)	The general rules for rounding to the nearest millimeter do not apply for tumors between 1.0 and 1.5 mm, so that these cancers are not classified as microinvasive (T1mi) carcinomas (defined as invasive tumor foci 1.0 mm or smaller). Tumors $>$ 1 mm and $<$ 2 mm should be reported rounding to 2 mm.	II
Definition of primary tumor (T)	It is confirmed that the maximum invasive tumor size (T) is a reasonable estimate of tumor volume. Small, microscopic satellite foci of tumor around the primary tumor do not appreciably alter tumor volume and are not added to the maximum tumor size.	I
Definition of primary tumor (T)	The T categorization of multiple synchronous tumors is clarified. These are identified clinically and/or by macroscopic pathologic examination, and their presence documented using the (m) modifier for the T category. This new edition specifically continues using only the maximum dimension of the largest tumor for clinical (cT) and pathological (pT) T classification; the size of multiple tumors is not added.	I
Definition of primary tumor (T)	A clear definition is added that satellite tumor nodules in the skin must be separate from the primary tumor and macroscopically identified to categorize as T4b. Skin and dermal tumor satellite nodules identified only on microscopic examination and in the absence of epidermal ulceration or skin edema (clinical peau d'orange) do not qualify as T4b. Such tumors should be categorized based on tumor size.	I
Definition of regional lymph node (N)	The criteria for pathological measurement of lymph node metastases are clearly defined. The dimension of the area containing several or multiple tumor deposits is NOT used to determine pathological N (pN) category. The largest contiguous tumor deposit is used for pN; adjacent satellite tumor deposits are not added.	I
Definition of regional lymph node (N)	The expert panel affirmed that cNX is not a valid category unless the lymph node basin has been removed and cannot be examined by imaging or clinical examination; a cN0 category is to be assigned when any evaluation of the lymph nodes is possible and the physical examination or imaging examination is negative.	I
Definition of distant metastasis (M)	The expert panel affirmed that pM0 is not a valid category. All cases should be categorized as either cM0 or cM1; however, if cM1 is subsequently microscopically confirmed, pM1 is used (see Chapter 1 as well)	I
Postneoadjuvant therapy classification (ypTNM)	The expert panel clarified that the postneoadjuvant therapy pathological T category (ypT) is based on the largest focus of residual tumor, if present. Treatment-related fibrosis adjacent to residual invasive carcinoma is not included in the ypT maximum dimension. When multiple foci of residual tumor are present, the (m) modifier is included. The pathology report should include a description of the extent of residual tumor explaining the basis for the ypT categorization and, when possible, also should document the pretreatment cT category.	I
Postneoadjuvant therapy classification (ypTNM)	The expert panel clarified that the largest focus of residual tumor in the lymph nodes, if present, is used for ypN categorization. Treatment-related fibrosis adjacent to residual lymph node tumor deposits is not included in the ypN dimension and classification.	I
Complete pathological response	The expert panel affirmed that any residual invasive carcinoma detected by pathological examination in the breast or lymph nodes precludes posttreatment classification as a complete pathological response (pCR). If a cancer is categorized M1 (clinical or pathological) prior to therapy, the cancer is categorized as M1 after neoadjuvant therapy, regardless of the observed response to therapy.	I
Collection of biomarkers (hormone receptor assays and HER2 assay)	The expert panel determined that all invasive carcinomas should have ER, PR, and HER2 status determined by appropriate assays whenever possible.	I

TABLE 1. *Continued*

CHANGE	DETAILS OF CHANGE	LEVEL OF EVIDENCE
Inclusion of multigene panels (when available) as stage modifiers—21-gene recurrence score (Oncotype Dx)	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 21-gene (Oncotype Dx) recurrence score less than 11, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0, and the tumor is staged using the AJCC prognostic stage group table as stage I.	I
Inclusion of multigene panels (when available) as stage modifiers—Mammaprint	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Mammaprint low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II
Inclusion of multigene panels (when available) as stage modifiers—EndoPredict	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 12-gene (EndoPredict) low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II
Inclusion of multigene panels (when available) as stage modifiers—PAM50 (Prosigna)	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a PAM50 risk–of-recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II
Inclusion of multigene panels (when available) as stage modifiers—Breast Cancer Index	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Breast Cancer Index in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II

Abbreviations: AJCC, American Joint Committee on Cancer; PAM50, prediction analysis of microarray 50.

histologic features that partially overlap the features of ductal carcinoma in situ (DCIS), including the potential to develop calcifications detectable by mammography. The expert panel debated whether to include this variant of LCIS in the pTis category; however, there are insufficient data in the literature regarding outcomes and reproducible diagnostic criteria for this LCIS variant. Cases exhibiting DCIS and LCIS are classified as pTis (DCIS). The only other Tis category, pTis (Paget), is for pure Paget disease without any underlying DCIS or invasive carcinoma.

The seventh edition staging manual included rules for rounding tumor size to the nearest millimeter. This was problematic for microinvasive carcinoma of the breast. The eighth edition manual explicitly defines microinvasive pathologic T1 tumors (pT1mi) as those measuring ≤ 1.0 mm and clarifies that tumors between 1.0 and 1.5 mm should be rounded up to 2.0 mm (pT1a). Table 2 lists the primary tumor size (T) classifications.

The eighth edition manual affirms that the TNM system for breast carcinoma is an estimate of total tumor volume; however, there are no easily applied and reproducible methods for calculating total primary tumor volume. The expert panel reaffirmed that the maximum tumor dimension is the best surrogate for volume and that additional small foci of tumor do not substantially alter the overall volume of tumor relative to the maximum dimension of the largest focus of tumor. Small satellite foci of microscopic tumor surrounding the main tumor mass do not alter the size or T classification of the tumor. Following similar principles, when synchronous tumors are present, the size of the largest tumor focus is used for T classification; the tumor sizes are not added.[3] Multifocal tumors are identified clinically or by macroscopic pathologic evaluation and are designated with the (m) modifier. A synchronous 1.5-cm and 0.6-cm tumor, for example, would be classified as pT1c(m). Generally, incidentally identified microscopic tumors in proximity to the main tumor mass would be considered satellite foci; however, occasionally, a synchronous invasive tumor may be macroscopically missed in a large excision or mastectomy specimen. In these situations, clinical judgment should be exercised, and it would be permissible to use the (m) modifier, particularly when the tumors have different histology, grade, or prognostic receptor status. The size of each macroscopic focus of tumor should be verified microscopically and compared with clinical and imaging dimensions to assist in establishing the best T classification. The new manual adds a clear definition indicating that satellite tumor nodules in the skin must be separate from the primary tumor and macroscopically identified to be classified as T4b. Skin and dermal tumor satellite nodules identified only on microscopic examination and in the absence of skin ulceration or skin edema (clinical peau d'orange) do not qualify as T4b.[4] In contrast, inflammatory carcinoma classified as T4d is primarily a clinical diagnosis based on diffuse erythema or edema of one-third or more of the breast. The expert panel discussed but did not create a specific T classification for the rare examples where there is clear evidence for the presence of invasive carcinoma but a primary breast invasive carcinoma

TABLE 2. American Joint Committee on Cancer Definition of Primary Tumor (T)—Clinical (cT) and Pathological (pT)

T CATEGORY	T CRITERIA
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)[a]	Ductal carcinoma in situ (DCIS)
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor $\leq$ 20 mm in greatest dimension
T1mi	Tumor $\leq$ 1 mm in greatest dimension
T1a	Tumor $>$ 1 mm but $\leq$ 5 mm in greatest dimension (round any measurement from $>$1.0-1.9 mm to 2 mm)
T1b	Tumor $>$ 5 mm but $\leq$ 10 mm in greatest dimension
T1c	Tumor $>$ 10 mm but $\leq$ 20 mm in greatest dimension
T2	Tumor $>$ 20 mm but $\leq$ 50 mm in greatest dimension
T3	Tumor $>$ 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma (see "Rules for Classification")

[a]Lobular carcinoma in situ is a benign entity and is removed from TNM staging in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, eighth edition.

was not identified. Examples of evidence of invasion include a lymph node with metastatic carcinoma or definitive lymphatic vascular invasion (LVI) in the breast without identification of definitive invasive carcinoma in the breast or only DCIS in the breast. In these situations, the T classification is pT0 or pTis (DCIS), as appropriate, and a comment should be added to the report indicating that the positive lymph node or LVI is evidence that invasive carcinoma is present but was not identified. These situations should prompt thorough attempts to identify a primary invasive carcinoma using additional pathologic, clinical, or imaging evaluation. Additional discussion of this situation can be found in Chapter 1 of the eighth edition manual.[5]

The expert panel did not recommend any major changes to N classification in the new edition of the staging manual (Table 3). However, the criteria for pathologic measurement of lymph node metastases are now more clearly defined. The dimension of the area containing several or multiple tumor deposits is not used to determine the pathologic lymph node (pN) category. The largest contiguous tumor deposit is used for pN; adjacent tumor deposits are not added together. In distinguishing pN0 tumors with lymph nodes containing isolated tumor cells (pN0[i+]) and pN1mi from other N categories, the clarifications follow the same principles outlined above for T classification, and estimates of tumor burden based on maximum size of the largest focus of tumor are used to estimate total tumor volume. The new manual incorporates supplemental figures that reinforce the concept that isolated tumor cell (ITC) clusters and micrometastases are more likely to be present as multiple tumor deposits, either in proximity to one another or dispersed in different locations within the lymph node, rather than as single tumor deposits. Only the size of the largest tumor deposit within a lymph node is used to classify that node, and the collective summary of all lymph nodes is used to determine the final N classification. For example, a lymph node with at least one tumor deposit $>$2.0 mm that also contains a few scattered micrometastases and ITC clusters would only be tabulated as a lymph node with a macrometastasis. If the patient had one additional involved lymph node with the largest tumor deposit qualifying as a micrometastasis and 2 additional involved lymph nodes with ITCs only, the 4 positive lymph nodes would be tabulated as 1 macrometastasis, 1 micrometastasis, and 2 ITCs, and the overall N classification would be pN1a. In other words, the tabulation of positive lymph nodes recognizes only the largest tumor deposit in each lymph node; and the sum of the tabulation of macrometastases, micrometastases, and ITCs is equivalent to the total number of lymph nodes containing metastatic tumor deposits. Lymph nodes with ITCs only are tabulated in the report

TABLE 3. American Joint Committee on Cancer Definition of Regional Lymph Nodes—Clinical (cN) and Pathological (pN)

CATEGORY	CRITERIA
cN[a]	
cNX[b]	Regional lymph nodes cannot be assessed (eg, previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I and II axillary lymph node(s)
cN1mi[c]	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I and II axillary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I and II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I and II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with level I and II axillary lymph node metastases;
	or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)
pN[d]	
pNX	Regional lymph nodes cannot be assessed (eg, not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase-polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary lymph nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel lymph nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary lymph nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I and II axillary lymph nodes;
	or in more than 3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary lymph nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Abbreviation: ITCs, isolated tumor cells. [a]The (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel lymph node biopsy or fine-needle aspiration/core needle biopsy, respectively. [b]The cNX category is used sparingly in patients with regional lymph nodes that were previously surgically removed or if there is no documentation of physical examination of the axilla. [c]cN1mi is rarely used but may be appropriate in patients who undergo sentinel lymph node biopsy before tumor resection, which is most likely to occur in patients who receive neoadjuvant therapy. [d]The (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel lymph node biopsy or fine-needle aspiration/core needle biopsy, respectively, with NO further resection of lymph nodes.

but do not contribute to overall N classification; the above example would not be considered pN2a. The new manual also clarifies that cNX is a category that should be rarely used and is generally not valid. A classification of cN0 should be used except in the rare event that the regional lymph node basin has been removed and cannot be evaluated by clinical or imaging examination. The expert panel considered but decided not to incorporate the lymph node ratio (LNR) as an alternative method for N classification and recognized that, when modest numbers of lymph nodes are removed for pathologic evaluation, the LNR performs as well or better than total positive lymph nodes for outcome prediction.[6–9] However, when only a few lymph nodes are removed, which commonly occurs with sentinel lymph node biopsy, the LNR can perform worse than total positive lymph nodes and may be misleading.

The eighth edition manual clarifies the use of M classification codes but does not make any changes to the M classification definitions (Table 4). The expert panel affirmed that pM0 is not a valid category, and all cases should be classified as cM0 or cM1. If cM1 is subsequently confirmed by pathologic examination, then pM1 is appropriate. A benign biopsy of a clinically suspicious lesion also does not indicate classification as pM0, because it does not guarantee the absence of metastatic lesions elsewhere. A classification of cM0(i+) is used if there is no clinical or imaging evidence of distant disease but there is molecular or microscopic evidence of circulating tumor cells or disseminated tumor cell deposits no larger than 0.2 mm in bone marrow or other nonregional lymph nodes. Table 5 illustrates the TNM anatomic stages.

Several clarifications of the postneoadjuvant therapy pathologic T classification (ypT) have been included in the new manual. When residual tumor is present in the breast, the largest focus of viable-appearing, residual tumor is used for ypT classification; treatment-related fibrosis or necrotic-appearing tumor around or adjacent to residual tumor is not included in the maximum dimension. When multiple foci of viable residual tumor are present, the (m) modifier should be appended to the ypT classification. When residual lymph node disease is present, the size of the largest focus of residual tumor is used to determine the ypN classification, and treatment-associated fibrosis is not included, analogous to the ypT classification. The pathology report should include a description of the residual tumor in the breast and regional lymph nodes that explains the basis of the ypT and ypN classifications; when possible, the report should also include the pretreatment cT and cN classifications. The expert panel affirmed that any residual, invasive tumor detected by pathological examination in the breast or regional lymph nodes precludes classification as a complete pathologic response. The finding of residual DCIS after neoadjuvant therapy is classified as ypTis. The expert panel discussed the situation in which the only residual disease detected is tumor within lymphatic vascular channels (LVI). Although there is no specific ypT classification for this situation, and there is no comprehensive outcome analysis for this event, it would not currently be considered a pathologic complete response. Regardless of response to therapy, if a cancer is classified pathologically or clinically as M1 before neoadjuvant therapy, then the cancer is classified M1 after therapy.

TABLE 4. American Joint Committee on Cancer Definition of Distant Metastasis (M)

CATEGORIES FOR DISTANT METASTASES—CLINICAL AND PATHOLOGICAL (CM0, CM1, PM1)	
M CATEGORY	**M CRITERIA**
M0	No clinical or radiographic evidence of distant metastases[a]
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or and no deposits no greater than 0.2 mm detected microscopically or by using molecular techniques in circulating blood, bone marrow, or other nonregional lymph node tissue in a patient without symptoms or signs of metastases
M1	Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

[a]Note that imaging studies are not required to assign the cM0 category.

The Incorporation of Biologic Factors Into AJCC Stage

The issue of incorporating biologic factors to include tumor grade, expression of hormone receptors and HER2, as well as multigene prognostic and predictive panels into staging was carefully reviewed and extensively deliberated by the breast expert panel. For the eighth edition, the breast expert panel concluded that the progress in biology, diagnostics, and therapeutics made incorporation of biology into the current staging system mandatory, recognizing the complexities and limitations involved. Clinicians often communicate with each other using biologic factors as well as TNM. For example, a colleague might say, "The patient has a T1N0M0, high-grade, triple-negative cancer."

The earliest prognostic biologic factor recognized by pathologists was tumor differentiation. Simply stated, this is how close or far from normal breast tissue a tumor appears microscopically. Tumors that closely resemble normal tissue are well differentiated, and those that are far from normal are poorly differentiated. Normal breast lobules are comprised of cells with round, regular nuclei arranged in well-formed glands or tubules, and with very few dividing cells. Today, the evaluation of these 3 factors has been standardized by the Nottingham group.[10,11] Each of the 3 factors—nuclear pleomorphism, gland or tubule

TABLE 5. American Joint Commission on Cancer TNM Anatomic Stage Groups[a]

WHEN T IS...	AND N IS...	AND M IS...	THEN THE STAGE GROUP IS...[b]
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

[a]The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available. Cancer registries in the United States must use the Prognostic Stage Group table for case reporting.
[b]Notes for Anatomic Stage Grouping:

- T1 includes micrometastases (T1mi).
- T0 and T1 tumors with lymph node micrometastases only are excluded from stage IIA and are classified as stage IB.
- M0 includes M0 with isolated tumor cells (i+).
- The designation pM0 is not valid; any M0 is clinical.
- If a patient presents with M1 disease before neoadjuvant systemic therapy, then the stage is stage IV and remains stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression and provided the patient has not received neoadjuvant therapy.
- Staging after neoadjuvant therapy is denoted with a "yc" or "yp" prefix to the T and N classification. No stage group is assigned if there is a complete pathological response (pCR) to neoadjuvant therapy: for example, ypT0ypN0cM0.

formation, and dividing cells or mitotic activity—is given a score from 1 to 3 (with 1 being the closest to normal). The scores are added and, if the combined tumor score is between 3 and 5, it is well differentiated or grade 1. If the combined score is 6 or 7, it is grade 2; and, if the combined score is 8 or 9, it is poorly differentiated or grade 3. The expert panel decided to incorporate Nottingham tumor grade in conjunction with other biomarkers, multigene assays, and panels to modify the assigned TNM stage.

The majority of available data regarding biomarkers and prognostic and predictive multigene panels are retrospective in nature and are confounded by the lack of a "no-treatment" control group of patients. With respect to biomarkers, large databases with complete data and adequate follow-up have not been available, largely because HER2 status was not routinely recorded by tumor registries until 2010. There are now data showing the value of incorporating biologic factors with TNM anatomic staging to refine prognostic categories in patients with breast cancer. In a study from The University of Texas MD Anderson Cancer Center (MD Anderson) that included 3728 patients who were treated between 1997 and 2006, investigators developed a staging system that incorporated grade and ER status with pathologic stage to facilitate improved stratification with respect to disease-specific survival (DSS) compared with pathologic stage alone.[12] This was validated with 26,711 patients from the Surveillance, Epidemiology, and End Results database. One important caveat of that work is that it predated the routine use of trastuzumab for patients with HER2-positive breast cancer. The investigators subsequently updated these analyses with a cohort of 3327 patients treated at MD Anderson from 2007 to 2013. That cohort included 306 patients (9.2%) with HER2-positive breast cancer, the majority of whom received trastuzumab. In this updated—although as yet unpublished—analysis, the inclusion of HER2 status, along with grade, ER status, and AJCC pathologic stage, further refined patient stratification with respect to DSS (E.A. Mittendorf, personal communication). These findings were validated using a cohort of 67,944 patients identified in the California Cancer Registry. The studies from MD Anderson included patients who received multidisciplinary treatment that included appropriate adjuvant systemic therapy and anti-HER2 agents, thus confirming the prognostic significance of biologic factors in appropriately treated patients.

Additional work from the MD Anderson group was discussed extensively by the breast expert panel while revisions of the AJCC staging system were ongoing. Data from the MD Anderson study of patients treated between 2007 and 2013 (n = 3327) were used to determine a risk profile and assign a score (Bioscore) to alter patient's stage. The MD Anderson staging system assigned points for each biologic factor and TNM pathologic stage with the number of points resulting in a Bioscore ranging from 0 to 4 based on the hazard ratio magnitude determined on multivariate analysis (Table 6). A patient would be determined to have a Bioscore ranging from 0 to 7 with a corresponding DSS of 100% to 33% (Table 7). Briefly, this system considers grade, ER status, and HER2 status. No points are assigned for grade 1 or2 tumors, ER-positive tumors, or HER2-positive tumors. One point is assigned for grade 3 tumors, ER-negative tumors, and HER2-negative tumors. Therefore, a risk-profile Bioscore from 0 to 3 is calculated. Within each TNM stage, the risk Bioscore can be used to further stratify patients.

TABLE 6. The University of Texas MD Anderson Cancer Center Univariate and Multivariate Analyses for Clinicopathologic Factors Associated With Disease-Specific Survival

		UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS		
FACTOR	5-YEAR DSS, %	HR	*P*	HR	*P*	BIOSCORE POINTS ASSIGNED
Pathologic stage						
IA/IB	99.1	Referent		Referent		0
IIA	98.0	2.8	.002	2.3	.01	1
IIB	95.6	4.8	< .0001	4.0	< .0001	2
IIIA	95.4	6.8	< .0001	7.2	< .0001	3
IIIC	79.5	26.6	< .0001	19.9	< .0001	4
ER status						
Positive	98.8	Referent		Referent		0
Negative	92.9	4.9	< .0001	2.5	.001	1
PR status						
Positive	98.8	Referent		Referent		
Negative	95.2	4.0	< .0001		NS	
HER2 status						
Positive	97.5	Referent		Referent		0
Negative	98.0	0.8	.5	2.2	.04	1
Nuclear grade						
1	99.8	Referent		Referent		0
2	98.9	5.0	.1	4.0	.2	0
3	95.3	25.0	.001	13.0	.01	1

Abbreviations: DSS, disease-specific survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NS, nonsignificant; PR, progesterone receptor. Source: Personal communication, E.A. Mittendorf (unpublished data).

For example, a patient with an anatomic stage IIB tumor that is grade 1, ER-positive, and HER2-negative would have a risk-profile score of 1 with a corresponding 5-year DSS rate of 97% and a 5-year OS rate of 95% in contrast to a patient with an anatomic stage IIB tumor that is grade 3, ER-negative, and HER2-negative, who would have a risk-profile score of 3 with 5-year DSS and OS rates of 92%. This risk-profile study was limited by the relatively small cohort in which the profile was developed. Although such a point-based staging system would perhaps improve staging accuracy, it would represent a complex departure from traditional TNM anatomic staging. The expert panel felt that validation in a larger cohort would be required before the risk profile could be considered for incorporation into AJCC staging; however, its data strongly support the incorporation of biomarkers into the TNM staging system.

There was a strong consensus among panel members that anatomic stage groups be maintained, as they could be applied to all patients with breast cancer worldwide, regardless of the availability of biomarker analysis or multigene assays. This recommendation acknowledged that there are many countries where biomarker assays and multigene panels are not routinely used, often because of the lack of resources to pay for such testing. Although anatomic staging has changed over the years, it still can be used as a link to the past for comparison of studies and patient populations as well as a common terminology for physicians regardless of country or available resources.

To address the importance of tumor biology, in addition to defining AJCC anatomic stage groups, the breast expert panel has defined biologic factor-based prognostic stage groups for the eighth edition that take into consideration tumor grade; HER2, ER, and PR status; and multigene panel (such as Oncotype DX) status. The incorporation of tumor grade and ER, PR, and HER2 status was determined based in part on an unpublished analysis performed by Dr. David J. Winchester, an expert panel member, using data from 238,265 women diagnosed with invasive breast cancer in 2010 who were included in the National Cancer Database. The analyses used conventional AJCC T, N, and M categories as well as tumor grade and ER, PR, and

TABLE 7. Five-Year Disease-Specific Survival Outcomes by Bioscore for The University of Texas MD Anderson Cancer Center Cohort (N = 3327)

BIOSCORE: POINTS ASSIGNED	DSS (95% CI), %
0, n = 36	100
1, n = 1204	99.4 (98.8-99.8)
2, n = 919	99.2 (98.0-99.7)
3, n = 667	97.2 (95.2-98.4)
4, n = 339	94.2 (90.1-96.7)
5, n = 129	92.0 (84.5-96.0)
6, n = 23	77.3 (53.6-89.9)
7, n = 10	33.3 (6.3-64.6)

Abbreviations: 95% CI, 95% confidence interval; DSS, disease-specific survival. Source: Personal communication, Mittendorf EA (unpublished data).

HER2 status to define prognostic subgroups. In the eighth edition, patients with triple-negative tumors, regardless of grade, have survival comparable to that of patients with disease one stage higher than those who have tumors expressing either HER2, ER, or PR. Similarly, patients with grade 3 tumors that are HER2-negative and positive for either ER or PR also have survival comparable to that of patients with disease one stage higher than those with tumors of a lower grade. This is supported by the analysis of Dr. David J. Winchester (personal communication), which is similar to findings of single-institution studies.[12,13] Table 8 illus- illustrates examples of the effect of grade and biomarkers on selected seventh edition TNM stage groups.

As stated above, the eighth edition prognostic stage groups also take into consideration multigene panel testing. Recently, early results from prospective clinical trials have begun to emerge, and the value of multigene panels for managing patients has progressed to the point where such panels are routinely incorporated into national guidelines and recommendations for treatment.[14,15] A few recent publications and abstracts have reported outcome data relative to multigene panel test results, although with limited follow up of only 3 to 5 years. Although the expert panel does not endorse any particular assay, the multigene panel used in the majority of these studies was the 21-gene Oncotype DX recurrence score,[16–20] whereas one study used the 70-gene MammaPrint in conjunction with Adjuvant! Online.[21,22] Table 9 summarizes 5-year outcome data from studies using multigene panels to define low-risk patients who were treated predominantly without systemic chemotherapy.[16–19,21] For such low-risk patients, downstaging to stage I based on biology is supported by the consistently low 5-year risk of recurrence. The major impact of a multigene panel in the eighth edition prognostic stage grouping is the downstaging of biologically low-risk T2 N0 from stage II to stage I for tumors with a low Oncotype DX recurrence score. This change in staging is supported by currently reported studies consistently demonstrating a very low risk of recurrence at 3 to 5 years in the low-risk subgroup of patients, as selected by low-risk biology determined by multigene panels. Caveats include only 3-year to 5-year results reported, differing clinical selection criteria, differing treatments used, differing molecular profiling tools used, and differing cutoff points used for selecting the low-risk subgroup of patients. As of this time, no upstaging is recommended based on multigene panel testing. Table 8 shows the impact of gene panels with Oncotype DX recurrence scores <11 on selected TNM stages from the seventh edition.

TABLE 8. Examples of Revisions to Breast Cancer Staging Using Biomarkers and Oncotype DX

T	N	M	G	HER2	ER	PR	SEVENTH EDITION ANATOMIC STAGE/ PROGNOSTIC GROUP	EIGHTH EDITION PROGNOSTIC STAGE GROUP
Biomarkers								
1	0	0	1	−	−	−	IA	IIA
1	0	0	3	−	+	−	IA	IIA
3	1-2	0	1	+	+	+	IIIA	IB
Oncotype DX recurrence score- < 11 for ER-positive tumors								
2	0	0	Any	−	+	Any	IIA	IB
1-2	1	0	Any	−	+	Any	IIA/IIB	IB
0-2	2	0	1-2	+	+	+	IIIA	IB

Abbreviations: −, negative; O+, positive; ER, estrogen receptor; G, grade; HER2, human epidermal growth factor receptor 2; M, metastasis classification; N, lymph node classification; PR, progesterone receptor; T, tumor classification.

TABLE 9. Comparison of Outcome Studies Using Multigene Panels to Define Patients With Low-Risk Biology[a]

	TAILORX STUDY (SPARANO 2015[16]	STEMMER 2015[17,18]	RASTER STUDY (DRUKKER 2013[21]	SHAK 2015[19]
Type of study	Prospective clinical trial, not randomized	Population-based, HMO (Israel)	Community-based (Netherlands)	SEER database (Netherlands)
Prospective decision-making based on multigene testing	Yes	Yes	Yes	No
Definition of low-risk biology	Recurrence score ≤ 10	Recurrence score < 18	Low MammaPrint and low Adjuvant! Online	Recurrence score < 18
No. of low-risk patients	1626	813	95	21,023
T classification T1c/T2	61%/31%[b]	Unk	Unk/0%	53%[c]/Unk
Systemic therapy	97-100% hormones, $< 1\%$ chemo	Unk hormones, 1% chemo	4% hormones, 3% chemo, and hormones	Unk hormones, 7% chemo
Median follow-up, y	5.75	5.9	5.1	3.25
5-Year outcomes for low-risk patients				
Invasive disease-free survival	93.8%			
Freedom from distant recurrence	99.3%	99.5%	94.3%	
Freedom from any recurrence	98.7%			
Overall survival	98.0%			
Breast cancer-specific survival		99.9%		99.3%-99.6%[d]
Distant recurrence-free interval			95.3%	

Abbreviations: Chemo, chemotherapy; HMO, health maintenance organization; RASTER, Microarray Prognostics In Breast Cancer; SEER, Surveillance, Epidemiology, and End Results; TAILORx, Trial Assigning Individualized Options for Treatment; Unk, unknown. [a]The analysis was restricted to studies that reported 5-year outcomes. [b]T1c and T2 tumors measured 1.0 to 1.9 cm and $\geq$ 2.0 cm, respectively. [c]Classification is for all patients, not just those with low recurrence scores. [d]Values indicate breast cancer-specific survival for patients with chemo vs no/unknown chemo, respectively.

It should be noted that Oncotype DX is the only multigene panel included in the prognostic stage group table of the eighth edition, because it is supported by level 1 data. In addition, it is a strong recommendation of the expert panel that prognostic and predictive markers should not be used as part of the staging system without knowledge of basic tumor markers (ER, PR, and HER2) as a necessary prerequisite. A second recommendation is that multigene panels would be incorporated into the staging system only for selected subsets of breast cancer (eg, hormone receptor-positive, HER2-negative, tone-half, lymph node-negative). Third, multigene panels currently in clinical use may simply represent a substitute for measuring proliferation. The Ki-67 labeling index as a single marker of proliferation was not considered sufficiently reliable to add to staging because of its known lack of reproducibility, especially between different laboratories, as well as the lack of agreement on an optimal cutoff point.[14,23]

The staging complexity of this new edition is clearly increased by the addition of contemporary multigene expression panels. The US Food and Drug Administration has approved for clinical use a panel for women younger than 61 years with TNM stage I or II lymph node-negative breast cancer. In addition, the Tumor Marker Guidelines Committee of the American Society of Clinical Oncology has recommended that a second multigene panel based on expression of 21 genes, as determined by reverse transcriptase-polymerase chain reaction, "may be used" to determine prognosis for patients with ER-positive breast cancer and tumor-free lymph nodes who will be treated with tamoxifen systemic therapy. The Breast Cancer Guideline Committee of the National Comprehensive Cancer Network (NCCN) has stated that using genomic and gene-expression arrays that also incorporate prognostic/predictive biomarkers like the Oncotype Dx recurrence score may provide prognostic and predictive information in addition to anatomic staging and ER/PR and HER2 status. Clinical validation of these assays is accumulating, supporting their use as prognostic and predictive tools and leading to this modification of the staging system for breast cancer.

The incorporation of biomarkers and multigene panels into the eighth edition AJCC staging system allows for more refined staging that reflects the prognostic and predictive significance of biologic factors. The expert panel realizes that not all oncologists use biomarker assays, and this could result in staging disparities. However, many oncologists do, and the NCCN guidelines recognize their use. The incorporation of multigene panels with the Oncotype DX or any gene panel creates its own problems. Some clinicians may decide not to order the test because of the patient's comorbidities or finances. This could result in a

staging discrepancy based on physician choice or even socioeconomic reasons. The panel clearly recognizes this problem; however, because the multigene assays are incorporated into national guidelines, it seems appropriate to recognize their undisputed value. The expert panel anticipates that biomarker utilization will continue to increase and believes that this initial effort in incorporating biology into staging was critical in maintaining the clinical relevance of the staging system. It is anticipated that future modifications based on biology will undoubtedly be needed with the reporting of additional outcome studies with different panels and longer follow-up, particularly as prospectively designed studies mature.

Conclusion

The eighth edition of the AJCC staging system for breast cancer is based on the anatomy-based and histology-based original TNM staging system and uses the addition of various biomarkers to refine the prognostic information for better selection of therapy with improved outcome. It is now possible to identify a group of patients who have invasive breast cancer with a prognosis so favorable that they may forgo systemic chemotherapy. The ability to predict benefit from or resistance to specific treatments is of major clinical relevance. The eighth edition expert panel formulated their recommendations before the publication of an additional prospective randomized study using a 70-gene signature (MammaPrint) to evaluate the impact of chemotherapy on women deemed to be at high risk of metastases because of clinical factors but found to be at low genomic risk based on their 70-gene assay.[24] This MINDACT study showed that women at low genomic risk who, despite their high clinical risk, did not receive adjuvant systemic chemotherapy had a high 5-year survival similar to that of patients who received chemotherapy. Although these data were not available for inclusion in the eighth edition of the AJCC staging manual, they are consistent with the recommendation of the expert panel for downstaging selected tumors with low-risk genomic profiling to stage I and will be incorporated in the future.

To preserve the relevance of anatomic staging for the entire world where such markers may not be available, the panel elected to integrate biomarkers as a second tier of prognostic modifiers similar to the use by expert panels evaluating other disease sites within the AJCC manual. The purely anatomic staging system provides clinicians throughout the world the ability to determine an anatomic stage and confers historical relevance to the current staging system. Most cancer deaths are not in developed countries, and ignoring anatomic staging would be detrimental to the well being of patients in developing countries.

The rapid expansion of knowledge of the biology of breast cancer is likely to lead to frequent online modifications of the eighth edition staging system as peer-reviewed, validated information becomes available. The eighth edition of the AJCC staging manual is intended to be relevant for the present and adaptable for the future but will remain firmly anchored to the past. ■

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