Staging system for breast cancer: revisions for the 6th edition of the *AJCC Cancer Staging Manual*

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Proper staging of breast cancer assists physicians in making appropriate treatment decisions and in evaluating the results of different treatment regimens. With a uniform staging system, patient outcomes can be compared across different institutions on a national and international basis, accelerating the accumulation of knowledge about the effectiveness of management strategies. In 1959, the American Joint Committee on Cancer (AJCC) was organized (originally as the American Joint Committee for Cancer Staging and End-Results Reporting) to develop a uniform system of cancer staging that reflected the existing state of knowledge about the clinical outcomes of cancer. Since that time, the staging manual developed by the AJCC has gone through periodic revisions, reflecting advances in our understanding of cancer.

Since the publication of the 5th edition of the *AJCC Cancer Staging Manual* in 1997 [1], significant developments have occurred in the field of breast cancer diagnosis and management, dictating the need for substantive changes in the staging system for breast cancer. First, with the increasing use of screening mammography, the average size of breast tumors when they are first detected has decreased significantly [2]. Although some of these small tumors could be effectively treated with minimal local therapy, others are inherently more malignant. The heterogeneity of outcomes among these small tumors has underscored the need for a finer delineation of classification in the lower levels of the staging system. A large number of recent studies have looked at histologic, biochemical, and molecular biological factors that might predict outcome independently of the factors

used in the traditional TNM staging system (<u>T</u>umor size, presence of <u>N</u>odal metastasis, and presence of distant <u>M</u>etastasis).

Second, the smaller tumors being detected with screening mammography have a reduced probability of being associated with axillary lymph node metastases [3]. This has led to a rethinking of the optimal approach to assessing lymph nodes—one that will retain accuracy while decreasing the sometimes significant morbidity associated with a standard axillary lymph node dissection (ALND) [4]. Within the last 5 years, sentinel lymph node dissection (SLND) has begun to replace ALND for the assessment of axillary lymph node status in early stage breast cancer. SLND is based on the observation that specific areas of the breast tend to drain primarily through a ''sentinel'' node to the other nodes in the axillary basin. If the sentinel node can be detected and removed, its status reflects the status of the remaining nodes in a significant majority of cases ($>95\%$) [5]. Thus, if the sentinel node is negative, complete dissection of the remaining nodes may not be necessary. Because only one or two nodes are removed in this approach, it has become feasible to use extensive sectioning, immunohisto-chemical (IHC) staining, and molecular biological detection (reverse transcriptase polymerase chain reaction, or RT-PCR) to examine the nodes in much greater detail than would be possible for all of the nodes in the axillary basin. This has led to the increased detection of minute lesions, some at the level of single cells or small clusters of cells, the clinical significance of which is still largely unknown. An important part of the new staging system will be to facilitate the accrual of data about the usefulness of these new approaches.

Third, the careful collection and assessment of recent clinical data has led to the reassessment of some decisions that were made in previous editions of the staging manual. The clinical significance of total number of affected axillary lymph nodes was largely ignored in the past, although a large body of clinical data suggests that this is an extremely important prognostic factor. The clinical importance of metastases to level III axillary lymph nodes and to nodal basins outside of the axilla has also been re-evaluated.

The process of revising the breast cancer staging system has progressed through several stages, beginning almost immediately after the publication of the last edition. In January 1998, an AJCC consensus conference on cancer prognostic factors assessed available data on serum markers or tumor markers to determine if any such factors were strong independent predictors of outcome for breast cancer [6]. The AJCC staging system has focused exclusively on prognostic factors. These are factors principally associated with risk of subsequent recurrence, metastasis, and death after primary therapy (surgery, radiation), independent of systemic therapy. The AJCC has not included predictive factors in the staging system. These are factors that are associated with the likelihood of response or benefit from specific therapeutic approaches, such as the presence of estrogen receptor and response to endocrine therapy. The AJCC consensus committee

concluded that presently available circulating markers were not independent prognostic factors in patients with newly diagnosed, nonmetastatic breast cancer. Many of the newer tissue-based molecular factors appear to be predictive factors specific to individual systemic therapies, as is the case for HER2/*neu* amplification or overexpression and response to trastuzumab. Their conclusion, which was later supported in separate consensus statements from the College of American Pathologists [7] and the American Society of Clinical Oncology [8], was that there were insufficient data to support the incorporation of any of these markers into the TNM system. The AJCC consensus committee recommended other changes to the breast cancer staging system, all of which were considered for the current revision.

Two years ago, the Breast Task Force was appointed by the AJCC to recommend changes for the breast cancer chapter in the 6th edition of the *AJCC Cancer Staging Manual* [9]. This task force was composed of 19 internationally known experts in the field of breast cancer management. They were charged with developing revisions that would reflect available clinical data or widespread clinical consensus about appropriate standards for the management of breast cancer.

This article presents the revised AJCC staging system for breast cancer that was officially adopted for use in tumor registries in January 2003. The major changes considered for this revision are discussed in detail to explain the rationale for including (or not including) them in the 6th edition.

The revised AJCC staging system for breast cancer

The revised AJCC staging system for breast cancer is shown in Table 1, and the stage groupings are shown in Table 2. The major changes in this revision fall into two major categories: (1) changes related to the detection and description of microscopic metastatic lesions, and (2) changes related to the location and number of lymph node metastases. The inclusion of histologic tumor grade in the TNM system was considered but ultimately rejected.

Rationale for changes in the 6th edition

Changes related to the detection and description of microscopic metastatic lesions

Major changes related to the detection and description of microscopic metastatic lesions are as follows:

1. Micrometastases are distinguished from isolated tumor cells on the basis of *size*. They are more likely to show histologic evidence of malignant activity, but this is not an absolute requirement.
2. Identifiers have been added to indicate the use of sentinel lymph node dissection and immunohistochemical or molecular techniques.

Table 1
TNM staging system for breast cancer

Primary tumor (T)	Assessment
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's disease of the nipple with no tumor
	Note: Paget's disease associated with a tumor is classified according to the size of the tumor.
T1	Tumor 2 cm or less in greatest dimension
T1 mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
Tlb	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) 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)	Assessment
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[a] 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[a] 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[a] 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)

(*continued on next page*)

Table 1 (*continued*)

Regional lymph nodes (N)	Assessment
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)[b]	Assessment
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 (ITC)[c]
pN0(i−)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0(mol−)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[d]
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[d]
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1	Metastasis in 1 to 3 axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[e]
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[e]
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[e,f]
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent[a] internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent[a] 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[a] ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 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 greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent[a] ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.[e]
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

Table 1 (continued)

Distant metastasis (M)	Assessment
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

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

[b] 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." [eg, pN0(i +)(sn)].

[c] Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of metastatic activity (eg, proliferation or stromal reaction).

[d] RT-PCR: reverse transcriptase/polymerase chain reaction.

[e] *Not clinically apparent* is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

[f] If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.

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Micrometastases and isolated tumor cells

The importance of size. Pathologists can now use IHC or RT-PCR to detect lesions down to the level of isolated tumor cells, but the clinical relevance of these minute lesions is unclear. Although micrometastatic lesions no greater than 2.0 mm in diameter were recognized as having possible clinical significance in the 5th edition of the *AJCC Cancer Staging Manual* [1], it seems likely that at some lower size limit these lesions may cease to have an impact on patient outcome. Unfortunately, there are not yet sufficient data to define that lower size limit. This is largely because there has been no adequate system in place to track such data, and because physicians have tended to treat all patients with IHC-identified nodal metastases as node-positive, regardless of the size of the metastatic lesion. A large body of outcome data is needed in which the distinction between micrometastases and isolated tumor cells has been made based on uniform quantitative criteria.

One of the most significant changes in the 6th edition of the *AJCC Cancer Staging Manual* [9] is the assignment of a specific lower size limit to micrometastases, now defined as metastatic lesions larger than 0.2 mm in diameter but no larger than 2.0 mm in diameter. Isolated tumor cells are now defined as metastatic lesions no larger than 0.2 mm in diameter. The upper size limit of 2.0 mm for micrometastases is consistent with that originally proposed by Huvos and colleagues in 1971 [10] and used in the 5th edition of the *AJCC Cancer Staging Manual* [1]. The lower limit of 0.2 mm, although somewhat arbitrary, was selected because it would significantly reduce the probability that isolated tumor cells (ITCs) would be classified as micrometastases, without requiring the pathologist to estimate actual cell numbers.

Table 2
TNM stage grouping for breast cancer

Stage grouping			
0	Tis	N0	M0
I	T1[a]	N0	M0
IIA	T0	N1	M0
	T1[a]	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1[a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

[a] T1 includes T1mic.

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A critical element of this definition is that the distinction between micrometastases and isolated tumor cells is being made based on size alone. Both types of tumor cell deposits may or may not show histologic evidence of malignant activity (such as proliferation or stromal reaction), although such evidence would be more likely in the larger lesions. Importantly, as will be discussed in the next section, the method of detection is not a factor in making this distinction. Metastatic cell deposits seen with IHC staining alone are considered to be equivalent to those seen on standard hematoxylin and eosin (H&E) staining.

Pending the collection of additional data, a finding of isolated tumor cells in the absence of any other nodal metastases will be classified as node-negative. It was the consensus of the Breast Task Force that the morbidity resulting from treating these lesions would outweigh any potential benefits.

Method of detection of microscopic lesions. H&E staining viewed with conventional light microscopy has long been considered the gold standard for assessing axillary lymph nodes for the presence of metastatic lesions. It provides permanent preparations that exhibit a fine level of detail, allowing pathologists to detect definitive histologic evidence of malignancy that may not be visible with IHC staining. However, small lesions that might be missed on H&E staining can be strikingly visible in the high-contrast IHC preparations. Reflecting this, IHC staining techniques have reportedly detected micrometastases in 12% to 29% of patients who were node-negative

by H&E staining [11–15], with some studies reporting reduced disease-free survival associated with IHC-detected micrometastases [11–13]. Although follow-up verification with H&E staining has been the recommended procedure, this approach is being abandoned in many institutions. The growing consensus among pathologists is that the clinical significance of a lesion, most directly reflected by size of the lesion, is more important than the staining method used to look for a lesion. This is still an area of some controversy, however. The Breast Task Force believed that the introduction of additional descriptors to reflect the method of detection would aid in the accrual of additional information on this issue. Thus, the 6th edition of the *AJCC Cancer Staging Manual* [9] uses an additional descriptor [(i +) or (i−)] to denote those cases that are histologically negative for lymph node metastasis by standard H&E staining and in which IHC staining was used. For example, pN0(i +) would indicate a case that was H&E negative in which an isolated tumor cell deposit no larger than 0.2 mm in diameter was detected by IHC, while pN0(i−) would indicate a case that was both H&E negative and IHC negative.

The RT-PCR technique has revolutionized many fields of biological and medical research. Through repeated amplification of single strands of mRNA, this technique is technically capable of detecting a single malignant cell. A growing number of researchers are investigating the use of this technique to detect minute lesions in sentinel lymph nodes [16–18]. While the most straightforward approach involves the amplification of mRNA from mammoglobin, researchers are also examining the possibility of using a multigene marker panel in conjunction with quantitiative real-time RT-PCR [18]. With all of these approaches, the most important question is whether the minute lesions detected by RT-PCR have any clinical significance. Isolated tumor cells are unlikely to escape the immunosurveillance of the body and survive to develop into significant metastatic foci. In the blood stream, for example, less than 0.05% of isolated tumor cells develop into a metastatic focus [19]. Reflecting the current state of knowledge, this edition of the *AJCC Cancer Staging Manual* designates lesions identified by RT-PCR alone as pN0, as they would have been classified under H&E staining. Clearly, however, this is another area requiring the accrual of additional clinical data. Thus, an additional descriptor [(mol +) or (mol−)] will be used to designate cases that are negative by H&E staining for regional lymph node metastasis and in which RT-PCR was used to assess the node for tumor cells. As an example, pN0(mol +) would indicate a case that was histologically negative but in which isolated tumor cells had been identified using RT-PCR, and pN0(mol−) would indicate a case that was histologically negative and also negative by RT-PCR.

Sentinel lymph node dissection

Treatment standards for management of the axillary lymph nodes are in a state of transition. SLND is rapidly becoming the preferred approach for

clinically node-negative patients with small tumors (eg, T1, T2) and is also being considered in patients with locally advanced breast cancer who have received preoperative chemotherapy [20–22]. Many questions remain unanswered, however. For example, in most cases ($\sim$60%) in which the sentinel lymph node is positive, it is the only positive node [5]. What are the clinical consequences of omitting ALND in a patient with a positive sentinel node? If a sentinel node is negative by standard histological staining but positive by IHC staining, should axillary dissection be performed? These questions are being addressed in several long-term prospective trials (the Z0010 and Z0011 trials from the American College of Surgeons and the B-32 trial from the National Surgical Adjuvant Breast and Bowel Project). This revised staging system includes descriptors that will allow national databases to collect relevant data. If a staging classification is based solely on SLND, it will have the additional designation (*sn*), which stands for "sentinel node" [eg, pN1(sn)]. Note, however, that if a standard ALND is performed after a SLND, the final classification would be based on the total results (ALND + SLND) and would not carry the (*sn*) designation.

Changes related to the number and location of lymph node metastases

Major changes related to the number and location of lymph node metastases are as follows:

1. Major classifications of lymph node status are defined by the number of affected axillary lymph nodes detected by histologic staining (preferred) or by immunohistochemical staining.
2. Metastasis to the infraclavicular lymph nodes is classified as N3.
3. Metastasis to the internal mammary nodes is classified as N1, N2, or N3, based on the method of detection and the presence or absence of concurrent axillary nodal involvement.
4. Metastasis to the supraclavicular lymph nodes is reclassified as N3 rather than M1.

The total number of affected axillary lymph nodes

In previous editions of the *AJCC Cancer Staging Manual*, the number of affected lymph nodes did not affect major classifications. A patient with 1 positive lymph node and a patient with 10 positive nodes were both classified as N1. This was somewhat misleading, because clinicians have long recognized that the absolute number of positive lymph nodes is a strong prognostic factor in breast cancer [23]. This anomaly has been resolved in the 6th edition. In the new pathologic staging system, patients with 1 to 3 positive axillary lymph nodes are classified as pN1a, patients with 4 to 9 positive axillary lymph nodes are classified as pN2a, and patients with 10 or more positive axillary lymph nodes are classified as pN3a. (In all cases, at least one tumor deposit must be greater than 2.0 mm in diameter, and all

tumor deposits must be greater than 0.2 mm in diameter). The separation between patients with 1 to 3 positive nodes and patients with 4 or more positive nodes is based on data from the Surveillance, Epidemiology, and End Results (SEER) Program, as presented by Carter and colleagues [24]. In 24,470 breast cancer cases grouped by tumor size, overall survival was inversely proportional to the total number of positive nodes in each size group. Patients with 10 or more positive axillary lymph nodes are clinically recognized as an especially high-risk group [25–27]. Nemoto and colleagues [28] demonstrated this in a study of 20,547 cases of breast carcinoma collected by the American College of Surgeons, where expected survival was inversely proportional to number of histologically positive axillary lymph nodes up to a total of 21 positive nodes.

Metastasis to infraclavicular lymph nodes

Although the infraclavicular lymph nodes (axillary level III) have historically been grouped with other axillary lymph nodes, recent data indicate that metastasis to these lymph nodes is associated with a very poor prognosis. Newman and colleagues [29] detected infraclavicular disease in nearly one third of patients examined with ultrasound. They reported that involvement of infraclavicular lymph nodes resulted in a significantly worse disease-free and overall survival compared with patients with no infracla-vicular node involvement (50% versus 68% and 58% versus 83%, respectively). The Breast Task Force was in agreement with these findings and recommended that metastasis to the infraclavicular lymph nodes be added to the classification system as N3a.

Metastasis to nonaxillary lymph nodes

Internal mammary nodes. The internal mammary (IM) nodes lie along the edge of the sternum in the endothoracic fascia. Metastasis to these nodes was previously classified as N3, because it was generally believed that there was a poor prognosis in IM+ versus IM− patients. A major study that supported this viewpoint did not, however, consider IM status independently of axillary lymph node (AL) status [30]. Klauber-Demore and colleagues [31] recently reviewed five studies related to this issue and found that there is a synergistic affect on survival between IM metastasis and AL metastasis. While similar survival rates are seen in IM+/AL− patients and IM−/AL+ patients (mean percentage of survival: 62% and 72%, respectively), a significant decrease in survival is observed in patients who are both IM+ and AL+ (mean percentage of survival: 40%). The size of the metastasis within the internal mammary nodes is also associated with survival. Nodes detected by sentinel node mapping but not large enough to be detectable by imaging studies (not including lymphoscintigraphy) have a better prognosis than nodes that are large enough to be detected by clinical examination or imaging studies. To reflect these complex findings, the 6th edition of the *AJCC Cancer Staging Manual* [9] classifies metastases to the

Table 3
AJCC classification of internal mammary node (IM) metastasis as a function of axillary lymph node status and method of detection

No. of positive axillary lymph nodes	AJCC classification	
	IM metastasis found with sentinel lymph node biopsy[a]	IM metastasis found with clinical examination or imaging[b]
0	pN1b	pN2b
1–3	pN1c	pN3b
More than 3	pN3b	pN3b

[a] Positive internal mammary nodes detected by sentinel lymph node dissection but not by imaging studies (including lymphoscintigraphy).
[b] Positive internal mammary nodes detect by clinical examination or imaging studies (including CT scan or ultrasound, but excluding lymphoscintigraphy).

internal mammary nodes as N1, N2, or N3, as shown in Table 3. The lowest classification (and the best prognosis) is seen in IM metastases detected with sentinel lymph node biopsy in the absence of positive axillary lymph nodes. The highest classifications and worst prognosis are assigned to IM metastases found in conjunction with AL metastases, especially in cases where the IM metastases are found on clinical examination or imaging. It is important to note that the decision to pursue nodes in these areas is still left to the discretion of the surgeon. Currently, the internal mammary nodes are not biopsied in the great majority of cases.

Supraclavicular lymph nodes. The poor prognosis associated with supra-clavicular lymph nodes (SCLN) was first reported by Halsted in 1907 [32]. Patients with positive SCLNs have 5-year survival rates ranging from 5% to 34% [33]. To reflect this, the previous edition of the *AJCC Cancer Staging Manual* classified SCLN metastasis as M1, in the same category as distant metastases to the bone, lung, or brain. Such patients are typically not treated with intent to cure; rather, they are offered palliative treatment options. A recent study by Brito and colleagues [34] has presented data indicating that this may be inappropriate. They examined survival outcomes in 70 patients with locally advanced breast cancer (LABC) who were positive for ipsilateral SCLN metastasis but otherwise negative for distant metastasis. Patients were treated with aggressive combined modality therapy consisting of chemo-therapy (pre- and postoperative), surgery, and radiotherapy. At 5 and 10 years after initial diagnosis, the overall survival rates were 41% and 31%, respectively, with a median overall survival of 3.5 years. These survival rates were equivalent to those seen in LABC patients without distant metastasis, and significantly better than those seen in stage IV patients with metastases at other distant sites. Based on these data, the 6th edition of the *AJCC Cancer Staging* Manual [9] has reclassified SCLN metastasis from M1 to N3c/pN3c. Stage IIIC (new to this revision) includes any T,N3 (pN3a, pN3b, pN3c).

Histologic grade as a prognostic factor for breast cancer

The relationship between the morphological appearance of tumors and their degree of malignancy has been recognized for over 100 years [35], and formal histologic grading systems have been proposed for almost as long [36]. Although few would question that histologic grade may offer valuable prognostic information for breast cancer, the question has been whether any existing grading system is sufficiently reproducible to allow comparison of data from institution to institution.

Tumor grading is subjective by nature, and successive grading systems have sought to introduce a more quantitative element. In the early 1990s, Elston and Ellis introduced the Nottingham combined histologic grade, a modification of the Bloom and Richardson grading system [37,38]. The Nottingham system evaluates percentage of tubule formation, degree of nuclear pleomorphism, and mitotic count in a defined area. Each feature is assigned a numerical score, and the three scores are used to compile the overall grade. Compared with previous systems, the Nottingham combined histologic grade has shown a very strong correlation with long-term survival as well as improved interobserver agreement. It is currently recommended in the College of American Pathologists Consensus Statement [7].

The Breast Task Force debated the issue of whether histologic grade should be incorporated into the existing TNM staging system, and how this might be done most effectively. An important point of consideration was whether the addition of histologic grade to the staging system would affect treatment decisions. Adjuvant chemotherapy is almost always recommended for large tumors (T3, T4), so the addition of histologic grade would have little effect on treatment recommendations. On the other hand, small node-negative tumors (T1, T2) present a wide spectrum of possible outcomes, and histologic grade could be of value in determining which of these small lesions would benefit from aggressive treatment. Currently, however, the available data related to the effect of histologic grade on outcome in patients with early stage breast cancer are difficult to assess and contradictory. The 11 studies reviewed in Table 4 vary in patient description, follow-up time, measured outcome, and type of grading system used [39–49]. Across all studies, outcomes for grade 1 tumors are clearly differentiated from grade 3 tumors. The relative position of grade 2 tumors varies among studies, sometimes grouping with grade 1 and sometimes with grade 3. In the 4 studies that used the Nottingham combined histologic grade and looked at early stage node-negative tumors [42,45,46,49], grade 2 tended to cluster with grade 3 at follow-up times ranging from 10 to 13 years.

Because of the small number of available studies and the significant variability in results, the consensus of the Breast Task Force was that a sufficient body of data does not yet exist to justify the inclusion of histologic grade in the TNM staging system for breast cancer.

Table 4
Histologic grade and outcome in patients with early stage breast cancer

Authors	Patient description	No. of patients	Follow-up (years)	Grading System[a]	Outcome measured[b]	Outcome		
						Grade 1	Grade 2	Grade 3
Rosen et al, 1989 [47]	T1,N0	644	20	NS	Relapse	10%	23%	30%
Henson et al, 1991 [41]	T1,N0 or T0,N1	22,616	10	NS	Relative survival	95%	91%	84%
	T1/2,N1 or T2N0		10	NS	Relative survival	82%	71%[c]	63%[c]
Rosner & Lane, 1991 [48]	T1a/b	113	7	BR	DFR		100%[c]	91%
	T1c	125	7	BR	DFR		91%[c]	79%
	T2	132	7	BR	DFR		65%[c]	70%
Genestie et al, 1998 [40]	T1/2,N0/1	877	5	N	OS	96%	88%	80%
					MFS	91%	81%	78%
Kollias et al, 1999 [42]	T1a/b,N0	318	10	N	OS	95%	91%	91%
Leitner et al, 1999 [43]	T1a/b	218	7	WHO	RFS	100%	97%	88%
Reed et al, 2000 [46]	T1/2,N0	228	10	N	RFS	90%	70%	69%
					OS	94%	86%	78%
D'Eredita et al, 2001 [39]	T1/2,N0/1	402	16	N	OS	78%	60%	29%
Lundin et al, 2001 [44]	T1N0	665	5	WHO	DDFS	98%	86%	87%
	T2N0	244	5	WHO	DDFS	96%	78%	69%
Page et al, 2001 [45]	T1/2,N0	311[d]	12	N	DFR[e]	76%	55%	54%
Frkovic-Grazio & Bracko, 2002 [49]	T1,N0	270	13	N	DSS	96%	79%	78%

[a] DFR: disease-free rate; OS: overall survival; MFS: metastasis-free survival; RFS: relapse-free survival; DDFS: distant-disease free survival; DSS: disease-specific survival.
[b] Original grades 3 and 4 showed no significant difference and were collapsed into Grade 3 for this review.
[c] Original grades 1 and 2 collapsed into one category in original study.
[d] Restricted to patients receiving no adjuvant therapy.
[e] Estimated from actuarial curves for time to recovery.

Abbreviations: NS, grading system not specified; BR, Bloom-Richardson; N, Nottingham combined histologic grade; WHO, World Health Organization.
Updated from AJCC Cancer staging Manual. 6th Edition. New York: Springer-Verlag, 2002; with permission.

Summary

Since its inception, the AJCC staging system for breast cancer has been in an almost constant state of evolution, striving with each revision to reflect the most up-to-date clinical research as well as the widespread consensus among physicians about appropriate diagnostic and treatment standards. To date, these revisions have essentially represented a ''fine-tuning'' of the initial judgment that tumor size, lymph node status, and presence of distant metastases are the most significant prognostic factors for breast cancer. With the problems of standardization and reproducibility being resolved, it is likely that histologic grade will join this group of independent markers and be incorporated into the AJCC staging system in the near future. Over the last 15 years, considerable attention has been focused on the discovery of new markers visualized with immunohistochemistry and RT-PCR that may be validated as independent prognostic indicators (reviewed by Mirza et al [50]). To date, the usefulness of many of these markers has been limited by lack of standardization in measurement techniques, but several show great promise for the future. By increasing the number of prognostic markers that can give independent information about patient outcome, physicians will be better able to determine optimal treatment approaches for individual patients.

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