PART VII

Breast

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Breast

At-A-Glance

SUMMARY OF CHANGES

Tumor (T)

- Identified specific imaging modalities that can be used to estimate clinical tumor size, including mammography, ultrasound, and magnetic resonance imaging (MRI)
- Made specific recommendations that (1) the microscopic measurement is the most accurate and preferred method to determine pT with a small invasive cancer that can be entirely submitted in one paraffin block, and (2) the gross measurement is the most accurate and preferred method to determine pT with larger invasive cancers that must be submitted in multiple paraffin blocks
- Made the specific recommendation to use the clinical measurement thought to be most accurate to determine the clinical T of breast cancers treated with neoadjuvant therapy. Pathologic (posttreatment) size should be estimated based on the best combination of gross and microscopic histological findings
- Made the specific recommendation to estimate the size of invasive cancers that are unapparent to any clinical modalities or gross pathologic examination by carefully measuring and recording the relative positions of tissue samples submitted for microscopic evaluation and determining which contain tumor
- Acknowledged "ductal intraepithelial neoplasia" (DIN) as uncommon, and still not widely accepted, terminology encompassing both DCIS and ADH, and clarification that only cases referred to as DIN containing DCIS (±ADH) are classified as Tis (DCIS)
- Acknowledged "lobular intraepithelial neoplasia" (LIN) as uncommon, and still not widely accepted, terminology encompassing both LCIS and ALH, and clarification that only cases referred to as LIN containing LCIS (±ALH) are classified as Tis (LCIS)
- Clarification that only Paget's disease NOT associated with an underlying noninvasive (i.e., DCIS and/or LCIS) or invasive breast cancer should be classified as Tis (Paget's) and that Paget's disease associated with an underlying cancer be classified according to the underlying cancer (Tis, T1, etc.)
- Made the recommendation to estimate the size of noninvasive carcinomas (DCIS and LCIS), even though it does not currently change their T classification, because noninvasive cancer size may influence therapeutic decisions, acknowledging that providing a precise size for LCIS may be difficult
- Acknowledged that the prognosis of microinvasive carcinoma is generally thought to be quite favorable, although the clinical impact of multifocal microinvasive disease is not well understood at this time
- Acknowledged that it is not necessary for tumors to be in separate quadrants to be classified as multiple simultaneous ipsilateral carcinomas, providing that they can be unambiguously demonstrated to be macroscopically distinct and measurable using available clinical and pathologic techniques

continued

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SUMMARY OF CHANGES (CONTINUED)

- Maintained that the term "inflammatory carcinoma" be restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer
- Recommend that all invasive cancer should be graded using the Nottingham combined histologic grade (Elston-Ellis modification of Scarff–Bloom–Richardson grading system)

Nodes (N)

- Classification of isolated tumor cell clusters and single cells is more stringent. Small clusters of cells not greater than 0.2 mm, or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section are classified as isolated tumor cells
- Use of the (sn) modifier has been clarified and restricted. When six or more sentinel nodes are identified on gross examination of pathology specimens the (sn) modifier should be omitted
- Stage I breast tumors have been subdivided into Stage IA and Stage IB; Stage IB includes small tumors (T1) with exclusively micrometastases in lymph nodes (N1mi)

Metastases (M)

- Created new M0(i+) category, defined by presence of either disseminated tumor cells detectable in bone marrow or circulating tumor cells or found incidentally in other tissues (such as ovaries removed prophylactically) if not exceeding 0.2 mm. However, this category does not change the Stage Grouping. Assuming that they do not have clinically and/or radiographically detectable metastases, patients with M0(i+) are staged according to T and N

Postneoadjuvant Therapy (yc or ypTNM)

- In the setting of patients who received neoadjuvant therapy, pretreatment clinical T (cT) should be based on clinical or imaging findings
- Postneoadjuvant therapy T should be based on clinical or imaging (ycT) or pathologic findings (ypT)
- A subscript will be added to the clinical N for both node negative and node positive patients to indicate whether the N was derived from clinical examination, fine needle aspiration, core needle biopsy, or sentinel lymph node biopsy
- The posttreatment ypT will be defined as the largest contiguous focus of invasive cancer as defined histopathologically with a subscript to indicate the presence of multiple tumor foci. Note: definition of posttreatment ypT remains controversial and an area in transition
- Posttreatment nodal metastases no greater than 0.2 mm are classified as ypN0(i+) as in patients who have not received neoadjuvant systemic therapy. However, patients with this finding are not considered to have achieved a pathologic complete response (pCR)
- A description of the degree of response to neoadjuvant therapy (complete, partial, no response) will be collected by the registrar with the posttreatment ypTNM. The registrars are requested to describe how they defined response [by physical examination, imaging techniques (mammogram, ultrasound, magnetic resonance imaging (MRI)) or pathologically]
- Patients will be considered to have M1 (and therefore Stage IV) breast cancer if they have had clinically or radiographically detectable metastases, with or without biopsy, prior to neoadjuvant systemic therapy, regardless of their status after neoadjuvant systemic therapy

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PROGNOSTIC FEATURES

New biomarkers are added and recommended for collection in addition to hormone receptors (estrogen receptor, ER; progesterone receptor, PgR). These are HER2 (also designated as erbB2 and c-neu) status and multigene signature "score" or classifications.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

ICD-O-3 TOPOGRAPHY CODES

C50.0 Nipple
C50.1 Central portion of breast
C50.2 Upper inner quadrant of breast
C50.3 Lower inner quadrant of breast
C50.4 Upper outer quadrant of breast
C50.5 Lower outer quadrant of breast
C50.6 Axillary tail of breast
C50.8 Overlapping lesion of breast
C50.9 Breast, NOS

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8940–8950, 8980–8981, 9020

Notes:

*T1 includes T1mi.

**T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered 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 that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

INTRODUCTION

This staging system for carcinoma of the breast applies to invasive (also designated infiltrating) as well as in situ carcinomas, with or without microinvasion. Microscopic confirmation of the diagnosis is mandatory, and the histologic type and grade of carcinoma should be recorded. For all sites (T, N, M), clinical staging (c) is determined using information identified prior to surgery or neoadjuvant therapy. Pathologic staging (p) includes information defined at surgery. With neoadjuvant therapy a posttherapy pathologic staging is recorded using the "yp" designator.

The year 2009 marks the 50th anniversary of codification of tumor staging into the TNM system by the American Joint Committee on Cancer (AJCC; originally designated the American Joint Committee for Cancer Staging and End-Results Reporting). Beginning with that initiative, six editions of the AJCC Staging Manual have been published, in which careful definitions of the primary tumor (T), the status of the surrounding lymph nodes (N), and the presence of distant

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metastases have been refined to reflect updates in technology and clinical evidence.[1] In each case, changes in the TNM system were made cautiously, so as to reflect modern clinical approaches while maintaining connections with the past. The recommendations by the Breast Cancer Task Force for the seventh edition are made in the same spirit.

Rapid advances in both clinical and laboratory science and in translational research have raised questions about the ongoing relevance of TNM staging, especially in breast cancer. For the most part, the TNM system was developed in 1959 in the absence of effective systemic therapy and certainly in a void of the understanding of the biology of breast cancer that exists today. The system was generated to reflect the risk of distant recurrence and death subsequent to local therapy, which at the time was almost universally aggressive surgery (radical mastectomy) and postoperative radiation to the chest wall. Therefore, the primary objective of TNM staging was to provide a standard nomenclature for prognosis of patients with newly diagnosed breast cancer, and its main clinical utility was to prevent apparently futile therapy in those patients who were destined to die rapidly in spite of aggressive local treatments.

Over the succeeding decades, remarkable progress has led to (1) less disfiguring surgery with modified radical mastectomies and breast conserving therapy, (2) dramatic improvements in the delivery and safety of radiation, (3) the recognition that early (adjuvant) systemic therapy reduces recurrences and mortality, and (4) a better understanding of biologic markers of prognosis, and perhaps more importantly, of prediction of response to selective categories of systemic therapy, such as those targeting cancer cells positive for estrogen receptors (ER) and HER2 overexpression.[2] TNM staging has been used as a guide to select whether to apply systemic therapy based on anatomic prognosis. Increasingly, biologic factors, such as ER and HER2, have become important to select which therapy to give.

These advances raise the questions: Is TNM staging still relevant for breast cancer in the twenty-first century and what, exactly, is the objective of TNM staging for patients with this disease? There are three potential answers to the second question: (1) To permit breast cancer investigators to remain linked to the past, in regards to studying categories of patients that accurately reflect prior groupings over the last six decades, (2) to permit current investigators in the field to communicate with one another in the same manner, and/or (3) to improve individual patient care. The AJCC Breast Cancer Task force has struggled with these questions, both for the seventh edition as well as for past editions. Indeed, the Breast Cancer Task Force made a major change from the fifth edition to the sixth edition in recommending that the N staging category be divided into three categories based on the number of axillary lymph nodes involved. In this regard, the current Breast Cancer Task Force came to the conclusion that although the TNM staging system provides insight into whether a patient's prognosis is so favorable the patient might forego systemic therapy, it is becoming anachronistic with regard to making recommendations for specific types of systemic therapy.

Although T, N, and M do still provide some value in determining a patient's future outcome, the average clinician today must take into account multiple factors that relate both to prognosis and prediction. For example, testing for estrogen and progesterone receptor content as well as HER2 status is now considered standard of care.[3] Although these factors do have intrinsic prognostic value in regards to the risk of subsequent recurrence for patients who do not receive systemic therapy, their main utility is to guide whether a patient should or should not receive adjuvant endocrine (anti-estrogen) or anti-HER2 (such as trastuzumab) therapy. The use of these factors as predictive, rather than prognostic, markers is fundamentally important in evaluation and care of patients with newly diagnosed breast cancer, but the Committee found it difficult to devise a scheme in which they might be incorporated into the TNM system.

The situation has become even more complex with the availability of multigene expression assays.[4] One such assay, based on a 70-gene prognostic signature developed by investigators from Amsterdam,[5] has been cleared by the United States Food and Drug Administration for use in women who are less than 61 years old and who have stage I or II, node negative breast cancer, explicitly to "assess a patient's risk for distant metastases." (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=24303). The Tumor Marker Guidelines Committee of the American Society of Clinical Oncology (ASCO) has recommended that a second multigene assay, which is based on expression of 21-genes as determined by RT-PCR (designated the "21-gene recurrence score assay") "can be used" to determine prognosis for patients with ER positive breast cancer and uninvolved lymph nodes who will, at the least, receive adjuvant tamoxifen,[2] and the Breast Committee of the National Comprehensive Cancer Network (NCCN) Guidelines states that "the use of genomic/gene expression arrays which also incorporate additional prognostic/predictive biomarkers (e.g., Oncotype Dx recurrence score) may provide additional prognostic and predictive information beyond anatomic staging and determination of ER/PR and HER2 status."[3] How do such assays become incorporated into the TNM staging system, since they portend future outcomes in several ways? (1) As pure prognostic factors (the profile predicts the odds of recurrence independent of systemic therapy),[6,7] (2) as markers of residual risk assuming the patient will receive endocrine therapy (the profile predicts favorable or unfavorable chances of recurrence presumably due to both prognosis and prediction of benefit or resistance to endocrine therapy),[5,8,9] and (3) perhaps as predictive factors for specific types of, or all, chemotherapies.[10,11]

Should these multiparameter prognostic assays that appear to predict outcomes in newly diagnosed breast cancer patients be included in staging? Since their value may be as much a predictor of response to chemotherapy regardless of TNM stage than as a prognostic factor, should an entirely new category related to prediction of benefit from systemic therapy be incorporated into the TNM staging system? In other words, increasingly in the modern era, many treatment decisions for patients with newly diagnosed breast cancer are

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not, or will not be, based on TNM stage. Although the size of the invasive cancer is a factor, the type of surgery for an individual patient is usually determined by multicentricity and tumor margins, neither of which is part of TNM. Perhaps the only exception is the almost universal recommendation of mastectomy, regardless of other factors, for patients with inflammatory breast cancer. Large tumor size (T3 vs. T1, 2) and lymph node (N 1, 2, or 3 vs. N0) status do play a role in deciding whether radiation should be used after mastectomy or for directing the fields of radiation for women undergoing breast preservation and in the recommendation for axillary dissection. However, in an era when many invasive cancers are detected at very small sizes when breast screening is used, multicentricity and tumor margins appear to be as important as T or N in determining optimal local treatment approaches. In the past, recommendations for most systemic therapy, especially chemotherapy, have been based on nodal status, and in the absence of involved lymph nodes, tumor size.[12,13] However, biologic features such as ER, progesterone receptor, HER2, and to some extent, grade, all play a role in a complex dance involving both prognosis and prediction for the specific therapies. With ongoing advances in molecular biology and technology, coupled with increasing options for novel systemic therapies, such as agents that interfere with angiogenesis, we anticipate that anatomic staging with tumor size, lymph node status, and the presence of clinical and radiographically evident metastases may play increasingly less important roles than understanding of the biology of the cancer.

While the advances in molecular diagnosis have provided new insights into cancer therapy, the Committee understands that much of this consideration is relevant only to the societies in which resources permit widespread screening, molecular evaluation of tumor tissue, and application of cutting edge biological-directed therapies. Projecting to 2010, the annual global burden of new breast cancer cases will be 1.5 million and an ever-increasing fraction will be from low and middle income countries (LMCs).[14] Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths each year in fact occur in developing rather than developed countries. In this regard, LMCs may simply not be able to afford testing for individual molecular events or multiparameter profiles, nor will they be able to provide expensive therapies directed against HER2 or other emerging targets. Tissue assays as basic as ER and PR may be unavailable in low income settings, even when oral endocrine therapies can be provided. Further complicating these resource limitations, women in LMCs typically present with locally advanced (Stage III) or metastatic disease (Stage IV) at diagnosis. In these settings, downstaging of disease through early detection programs may be the most practical approach to improving cancer outcome at the population level.[14] Thus, anatomic (TNM) staging remains a key aspect of cancer control in LMCs, because it directly reflects the degree to which early detection programs are working. While it is of value to continue education regarding the exciting advances in molecular oncology in LMCs, anatomic staging will remain the fundamental cornerstone on which evaluation and treatment decisions of newly diagnosed breast cancer patients will be made.

Ultimately, and after much deliberation, the Task Force has elected to make minor to modest adjustments to the T, N, and M categories for the seventh edition to reflect new technologies and new clinical outcome data since the sixth edition. The Task Force has also substantially enhanced the "yp" category to distinguish stage after preoperative, or "neoadjuvant" systemic therapy and surgery. This designation has already been used by other disease groups, and its incorporation into the seventh edition seems appropriate in light of the growing application of this strategy.[15]

Nonetheless, the Breast Cancer Task Force does not want to ignore the importance of tumor biology, both in predicting recurrence and benefits from therapy. The Task Force did consider adding a "B" category (for biology), in which the status of ER, PR, HER2, and even multigene expression profiles would be incorporated and ultimately added to the Stage Grouping. However, for the reasons above, the Breast Cancer Task Force decided such a step would add little, since they are already used to care for individual patients. Such a change would, by definition, completely abrogate at least the first objective of TNM staging elucidated above (linkage to the past), and it would almost certainly confuse the second (discussion among peers), since not all clinicians worldwide have access to the necessary assays to determine them, especially the newer multigene assays. Therefore, although the Breast Cancer Task Force has not recommended changes to the TNM staging system to incorporate biology, we have requested that the invasive cancer data, if available, be collected in a highly detailed manner for inclusion into the National Cancer Database (NCDB) and other central registry databases. Although we recognize that the "prognostic" value of these data will be highly confounded by the effects of systemic therapy we hope this inclusion will permit future investigators to further define the role of these important features in future TNM deliberations.

ANATOMY

Primary Site. The mammary gland, situated on the anterior chest wall, is composed of glandular tissue with a dense fibrous stroma. The glandular tissue consists of lobules that group together into 8–15 lobes, occasionally more, arranged approximately in a spoke-like pattern. Multiple major and minor ducts connect the milk-secreting lobular units to the nipple. Small milk ducts course throughout the breast, converging into larger collecting ducts that open into the lactiferous sinus at the base of the nipple. Each duct system has unique anatomy: the smallest systems may comprise only a portion of a quadrant whereas the largest systems may comprise more than a quadrant. The periphery of each system overlaps along their radial boundaries. Most cancers form initially in the terminal duct lobular units of the breast. Carcinoma spreads along the duct system in the radial axis of the lobe; invasive carcinoma is more likely to spread in a centripetal orientation in the breast stroma from the initial locus

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of invasion, although opportunistic intraductal spread may be enhanced along the radial axes. Glandular tissue is more abundant in the upper outer portion of the breast; as a result, half of all breast cancers occur in this area.

Chest Wall. The chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not the pectoral muscles. Therefore, involvement of the pectoral muscle does not constitute chest wall invasion.

Regional Lymph Nodes. The breast lymphatics drain by way of three major routes: axillary, transpectoral, and internal mammary. Intramammary lymph nodes reside within breast tissue and are coded as axillary lymph nodes for staging purposes. Supraclavicular lymph nodes are classified as regional lymph nodes for staging purposes. Metastases to any other lymph node, including cervical or contralateral internal mammary or axillary lymph nodes, are classified as distant (M1) (Figure 32.1.)

The regional lymph nodes are as follows:

1. Axillary (ipsilateral): interpectoral (Rotter's) nodes and lymph nodes along the axillary vein and its tributaries that may be (but are not required to be) divided into the following levels:
   a. Level I (low-axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle.
   b. Level II (mid-axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes.
   c. Level III (apical axilla): lymph nodes medial to the medial margin of the pectoralis minor muscle and inferior to the clavicle. These are also known as apical or infraclavicular nodes. Metastases to these nodes portend a worse prognosis. Therefore, the infraclavicular designation will be used hereafter to differentiate these nodes from the remaining (level I, II) axillary nodes.
2. Internal mammary (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia.
3. Supraclavicular: lymph nodes in the supraclavicular fossa, a triangle defined by the omohyoid muscle and tendon (lateral and superior border), the internal jugular vein (medial border), and the clavicle and subclavian vein (lower border). Adjacent lymph nodes outside of this triangle are considered to be lower cervical nodes (M1).
4. Intramammary: lymph nodes within the breast; these are considered axillary lymph nodes for purposes of N classification and staging.

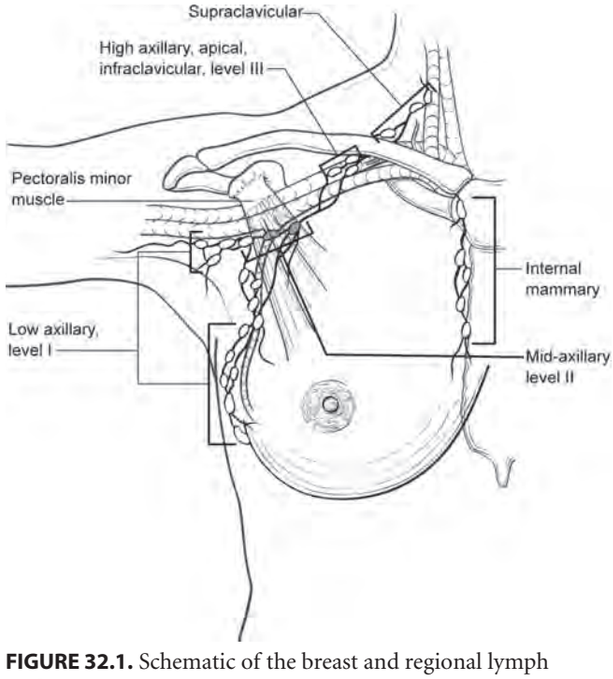

FIGURE 32.1. Schematic of the breast and regional lymph nodes.

Metastatic Sites. Tumor cells may be disseminated by either the lymphatic or the blood vascular system. The four major sites of involvement are bone, lung, brain, and liver, but tumor cells are also capable of metastasizing to many other sites. Bone marrow micrometastases, circulating tumor cells, and tumor deposits no larger than 0.2 mm detected inadvertently, such as in prophylactically removed ovarian tissue, are collectively known as microscopic disseminated tumor cells (DTCs). These deposits do not alone define or constitute metastatic disease, although there are data that demonstrate that, in early stage disease, DTCs correlate with recurrence and mortality risk, and in patients with established M1 disease, circulating tumor cells (CTCs) are prognostic for shorter survival.

RULES FOR CLASSIFICATION

Clinical Staging. Clinical staging includes physical examination, with careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supraclavicular, and cervical), imaging, and pathologic examination of the breast or other tissues as appropriate to establish the diagnosis of breast carcinoma. The extent of tissue examined pathologically for clinical staging is not as great as that required for pathologic staging (see "Pathologic Staging" below). Imaging findings are considered elements of staging if they are collected within 4 months of diagnosis in the absence of disease progression or through completion of surgery, whichever is longer. Such imaging findings would include the size of the primary invasive cancer and of chest wall invasion, and the presence or absence of regional or distant metastases. Imaging and clinical findings obtained after a patient has been treated with neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy are not considered elements of initial clinical staging. If recorded in the medical record, these should be denoted using the modifier prefix "yc."

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Pathologic Staging. Pathologic staging includes all data used for clinical staging, plus data from surgical exploration and resection as well as pathologic examination (gross and microscopic) of the primary carcinoma, regional lymph nodes, and metastatic sites (if applicable), including not less than excision of the primary carcinoma with no macroscopic tumor in any margin of resection by pathologic examination. A cancer can be classified pT for pathologic stage grouping if there is only microscopic, but not macroscopic, involvement at the margin. If there is transected tumor in the margin of resection by macroscopic examination, the pathologic size of the tumor may be estimated from available information but will not necessarily be the sum of the sizes of multiple resected pieces of tumor.

If the primary tumor is invasive (with a possible exception of microinvasive cancer), resection of at least the low axillary lymph nodes (Level I) – that is, those lymph nodes located lateral to the lateral border of the pectoralis minor muscle – should be performed for pathologic (pN) classification. Such a resection will ordinarily include six or more lymph nodes. Alternatively, one or more sentinel lymph nodes may be resected and examined for pathologic classification [pN(sn)]. Certain histologic invasive cancer types [classic tubular carcinoma <1 cm, classic mucinous carcinoma <1 cm, and microinvasive carcinoma (pT1mi)] have a very low incidence of axillary lymph node metastases and may not require an axillary lymph node dissection, although sentinel lymph node biopsy may be appropriate. Cancerous nodules in the axillary fat adjacent to the breast, without histologic evidence of residual lymph node tissue, are classified as regional lymph node metastases (≥N1). Pathologic stage grouping includes the following two combinations of pathologic and clinical classifications: pT pN pM, or pT pN cM. If surgery occurs after the patient has received neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy, the prefix "yp" should be used with the TNM classification, for example, ypTNM.

Primary Tumor (T)

Determining Tumor Size. The original size of a primary tumor (T) can be measured based on clinical findings (physical examination and imaging modalities such as mammography, ultrasound, and MRI) and pathologic findings (gross and microscopic measurements). Clinical tumor size (cT) should be based on the clinical findings that are judged to be most accurate for a particular case, although it may still be somewhat inaccurate because the extent of some breast cancers is not always apparent with current imaging techniques, and because tumors are composed of varying proportions of noninvasive and invasive disease, which these techniques are currently unable to distinguish. Pathologic tumor size (pT) based on gross measurement may also be somewhat inaccurate for the same reasons, although microscopic assessment is able to distinguish noninvasive and invasive carcinoma, and microscopically determined pT should be based on measuring *only the invasive component*. For small invasive tumors that can be submitted in one section/paraffin block, the microscopic measurement is the most accurate way to determine pT. If an invasive tumor is too large to be submitted for microscopic evaluation in one tissue section/block, the gross measurement is the preferred method of determining pT. Whichever method is used, pT should be recorded to the nearest millimeter. The size of the primary tumor is measured for T classification before any tissue is removed for special purposes, such as prognostic biomarkers or tumor banking. In patients who have undergone diagnostic core biopsies prior to surgical excision (particularly vacuum-assisted core biopsy sampling), measuring only the residual tumor may result in underclassifying the T component and understaging the tumor, especially with smaller tumors. In such cases, the original invasive cancer size should be estimated and verified based on the best combination of imaging, gross, and microscopic histological findings. Adding the maximum invasive cancer dimension on the core biopsy to the residual invasive tumor in the excision is not recommended as this often overestimates maximum tumor dimension. In general, the maximum dimension in either the core biopsy or the excisional biopsy is used for T classification unless imaging dimensions suggest a larger invasive cancer.

For patients who receive neoadjuvant systemic or radiation therapy, it is not possible to determine a pretreatment pathologic size. Therefore, pretreatment T is defined as clinical (cT). Pretreatment staging is clinical, and the clinical measurement defined from examination and imaging is recorded (cT). Posttreatment (ypT) size should be estimated based on the best combination of imaging, gross, and microscopic histological findings. The size of some invasive cancers, regardless of previous biopsy or chemotherapy, may be unapparent to any imaging modalities or gross pathologic examination. In these cases, invasive cancer size can be estimated by carefully measuring and recording the relative positions of tissue samples submitted for microscopic evaluation and determining which contain invasive cancer.

Tis Classification. Pure noninvasive carcinoma, or carcinoma in situ, is classified as Tis, with an additional parenthetical subclassification indicating the subtype. Three subtypes are currently recognized, including ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and Paget's disease of the nipple with no underlying invasive cancer. These are categorized as Tis (DCIS), Tis (LCIS), and Tis (Paget's), respectively. "Intraductal carcinoma" is an outmoded term for DCIS, which is still used occasionally, and tumors referred to in this manner (which is discouraged) should be categorized as Tis (DCIS). "Ductal intraepithelial neoplasia" (DIN) is a recently proposed but uncommonly used terminology encompassing both DCIS and atypical ductal hyperplasia (ADH), and only cases referred to as DIN containing DCIS (±ADH) should be classified as Tis (DCIS).[16,17] Similarly, "lobular intraepithelial neoplasia" (LIN) is an uncommon terminology encompassing both atypical lobular hyperplasia (ALH) and LCIS, and only cases referred to as LIN containing LCIS (±ALH) should be classified as Tis (LCIS).[18] DIN and LIN are not widely accepted terminology. "Lobular neoplasia

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in situ" is an outmoded term also encompassing both ALH and LCIS, and only tumors referred to in this manner (which is discouraged) containing LCIS (±ALH) should be classified as Tis (LCIS). If DCIS and LCIS are both present, the tumor is currently classified as Tis (DCIS). A recently published Cancer Protocol and Checklist from the College of American Pathology provides much greater detail regarding definition and evaluation of in situ cancer of the breast[19] (http://www.cap.org).

Paget's disease is characterized clinically by an exudate or crust of the nipple and areola caused by infiltration of the epidermis by noninvasive breast cancer epithelial cells. This condition usually occurs in one of the following three settings[20]: (1) Associated with an invasive carcinoma in the underlying breast parenchyma. The T classification should be based on the size of the invasive disease. (2) Associated with an underlying noninvasive carcinoma, usually DCIS but rarely LCIS. T classification should be based on the underlying tumor as Tis (DCIS) or Tis (LCIS), accordingly. However, the presence of Paget's disease associated with invasive or noninvasive carcinomas should still be recorded. (3) Not associated with identifiable underlying invasive or noninvasive disease. These are the only lesions that should be classified as Tis (Paget's).

The size of noninvasive carcinomas does not change their T classification. However, because tumor size may influence therapeutic decisions, an estimate of size should be still provided based on the best combination of imaging, gross, and microscopic histological findings.[19] Sizing of LCIS may be difficult, but an attempt to do so, based on either clinical/radiographic and/or pathologic features, is recommended.

Microinvasive Carcinoma. Microinvasive carcinoma is defined as an invasive carcinoma with no focus measuring >1 mm. In cases with only one focus, its microscopic measurement should be provided. In cases with multiple foci, the pathologist should attempt to quantify the number of foci and the range of their sizes, including the largest, but should not report the size of the tumor as the sum of the sizes. If there are multiple foci, reporting of the number may be difficult. In these cases, it is recommended that an estimate of the number be provided, or alternatively a note that the number of foci of microinvasion is too numerous to quantify, but that no identified focus is larger than 1.0 mm. Microinvasive carcinoma is nearly always encountered in a setting of DCIS (or, less often, LCIS) where small foci of tumor cells have invaded through the basement membrane into the surrounding stroma, although rare cases are encountered in the absence of noninvasive disease. The prognosis of microinvasive carcinoma is generally thought to be quite favorable, although the clinical impact of multifocal microinvasive disease is not well understood at this time.

Multiple Simultaneous Ipsilateral Primary Carcinomas. Multiple simultaneous ipsilateral primary carcinomas are defined as infiltrating carcinomas in the same breast, which are grossly or macroscopically distinct and measurable using available clinical and pathologic techniques. T stage assignment in this setting should be based only on the largest tumor, and the sum of the sizes should not be used. However, the presence and sizes of the smaller tumor(s) should be recorded using the "(m)" modifier as defined by the TNM rules in Chap. 1.

Invasive cancers that are in close proximity, but are apparently separate grossly, may represent truly separate tumors or one tumor with a complex shape. Distinguishing these two situations may require judgment and close correlation between pathologic and clinical findings (especially imaging), and preference should be given to the modality thought to be the most accurate in a specific case. When macroscopically apparently distinct tumors are very close (e.g., <5 mm), especially if they are similar histologically, they are most likely one tumor with a complex shape, and their T category should be based on the largest combined dimension. Careful and comprehensive microscopic evaluation often reveals subtle areas of continuity between tumor foci in this setting. However, contiguous uniform tumor density in the intervening tissue is needed to justify adding two grossly distinct masses. These criteria apply to multiple macroscopically measurable tumors and do not apply to one macroscopic carcinoma associated with multiple separate microscopic (satellite) foci. Tumors along the same approximate radial axis are frequently related and have arisen in the same duct system.

Simultaneous Bilateral Primary Carcinomas. Each carcinoma is staged as a separate primary carcinoma in a separate organ based on its own characteristics, including T category as specified in the TNM rules (see Chap. 1).

Inflammatory Carcinoma. Inflammatory carcinoma is a clinical-pathologic entity characterized by diffuse erythema and edema (peau d'orange) involving a third or more of the skin of the breast.[21] The tumor of inflammatory carcinoma is classified T4d. It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. On imaging, there may be a detectable mass and characteristic thickening of the skin over the breast. An underlying mass may or may not be palpable, although imaging modalities often reveal one. The skin changes are due to lymphedema caused by tumor emboli within dermal lymphatics, which may or may not be obvious in a small skin biopsy. However, a tissue diagnosis is still necessary to demonstrate an invasive carcinoma in the underlying breast parenchyma or at least in the dermal lymphatics, as well as to determine biologic markers, such as estrogen receptor, progesterone receptor, and HER2 status. Tumor emboli in dermal lymphatics without the clinical skin changes described above do not qualify as inflammatory carcinoma. Locally advanced breast cancers directly invading the dermis or ulcerating the skin without the clinical skin changes and tumor emboli in dermal lymphatics also do not qualify as inflammatory carcinoma. Thus, the term *inflammatory carcinoma* should not be applied to a patient with neglected locally advanced cancer of the breast presenting late in the course of her disease. The rare case that exhibits all the features of inflammatory breast carcinoma, but in which skin changes

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involve less than one third of the skin, should be classified as T4b or T4c.

Skin of Breast. Dimpling of the skin, nipple retraction, or any other skin change except those described under T4b and T4d may occur in T1, T2, or T3 without changing the classification.

Regional Lymph Nodes (N)

Macrometastases. Cases in which regional lymph nodes cannot be assessed (previously removed or not removed for pathologic examination) are designated NX or pNX. Cases in which no regional lymph node metastases are detected are designated cN0 or pN0.

For patients who are clinically node-positive, cN1 designates metastases to one or more movable ipsilateral level I, II axillary lymph nodes, cN2a designates metastases to level I, II axillary lymph nodes that are fixed to each other (matted) or to other structures, and cN3a indicates metastases to ipsilateral infraclavicular (level III axillary) lymph nodes. Metastases to the ipsilateral internal mammary nodes are designated as cN2b when they are detected by imaging studies (including CT scan and ultrasound, but excluding lymphoscintigraphy) or by clinical examination and when they do not occur in conjunction with metastases to the level I, II axillary lymph nodes. Metastases to the ipsilateral internal mammary nodes are designated as cN3b when they are detected by imaging studies or by clinical examination and when they occur in conjunction with metastases to the level I, II axillary lymph nodes. Metastases to the ipsilateral supraclavicular lymph nodes are designated as cN3c regardless of the presence or absence of axillary or internal mammary nodal involvement. Since lymph nodes that are detected by clinical or imaging examination are frequently larger than 1.0 cm, the presence of tumor deposits should be confirmed by fine needle aspirate or core biopsy with cytologic/histologic examination if possible. Lymph nodes classified as malignant by clinical or imaging characteristics alone, or only by fine needle aspirate cytology examination or core biopsy, and not by formal surgical dissection and pathologic review, are presumed to contain macrometastases for purposes of clinical staging classification. When confirmed by fine needle aspirate or core biopsy, the (f) modifier should be used to indicate cytologic/histologic confirmation, for example, cN2a(f). Pathologic classification rules apply when lymph nodes are removed by surgical excisional biopsy and examined histopathologically.

For patients who are pathologically node-positive with macrometastases, at least one node must contain a tumor deposit greater than 2 mm and all remaining quantified nodes must contain tumor deposits greater than 0.2 mm (at least micrometastases); nodes containing only tumor deposits ≤0.2 mm (ITCs) are excluded from the positive node count for purposes of N classification but should be recorded as additional ITC involved nodes and should be included in the total nodes evaluated. Cases with 1–3 positive level I/II axillary lymph nodes are classified pN1a; cases with 4–9 positive axillary lymph nodes are classified pN2a, and cases with 10 or more positive axillary lymph nodes are classified pN3a. Cases with histologically confirmed metastases to the internal mammary nodes, detected by sentinel lymph node dissection but not by clinical examination or imaging studies (excluding lymphoscintigraphy), are classified as pN1b if occurring in the *absence* of metastases to the axillary lymph nodes and as pN1c if occurring in the *presence* of metastases to 1–3 axillary lymph nodes. If four or more axillary lymph nodes are involved, and internal mammary sentinel nodes are involved, the classification pN3b is used. Pathologic classification is used when axillary nodes have been histologically examined and clinical involvement of the ipsilateral internal mammary nodes is detected by imaging studies (excluding lymphoscintigraphy); in the absence or presence of axillary nodal metastases, pN2b and pN3b classification is used, respectively.

Histologic evidence of metastases in ipsilateral supraclavicular lymph node(s) is classified as pN3c. A classification of pN3, regardless of primary tumor size or grade, is classified as Stage IIIC. A case in which the classification is based only on sentinel lymph node biopsy is given the additional designation (sn) for "sentinel node" – for example, pN1(sn). For a case in which an initial classification is based on a sentinel lymph node biopsy but a standard axillary lymph node dissection is subsequently performed, the classification is based on the total results of both the axillary lymph node dissection and the sentinel node biopsy, and the (sn) modifier is removed. The (sn) modifier indicates that nodal classification is based on less than an axillary dissection. When the combination of sentinel and nonsentinel nodes removed is less than a standard low axillary dissection (less than six nodes) the (sn) modifier is used. The number of quantified nodes for staging is generally the number of grossly identified, histologically confirmed lymph nodes. Care should be taken to avoid overcounting sectioned nodes or sectioned adipose tissue with no grossly apparent nodes.

The first priority in pathologic evaluation of lymph nodes is to identify all macrometastases (metastases larger than 2.0 mm). The entire lymph node should be submitted for evaluation and larger nodes should be bisected or thinly sliced no thicker than 2.0 mm. A single histologic section of each slice has a high probability of detecting all macrometastases present although the largest dimension of the metastases may not be represented. More comprehensive evaluation of lymph node paraffin blocks is not required for staging; however, techniques such as multilevel sectioning and immunohistochemistry will identify additional tumor deposits, typically less than or equal to 2.0 mm [micrometastases and isolated tumor cell clusters (ITCs)]. It is not recommended that nodal tissue that may contain a macrometastasis be diverted for experimental or alternative testing, such as molecular analysis, if this diversion would potentially result in the pathologist missing macrometastases detectable by routine microscopic examination.

Isolated Tumor Cell Clusters and Micrometastases. ITCs are defined as small clusters of cells not greater than 0.2 mm

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in largest dimension, or single cells, usually with little if any histologic stromal reaction. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. When no single metastasis larger than 0.2 mm is identified, regardless of the number of nodes containing ITCs, the regional lymph nodes should be designated as pN0(i+) or pN0(i+)(sn), as appropriate, and the number of ITC-involved nodes should be noted.

Approximately 1,000 tumor cells are contained in a three-dimensional 0.2-mm cluster. Thus, if more than 200 individual tumor cells are identified as single dispersed tumor cells or as a nearly confluent elliptical or spherical focus in a single histologic section of a lymph node there is a high probability that more than 1,000 cells are present in the lymph node. In these situations, the node should be classified as containing a micrometastasis (pN1mi). Cells in different lymph node cross or longitudinal sections or levels of the block are not added together; the 200 cells must be in a single node profile even if the node has been thinly sectioned into multiple slices. It is recognized that there is substantial overlap between the upper limit of the ITC and the lower limit of the micrometastasis categories due to inherent limitations in pathologic nodal evaluation and detection of minimal tumor burden in lymph nodes. Thus, the threshold of 200 cells in a single cross-section is a guideline to help pathologists distinguish between these two categories. The pathologist should use judgment regarding whether it is likely that the cluster of cells represents a true micrometastasis or is simply a small group of isolated tumor cells.

Micrometastases are defined as tumor deposits greater than 0.2 mm but not greater than 2.0 mm in largest dimension. Cases in which at least one micrometastasis is detected but no metastases greater than 2 mm (macrometastases) are detected, regardless of the number of involved nodes, are classified pN1mi or pN1mi(sn), as appropriate, and the number of involved nodes should be noted.

The size of a tumor deposit is determined by measuring the largest dimension of any group of cells that are touching one another (confluent or contiguous tumor cells) regardless of whether the deposit is confined to the lymph node, extends outside the node (extranodal or extracapsular extension), or is totally present outside the lymph node and invading adipose. When there are multiple tumor deposits in a lymph node, whether ITCs or micrometastases, the size of only the largest contiguous tumor deposit is used to classify the node; do not use the sum of all individual tumor deposits. When a tumor deposit has induced a fibrous (desmoplastic) stromal reaction, the combined contiguous dimension of tumor cells and fibrosis determines size of the metastasis. When a single case contains multiple positive lymph nodes and the largest tumor deposit in each node is categorically distinct, the number of nodes in each category (macrometastases, micrometastases, ITCs) may be recorded separately to facilitate N classification as described previously.

If histologically negative lymph nodes are examined for evidence of unique tumor or epithelial cell markers using molecular methods [reverse transcriptase–polymerase chain reaction (RT-PCR)] and these markers are detected, the regional lymph nodes are classified as pN0(mol+) or pN0(mol+)(sn), as appropriate. Sacrificing lymph node tissue for molecular analysis that would otherwise be available for histologic evaluation and staging is not recommended particularly when the size of the sacrificed tissue is large enough to contain a macrometastasis. If these data are generated, they should be collected by the registrar.

Distant Metastases (M). Cases in which there are no distant metastases as determined by clinical and/or radiographic methods are designated cM0, and cases in which one or more distant metastases are identified by clinical and/or radiographic methods are designated cM1. Positive supraclavicular lymph nodes are classified as N3 (see previous discussion). A case is classified as clinically free of metastases (cM0) unless there is documented evidence of metastases by clinical means (cM1) or by biopsy of a metastatic site (pM1). M stage of breast cancer refers to the classification of clinically significant distant metastases, which typically distinguishes whether or not there is a potential for long-term cure. The ascertainment of M stage requires evaluations consisting of a review of systems, physical examination and often also includes radiographic imaging, blood work, and tissue biopsy. The types of examinations needed in each case may vary and guidelines for these are available.[22] M classification is based on best clinical and radiographic interpretation, but pathologic confirmation is recommended, although it may not be obtained for reasons of feasibility or safety. Additionally, M stage assessment may not yield a definitive answer on the initial set of evaluations, and follow-up studies may be needed such that the final determination is a recursive and iterative process, assuming that the area of question was present at the time of diagnosis of the primary breast cancer. In these cases, the designated stage should remain M0 unless a definitive designation is made that the patient truly had detectable metastases at the time of diagnosis, based on the guidelines that follow. Subsequent development of new metastases in areas not previously thought to be suspicious does not change the patient's original stage and the patient would now be considered to have converted to recurrent Stage IV, which is considered recurrent disease without altering the original stage.

Physical Examination. Detection of metastatic disease by clinical exam should include a full physical examination with focused detail based on symptoms and radiographic findings. When appropriate, serial physical examinations based on evolving symptoms, physical findings, radiographic findings, and/or laboratory findings should be done on an iterative basis. Physical findings alone rarely will provide the basis for assigning M1 stage, and radiographic studies are almost always required. Whenever feasible, biopsy confirmation should be performed.

Radiographic Studies. It is not necessary for the patient to have radiological evaluation of distant sites to be classified as clinically free of metastases. The indication for the indicated radiographic evaluation for the presence of an M lesion in the

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staging of breast cancer is uncertain and varies by T and N stage category. Certainly, all guidelines stipulate that suspicious findings in the history or physical examination, and/or elevated serologic tests for liver or bone function, are indications to proceed with radiographic systemic imaging, such as bone or body scintigraphy or anatomic, cross-sectional imaging. Most experts agree that systemic radiographic staging evaluation for metastases is not warranted in asymptomatic patients with normal blood tests who have T1-2, N0 breast cancer, and likewise most experts agree that staging is appropriate for patients with Stage III disease (clinical or pathologic). Recommendations are mixed for patients with T2N1.

Regardless, staging studies should focus on common sites of metastatic disease and/or sites indicated by symptoms or blood tests. Certain findings such as multiple lesions with classical characteristics of metastases, and clear changes from earlier studies may provide a very high index of suspicion and result in M1 classification. With radiographic screening or evaluation for another cause, false positive staging studies in patients with newly diagnosed breast cancer are relatively common. Pathologic confirmation of metastatic disease should be performed whenever feasible.

Tissue Biopsy. The type of biopsy of a suspicious lesion should be guided by the location of the suspected metastases along with patient preference, safety, and the expertise and equipment available to the care team. Fine needle aspiration (FNA) is adequate, especially for visceral lesions and with the availability of experienced cytopathologic interpretation. Negative FNA or cellular atypia might carry a significant risk of false negativity, especially in bony or scirrhous lesions, so consideration of repeat FNA or other biopsy techniques such as core needle or open surgical biopsy may be warranted. Histopathologic examination should include standard H&E staining and in some cases may require additional immunohistochemical staining or other specialized testing for confirmation of breast cancer or other cancer type. If adequate biomarker data (estrogen receptor, progesterone receptor, HER2) are not available from the primary tumor, these should be obtained on any other biopsy that shows cancer on H&E staining. Special caution should be taken with evaluation of tumor markers in tissue collected from bone biopsies. Decalcification procedures may create false negative results for both immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). Incidentally detected cancer cells, clusters of cancer cells or foci ≤0.2 mm, or circulating tumor cells that are otherwise clinically and radiographically silent should not alone constitute M1 disease and are discussed below.

Laboratory Abnormalities. Patients with abnormal liver function tests should undergo liver imaging, whereas those with elevated alkaline phosphatase or calcium levels, or suggestive symptoms, should undergo bone imaging and/or scintigraphy. Unexplained anemia and other cytopenias require a full hematologic evaluation (e.g., examination of the peripheral smear, iron studies, B12/folate levels) and should be investigated with bone imaging and a bone marrow biopsy depending on the results of the evaluation. Other unexplained laboratory abnormalities such as elevations in renal function should also prompt appropriate imaging tests. Elevated tumor markers are known to be associated with variable degrees of false positivity and their use has not been shown to improve outcome. The routine ordering of these tests, such as CA 15-3, CA 27.29, CEA, and other protein-based markers for staging is not indicated.[2]

Circulating Tumor Cells, Bone Marrow Micrometastases, and Disseminated Tumor Cells. The presence of circulating tumor cells (CTCs) in the blood or micrometastases (≤0.2 mm) in the bone marrow or other nonregional nodal tissues should not be used to define M stage in the absence of other apparent clinical and/or radiographic findings that correspond to pathologic findings. However, an increasing number of studies are showing microscopic bone marrow and circulating tumor cells in M0 disease to be prognostic for recurrence or survival. Thus, denotation of histologically visible micrometastases in bone marrow, blood, or other organs distant from the breast and regional lymph nodes should be denoted by the term M0(i+). For M1 stage breast cancer (clinically and/or radiographically detectable metastases), the enumeration of CTCs at the time of diagnosis of metastatic disease has been shown to strongly correlate with survival, but neither the presence nor the number of CTCs will change the overall classification.

OUTCOMES

Figure 32.2 shows percent survival at 5 years by size of primary tumor and number of nodes involved. Figure 32.3 shows observed survival rates for 211,645 cases with carcinoma of the breast diagnosed in years 2001–2002.

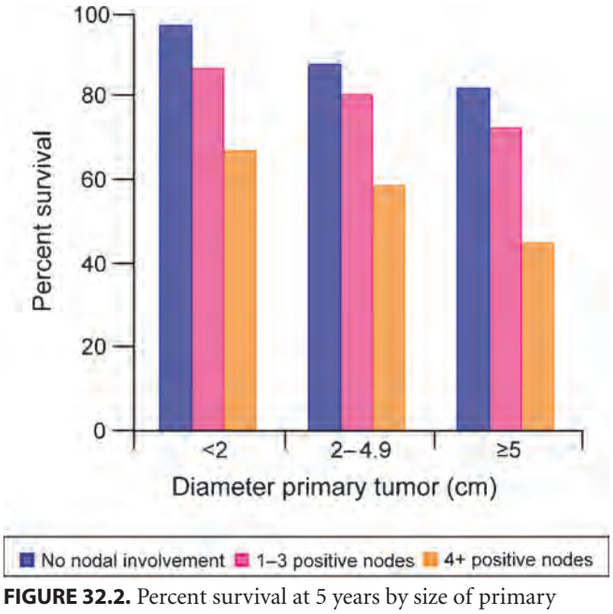

FIGURE 32.2. Percent survival at 5 years by size of primary tumor and number of nodes involved.

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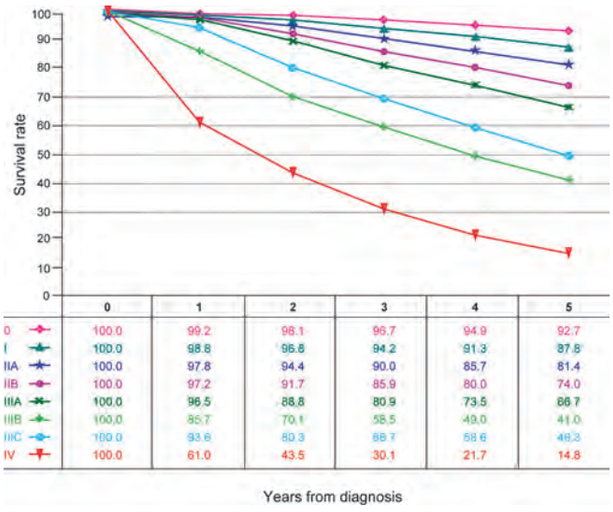

	0	1	2	3	4	5
0	100.0	99.2	98.1	96.7	94.9	92.7
I	100.0	98.8	96.8	94.2	91.3	87.8
IIA	100.0	97.8	94.4	90.0	85.7	81.4
IIB	100.0	97.2	91.7	85.9	80.0	74.0
IIIA	100.0	96.5	88.8	80.9	73.5	66.7
IIIB	100.0	85.7	70.1	58.5	49.0	41.0
IIIC	100.0	93.6	80.3	68.7	58.6	48.3
IV	100.0	61.0	43.5	30.1	21.7	14.8

FIGURE 32.3. Observed survival rates for 211,645 cases with carcinoma of the breast. Data from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) diagnosed in years 2001–2002. Stage 0 includes 30,263; Stage I, 85,278; Stage IIA, 43,047; Stage IIB, 17,665; Stage IIIA, 13,983; Stage IIIB, 4,533; Stage IIIC, 6,741; and Stage IV, 10,135.

DEFINITIONS OF TNM

The increasing use of neoadjuvant therapy in breast cancer and the documented prognostic impact of postneoadjuvant extent of disease and response to therapy warrant clear definitions of the use of the "yp" prefix and response to therapy. The use of neoadjuvant therapy does not change the clinical (pretreatment) stage. As per TNM rules, the clinical stage is identified with the prefix "c". In addition, the use of fine needle aspiration and sentinel lymph node biopsy before neoadjuvant therapy is denoted with the subscripts "f" and "sn," respectively. Nodal metastases detected by FNA or core biopsy are classified as macrometastases (N1) regardless of the size of the tumor focus in the final pathologic specimen. For example, if, prior to neoadjuvant systemic therapy, a patient has no palpable nodes but has an ultrasound-guided FNA biopsy of an axillary lymph node that is positive, the patient will be categorized as cN1 (f) for her clinical (pretreatment) staging and would be considered as stage IIA. Likewise, if the patient has a positive axillary sentinel node identified prior to neoadjuvant systemic therapy, the patient will be categorized as cN1 (sn) (Stage IIA).

As per TNM rules, with the absence of pathologic T evaluation (removal of the primary tumor), microscopic evaluation of nodes before neoadjuvant therapy is still classified as clinical "c."

Primary Tumor (T)

The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

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's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤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 skin nodules).

Note: Invasion of the dermis alone does not qualify as T4

T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma (see "Rules for Classification")

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Posttreatment ypT. Clinical (pretreatment) T will be defined by clinical and radiographic findings, while y pathologic (posttreatment) T will be determined by pathologic size and extension. The ypT will be measured as the largest single focus of invasive tumor, with the modifier "m" indicating multiple foci. The measurement of the largest tumor focus should not include areas of fibrosis within the tumor bed. The inclusion of additional information in the pathology report such as the distance over which tumor foci extend, the number of tumor foci present, or the number of slides/blocks in which tumor appears may assist the clinician in estimating the extent of disease. A comparison of the cellularity in the initial biopsy to that in the posttreatment specimen may also aid in the assessment of response.

Note: If a cancer was designated as inflammatory before neoadjuvant chemotherapy, the patient will be designated to have inflammatory breast cancer throughout, even if the patient has complete resolution of inflammatory findings.

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

**Note*: *Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

Pathologic (pN)*

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i−)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0 (mol−)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0 (mol+)	Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

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Pathologic (pN) (Continued)*	
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes andin internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Notes:
*Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

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

***"Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

****"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Posttreatment ypN

- Post-treatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "sn" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by axillary node dissection (AND).
- The X classification will be used (ypNX) if no yp posttreatment SN or AND was performed
- N categories are the same as those used for pN.

Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Posttreatment yp M classification. The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

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Notes:
*T1 includes T1mi.

**T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered 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 that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS) (Recommended for Collection)

Required for staging	None
Clinically significant	Paget's disease Tumor grade (Scarff–Bloom–Richardson system) Estrogen receptor and test method (IHC, RT-PCR, other) Progesterone receptor and test method (IHC, RT-PCR, other) HER2 status and test method (IHC, FISH, CISH, RT-PCR, other) Method of lymph node assessment (e.g., clinical, fine needle aspiration; core biopsy; sentinel lymph node biopsy) IHC of regional lymph nodes Molecular studies regional lymph nodes Distant metastases method of detection (clinical, radiographic, biopsy) Circulating tumor cells (CTC) and method of detection (RT-PCR, immunomagnetic separation, other) Disseminated tumor cells (DTC; bone marrow micrometastases) and method of detection (RT-PCR, immunohistochemical, other) Multigene signature score
Response to neoadjuvant therapy	Will be collected in the registry but does not affect the postneoadjuvant stage
Complete response (CR)	Pathologic complete response can only be determined by histopathologic evaluation and is defined by the absence of invasive carcinoma in the breast and lymph nodes. Residual in situ cancer, in the absence of invasive disease, constitutes a pCR. Patients with isolated tumor foci in lymph nodes are not classified as having a CR. The presence of axillary nodal tumor deposits of any size, including cell clusters less than or equal to 0.2 mm, excludes a complete response. These patients will be categorized as ypN0(i+).
Partial response (PR)	A decrease in either or both the T or N category compared to the pretreatment T or N, and no increase in either T or N. After chemotherapy, one should use the method that most clearly defined tumor dimensions at baseline for this comparison, although prechemotherapy pT cannot be measured. Clinical (pretreatment) T will be defined by clinical and radiographic findings. y pathologic (posttreatment) T will be determined by pathologic size and extension. Nodal response should be determined by physical examination or radiologic evaluation, if the nodes are palpable or visible before chemotherapy. If prechemotherapy pathologic lymph node involvement is demonstrated by fine needle aspiration, core biopsy, or sentinel node biopsy, it should be recorded as such. Absence of posttreatment pathologic nodal involvement should be used to document pathologic complete response, and should be recorded, but does not necessarily represent a true "response" since one does not know whether lymph nodes removed surgically postchemotherapy were involved prior to chemotherapy.
No response (NR)	No apparent change in either the T or N categories compared to the clinical (pretreatment) assignment or an increase in the T or N category at the time of y pathologic evaluation. Clinical (pretreatment) T will be defined by clinical and radiographic findings. yp (posttreatment) T will be determined by pathologic size. The response category will be appended to the y stage description. For example: • ypTisypN0cM0CR; ypT1ypN0cM0PR; ypT2ypN1cM0NR

HISTOLOGIC GRADE (G)

All invasive breast carcinomas should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff–Bloom–Richardson grading system) is recommended.[2,23] The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism,

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and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3–5 points is designated as grade 1; a combined score of 6–7 points is grade 2; a combined score of 8–9 points is grade 3.

HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)

GX Grade cannot be assessed
G1 Low combined histologic grade (favorable)
G2 Intermediate combined histologic grade (moderately favorable)
G3 High combined histologic grade (unfavorable)

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

In situ Carcinomas

NOS (not otherwise specified)
Intraductal
Paget's disease and intraductal

Invasive Carcinomas

NOS
Ductal
Inflammatory
Medullary, NOS
Medullary with lymphoid stroma
Mucinous
Papillary (predominantly micropapillary pattern)
Tubular
Lobular
Paget's disease and infiltrating
Undifferentiated
Squamous cell
Adenoid cystic
Secretory
Cribriform

SPECIFIC CONSIDERATIONS FOR EVIDENCE-BASED CHANGES TO THE *AJCC CANCER STAGING MANUAL*, SEVENTH EDITION

Revisit of Considerations Between Fifth and Sixth Editions

Q: *Should histologic grade (Nottingham combined histologic grade recommended) be incorporated into the TNM classification system?*
A: No; see "Considerations" below; T category.

Q: *Should the classification of pathologic lymph node status in node-negative patients be amplified to include information about isolated tumor cells detected by immunohistochemical techniques?*
A: Yes, in part and now further clarified; see "Considerations" below; N category

Q: *Should micrometastases (pN1mi) detected by immunohistochemical staining and not verified by H&E staining be classified as pN1?*
A: Yes; see "Considerations" below; N category. The definition is now based on size, NOT how they were detected.

Q: *Should size criteria be used to distinguish between isolated tumor cells and micrometastases?*
A: Yes; see "Considerations" below; N category. The definition is now based on size, NOT how they were detected.

Q: *How should RT-PCR be used in the detection of small tumor deposits?*
A: If collected, it should be collected by the registrar, but not used for staging; see "Considerations" below; N category

Q: *Should the classification of pathologic lymph node status in node-positive (all nodes with deposits greater than 0.2 mm) patients be changed to reflect more clearly the prognostic significance of number of affected nodes?*
A: It was changed in sixth edition; no change in seventh edition.

Q: *Should a finding of positive internal mammary lymph nodes retain a current classification of N3?*
A: It was reclassified pN2b in the sixth edition. In the seventh edition, if positive internal mammary lymph nodes are identified in the absence of axillary lymph node positivity, then it is classified N2b. If positive lymph nodes are identified in the presence of axillary lymph node positivity, then it is classified N3b.

Q: *Should a finding of positive supraclavicular lymph nodes be classified as N3 rather than M1?*
A: It was reclassified pN3 from M1 in the sixth edition. No change in the seventh edition.

Q: *Are there other prognostic factors that are powerful enough to consider for inclusion in the TNM grading system?*
A: No. See "Considerations" below; B category regarding multiparameter assays.

New Considerations Between Sixth and Seventh Editions. The Breast Cancer Task Force deliberated many important issues regarding the TNM staging system for the seventh edition. These can be divided into subtle, but important changes in rules regulating how to collect or interpret already existing factors, such as T, N, and M, and whether new markers and/or technologies should be incorporated into any of these categories. The following discussions highlight these

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considerations and justify the changes that have been recommended.

Of note, the Breast Cancer Task Force did not feel that any new factors have reached a level of evidence to justify inclusion into the staging system. Indeed, a literature search using the terms "breast cancer" and "prognostic factors" yielded over 1,800 publications in the English literature during the 5-year period 2003–2007. These factors included ethnic origin, pre- and post-diagnostic life styles and body habitus, means of diagnosis and apparent radiographic character of the tumor, germ line polymorphisms in candidate genes related to tumor behavior and/or distribution and activity of therapeutic agents, somatic biologic changes in the primary cancer, and evidence of distant, microscopic metastases using sensitive radiographic, molecular, and cellular detection systems. In most, if not all of these studies, the authors conclude that the investigational factor was statistically significantly associated with outcome. However, the studies were often conducted using datasets and tissue specimens that were conveniently available rather than as prospective, well-designed investigations. Importantly, the effects of systemic therapy, either in the adjuvant or metastatic settings, were often ignored or not even considered. Therefore, one is unable to determine if differential outcomes between those patients who were positive vs. those who were negative occurred because of, or in spite of, the marker. Such considerations must be taken into account in the design, conduct, analysis, and reporting of tumor marker studies.[24–30]

Primary Tumor (T)

Should histologic grade (Nottingham combined histologic grade recommended) be incorporated into the TNM classification system?

As noted, the issue of inclusion of histologic grade was very seriously considered by the Breast Cancer Task Force in preparation of the sixth edition. Ultimately, after careful deliberation of all of the identified published literature on the subject, the Task Force elected not to include grade as a stage modifying factor in the TNM system.[23] The Task Force acknowledged the consistent differences in outcomes between women whose tumors were grade 1 vs. those that were grade 3, using the modified Scarff–Bloom–Richardson scoring system. However, the majority of breast cancers are classified as grade 2, and the prognostic significance of this category inconsistently tracked with either of the other two grades, depending on the study. Moreover, persistent concerns about grading inconsistency between observers contributed to the decision not to include grade.

Several new studies have been published since the sixth edition, but none has clarified the issue any further than what were available to the Task Force at that time. Additionally, several authors have addressed specific molecular components of grade, such as proliferative markers and multigene expression arrays that appear to reflect grade.[31–33] However, these assays are either not widely available, or, like standard histopathologic analyses, reproducibility has been an issue. However, the Task Force does recommend collection of tumor grade, using the standardized Nottingham combined histologic score with calibrated mitotic counts, for inclusion in registry databases.

Should T4 be distilled to inflammatory carcinoma only?

Recent studies have suggested that the T4 designation should be restricted to inflammatory carcinoma (T4d) only, with the consideration that T4 a, b, and c categories have outcomes similar to those in the T3 category, and substantially better than those with true inflammatory breast cancer, if carefully defined.[34–36] In this case, the other subcategories (T4a, T4b, T4c) would then be categorized based on the size of the tumor in each case, regardless of skin or chest wall involvement.

The Breast Cancer Task Force concluded that the data from the main study suggesting this change were interesting, but size of the study was modest and the analyses were not comprehensive. Therefore, the Task Force requested an analysis of 5-year survival rates in T4 lesions in the National Cancer Database from 1998 to 2000. In this analysis of 9,865 cases, significantly different outcomes were observed for each of the T4 categories (T4a = 47%, T4b = 40%, T4c = 28%, T4d = 34%; $p < 0.0001$ all pair-wise comparisons). However, without a comprehensive comparison to tumors of similar size/stage but <T4, the Task Force could not conclude that restricting T4 to T4d was appropriate. The group concluded that the data were insufficient at this time to recommend a change, but that they do warrant further study and future consideration.

Should the term "inflammatory carcinoma" be restricted to cases with typical clinical skin changes AND the presence of histologically confirmed invasive carcinoma involving dermal lymphatics?

The Task Force carefully considered this issue and elected not to recommend changes in the seventh edition. The definition of inflammatory breast cancer will remain clinical and does not require the finding of dermal lymphatic involvement, although it does, of course, require histologic confirmation of cancer either in breast parenchyma or skin. Dermal lymphatic involvement supports the diagnosis of inflammatory breast cancer but is not necessary, nor is it sufficient, in the absence of classical clinical findings, for the diagnosis of inflammatory breast cancer. The Task Force acknowledges that this recommendation is not based so much on new data but rather a perceived need to clarify the definition in the sixth edition, which was considered ambiguous.

Should the size of multiple separate ipsilateral tumors be taken into account when determining T category and Stage?

In prior editions of the *Staging Manual*, T stage assignment for patients with multiple, concurrent ipsilateral breast cancers has been based only on the largest tumor, and the sum of the sizes has not been used. Although some studies suggest that multiple tumors may have a somewhat worse prognosis than single tumors in the same T category, the data are insufficient to change the current rules for staging.[37] However, the presence and sizes of the smaller tumor(s) should be recorded. The Breast Cancer Task Force does express concern about this issue and suggests it warrants further study.

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Regional Lymph Nodes (N)

Should the size thresholds for isolated tumor cell clusters and micrometastases be changed from the current limits of 0.2 and 2.0 mm?

The prognostic significance of axillary metastases above a 2.0-mm threshold was confirmed by two studies reported over 3 decades ago.[38,39] Following the first study, a subcategory for micrometastases was added to the *Cancer Staging Manual*. The introduction of sentinel lymph node biopsy and widespread use of immunohistochemistry facilitated detection of minimal disease in axillary lymph nodes and the sixth edition of the *Staging Manual* established a lower limit for micrometastases of >0.2 mm creating a new category of minimal nodal disease. This limit was ten times smaller than the upper limit for micrometastases and had been tested in one retrospective study of occult metastases.[40] It was not a limit based on firm medical evidence and should be periodically reevaluated.

Testing these thresholds is not an easy task. Doing so requires excluding the presence of metastases above the suggested threshold prior to comparing differences in outcome for subgroups with smaller metastases, and then either accepting the confounding effects of systemic therapy or identifying datasets of untreated patients. To date, no study has evaluated differences in disease free or overall survival for metastases above and below a 1.0-mm threshold after excluding all metastases above 2.0 mm. When these data become available, the upper limit of 2.0 mm for micrometastases could be reconsidered.

Evaluating the upper limit for isolated tumor cell clusters is more problematic because it requires excluding all patients with metastases larger than 0.2 mm prior to comparing subgroups with metastases below this threshold. Creating a "true node negative" comparison group is probably not practical with standard histologic techniques. In other words, any "node negative" group will contain some patients with occult metastatic disease. Two limiting principles emerge when evaluating these thresholds; the first is lymph node sectioning strategies and the second is section screening. The possibility of missing a metastasis is proportional to the thickness of unexamined tissue, the number of sections examined, and the capability of the slide screening system to detect disease.[41–44] For example, if evaluation of serial sections from a lymph node is negative, but if a pathologist leaves 1.0 mm of unexamined tissue in the paraffin lymph node block, one can only conclude that there is no metastasis larger than 1.0 mm; there is no guarantee the node does not contain occult disease. Single cells are routinely detected on histologic sections, but metastases as large as 0.1 mm may be missed by a pathologist screening slides.[43,44]

It has been theorized that isolated tumor cell clusters should be distinguishable from micrometastases on the basis of metastatic characteristics, such as proliferation or stromal reaction, and indeed this observation was included in the sixth edition.[23,45] However, in consideration of the seventh edition, the Breast Cancer Task Force perceived that this distinction can be highly subjective and expressed concern that replication among pathologists and among institutions may be difficult. For the seventh edition, the Breast Cancer Task Force continues to define isolated tumor cell clusters as not greater than 0.2 mm in diameter and micrometastases as greater than 0.2 mm and not greater than 2.0 mm in diameter. However, the Task Force has recommended additional stringency to the isolated tumor cell cluster (ITC) category. A 0.2-mm metastasis contains approximately 1,000 tumor cells and a 2.0-mm metastasis contains approximately one million tumor cells. The use of 0.2 mm as a lower limit was selected because it significantly reduces the likelihood that ITCs will be recorded as micrometastases without making it necessary to estimate actual cell number counts in ITCs. However, pathologists have had difficulty applying the size criterion when a large number of nonconfluent tumor cells are present in a lymph node such as may occur in some invasive lobular carcinomas.[46] For this reason, additional guidance has been incorporated in this edition. When more than 200 nonconfluent or nearly confluent tumor cells are present in a single histologic cross section of a lymph node, there is a high probability that more than 1,000 cells are present in the node, that the cumulative volume of these cells exceeds the volume of an ITC, and the node should be classified as containing a micrometastasis. The classification of patients with metastatic tumor deposits no greater than 0.2 mm as pN0 is consistent with the low recurrence rates typically seen in this patient group. The use of 2.0 mm as an upper size limit for micrometastases, originally proposed by Huvos and colleagues in 1971, is consistent with standards already used in the AJCC staging system.[38] These thresholds are meant to be guidelines, and not absolute cutoffs, to help pathologists determine if the tumor burden in a given lymph node is likely to be clinically important or not. The pathologist should use judgment, and not an absolute cutoff of 0.2 mm or exactly 200 cells, in determining the likelihood of whether the cluster of cells is an ITC or a true micrometastasis.

There is significant theoretic overlap in nodal tumor burden at the upper limit of the ITC category and the lower limit of the micrometastasis category that is due to practical and economic constraints in the pathologic evaluation of lymph nodes. After considering these limitations in lymph node examination and the absence of outcome data on clinical significance of isolated tumor cell clusters and micrometastases *after* systematic exclusion of macrometastases, the Breast Cancer Task Force perceived no compelling reason to change the current thresholds.

Should nodal micrometastases be considered different from nodal macrometastases for purposes of overall stage grouping?

The *AJCC Cancer Staging Manual* has traditionally grouped breast cancer cases with exclusively nodal micrometastases (pN1mi) as having the same prognostic significance as macrometastases with respect to assigning an overall stage grouping based on T, N, and M categorical classifications. A recent analysis of data in the United States Surveillance, Epidemiology, and End Results (SEER) national cancer database has demonstrated that when nodal tumor deposits no larger than 2.0 mm are the only finding in lymph nodes and the primary tumor is less than or equal to 2 cm (pT1) the incremental decrease in survival at 5 and 10 years was only 1% compared

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to patients with no nodal metastases detected.[47] Patients with tumors no larger than 2.0 cm (T1) represented 70% of the total population in the analysis, and in this subset calculated 10-year survival decreased from 78% to 77% to 73% for pN0, pN1mi, and pN1a, respectively. This does not justify classifying pN1mi cases with Stage II tumors. This analysis included data from 1992 to 2003 spanning the introduction and widespread adoption of sentinel lymph node biopsy. In this edition of the manual, T1 tumors with nodal micrometastases (pN1mi) will be classified as Stage IB to indicate the better prognosis for the subset of breast cancer patients and to facilitate further investigation.

How should RT-PCR be classified in the detection of nodal tumor deposits?

An even finer level of resolution in the detection of isolated tumor cells and micrometastases is available with the use of reverse transcriptase-polymerase chain reaction (RT-PCR). This technique was able to identify epithelial markers in a significant percentage of sentinel nodes that were negative for disease by both histologic and immunohistochemical staining.[48] This is not surprising given that RT-PCR is theoretically capable of identifying single cells. However, it seems unlikely that minimal tumor burden would be as significant as clinically detected disease or macrometastases. Furthermore, because lymph node tissue is digested and consumed in preparation for RT-PCR, it is technically challenging to determine the exact size of the original metastatic focus. RT-PCR assays have been offered as an adjunct to standard histological analysis of sentinel lymph node biopsy to assist in intraoperative decision making regarding the performance of completion axillary node dissection.[49] The prognostic or staging significance of such RT-PCR assay results remains unclear. There is evidence that such highly-sensitive tests produce false positive results despite efforts to calibrate RT-PCR results with traditional histologic measurements.[41] Correlation between RT-PCR testing and histology has been performed but there is continued and justified concern that RT-PCR assays do not provide the same data as routine histologic measurement and categorization of nodal metastases. A lymph node that is exclusively positive by molecular assay alone (mol+) may contain isolated tumor cell clusters, micrometastases, macrometastases, or be a false positive result due to sampling, contamination, or features intrinsic to the assay. Presently, there are insufficient data to suggest that RT-PCR assay of lymph nodes should replace or substitute for traditional histologic evaluation of lymph nodes. Staging is further complicated when some nodes or portions of some nodes are evaluated by RT-PCR and other nodes are evaluated by histology.

Pending further developments in this area, this edition of the *AJCC Cancer Staging Manual* will continue to classify any lesion identified by RT-PCR alone as pN0 for the purposes of staging. In addition, any case that is histologically negative for regional lymph node metastases and in which examination for epithelial markers was made with RT-PCR and the examination was considered positive will have the appended designation (mol+). It is recommended that the first priority in evaluating lymph nodes is histologic identification of macrometastases (metastases larger than 2.0 mm). Thus, it is not recommended to divert portions of nodal tissue for molecular analysis that might contain a macrometastasis. When lymph nodes contain tumor deposits detected by histologic evaluation and molecular techniques, N classification based on histologic findings and measurements is utilized.

Distant Metastases (M)

How should circulating tumor cells or microscopic tumor cells be handled in the absence of overt clinical finding?

Circulating tumor cells (CTCs) and microscopic tumor cells detected in the bone marrow are collectively designated as DTCs. Several studies have shown a relationship between bone marrow DTCs and recurrence risk and mortality in M0 stage breast cancer.[50,51] However, the Breast Cancer Task Force concluded that although the presence of positive bone marrow micrometastases has been statistically significantly associated with worse outcomes, the difference in recurrence and mortality rates between patients who have them and those who do not was not sufficiently large to recommend a change in the M staging system. In particular, patients who already have a favorable prognosis (T1, N0) do not appear to have a substantially worse outcome if they have positive bone marrow micrometastases.[50]

Although several recent studies have suggested that CTC are commonly detected in patients with early stage breast cancer and may be prognostic, the Task Force concluded that most of these studies were small with short follow-up and were confounded by the effects of systemic therapy.[2,28,52–60]

In summary, the designation of M1 has generally been used to determine a relative, or even, absolute state of incurability. Thus, many clinicians revert to a philosophy of palliative, rather than curative intent, for patients who are designated M1. There are no data to suggest that detection of DTCs in any tissue (bone marrow, ovary, blood) in the absence of clinical and/or radiographic findings confers incurability. Therefore, the Task Force recommends that in the absence of overt metastases detected by clinical examination or imaging abnormalities, DTCs should not affect M staging.

The Task Force has recommended that, for data collection purposes, the DTC designation should be expanded to include any cluster of malignant cells not greater than 0.2 mm found in any tissue outside of the breast and surrounding regional lymph nodes in the absence of clinical or radiographic signs of metastases. DTC assessment is not required or recommended as part of staging at the current time outside of the investigational setting in patients with clinical M0 disease. However, if DTCs are detected, the staging category should be denoted as M0(i+) and the data should be collected by the registrars.

Should DTC (bone marrow micrometastases or CTC) be incorporated to subdivide the M1 category?

The Task Force considered whether the TNM system might be used to further subdivide patients with M1 disease. In patients with overt metastases (M1), the presence and number of CTCs

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at the time of diagnosis have been shown to be prognostic for both disease progression and mortality.[51,58,61–67] Changes in CTCs after treatment are also predictive of response to therapy and prognostic for recurrence and mortality, although the American Society of Clinical Oncology Tumor Marker Guidelines Panel has not recommended routine use of CTC in management of patients with metastatic breast cancer, since the utility of this assay in patient management decisions has not been demonstrated.[2] After careful deliberation, the Task Force decided that the TNM system has not, in the past, dealt with prognosis in those patients with established, clinically or radiographically detectable metastases, and the Task Force elected not to recommend that CTC presence or number be used to further subclassify M1 staging.

y Pathologic (Postneoadjuvant) Systemic Therapy

Why add a postneoadjuvant systemic therapy staging system?
Neoadjuvant therapy, also designated preoperative, presurgical, or primary adjuvant systemic therapy, has been increasingly studied and applied for patients with operable, as well as traditionally inoperable breast cancer.[68] While most commonly considered for chemotherapy, neo- or preoperative adjuvant endocrine therapy has also been studied extensively.[68] The increasing importance of this strategy mandates that the staging system provide the information necessary to assess prognosis in this diverse group of patients. Clearly, outcomes after neoadjuvant systemic therapy differ among patients, so that a staging system should reflect potential prognosis. Thus, the Breast Cancer Task Force has included a staging system to be applied for patients treated in this manner, which will be designated with the prefix y, y pathologic or yp, in accordance with AJCC policy in other disease sites.

What is the proper definition of complete response after neoadjuvant systemic therapy?
The prognostic importance of a histologic complete response (CR) to neoadjuvant chemotherapy was first documented in patients with locally advanced breast cancer.[69] This observation was subsequently confirmed in randomized trials involving patients with operable disease.[70] In several studies, a variety of different definitions of CR have been employed, making a comparison of the outcomes of different treatment regimens difficult. For this reason, the Task Force proposed a standard set of response definitions to be included with the posttreatment stage.

Although an international expert panel proposed that a CR be defined as the absence of invasive and *noninvasive* tumor in the breast,[71] the Task Force recommends that the AJCC definition of CR should be the absence of invasive carcinoma in the breast and the axillary nodes, since the presence of noninvasive cancer, while important in the selection of local therapy, is not a determinant of survival. A retrospective review from the MD Anderson Cancer Center compared the outcome of 78 patients with a pathologic CR and no residual tumor of any kind to that of 199 patients with residual DCIS only and 2,025 patients with residual invasive cancer. The 5 and 10 year disease-free and overall survival rates for patients with a pathologic CR with and without DCIS did not differ significantly, but were significantly better than the survival rates of patients with invasive cancer.[72] Similar findings were reported by Jones et al. in a study of 435 patients.[73]

What is the optimal method of determining T after neoadjuvant systemic therapy?
An unresolved problem in defining the yp posttreatment stage is how to determine the best method for measuring tumor size after neoadjuvant/preoperative chemotherapy. In the absence of a CR, the assessment of the extent of response in the tumor and the measurement of tumor size remain problematic. Partial response in the NSABP protocol B18[74] and in the grading system proposed by Chevillard et al.[75] is identified by nests of tumor in a desmoplastic or fibrotic stroma. In contrast, the Miller–Payne grading system[76] and a system used at the M.D. Anderson Cancer Center[77] rely upon loss of cellularity to describe the degree of response. No single method of assessing response has been shown to be a superior predictor of outcome, and concerns about reproducibility exist for all these measures. The combination of tumor size and an assessment of changes in cellularity are useful in documenting pathologic evidence of response. However, pretreatment biopsies are not always available to the pathologist assessing the posttreatment specimen. For this reason, the Breast Cancer Task Force has defined the pathologic T size by the largest contiguous tumor focus, with a suffix to alert the clinician when multiple scattered tumor foci are observed. When nests of tumor cells in fibrotic stroma are observed posttreatment, the T should be determined based on the largest contiguous area of invasive carcinoma, excluding surrounding areas of fibrosis. This method of T determination has been shown to correlate with survival in the study of Carey et al.[78] Additional information that is important for planning local therapy such as the distance over which the tumor extends (when scattered foci are present) or the number of slides/blocks in which tumor is seen should be included in the pathology report, but is not part of TNM.

How should isolated tumor cells be considered after neoadjuvant therapy?
In patients who have not received neoadjuvant therapy, nodes with ITCs are classified pN0, reflecting uncertainty about their prognostic significance. After neoadjuvant therapy, ITCs could represent the presence of minimal nodal disease pre-treatment which did not respond to therapy or the remnants of macroscopic nodal disease which has had a partial response. Until further data are available to address the prognostic significance of ITCs post-treatment, the presence of ITC precludes classifying the patient as having a complete response to therapy. However, these patients will be classified as ypN0(i+) to maintain standard definitions throughout the TNM system.

Should the same considerations be used for preoperative endocrine (anti-estrogen) or other targeted therapy?
The overwhelming majority of the available information regarding the prognostic significance of CR comes from

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patients treated with chemotherapy. Limited information is available about the prognostic significance of the degree of response when targeted therapies directed against ER or HER2 are used. Pathologic CR is rarely seen in patients receiving 3–4 months of neoadjuvant endocrine therapy, and its absence should not be considered evidence of endocrine resistance or poor prognosis.[79,80] Complete response in patients overexpressing HER2 and treated with trastuzumab plus chemotherapy was associated with a significant survival improvement compared with that in women who did not have pathologic CR.[81] Additional information regarding the relationship between response and survival is needed for the newer targeted therapies, and therefore the Breast Cancer Task Force recommends collection of postneoadjuvant therapy TNM data by the registrars.

What are the difficulties in evaluating partial response?

The Breast Cancer Task Force recognizes that the definition of partial response (PR), requiring a decrease in the T or N category, may fail to capture some patients with a reduction in tumor volume. However, modalities such as physical examination, mammography, ultrasound, and MRI, which may be used to determine the clinical (pretreatment) tumor size, have been demonstrated to significantly overestimate and underestimate the extent of tumor when compared with pathologic examination,[82] making definitions of response based on small changes in the clinically determined pretreatment tumor size compared to the y pathologic posttreatment tumor size potentially inaccurate. In this regard, the most accurate predictor of outcome after neoadjuvant chemotherapy is pathologic complete response.[68,79] However, a rough estimate of response should be determined comparing posttreatment clinical, radiographic, and pathologic assessments with those made prior to initiation of systemic therapy, and this should be recorded.

Should TNM stage prior to neoadjuvant systemic (clinical stage) be considered in y pathologic posttreatment staging?

An increasing body of data suggests that prognosis after neoadjuvant therapy is determined by the posttreatment pathologic stage, degree of response, and the pretreatment stage. Carey et al. demonstrated that the AJCC TNM posttreatment (yp) stage was a significant predictor of both 5-year disease-free and overall survival.[78] However, even in patients with a pathologic CR, the clinical TNM at presentation provides valuable prognostic information. In a group of 226 patients treated at the MD Anderson Cancer Center and having a pathologic CR to neoadjuvant therapy, statistically significant differences in the 10-year metastases-free survival were noted on the basis of stage at presentation.[83] Similar findings were noted for locoregional recurrence (LRR), with patients with clinical Stage I or II disease and a pathologic CR to neoadjuvant therapy having a 0% 10-year incidence of LRR without radiation therapy compared with 33% for those with clinical Stage III disease and a pathologic CR treated without radiotherapy.[10] The relative importance of pretreatment stage, posttreatment stage, and degree of response in predicting survival remains to be defined, and therefore the Task Force does not recommend inclusion of pretreatment TNM data in calculating a posttreatment stage ("yp"), unless the patient was M1 prior to initiation of therapy. In this case, her M status is considered M1 regardless of response to therapy. However, the Task Force does recommend inclusion of response in the data routinely collected in patients receiving neoadjuvant therapy and the definition of the method of determining pretreatment nodal status will allow these relationships to be more carefully assessed.

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