Part XI

Breast

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Breast

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CHAPTER SUMMARY

Cancers Staged Using this Staging System

Invasive (infiltrating) carcinoma of the breast, ductal carcinoma *in situ* of the breast.

Cancers Not Staged Using this Staging System

These histopathologic types of cancer…	Are staged according to the classification for…	And can be found in chapter…
Breast sarcomas	Soft tissue sarcoma of the trunk and extremities	41
Phyllodes tumor	Soft tissue sarcoma – unusual histologies and sites	45
Breast lymphomas	Hematologic malignancies	79–81

Summary of Changes

Change	Details of change	Level of evidence
AJCC Anatomic, Clinical Prognostic Stage and Pathological Prognostic Stage Groups	There are three stage group tables presented in this chapter: 1. Anatomic Stage table. This is based solely on anatomic extent of cancer as defined by the T, N, and M categories. This is intended for use in settings around the world where biomarker analysis is not available. When biomarkers are available, cancers are to be staged using the Clinical and Pathological Prognostic Stage tables. 2. Clinical Prognostic Stage table. This is to be used to assign stage for ALL patients based on history, physical examination, imaging studies performed (not required) and relevant biopsies. Clinical Prognostic Stage is determined by T, N, M, tumor grade, human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) status. 3. Pathological Prognostic Stage table. This is to be used to assign stage for patients who have surgical resection as the initial treatment of their cancer before receipt of any systemic or radiation therapy. It is based on all clinical information, biomarker data, and findings from surgery and resected tissue.	I/II
Selecting the Appropriate Stage Group Table	The Prognostic Stage Group tables are preferred for patient care and are to be used for reporting of all cancer patients in the U.S. The Anatomic Stage Group table is provided so that stage can be assigned in settings and regions of the world where the biomarkers cannot be routinely obtained.	N/A

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Change	Details of change	Level of evidence
Definition of Primary Tumor (T)	Lobular carcinoma *in situ* (LCIS) is removed as a pTis category for T categorization. Lobular carcinoma *in situ* is treated as a benign entity and is removed from TNM staging.	I
Definition of Primary Tumor (T)	The general rules for rounding to the nearest millimeter do not apply for tumors between 1.0 and 1.5 mm, so as to not classify these cancers as microinvasive (T1mi) carcinomas (defined as invasive tumor foci 1.0 mm or smaller). Tumors >1 mm and <2 mm should be reported rounding to 2 mm.	II
Definition of Primary Tumor (T)	Confirmed that the maximum invasive tumor size (T) is a reasonable estimate of tumor volume. Small microscopic satellite foci of tumor around the primary tumor do not appreciably alter tumor volume and are not added to the maximum tumor size.	I
Definition of Primary Tumor (T)	Clarified the T categorization of multiple synchronous tumors. These are identified clinically and/or by macroscopic pathological examination and their presence documented using the (m) modifier for the T category. This new edition specifically continues using only the maximum dimension of the largest tumor for cT and pT; the size of multiple tumors is not added.	I
Definition of Primary Tumor (T)	Added a clear definition that satellite tumor nodules in the skin must be separate from the primary tumor and macroscopically identified to categorize as T4b. Skin and dermal tumor satellite nodules identified only on microscopic examination and in the absence of epidermal ulceration or skin edema (clinical peau d'orange) do not qualify as T4b. Such tumors should be categorized based on tumor size.	I
Definition of Regional Lymph Node (N)	The criteria for pathological measurement of lymph node metastases are clearly defined. The dimension of the area containing several or multiple tumor deposits is NOT used to determine pN category. The largest contiguous tumor deposit is used for pN; adjacent satellite tumor deposits are not added.	I
Definition of Clinical Regional Lymph Node (cN)	The Expert Panel affirmed that cNX is not a valid category unless the nodes in the relevant node basin have been removed and cannot be examined by imaging or clinical examination. A cN0 category is to be assigned when any evaluation of the nodes is possible and the physical examination or imaging examination is negative.	I
Definition of Distant Metastasis (M)	The Expert Panel affirmed that pM0 is not a valid category. All cases should be categorized as either cM0 or cM1; however, if cM1 is subsequently microscopically confirmed, pM1 is used. See Chapter 1 for more information.	I
Post Neoadjuvant Therapy Pathological Tumor Categorization (ypT)	The Expert Panel clarified that the post neoadjuvant therapy pathological T category (ypT) is based on the largest continuous focus of residual invasive cancer, if present. Treatment-related fibrosis adjacent to residual invasive carcinoma or between foci of residual cancer is not included in the ypT maximum dimension. When multiple foci of residual tumor are present, the (m) modifier is included. The pathology report should include a description of the extent of residual tumor explaining the basis for the ypT categorization.	II
Post Neoadjuvant Therapy Pathological Node Categorization (ypN)	The Expert Panel clarified that the largest continuous focus of residual cancer in the lymph nodes, if present, is used for ypN categorization. Treatment-related fibrosis adjacent to residual nodal tumor deposits or between foci of residual cancer is not included in the ypN dimension and classification.	II
Complete Pathological Response	The Expert Panel affirmed that any residual invasive carcinoma detected by pathological examination in the breast, including cancer within blood or lymph vessels (LVI) or lymph nodes precludes posttreatment classification as a complete pathological response (pCR).	I
Complete Pathological Response – Metastasis categorization (M)	If a cancer is categorized M1 (clinical or pathological) prior to or during neoadjuvant therapy, the cancer is categorized as M1 following neoadjuvant therapy, regardless of the observed response to therapy.	N/A
Histologic Grade (G) for invasive cancer	Tumor grade defined by the histologic grading system of Scarff, Bloom, and Richardson, as updated and standardized by the Nottingham group, is now a required element for assigning breast cancer stage for invasive cancer.	I

Change	Details of change	Level of evidence
Nuclear Grade for Ductal Carcinoma in situ (DCIS)	For ductal carcinoma *in situ*, the assigned grade should be nuclear grade.	I
Collection of Biomarkers (Hormone receptor assays and HER2 assay)	The Expert Panel determined that all invasive carcinomas should have estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status determined by appropriate assays whenever possible.	I
Inclusion of Genomic Profiles, Multigene Panels	Multigene panels may provide prognostic and therapy-predictive information that complements T, N, M and biomarker information. Use of these assays is not required for staging. The Breast Expert Panel included one multigene panel in Pathological Prognostic Staging, but others may be equally useful for clinical decision making. Inclusion in the staging system does not imply recommendation or endorsement of one multigene panel over any other for use in clinical care.	N/A
Inclusion of Multigene Panels (when available) as Stage Modifiers – 21 Gene Recurrence Score (Oncotype Dx®)	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 21-gene (Oncotype Dx®) recurrence score less than 11, places the tumor into the same prognostic category as T1a–T1b N0 M0. Such cancers are staged as Stage IA using the AJCC Pathological Prognostic Stage table.	I
Inclusion of Multigene Panels (when available) as Stage Modifiers – Breast Cancer Index	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Breast Cancer Index in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II
Inclusion of Multigene Panels (when available) as Stage Modifiers - EndoPredict®	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 12-gene (EndoPredict) low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b N0 M0.	II
Inclusion of Multigene Panels (when available) as Stage Modifiers – Mammaprint®	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Mammaprint® low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b N0 M0.	II
Inclusion of Multigene Panels (when available) as Stage Modifiers – PAM 50® (ProSigna)	For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a PAM50 risk of recurrence (ROR) score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b N0 M0.	II

ICD-O-3 Topography Codes

Code	Description
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

Histology Codes

This list includes histology codes and preferred terminologies from the *WHO Classification of Tumors* and the *International Classification of Diseases for Oncology* (ICD-O-3). Sometimes there are duplicate histology codes for different behaviors. For cancer reporting purposes, behavior codes /2 (denoting *in situ* neoplasms), /3 (denoting malignant neoplasms) and in some cases /1 (denoting neoplasms with uncertain or unknown behavior) may be appended to the 4-digit histology codes to create a complete morphology code.

Code	Description
8022	Pleomorphic carcinoma
8032	Spindle cell carcinoma
8035	Carcinoma with osteoclast-like stromal giant cells
8041	Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)
8070	Squamous cell carcinoma
8200	Adenoid cystic carcinoma
8201	Cribriform carcinoma
8211	Tubular carcinoma
8246	Neuroendocrine tumor, well-differentiated
8290	Oncocytic carcinoma
8314	Lipid-rich carcinoma
8315	Glycogen-rich clear cell carcinoma
8410	Sebaceous carcinoma
8430	Mucoepidermoid carcinoma
8480	Mucinous carcinoma
8500	Ductal carcinoma *in situ*

Code	Description
8500	Invasive carcinoma of no special type (NST) with medullary features
8500	Invasive carcinoma of no special type (NST)
8502	Secretory carcinoma
8503	Intraductal papillary carcinoma
8503	Intraductal papilloma with ductal carcinoma *in situ*
8503	Invasive papillary carcinoma
8504	Encapsulated papillary carcinoma
8504	Encapsulated papillary carcinoma with invasion
8507	Invasive micropapillary carcinoma
8509	Solid papillary carcinoma
8510	Medullary carcinoma
8513	Atypical medullary carcinoma
8520	Invasive lobular carcinoma
8525	Polymorphous carcinoma
8530	Inflammatory carcinoma
8540	Paget disease of the nipple
8550	Acinic cell carcinoma
8570	Low-grade adenosquamous carcinoma
8571	Metaplastic carcinoma with mesenchymal differentiation, chondroid differentiation
8571	Metaplastic carcinoma with mesenchymal differentiation, osseous differentiation
8572	Fibromatosis-like metaplastic carcinoma
8574	Carcinoma with neuroendocrine differentiation
8575	Metaplastic carcinoma of no special type
8575	Mixed metaplastic carcinoma
8575	Metaplastic carcinoma with mesenchymal differentiation, other types of mesenchymal differentiation
8982	Myoepithelial carcinoma
8983	Adenomyoepithelioma with carcinoma
*8000**	*Neoplasm, malignant*
*8010**	*Carcinoma, NOS*
*8140**	*Adenocarcinoma, NOS*
*8255**	*Adenocarcinoma with mixed subtypes*
*8401**	*Apocrine adenocarcinoma*
*8501**	*Comedocarcinoma, NOS*
*8501**	*Comedocarcinoma, noninfiltrating*
*8521**	*Infiltrating ductular carcinoma*
*8522**	*Infiltrating duct and lobular carcinoma (invasive type only)*
*8523**	*Infiltrating duct mixed with other types of carcinoma*
*8524**	*Infiltrating lobular mixed with other types of carcinoma*
*8541**	*Paget disease and infiltrating duct carcinoma of breast*
*8543**	*Paget disease and intraductal carcinoma*

*Histology is not ideal for clinical care, as the staging system was not created using these cases. Data collectors may use this code if there is not enough information in medical record to document a more specific diagnosis.

Lakhani SR, Ellis IO, Schnitt SJ, Hoon Tan P, van de Vijver MJ, eds. *World Health Organization Classification of Tumours of the Breast.* Lyon: IARC; 2012. Used with permission.

International Agency for Research on Cancer, World Health Organization. International Classification of Diseases for Oncology. ICD-O-3-Online. http://codes.iarc.fr/home. Accessed August 16, 2017. Used with permission.

INTRODUCTION

This staging system for carcinoma of the breast applies to both invasive carcinoma (also designated infiltrating) and ductal carcinoma *in situ,* 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 clinical staging (c) is determined using information identified prior to surgery or neoadjuvant therapy. Pathological staging (p) includes information defined at surgery. Following neoadjuvant systemic therapy, posttherapy pathological staging is recorded using the "yp" designator. A major change in breast cancer staging is the addition of tumor grade, HER2, estrogen receptor (ER), progesterone receptor (PR) and genomic assays as elements required to assign stage in conjunction with anatomic information on the tumor (T), regional nodes (N), and distant metastases (M) categories. Another major change is that the benign entity termed "lobular carcinoma *in situ*" or "lobular neoplasia" is not included in this staging system.

Evolving knowledge of breast cancer biology and the increased validation of various biomarkers of prognosis and prediction of treatment benefit or resistance also suggest that several biomarkers should be documented at the time of initial diagnosis whenever this is possible. These biomarkers include histologic grade, hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]), human epidermal growth factor receptor-2 (HER2), a marker of proliferation (such as Ki-67 or a mitotic count), and for appropriate subgroups of tumors, a genomic prognostic panel (such as Oncotype Dx®, Mammaprint®, Endopredict, PAM50 (ProSigna), Breast Cancer Index, etc.), if available.

Codification of tumor staging into the TNM system by the American Joint Committee on Cancer (AJCC) started in 1959 (when the AJCC was operating as the American Joint Committee for Cancer Staging and End-Results Reporting). Since then, seven editions of the AJCC Cancer Staging Manual have been published, in which careful definitions of categories for the primary tumor (T), the status of the surrounding lymph nodes (N), and the presence of distant metastases have been refined to reflect updates in technology and clinical evidence.[1] During these five decades, changes to the TNM system in each revision were made cautiously, to reflect modern clinical approaches while maintaining connections with the past. As much as possible, changes were based on the highest level of evidence in the peer-reviewed literature.

Over the past decade, there have been fundamental changes in our understanding of the biology of breast cancer. We now think of breast cancer as a group of diseases with different molecular characteristics (identified by gene expression profiling, immunohistochemistry, proteomics, next-generation sequencing, and other molecular techniques) that originate in breast epithelial tissue but have different prognoses, patterns of recurrence, and dissemination after

primary multidisciplinary treatments and have different sensitivities to available therapies.[2] This enhanced knowledge has led to significant changes in diagnostic and therapeutic approaches, and such changes must be reflected in the *AJCC Cancer Staging Manual, Eighth Edition* (8th Edition).

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. The TNM system was developed in 1959 in the absence of effective systemic therapy and based on limited understanding of the biology of breast cancer as well as the then-widely accepted paradigm of orderly progression for the tumor to regional nodes and thence to distant sites, which supported the use of the Halsted radical mastectomy introduced in the late 1800s. The TNM 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 challenged this Halstedian view of tumor progression with the understanding of the potential for distant systemic spread of all invasive cancers irrespective of node involvement and with demonstration of the value of adjuvant systemic therapy. This led to (1) more limited surgical management, with breast-conserving surgery being preferred for most patients with early-stage breast cancers and total mastectomy with axillary dissection for more advanced disease; (2) reduction in the extent of axillary staging, with sentinel lymph node biopsy becoming the leading approach for patients with clinically negative axillae; (3) dramatic improvements in the delivery and safety of radiation treatment; (4) the recognition that early (adjuvant) systemic therapy reduces the chance of recurrence and mortality; (5) the increasing implementation of preoperative (or neoadjuvant) systemic therapies for treatment of larger operable tumors and locally advanced breast cancer; and (6) a better understanding of biologic markers of prognosis and, perhaps more important, of prediction of response to selective categories of systemic therapy, such as those targeting cancer cells positive for ER and HER2 overexpression or amplification.[3] Heretofore, TNM staging based solely on the anatomic extent of disease has been used as a prognostic guide to select whether to apply systemic therapy. Based on such progress, biologic factors—such as grade, hormone receptor expression, HER2 overexpression/amplification, and genomic panels—have become as or more important than the anatomic extent of disease to define prognosis, select the optimal combination of systemic therapies,[3] and increasingly, influence the selection of locoregional treatments.[4]

Much of this biological information had started to appear at the time the 6th and 7th editions of the *AJCC Cancer Staging Manual* were being developed, but published information with high enough level of evidence to incorporate biomarkers into the TNM classification was lacking or incomplete. As an example, it has been known for several decades that the expression of the ER in primary breast cancer conferred a more favorable prognosis than its absence to groups of patients in various clinical stages. However, precise analysis to demonstrate that within specific TNM stages, the presence of ER modified prognosis was not available. Similar statements can be made about grade, markers of proliferation, and HER2. Population-based registries have started to collect information about hormone receptors only within the past 10–15 years, and information about HER2 was not integrated into national databases (National Cancer Database [NCDB]; National Program of Cancer Registries [NPCR]; Surveillance, Epidemiology, and End Results [SEER]; and others) until 2010. In the meantime, clinical practice evolved rapidly, integrating modern biological knowledge into the selection of systemic treatments.[5] ER, PR, grade, and HER2 started to be collected by most clinical laboratories, and clinicians integrated these concepts into prognostication and selection of therapies. The widespread adoption of the concept of biologic intrinsic subtypes led to different treatment strategies for the three major biological subsets of breast cancer: (1) hormone receptor-positive (ER and/or PR positive), HER2-negative tumors (also referred to as luminal-type); (2) HER2-amplified or overexpressed breast cancers; and (3) breast cancers that do not express hormone receptors or HER2 (also known as triple-negative tumors).[3] More recently, it also was recognized that in the presence of HER2 overexpression/amplification, the presence or absence of hormone receptor expression was associated with different prognoses and responsiveness to anti-HER2 therapy. Based on that observation, the HER2-positive population is now approached differently based on the expression of hormone receptors. These advances raise two questions. (1) Is anatomic-based TNM staging still relevant for breast cancer? (2) What, exactly, is the objective of TNM staging for patients with this disease? The answer to the first question is twofold: The TNM staging classification based solely on anatomical/histological parameters is clearly relevant to that part of the world where that is the only information available to practitioners. It also remains useful as the foundational basis of staging classification for areas of the world where biological information is an integral part of the initial evaluation. However, in these regions, staging needs to expand to incorporate the prognostic and predictive value of biomarkers. The second question, on the objective of TNM staging, has three potential answers: (1) to provide continuity to breast cancer investigators, 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 using a standardized language that reflects disease burden and tumor biology, and (3) to improve individual patient care. The AJCC Breast Cancer Expert Panel has struggled with these questions for the past several editions and especially with the 8th Edition. The current Breast Cancer Expert Panel came to the conclusion that although the anatomy- and histology-based TNM staging system provides important insight into a patient's prognosis, the addition of various biomarkers refines the prognostic information and leads to better selection of systemic therapies and, therefore, better outcomes. For example, the ability to identify a group of patients with invasive breast cancer with prognosis that is so favorable that the patient might forego systemic therapy is an important feature of anatomical and biological staging. The ability to predict benefit from or resistance to specific treatments also is of critical importance.

Although anatomic T, N, and M still provide value in determining a patient's future outcome, the clinician today must take into account multiple factors that relate both to prognosis and prediction. For example, testing for ER and PR expression, HER2 status, and where appropriate, results of genomic profile assays is now considered a prerequisite to treatment because it is factored into all prognostic and treatment decisions.[5] Although these factors individually have some limited intrinsic prognostic value in regards to the risk of subsequent recurrence for patients who do not receive systemic therapy, their main utility is prediction of benefit from therapy, guiding whether a patient should or should not receive adjuvant endocrine (anti-estrogen) or anti-HER2 (such as trastuzumab) therapy. However, among patients who receive treatment, the prognosis varies widely for cancers of the same T and N status based on the expression of these biomarkers. The use of these factors as both prognostic and predictive markers is fundamentally important in evaluation and care of patients with newly diagnosed breast cancer, as well as for patients with metastatic breast cancer.

The situation has become even more complex with the availability of multigene expression assays. One such assay, based on a 70-gene prognostic signature (Mammaprint®) developed by investigators from Amsterdam has been cleared by the US Food and Drug Administration (FDA) for use in women who are younger 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.fda.gov/ForConsumers/ConsumerUpdates/ucm048477.htm).[6, 7] The use of the 70-gene prognostic signature was evaluated in a prospective study called the MINDACT study.[8] This study examined outcome for women with high and low risk of recurrence based on the 70-gene prognostic score coupled with an high or low clinical risk of recurrence based on estimates from the on-line tool Adjuvant! Online (www.adjuvantonline.com). Women with a low 70-gene prognostic risk and a high clinical risk were randomized to receive chemotherapy or not. Survival for those on the study with ER positive, HER2 negative cancers, with positive or negative nodes was similar with or without chemotherapy. The use of the 70-gene prognostic signature for directing use of adjuvant therapy for those with a low risk signature was endorsed in an American Society of Clinical Oncology (ASCO) Guideline in 2017.[9]

The Tumor Marker Guidelines Committee of the ASCO previously recommended that a second multigene assay, which is based on expression of 21 genes as determined by reverse transcriptase–polymerase chain reaction (RT-PCR) (designated the "21-gene recurrence score assay" or by its proprietary name, Oncotype Dx®) 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.[3] Similarly, the Breast Cancer Guideline Committee of the National Comprehensive Cancer Network (NCCN) 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."[5] Additional clinical validation of these assays continues to accumulate. The initial results of the ECOG-ACRIN Cancer Research Group-led *Trial Assigning Individualized Options for Treatment (Rx) (TAILORx)* trial were published in late 2015, documenting that the group of patients with hormone receptor-positive, HER2-negative, lymph node-negative breast cancer who had a Recurrence Score lower than 11 by the Oncotype Dx® assay had a 5-year distant recurrence-free survival of 99.3% with adjuvant endocrine therapy alone.[10] Two additional reports confirmed the ability of the 21-gene genomic assay to identify the group of patients who can safely forgo chemotherapy and still have an excellent prognosis.[11, 12]

Given the clear impact that genomic profiling will increasingly have in breast cancer treatment, the Expert Panel deliberated with the question of whether it was of value, and if so, how these gene profile assays could be incorporated into the TNM staging system. First and foremost, the Expert Panel affirmed that it is not formed as a practice guideline unit, and that it is not in the position to recommend or endorse the use of any genomic panel in determining appropriate treatment for individuals. The evidence supporting the available multigene panel continues to evolve rapidly and it is also likely that heretofore undescribed panels or other tools for these purposes will become available. Clinicians and patients should base therapy on the evidence available at the time of treatment as it relates to their individual circumstance.

The Panel considered if it was useful to use one or more of the existing multigene panels to assign prognostic stage. If so, should they be used (1) as pure prognostic factors that

serve as secondary modifiers of the basic TNM classification,[13, 14] (2) as components of multifactorial prognostic models that calculate individual risk of recurrence and perhaps individual sensitivity to therapy,[15–19] or (3) as components of simple prognostic scoring systems that add to, but do not alter the basic structure of, the TNM staging classification?[20] Should the multiparameter prognostic assays (Oncotype Dx®, Mammaprint®, PAM50, EndoPredict®, Breast Cancer Index®, IHC4, etc.) that appear to predict outcomes in newly diagnosed breast cancer patients be included in staging? Because their value may be as much a predictor of response to chemotherapy regardless of TNM stage as a prognostic factor, should an entirely new category related to prediction of benefit from systemic therapy be incorporated into the TNM staging system?

Inclusion of Biologic Factors in Staging and the Need for Anatomic Stage

Increasingly in the modern era, many treatment decisions for patients with newly diagnosed breast cancer are not based on anatomic TNM stage, and certainly not on stage alone. Large tumor size (T3 versus T1 or T2) and lymph node status (N1, N2, or N3 versus N0) influence decisions regarding whether radiation should be used after mastectomy or for directing the fields of radiation for women undergoing breast preservation and in recommendations for axillary dissection. However, in an era when many invasive cancers are detected at very small sizes due to breast screening, 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.[21, 22] Today, such decisions are largely reached based on the biologic characteristics of the primary tumor, rather than the extent of disease.

In 2013, 1.8 million women were diagnosed with breast cancer around the world and 471,000 died of this neoplasm.[23] Although the majority of breast cancers in the industrialized world are diagnosed in early stages and the great majority are cured, more than half of patients with breast cancer in the low- and middle-income countries (LMCs) are diagnosed in late stages (III and IV), with the majority of them dying of metastatic breast cancer. It is projected that the annual global burden of new breast cancer cases will continue to increase and an ever-increasing fraction will be from LMCs.[24] 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 LMCs.[23] LMCs simply may not be able to afford testing for individual molecular events or multiparameter profiles, nor will they be able to provide expensive therapies directed against ER, HER2, CDK 4/6, 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. 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. In LMCs, anatomic staging will remain the cornerstone on which evaluation and treatment decisions of newly diagnosed breast cancer patients will be made.

Although the advances in molecular diagnosis have provided compelling new insights into cancer therapy, the Expert Panel understands that economic considerations limit the relevance of these observations to the societies in which resources permit widespread screening, molecular evaluation of tumor tissue, and application of cutting-edge biologically directed therapies. Nonetheless, as survival data continue to accumulate, these and other molecular assays must be incorporated into future updates of AJCC breast cancer staging.

Expert Panel Decisions on Anatomic and Prognostic Staging

After much deliberation, the Expert Panel determined that, in addition to modest adjustments to the T, N, and M categories for the 8th Edition, progress in biology, diagnostics, and therapeutics made incorporation of basic biomarkers into the TNM classification an absolute necessity. Therefore, the Breast Cancer Expert Panel made changes to the TNM staging system incorporating the basic biomarkers in widespread use today that have demonstrated clinical utility. These biomarkers are collected by the NCDB, NPCR, SEER, and other population-based registry databases in the United States. To preserve the relevance of the TNM classification and recognizing the need for anatomic staging for the entire world, the Expert Panel elected to integrate biomarkers as a second tier of prognostic modifiers, as have other tumor-specific Expert Panels within AJCC (e.g., esophagus and esophagogastric junction, prostate, gestational trophoblastic neoplasms, testis, and others).

The biomarkers are included in two Prognostic Stage tables for breast cancer staging.

1. Clinical Prognostic Stage. This is for use on ALL patients to provide guidance for initial treatment, to provide a base for comparison for all patients regardless of the sequence of treatments (e.g. initial surgery with adjuvant therapy vs. neoadjuvant therapy. It is the primary prognostic staging for patients who receive systemic therapy or radiation before surgery or for those who do not receive surgery. Clinical Prognostic Stage is based on clinical information

obtained from history, physical examination, and any imaging, cytology or histology biopsy obtained before treatment. Clinical Prognostic Stage includes cT, cN, c/pM, grade, HER2, ER and PR.

2. Pathological Prognostic Stage. This applies to patients who undergo surgical resection as the initial treatment of the cancer. A separate table is provided for defining Pathological Prognostic Stage using pT, pN, c/pM, grade, HER2, ER and PR and genomic assays for the T1–2 N0, ER positive, HER2 negative group.

Pathological Prognostic Stage is not applicable for patients who receive neoadjuvant therapy. Information recorded on these patients should include the Clinical Prognostic Stage; the category information for either the clinical response to therapy (ycT and ycN) if surgery not performed; or if surgery is performed, the pathological response to therapy (ypT and ypN) and the degree of response (complete response, partial response, no response).

The Expert Panel considered incorporating results from multigene genomic profile assays into Pathological Prognostic Stage. It decided to assign Pathological Prognostic Stage Group IA for those with T1 or T2, N0, M0 cancers that are ER positive and HER2 negative, and have an OncotypeDx® recurrence score of less than 11. This decision was based on the published information from a prospective clinical trial indicating that for a specific group of patients (ER+, LN-, RS < 11), the prognosis was excellent and comparable to patients with T1a-T1b N0 breast cancer with similar characteristics.[10] In addition, two additional prospective studies, and a population-based analysis (SEER database) provided similarly excellent outcomes for this group of patients.[11, 25, 26]

After extensive discussion the Expert Panel decided not to include the specific results of other genomic profile or multigene assays to assign Pathological Prognostic Stage in the staging table. This reflects the more limited Level I evidence for other profiles, and the difficulty in specifying exactly how they should be included in the tables. However, the Panel recognizes that the findings of other genomic profile assays provide relevant prognostic and potentially treatment-predictive information.[27] The Expert Panel does not intend by its decisions to specifically recommend or endorse the clinical utility of one multigene genomic profile test over another. This is a rapidly evolving field, and the clinician and patient must evaluate at the time of treatment the relevant evidence and which of these assays, if any, provide information valuable to assist in making appropriate treatment decisions. Finally, in subsequent updates of the staging system, anticipated to occur at shorter intervals than in the past, the Expert Panel will further consider refining criteria for including other prognostic tools in staging and incorporating other multigene prognostic panels into the Pathological Prognostic Staging tables.

At the same time, the Expert Panel agreed unanimously that the staging system must provide clinicians the ability to determine a purely anatomic-based stage. This allows usage around the world for patients who do not or cannot have the standard biomarker assays performed. It also provides for comparison of cases across time to continue to evaluate progress in breast cancer care on a population-wide basis.

The Expert Panel discussed at length the confounding effect of treatment on defining stage groupings. Data are not available on patients who do not receive treatment, a group historically considered the "gold standard" for a staging system. In reality, however, when the TNM classification was first developed, the great majority of breast cancers were receiving treatment with definitive surgery and, if indicated, radiotherapy. Therefore, from its inception, the TNM classification reflected prognosis of patients who had received definitive locoregional therapy. Today, almost six decades later, few patients with breast cancer fail to receive therapy, except for those who refuse or those with comorbid conditions severe enough to preclude treatment. Therefore, TNM staging reflects the prognosis of patients treated with the current standard multimodality treatment. In that sense, the incorporation of biomarkers into the staging system will refine the prognostic character of the classification as biomarkers guide the optimal selection of treatments for large subsets of patients with primary and/or metastatic breast cancer. It also will serve as the new platform to continue investigations that will lead to improvement of both prognostic and predictive ability in future staging systems. Updates for AJCC staging will depend upon the availability and validity of data for all predictors and prognosticators of breast cancer, including conventional TNM data, molecular markers, and genomic assays that influence survival.

It is important to recognize that the Clinical and Pathological Prognostic Staging systems reflect the prognosis in patients offered treatment appropriate for the clinical extent and biomarker status of the case. Lower stage disease reflects favorable biology, effective therapy or both. Lower stage does not denote the need for less treatment. For example a women with a T3, N1, Grade 2, HER2-positive, ER and PR-positive cancer is staged as Prognostic Stage IB. However to achieve the excellent prognosis this reflects, the patient should receive, if possible, systemic therapy appropriate for a larger HER2-positive cancer – systemic chemotherapy coupled with anti-HER2 therapy, followed by endocrine therapy.

Therefore, it is important that clinicians recognize that this new breast cancer staging system assigns stage group based on overall prognosis with treatment, and not simply on the anatomic extent of cancer. A cancer staged using the AJCC 7th Edition or earlier TNM system as a Stage II or Stage III cancer may now be staged as a Stage IB. This does not mean the patient can forego systemic therapy, but rather

that with administration of appropriate therapy based on the biomarkers and anatomic extent of the cancer, the patient has a better prognosis. Clinicians should recognize and accommodate this different paradigm for the use of "stage" than used in the past.

More advanced staging models will undoubtedly reflect contemporary clinical and scientific data but will require adequate follow-up to accurately determine survival. As the complexity of survival predictions increase, stage groupings may evolve into calculation models to assign survival and stage. This progression of knowledge is likely to lead to more frequent modifications of survival-based stage assignments than has been experienced over the typical lifespan of the previous seven editions of the AJCC staging manuals. It is therefore anticipated that updates will be made on a more frequent basis when relevant validated information is available, rather than the historical 6- to 8-year cycle of TNM revisions.

ANATOMY

Primary Site(s)

The mammary gland, situated on the anterior chest wall, is composed of glandular tissue with a dense fibrous stroma admixed with adipose tissue. 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 ducts course throughout the breast, converging into larger collecting ducts that open into the lactiferous sinuses at the base of the nipple. Each duct system has a 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 (Fig. 48.1). Most cancers form initially in the terminal duct lobular units of the breast. *In situ* 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 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 region.

Chest Wall

The chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not the pectoral muscles. Therefore, involvement of the pectoral muscle in the absence of invasion of these chest wall structures or skin does not constitute chest wall invasion, and such cancers are categorized on the basis of tumor size.

Regional Lymph Nodes

The breast lymphatics drain by way of three major routes: axillary, interpectoral, and internal mammary. Intramammary lymph nodes reside within breast tissue and are designated as axillary lymph nodes for staging purposes. Supraclavicular lymph nodes are categorized as regional lymph nodes for staging purposes. Metastases to any other lymph node, including cervical or contralateral internal mammary or contralateral axillary lymph nodes, are classified as distant metastases (M1) (Fig. 48.2).

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:

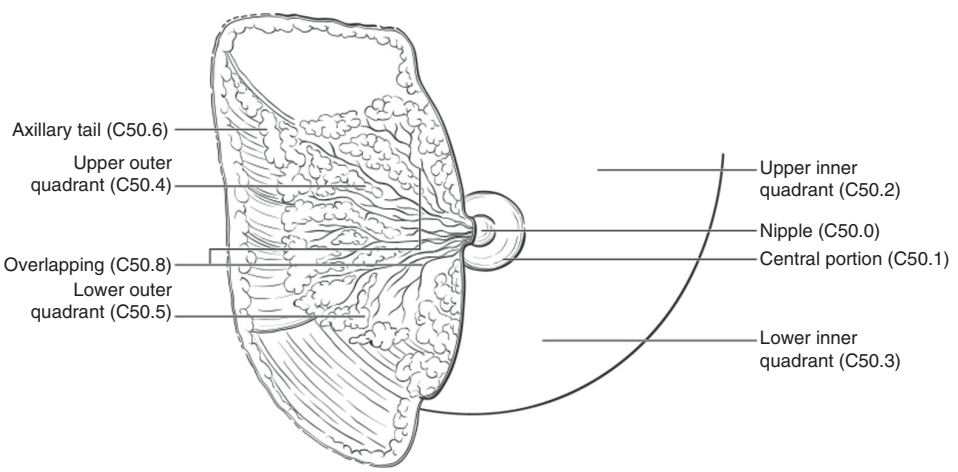

Fig. 48.1 Anatomic sites and subsites of the breast

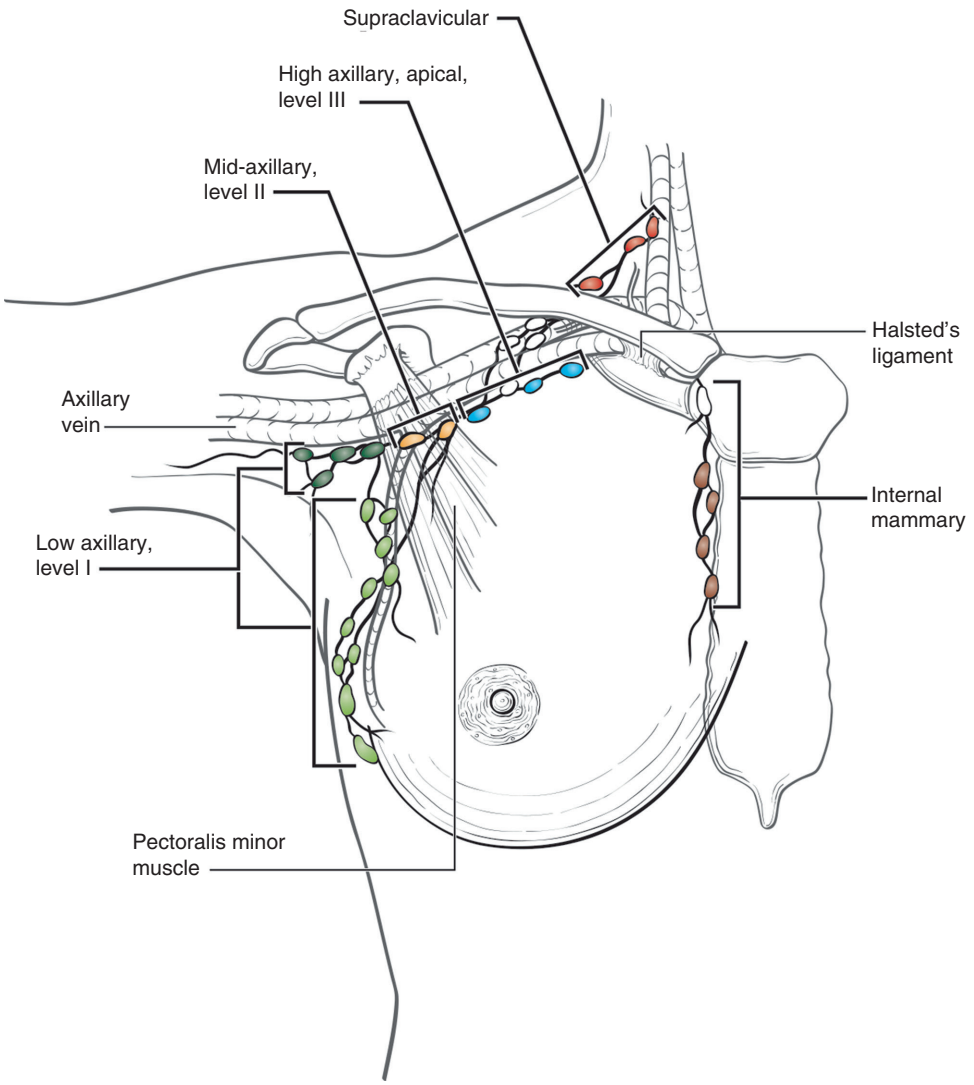

Fig. 48.2 Schematic diagram of the breast and regional lymph nodes

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. Level III infraclavicular nodes should be separately identified by the surgeon for microscopic evaluation.

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 categorization and staging.

Metastatic Sites

Tumor cells may be disseminated by either the lymphatic or the blood vascular system. The four most common sites of involvement are bone, lung, brain, and liver, but breast cancers also are capable of metastasizing to many other sites. Bone marrow micrometastases, circulating tumor cells (CTCs), 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 and clusters (DTCs). These deposits do not alone define or constitute metastatic disease, although data exist that demonstrate that, in early stage disease, DTCs correlate with recurrence and mortality risk, and in patients with established M1 disease, CTCs are prognostic for shorter survival.

RULES FOR CLASSIFICATION

The anatomic TNM system is a method for coding extent of disease. This is done by assigning a category of extent of disease for the tumor (T), regional lymph nodes (N), and distant metastases (M). T, N, and M are assigned by clinical means and by adding surgical findings and pathological information to the clinical information (see Chap. 1). The documented prognostic impact of post neoadjuvant 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 anatomic component of clinical stage is identified with the prefix "c" (e.g., cT). In addition, clinical staging can include the use of fine needle aspiration (FNA) or core needle biopsy and sentinel lymph node biopsy before neoadjuvant therapy. These are denoted with the postscripts "f" and "sn," respectively. Nodal metastases confirmed by FNA or core needle biopsy are classified as macrometastases (cN1), regardless of the size of the tumor focus in the final pathological specimen. For example, if, prior to neoadjuvant systemic therapy, a patient with a 1 cm primary 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 clinical (pretreatment) staging and is assigned to Stage IIA. Likewise, if the patient has a positive axillary sentinel node identified prior to neoadjuvant systemic therapy, the tumor is categorized as cN1 (sn) (Stage IIA). As per TNM rules, in the absence of pathological T evaluation (removal of the primary tumor), which is identified with prefix "p" (e.g., pT), microscopic evaluation of nodes before neoadjuvant therapy, even by complete removal such as sentinel node biopsy, is still classified as clinical (cN).

Clinical Classification

Clinical categorization of cancer is based on findings of history, physical examination, and any imaging studies that are done. Imaging studies are not required to assign clinical categories or stage. Cases with a biopsy of lymph nodes or metastatic sites may be staged clinically, including the biopsy information.

Physical Examination

Physical examination includes careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supraclavicular, and cervical), imaging, and pathological 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 pathological staging (see section "Pathological Classification" in this chapter).

Imaging

Imaging findings are considered elements of staging if they are collected within 4 months of diagnosis or through completion of surgery, whichever is longer in the absence of disease progression. Relevant imaging findings 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."

Breast cancer clinical T, N, and M categorizations are based on a combination of clinical examination and imaging findings. Clinical findings are usually integrated with imaging to determine the size of primary tumor and the presence or absence of multiple synchronous lesions involving the same breast quadrant or different breast quadrants (i.e., multifocal or multicentric disease, respectively). The imaging modalities most commonly used to help determine T and N features are mammography and ultrasound. The routine use of breast magnetic resonance (MR) imaging in newly diagnosed cancer patients has not been shown to have significant benefit in obtaining clear surgical margins[28–31] and its effect on improving local recurrence and survival is under debate.[32, 33] If MR imaging of the breast is performed, it should be done in consultation with the multidisciplinary treatment team, using a dedicated breast coil, and interpreted by a breast imaging team capable of performing MR imaging-guided biopsy. MR imaging is indicated in patients presenting with axillary breast cancer metastasis with no evident breast tumor on clinical, mammographic, and sonographic examination (occult breast primary) and may help facilitate breast-conserving therapy in this patient subgroup.

Primary Tumor (T) – Clinical and Pathological

The T category of the primary tumor is defined by the same criteria regardless of whether it is based on clinical or pathological criteria, or both. The T category is based primarily on the size of the invasive component of the cancer. See Figs. 48.3, 48.4 and 48.5 for illustrations of the T-categories. The maximum size of a tumor focus is used as an estimate of

disease volume. The largest contiguous dimension of a tumor focus is used, and small satellite foci of noncontiguous tumor are not added to the size. The cellular fibrous reaction to invasive tumor cells is generally included in the measurement of a tumor prior to treatment; however, the dense fibrosis observed following neoadjuvant treatment is generally not included in the pathological measurement because its extent may overestimate the residual tumor volume.

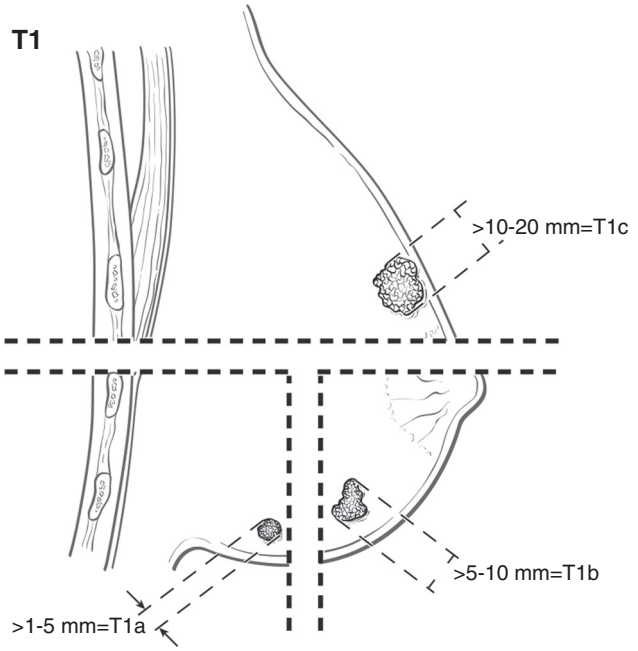

Fig. 48.3 T1 is defined as a tumor 20 mm or less in greatest dimension. T1mi is a tumor 1 mm or less in greatest diameter (not illustrated). T1a is defined as tumor more than 1 mm but not more than 5 mm in greatest dimension; T1b is defined as tumor more than 5 mm but not more than 10 mm in greatest dimension; T1c is defined as tumor more than 10 mm but not more than 20 mm in greatest dimension

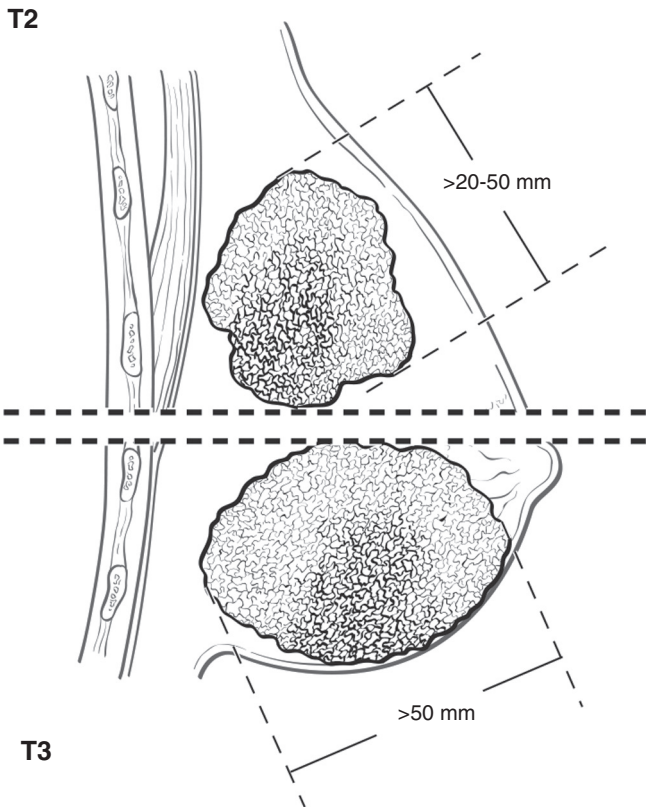

Fig. 48.4 T2 (above dotted line) is defined as tumor more than 20 mm but not more than 50 mm in greatest dimension, and T3 (below dotted line) is defined as tumor more than 50 mm in greatest dimension

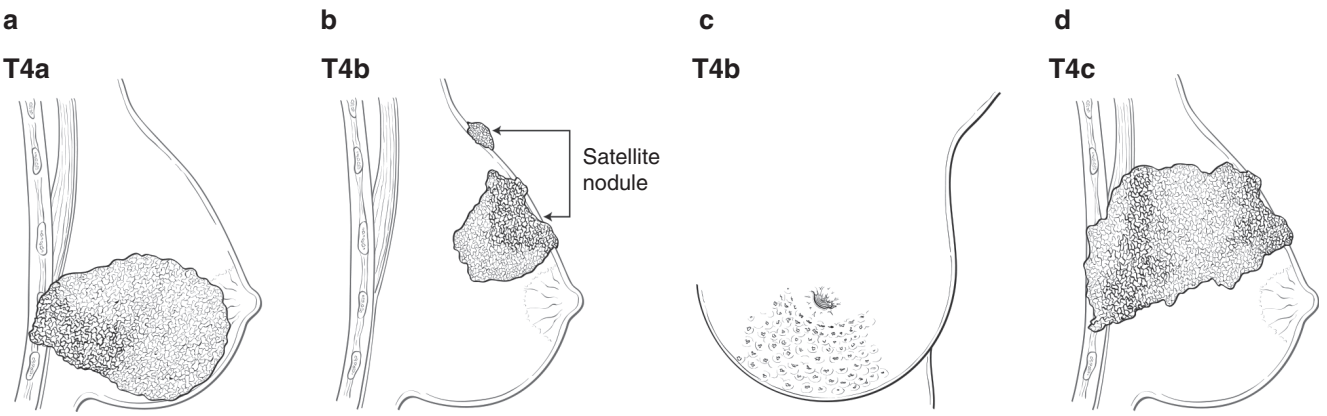

Fig. 48.5 T4 is defined as a tumor of any size with direct extension to chest wall and/or to the skin (ulceration or skin nodules). (**a**) T4a is extension to the chest wall. Adherence/invasion to the pectoralis muscle is NOT extension to the chest wall and is not categorized as T4. (**b**) T4b, illustrated here as satellite skin nodules, is defined as edema (including peau d'orange) of the skin, or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast. These do not meet the criteria for inflammatory carcinoma. (**c**) T4b illustrated here as edema (including peau d'orange) of the skin. (**d**) T4c is defined as both T4a and T4b. T4d (not illustrated) is inflammatory cancer (see text for definition)

Tumor Size

The clinical size of a primary tumor (T) can be measured based on clinical findings (physical examination and imaging modalities, such as mammography, ultrasound, and MR imaging) and pathological 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.

Imaging Classification of Tumor (T)

The American College of Radiology (ACR) BI-RADS lexicon provides general guidelines for the reporting of mammography, breast ultrasound, and breast MR imaging studies.[34] All breast imaging reports should follow these guidelines. Information relevant to primary tumor size should be accurately measured in at least the longest diameter in the plane of measurement and should be included in the report body and the final impression sections. If the primary tumor also is associated with such features as calcifications or architectural distortion, this combined size should be provided in the report. If present, extension of the primary tumor to the ipsilateral nipple, overlying skin, or underlying chest wall should be clearly indicated. MR imaging is more accurate than ultrasound and mammography in confirming chest wall involvement by demonstrating abnormal enhancement within chest wall structures.[35] When more than one malignant lesion is identified on imaging, the size and description of their locations (i.e., quadrant and/or distance from the nipple and/or distance to the index tumor) should be defined in the imaging report. The same tumor may have different measurements using different modalities (e.g., mammography versus ultrasound versus MR imaging). If available, MR imaging measurements could be used based on prior studies demonstrating better correlation with overall tumor size. However, if index tumor size difference between different imaging modalities, including that of MR imaging, significantly affects T classification or overall clinical stage, imaging-guided biopsy could be considered to confirm disease extent. Imaging-guided tissue biopsy can similarly be considered for any additional lesions suspicious for multifocal or multicentric secondary lesions that affect clinical management.

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, the size should be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 4.9 mm is reported as 5 mm, or a size of 2.04 cm is reported as 2.0 cm (20 mm). The exception to this rounding rule is for a breast tumor sized between 1.0 and 1.4 mm. These sizes are rounded up to 2 mm, because rounding down would result in the cancer's being categorized as microinvasive carcinoma (T1mi) defined as a size of 1.0 mm or less.

Inflammatory Carcinoma

Inflammatory carcinoma is a clinical-pathological entity characterized by diffuse erythema and edema (peau d'orange) involving approximately a third or more of the skin of the breast.[36] The tumor of inflammatory carcinoma is classified cT4d. 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. The skin changes may be due to lymphedema caused by tumor emboli within dermal lymphatics, which may or may not be obvious in a small skin biopsy. Therefore, the pathological finding of tumor in dermal lymphatics is not necessary to assign the diagnosis of inflammatory cancer. A tissue diagnosis is necessary to demonstrate an invasive carcinoma in the underlying breast parenchyma, or at least in the dermal lymphatics, and to determine biologic markers (ER, PR, HER2, and grade). Tumor emboli in dermal lymphatics without the clinical skin changes described above should be classified according to tumor size (T1, T2, or T3) and do not qualify as inflammatory carcinoma. Locally advanced breast cancers directly invading the dermis or ulcerating the skin without the clinical skin changes also do not qualify as inflammatory carcinoma. A characteristic of inflammatory carcinoma of the breast is its rapid evolution, from first symptom to diagnosis of less than 6 months.[36] 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.

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 tumors without changing the T classification.

The category should be made with the prefix "c" or "p" modifier to indicate whether the T category was determined by clinical information (physical examination with whatever breast imaging was done) or by clinical information supplemented by pathological measurements from surgical resection, respectively. In a few cases, such as for small tumors where the biopsy procedure may have removed a substantial portion of the tumor (e.g., vacuum-assisted core needle biopsy), such clinical information as imaging size and biopsy tumor dimension should be considered when assigning the final pathological size and category (pT).

Regional Lymph Nodes – Clinical (cN)

The definitions for clinical and pathological node categorization are different. See Fig. 48.6 for illustrations of the clinical categories for regional lymph nodes. Clinical categorization includes nodes detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed histologic macrometastasis based on FNA biopsy, core needle biopsy, or sentinel node biopsy. Confirmation of clinically detected metastatic disease by fine needle aspiration or core needle biopsy is designated with an (f) suffix, for example, cN3a(f). Histologic confirmation in the absence of assignment of a pT (through surgical resection) is classified as cN, including excision of a node; for example, an axillary sentinel node biopsy with a macrometastasis is classified cN1a(sn) when primary tumor classification is clinical (cT). The method of confirmation of the nodal status should be designated as either clinical (cN), FNA/core biopsy (cN(f)), or sentinel node biopsy (cN(sn)).

Imaging studies are not necessary to categorize the regional nodes as negative. The designation cN0, not cNX, should be used for an axilla that is negative solely by physical examination. Even when regional lymph nodes have been previously removed, if no disease is identified in the nodal

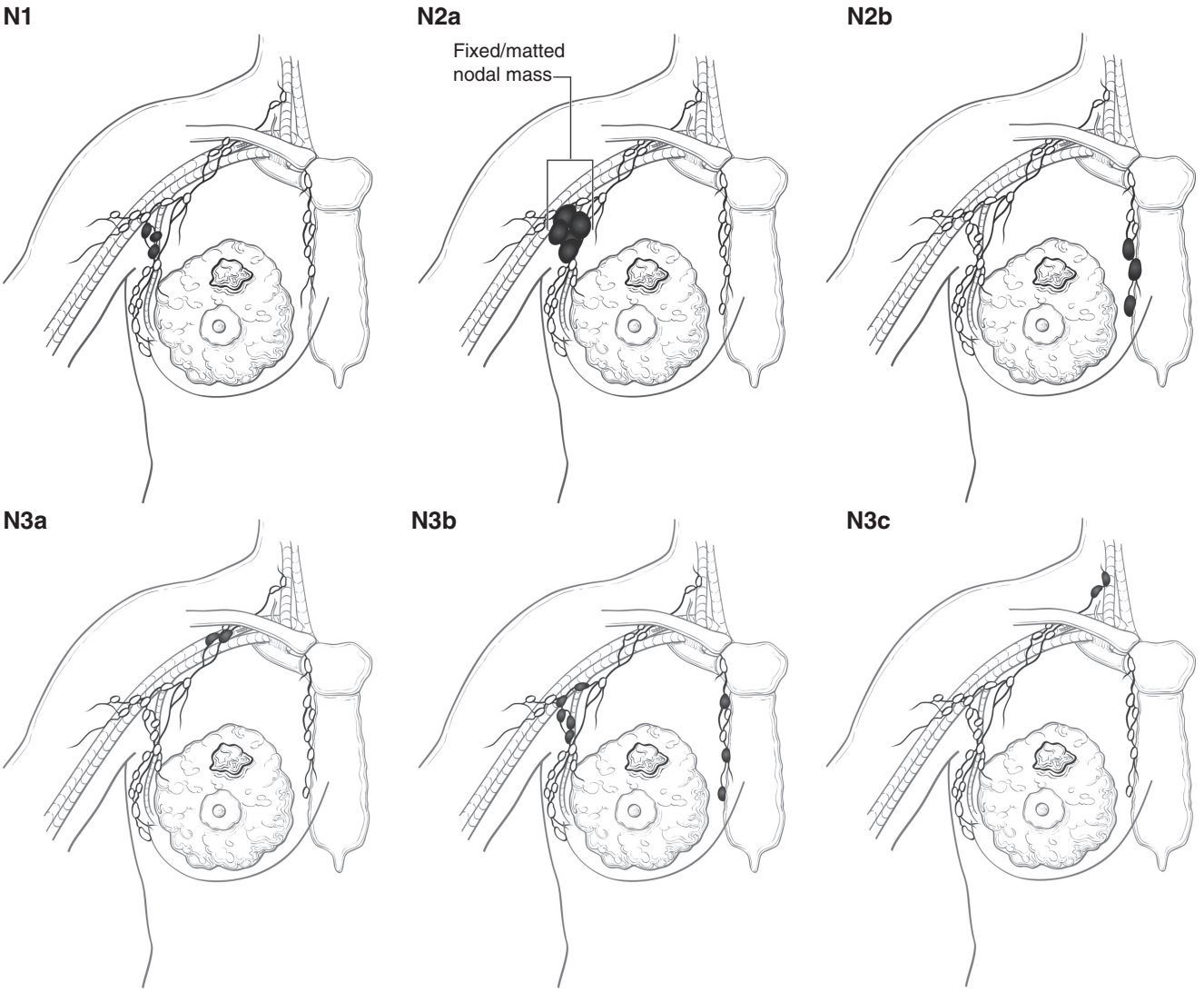

Fig. 48.6 Clinical Lymph Node Categories: cN1 is defined as metastasis in movable ipsilateral level I, II axillary lymph nodes. cN2a is defined as metastasis in ipsilateral level I, II axillary lymph nodes fixed to one another (matted). cN2b is defined as metastasis only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastasis. cN3a is defined as metastasis in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement. cN3b is defined as metastasis in clinically detected ipsilateral internal mammary lymph node(s) and clinically evident axillary lymph node(s). cN3c is defined as metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.

basin by imaging or clinical examination, it should be categorized as cN0.

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 detected by imaging studies (including computed tomography [CT] scan and ultrasound, but excluding lymphoscintigraphy) or by clinical examination are designated as cN2b when they do not occur in conjunction with metastases to the Level I, II axillary lymph nodes and cN3b when they occur in conjunction with axillary Level I, II metastases. Metastases to the ipsilateral supraclavicular lymph nodes are designated as cN3c regardless of the presence or absence of axillary or internal mammary nodal involvement. Because 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 FNA or core needle biopsy, with cytologic/histologic examination if possible, but biopsy is not necessary to categorize as lymph node-positive. Lymph nodes classified as malignant by clinical or imaging characteristics alone, or only FNA cytology examination or core needle biopsy, and not by formal surgical dissection and pathological review, are presumed to contain macrometastases for purposes of clinical staging classification. When confirmed by FNA or core needle biopsy, the (f) modifier should be used to indicate cytologic/histologic confirmation, for example, cN2a(f). If a lymph node or nodes are removed by surgical excisional biopsy or sentinel lymph node biopsy and examined histopathologically, and the primary tumor has not been removed, the N category is recorded as clinical (cN).

Imaging Classification of Regional Lymph Nodes (N)

Imaging is not necessary to assign the clinical node category. Routine use of axillary ultrasound in breast cancer patients is controversial. Meta-analyses[37, 38] suggest that among patients who prove to have positive nodes, clinically occult axillary nodal metastases can be detected in about half on preoperative ultrasound evaluation. In centers that routinely implement regional nodal ultrasound, imaging should include at least ipsilateral axillary levels I and II. Lymph node measurements are obtained by both long and short axis lengths on ultrasound. However, ultrasound measurements are operator- and technique-dependent. Ultrasound-guided needle biopsy of the index axillary node with clip placement should be considered in keeping with previously published guidelines.[21] Imaging or histopathological evidence of axillary Level I or II lymphadenopathy warrants consideration of imaging investigation of Level III axillary, internal mammary chain, and supraclavicular lymph node involvement. These sites can be imaged using ultrasound.[39] Alternatively, they may be evident on breast MR imaging or chest CT if performed. Ultrasound, CT, or positron emission tomography (PET)-CT may be used to demonstrate any possible metastatic supraclavicular lymph nodes. Lymph node measurements are obtained by the length of their short axis on cross-sectional imaging.

Distant Metastasis (M)

Clinical assessment for distant metastases is by clinical history, physical examination, and imaging studies.

History and Physical Examination

Detection of metastatic disease by clinical exam should include a full history and physical examination, focusing 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 cM1 category, and radiographic studies are almost always required. Whenever feasible, biopsy confirmation should be performed (pM1) and, if possible, tested for ER, PR, and HER2.

Imaging Classification of Metastases (M)

It is not necessary for the patient to have radiological evaluation of distant sites to be classified as clinically free of metastases (cM0). The indications for radiographic evaluation for the presence of metastases in the staging of breast cancer varies by T and N categorization. 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.[40] 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 large, node positive disease (clinical or pathologic).[41] Recommendations are mixed for patients with T2 N1. The value of staging imaging studies might be influenced by the anatomic extent of the cancer (tumor size, number of nodes, grade), and biomarker profile.

If imaging studies are indicated, these 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 categorization. With radiographic screening or evaluation for another cause, false-positive staging studies in patients with newly diagnosed breast cancer are relatively common.

In patients with T1 or T2 N0 or N1 cancer, routine use of imaging to detect occult distant metastasis is discouraged,[42] based on its previously demonstrated low yield and because of the risk of false-positive findings. For clinical Stages I–IIB, additional studies can be considered only if directed by the following signs or symptoms:

- Bone scan indicated if localized bone pain or elevated alkaline phosphatase
- Abdominal, with or without pelvic, diagnostic CT or MR imaging indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis
- Chest diagnostic CT if pulmonary symptoms present[21]

For patients with clinical Stage IIIA and higher locoregional disease, the above diagnostic tests can be considered in the absence of clinical signs or symptoms of distant metastasis.[34] 18-Fluorodeoxyglucose-PET (18F–FDG-PET) can be used in the workup of patients with locally advanced breast cancer Stage IIIB and higher as a "screen" for distant disease. If one or more suspicious findings are detected, they can be further evaluated with CT and/or MR imaging depending on location. 18F–FDG-PET reports should include standardized uptake values (SUVs) of the identified lesions.

Cases in which no distant metastases are determined by clinical methods (history, physical examination, and imaging if indicated) 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 categorized as N3 (see previous discussion). A case is categorized as clinically free of metastases (cM0) unless evidence of metastases is documented by clinical means (cM1) or by biopsy of a metastatic site (pM1). M categorization 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 categorization requires evaluations consisting of a review of systems and physical examination. It also may include radiographic imaging, blood tests, and tissue biopsy. The types of examinations needed in each case may vary and guidelines for these are available.[40] M categorization is based on best clinical and radiographic interpretation; pathological confirmation is recommended, although confirmation may not be possible for reasons of feasibility or safety. Whenever biopsy confirmation is possible and safe, repeat biomarker assessment (ER, PR, HER2) is recommended because differences in the biomarker profile of the metastases and the primary tumor affect treatment. Additionally, M category assessment may not yield a definitive answer on the initial set of evaluations, and follow-up studies may be needed, making the final determination 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 category 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 classification and the patient would now be considered to have converted to recurrent Stage IV, which is considered recurrent disease without altering the original stage.

Pathological confirmation of suspected metastatic disease should be performed whenever feasible. 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. 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-negative results, 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 hematoxylin and eosin (H&E) staining. In some cases, additional immunohistochemical staining or other specialized testing for confirmation of breast cancer or other cancer type is required. If adequate biomarker data (ER, PR, HER2) are not available from the primary tumor, these should be obtained on any other biopsy that shows cancer on H&E staining. Determination of biomarkers on the metastatic biopsy specimen is highly desirable, regardless of the availability of biomarker analysis on the primary tumor. 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 CTCs that are otherwise clinically and radiographically silent should not alone constitute M1 disease and are discussed in this chapter.

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, also should 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 cancer antigen (CA) 15–3, CA 27.29, carcinoembryonic antigen, and other protein-based markers—for staging is not indicated.[3]

Circulating Tumor Cells, Bone Marrow Micrometastases, and Disseminated Tumor Cells

The presence of CTCs in the blood or DTC clusters (≤ 0.2 mm) in the bone marrow or other nonregional nodal tissues does not constitute M1 in the absence of other apparent clinical and/or radiographic findings of metastases that correspond to pathological findings. However, an increasing number of studies are showing microscopic bone marrow and CTCs in M0 disease to be associated with adverse prognosis for recurrence or survival. Thus, denotation of histologically visible metastatic deposits ≤0.2 mm in bone marrow or other organs distant from the breast and regional lymph nodes should be denoted by the term cM0(i+). For breast cancer classified as cM1 (clinically 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.

When metastatic disease is confirmed by biopsy, the pM1 category may be used. When a biopsy fails to confirm M1 disease, the assignment of cM0 or cM1 is based on clinical and imaging data; pM0 is not a valid category for "M" (see Chap. 1).

Post Neoadjuvant Therapy Clinical Classification (yc)

Preoperative or "neoadjuvant systemic" therapy has been used for several decades for managing inflammatory and locally advanced breast cancer, and it is being used increasingly for managing earlier stages of the disease as well.[43]

Post Neoadjuvant Therapy ycT Classification

Clinical (pretreatment) T (cT) is defined by clinical and radiographic findings; clinical (posttreatment) T (ycT) is determined by the size and extent of disease on physical examination and imaging. The ycT is determined by measuring the largest single focus of residual tumor by examination or imaging.

If a cancer was classified as inflammatory (cT4d) before neoadjuvant chemotherapy, the cancer is classified as inflammatory breast cancer after therapy, even if complete resolution of the inflammatory findings is observed during treatment. The posttreatment clinical classification (ycT) should reflect the extent of identified residual disease on imaging. For example, a patient with several areas of residual disease measuring 2.0 mm to 9.0 mm in greatest dimension identified within a 2.2 cm area of tumor bed previously involved is classified as ycT1b(m), and a patient with no residual disease identified is classified as ycT0.

Post Neoadjuvant Therapy ycN Classification

Clinical pretreatment and posttreatment node status (cN and ycN) is defined by clinical and radiographic findings with or without FNA, core needle biopsy, or sentinel node biopsy of a suspicious node or excision of a palpable node. If definitive resection of the primary tumor and/or nodes is performed, the pathological information for this category is ypN.

Post Neoadjuvant Therapy M Classification

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

Pathological Classification

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

If the primary tumor is invasive, surgical evaluation of the axillary lymph nodes is usually performed. Exceptions may include microinvasive cancers, as well as some cases where the risk of axillary metastases is very low or where the presence of axillary metastases will not affect the use of systemic therapy (e.g., older women with small, hormone receptor-positive cancers). Evaluation of axillary nodes for pathological categorization requires surgical resection. Sentinel lymph node biopsy to remove one or more sentinel lymph nodes for pathological examination is commonly done for patients with clinically negative lymph nodes. The use of sentinel node biopsy is denoted by the "sn" modifier [e.g., pN(sn)]. Alternatively, dissection of the axillary lymph nodes may be performed. In women with clinically negative nodes, this

entails resection of the nodal tissue located lateral to the lateral border of the pectoralis minor muscle (Level I) and beneath that muscle to its medial border (Level II).

When T data are otherwise sufficient for pathological staging, it is necessary to have microscopic analysis of at least one lymph node to classify the lymph node pathologically. This may be FNA, core needle biopsy, excisional node biopsy, or sentinel node biopsy. A case may be assigned a pathological N category if any lymph nodes are microscopically examined, irrespective of the number of nodes removed. However, the number of nodes removed should be reported. In most cases, lymph node dissection of Level I and Level II of the axilla includes 10 or more lymph nodes.

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 surgery, although sentinel lymph node biopsy may be considered. Invasive tumor nodules in the axillary fat adjacent to the breast, without histologic evidence of associated lymph node tissue, are classified as regional lymph node metastases (pN).

Pathological staging groups may be assigned if pathological information is available for T and N using the clinical category for M (pT pN cM0 or pT pN cM1), or the pathological category for M if metastases are biopsy proven (pT pN pM1). 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, ypT ypN cM. Clinical prognostic stage should be assigned in this case.

Pathological Characterization of the Primary Tumor (T)

Determining Tumor Size

Pathological tumor size (pT) based on gross measurement also may be somewhat inaccurate for the same reasons as discussed in the clinical classification. Microscopic assessment is preferred because it is able to distinguish fibrosis, noninvasive, and invasive carcinoma. Microscopically determined pT should be based on measuring only the invasive component. For small invasive tumors that can be submitted in one section or paraffin block, 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 or block, the gross measurement is the preferred method of determining pT. In some situations, systematic pathology evaluation allows microscopic reconstruction of the tumor; however, reconstruction measurements should be correlated with gross and imaging size before assigning pT. Whichever method is used, pT should be recorded to the nearest millimeter. The size of the primary tumor is measured for T categorization 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 needle biopsy sampling), measuring only the residual tumor may result in underclassifying the T category 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 needle biopsy to the residual invasive tumor in the excision is not recommended, because this method often overestimates maximum tumor dimension. In general, the maximum dimension in either the core needle biopsy or the excisional biopsy is used for T categorization unless imaging dimensions suggest a larger invasive cancer.

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 not be apparent by any imaging modalities or gross pathological 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 (see section "Post Neoadjuvant Therapy ypT Classification").

Tis Classification

Pure noninvasive carcinoma, or carcinoma *in situ,* is classified as Tis, with an additional parenthetical subclassification indicating the subtype. Two subtypes are currently recognized: ductal carcinoma *in situ* (DCIS) and Paget disease of the nipple with no underlying invasive cancer. These are categorized as Tis (DCIS) and Tis (Paget), respectively. "Intraductal carcinoma" is an outmoded term for DCIS that 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 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).[44, 45] If both ductal and lobular *in situ* components (DCIS and LCIS) are present, the tumor currently is classified as Tis (DCIS). A recently published Cancer Protocol and Checklist from the College of American Pathology (CAP) provides much greater detail regarding definition and evaluation of *in situ* cancer of the breast (http://www.cap.org).[46]

Paget disease of the breast is characterized clinically by an exudate or crust of the nipple and areola caused by infiltration of the epidermis by noninvasive breast cancer epithe-

lial cells. This condition usually occurs in one of the following three circumstances:[47]

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 DCIS. T classification should be based on the underlying tumor as Tis (DCIS), accordingly. However, the presence of Paget disease associated with invasive or noninvasive carcinomas should still be recorded.
3. Paget disease without any associated identifiable underlying invasive or noninvasive disease is the only lesion classified as Tis (Paget). The very rare case of Paget Disease with LCIS in the breast parenchyma also is categorized as Tis (Paget).

The size of noninvasive (pTis) carcinomas does not change the T category. However, because tumor size may influence therapeutic decisions, an estimate of size should be provided based on the best combination of imaging, gross, and microscopic histological findings.[46] Recommendations for establishing and communicating the size of DCIS have been disseminated by CAP in its cancer protocols (www.cap.org).

LCIS, included in prior editions of the AJCC Cancer Staging Manual, is removed from the 8th Edition. LCIS is a benign condition and is not treated as a carcinoma. It is properly considered a proliferative disease with associated risk for developing a breast cancer in the future and, therefore, is no longer included in this cancer staging system.

One form of LCIS (often called "pleomorphic" LCIS or high-grade LCIS) has features overlapping DCIS, including high-grade nuclei and central necrosis, and some physicians believe it should be treated similarly to DCIS. Evidence is insufficient at present, primarily due to the low prevalence of this form of high-grade LCIS, to establish definitive recommendations for treatment. Thus, for the present, high-grade or pleomorphic LCIS also is not included in the pTis classification.

Microinvasive Carcinoma

Microinvasive carcinoma is defined as an invasive carcinoma with no focus measured larger than 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. The sum of the sizes should not be reported or used for determining pT. 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. Tumor foci larger than 1.0 mm should not be rounded down to 1.0 mm. If a registry system limits reporting to millimeter increments, those tumors that are larger than 1 mm but smaller than 2 mm should be reported as 2 mm. Microinvasive carcinoma is nearly always encountered in a setting of DCIS (or, infrequently, 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.

Categories for pathological tumor (pT) are the same as for clinical (cT); see section "Definitions of AJCC TNM" in this chapter.

Pathological Characterization of Regional Lymph Nodes (N)

Pathological classification (pN) is used only in conjunction with a pathological T assignment (surgical resection) (pT) and includes pathological evaluation of excised nodes from a sentinel lymph node biopsy and/or lymph node dissection. Classification based solely on sentinel lymph node biopsy with fewer than six nodes evaluated and without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn). Isolated tumor cell clusters (ITC) are defined as small clusters of cells not larger than 0.2 mm, or single tumor cells, or fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N categorization but should be included in the total number of nodes evaluated, and the number of nodes with only ITCs should be noted in the pathology report. When pT is assigned, the final pN classification may include clinical data; for example, when an ipsilateral internal mammary node is identified by imaging and meets criteria for cN3b and axillary or sentinel nodes have been removed for pathological evaluation, a pN3b classification may be assigned. See Figs. 48.10 and 48.11 for illustrations of the categories for pathological N (pN).

Macrometastases

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

The pN classification for breast carcinoma reflects the cumulative total regional lymph node burden of metastatic disease in the axillary, infraclavicular, supraclavicular, and ipsilateral internal mammary nodes. For patients who are

pathologically node-positive with macrometastases, at least one node must contain a tumor deposit larger than 2 mm, and all remaining quantified nodes must contain tumor deposits larger than 0.2 mm (at least micrometastases); nodes containing only ITCs are excluded from the calculated positive node count for purposes of N categorization, but they should be recorded as additional ITC-involved nodes and should be included in the total nodes evaluated. Cases with one to three positive Level I/II axillary lymph nodes are classified pN1a; cases with four to nine 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 one to three axillary lymph nodes. If four or more axillary lymph nodes are involved and internal mammary sentinel nodes are involved, the classification pN3b is used. Pathological 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, is classified as Stage IIIC.

A case in which the categorization is based only on sentinel lymph node biopsy is given the additional designation (sn) for "sentinel node"—for example, pN1a(sn). For a case in which an initial categorization is based on a sentinel lymph node biopsy but a standard axillary lymph node dissection is subsequently performed, the categorization 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 categorization 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 (fewer 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 over counting sectioned nodes or sectioned adipose tissue with no grossly apparent nodes.

The first priority in histologic evaluation of lymph nodes is to identify all macrometastases (metastases larger than 2.0 mm, see Fig. 48.7). 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 categorization; however, such techniques as multilevel sectioning and IHC will identify additional tumor deposits, typically micrometastases and ITCs. It is recommended that nodal tissue that may contain a macrometastasis not be diverted for experimental or alternative testing, such as molecular analysis, if this diversion would potentially result in the pathologist's missing macrometastases detectable by routine microscopic examination.

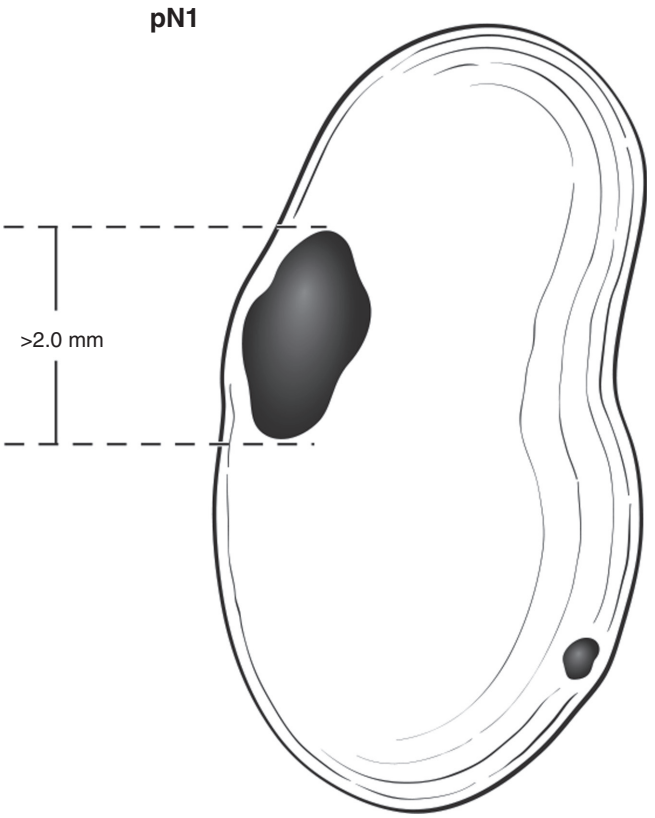

Fig. 48.7 Macrometastasis; pN1. At least one contiguous tumor deposit must be larger than 2.0 mm

Isolated Tumor Cell Clusters and Micrometastases

ITCs are defined as small clusters of cells not larger than 0.2 mm in largest dimension, or single cells, usually with little if any histologic stromal reaction. ITCs may be detected by routine histology or by 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. Multiple ITC clusters often are present, and only the size of the largest contiguous tumor cell cluster is used for pN category; neither the sum of the ITC cluster sizes nor the area in which the clusters are distributed is used for pN (Fig. 48.8).

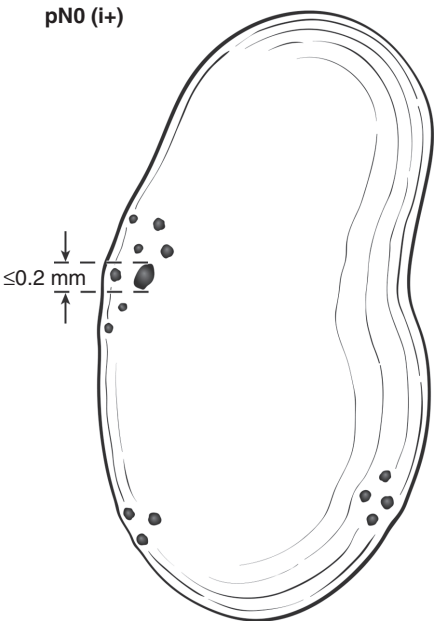

Fig. 48.8 Isolated tumor cell clusters (ITC); pN0(i+). The largest contiguous tumor deposit must be no larger than 0.2 mm. Multiple ITCs are often clustered and multiple foci are frequently present in a single node. The size of areas of noncontiguous adjacent ITCs are not added. When more than 200 single tumor cells are present in a single lymph node cross section, this signifies that the size of the deposit is likely greater than 0.2 mm and this should be classified as a micrometastasis

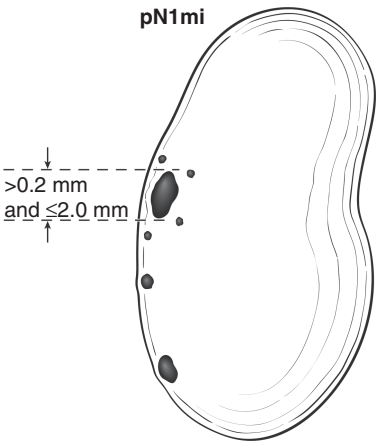

Fig. 48.9 Micrometastasis; pN1mi. At least one contiguous tumor deposit must be larger than 0.2 mm and the largest contiguous tumor deposit must be no larger than 2.0 mm. The sizes of noncontiguous adjacent tumor deposits are not added. Multiple micrometastases may be present in a single lymph node

A three-dimensional 0.2-mm cluster contains approximately 1000 tumor cells. 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 1000 cells are present in the lymph node. In these situations, the node may be classified as containing 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 because of inherent limitations in pathological 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 group of isolated tumor cells.

Micrometastases are defined as tumor deposits larger than 0.2 mm but not larger than 2.0 mm in largest dimension (Fig. 48.9). Cases in which at least one micrometastasis is detected but no metastases larger 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 extension), is totally present outside the lymph node and invading adipose, or is present within a lymphatic channel adjacent to the node. When multiple tumor deposits are present in a lymph node, whether ITCs or micrometastases, the size of only the largest contiguous tumor deposit is used to classify the node, not the sum of all individual tumor deposits or the area in which the deposits are distributed. When a tumor deposit has induced a fibrous (desmoplastic) stromal reaction, the combined contiguous dimension of tumor cells and fibrosis determines the size of the metastasis, except following neoadjuvant therapy. 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) should be recorded separately to facilitate N categorization as described previously.

If histologically negative lymph nodes are examined for evidence of unique tumor or epithelial cell markers using molecular methods (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 data from molecular analyses are generated, they should be recorded by the registrar (Figs. 48.10 and 48.11).

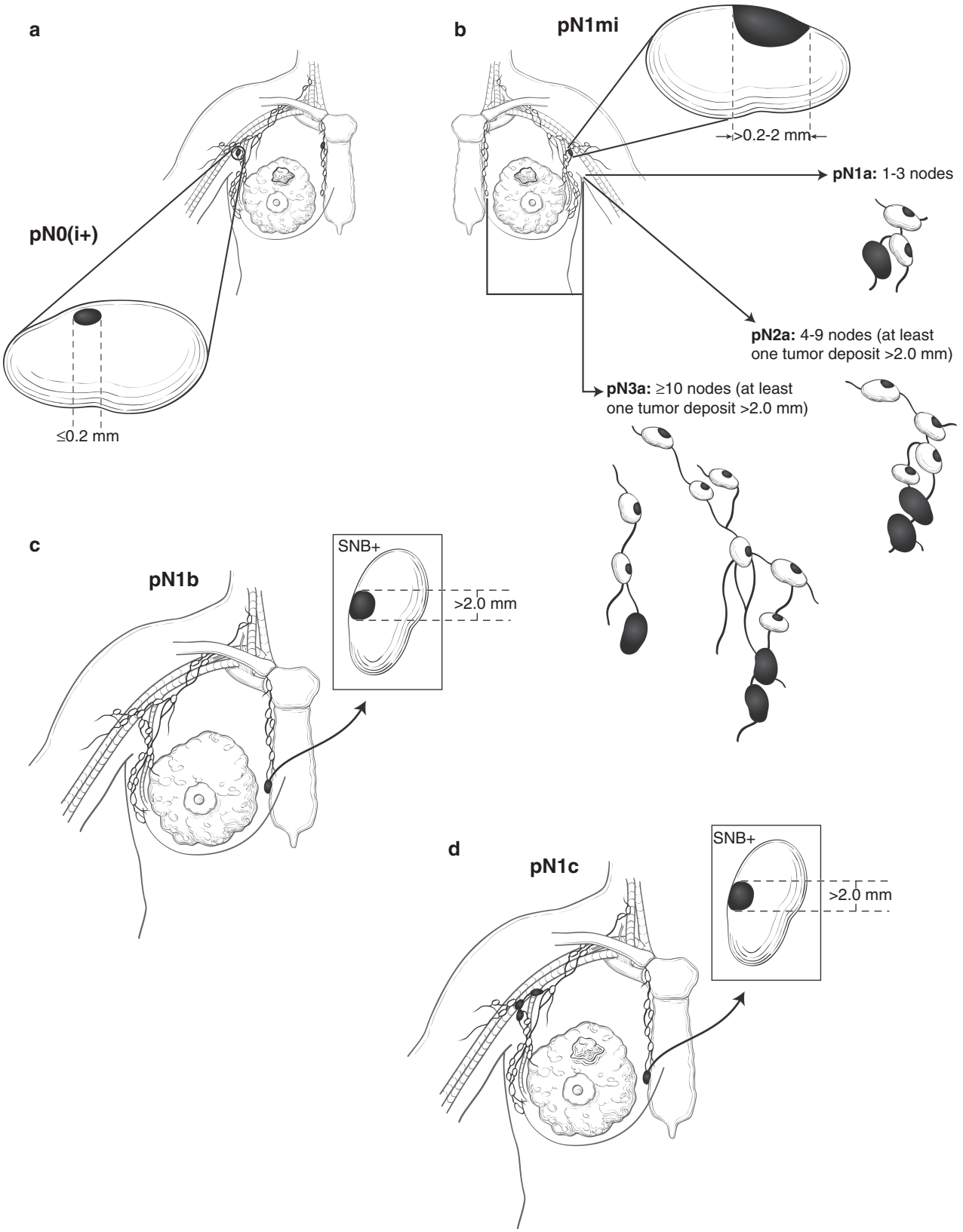

Fig. 48.10 Pathological nodal categories. (**a**) Isolated tumor cell clusters (ITC) are groups of tumor cells 0.2 mm or less and are categorized as pN0(i+). (**b**) The pN1 category includes pN1mi micrometastases defined as node deposits of tumor cells 0.2 – 2 mm; pN1a defined as 1–3 nodes with at least 1 node with a deposit greater than 2 mm; pN2a is 4–9 positive nodes; pN3a is 10 or more positive nodes. (**c**) pN1b is assigned with a positive internal mammary sentinel node with a deposit greater than 0.2 mm in the absence of axillary node metastases. (**d**) pN1c is with combined pN1a and pN1b

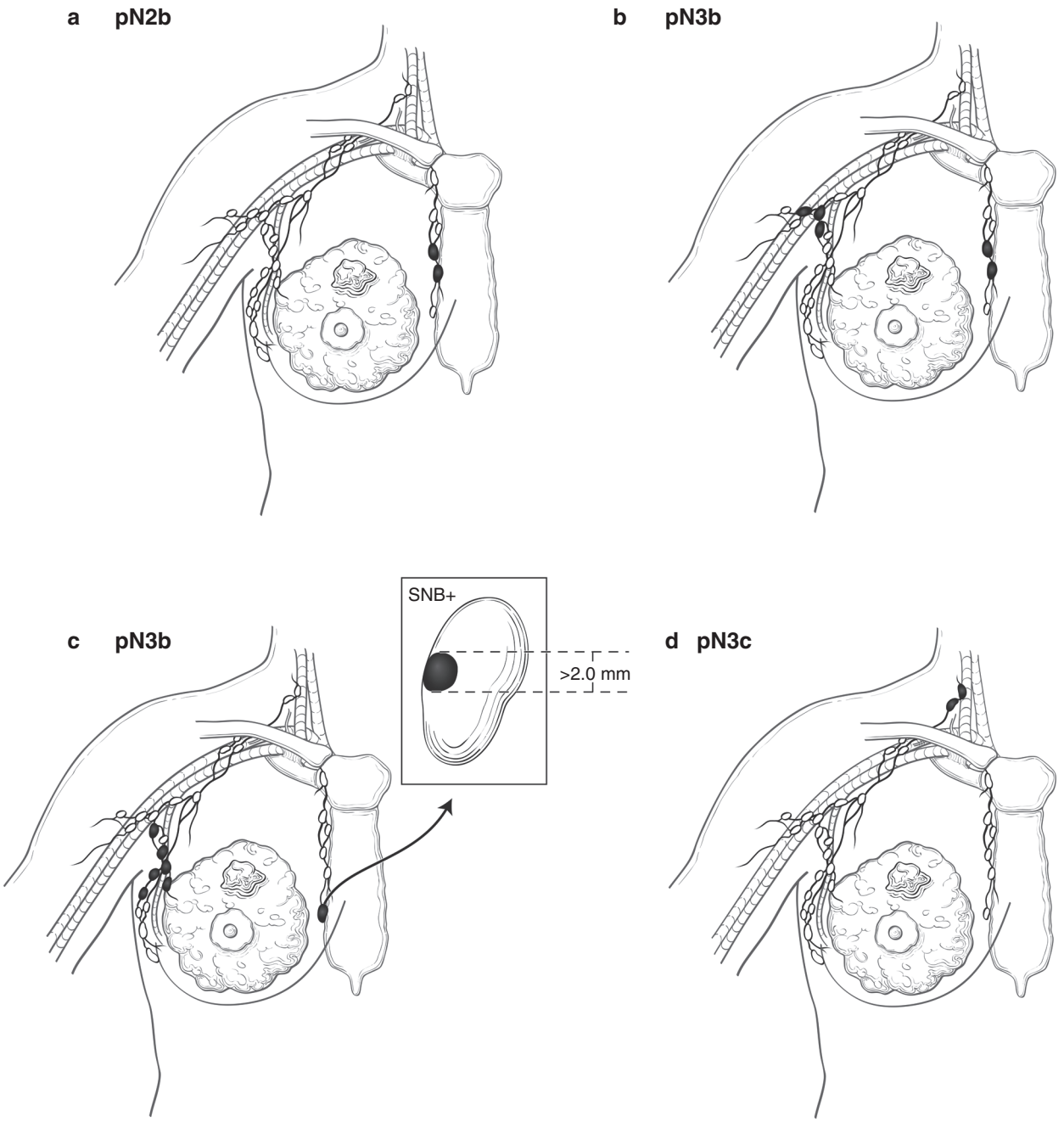

Fig. 48.11 Pathological Node Categories (continued). (**a**) pN2b is with clinically detected internal mammary nodes and negative axillary nodes; (**b** and **c**) pN3b is with pN1a or pN2a with clinically positive internal mammary nodes by imaging OR pN2a with pN1b; and (**d**) pN3c is metastases to ipsilateral supraclavicular lymph nodes with any other regional lymph node involvement.

Pathological Characterization of Distant Metastases (M)

Categories for pathological (pM) are the same as for clinical (cM); see previous discussion of distant metastases characterization and Definitions of AJCC TNM in this chapter.

Post Neoadjuvant Therapy Pathological Classification (yp)

Multiple prospective clinical trials demonstrated the prognostic value of response to preoperative (neoadjuvant) therapy.[48, 49] A pathological complete response (pCR) is

associated with significantly improved disease-free and overall survival for individual patients. A recent meta-analysis confirmed the reproducible prognostic value of pCR.[50]

Post Neoadjuvant Therapy ypT Classification

Preoperative or neoadjuvant systemic therapy has been used for several decades for managing inflammatory and locally advanced breast cancer, and it is being used increasingly for managing earlier stages of the disease, as well.[43] Clinical (pretreatment) T (cT) is defined by clinical and radiographic findings; pathological (posttreatment) T (ypT) is determined by the pathological size and extent of disease – this can only be determined if the primary site is resected after completing neoadjuvant therapy. The ypT is determined by measuring the largest contiguous focus of residual invasive tumor, with the modifier "m" indicating multiple foci of residual tumor. 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 may further assist the clinician in estimating the extent of residual disease. The residual cancer burden method (www.mdanderson.org/breastcancer_RCB) can be recommended, with demonstrated prognostic relevance within each molecular subtype of breast cancer, and provision of quantitative information that is complimentary to yp classification.[51, 52] Other methods, currently without subtype-specific prognostic evidence, semi-quantitatively compare the histopathology before and after treatment, e.g. Miller-Payne, Chevallier, Sataloff, or others.[53–56] Otherwise, description of the distance over which tumor foci extend, the number of tumor foci present, or the number of slides/blocks in which tumor appears, might be offered in the report.

If a cancer was classified as inflammatory (cT4d) before neoadjuvant chemotherapy, the cancer is still classified as inflammatory breast cancer after therapy, even if complete resolution of the inflammatory findings is observed during treatment. The posttreatment pathological classification (ypT) should reflect the extent of identified residual disease, and the pathology report should note that the pretreatment classification was cT4d. For example, a patient with several foci of microscopically confirmed residual disease measuring 2–9 mm in greatest dimension identified within a 22-mm^2 area of tumor bed fibrosis is classified as ypT1b(m), and a patient with no residual disease identified is classified as ypT0. When the only residual cancer in the breast is intravascular or intralymphatic (LVI), the ypT0 category is assigned, but the case cannot be classified as a complete pathological response (pCR).

Post Neoadjuvant Therapy ypN Classification

Clinical pretreatment node status (cN) is defined by clinical and radiographic findings with or without FNA, core needle biopsy, or sentinel node biopsy of a suspicious node or excision of a palpable node; pathological posttreatment N (ypN) is determined similar to pN. The "sn" modifier is used only if a sentinel node evaluation was performed after treatment and no axillary dissection has been performed. If no sentinel node or axillary dissection is performed, the (ypNX) classification is used.

The ypN categories are the same as those used for pN. Only the largest contiguous focus of residual tumor in the node evaluation is used for classification; any treatment-associated fibrosis is not included. Inclusion of additional information in the pathology report—such as the distance over which tumor foci extend and the number of tumor foci present—may assist the clinician in estimating the extent of residual disease.

Post Neoadjuvant Therapy M Classification

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

Other Rules for Classification – Functional Imaging, Multiple Primaries

Historically, TNM classification has been based on tumor morphology with size as the major indicator of prognosis and treatment efficacy. Although size is still the prime determinant in classification, the use of molecular breast imaging, CT, PET and MR imaging with contrast enhancement brings up many more measurement possibilities other than anatomic size. This includes biologic functional imaging characteristics that may be more accurate than size alone to evaluate prognosis and treatment options. At the moment, validated data are insufficient to incorporate these findings into staging. When sufficient data are accumulated these factors may be introduced into the staging system.

For patients who receive neoadjuvant systemic or radiation therapy pretreatment, T is defined as clinical (cT). Pretreatment staging is clinical, and the clinical measurement defined from examination and imaging is recorded (cT).

Multiple Simultaneous Ipsilateral Primary Carcinomas

Multiple simultaneous ipsilateral primary carcinomas in the same breast, which are grossly or macroscopically distinct and measurable using available clinical and pathological techniques, are defined as invasive carcinomas. T category

Table 48.1 Characterization of the response to neoadjuvant therapy

Treatment response category	Description
Complete Response(cCR and pCR) ycT0N0 ypT0N0 or ypTisN0	Clinical response is based on history, physical examination and whatever imaging studies are available. Clinical complete response (cCR) is defined as the absence of evidence of cancer in breast and lymph nodes based on this information. Pathological complete response (pCR) can only be determined by histopathologic evaluation if the primay site and nodes are removed after completing therapy and is defined by the absence of invasive carcinoma in the breast and lymph nodes. The presence of *in situ* cancer after treatment in the absence of residual invasive disease, constitutes a pCR. The presence of tumor within lymphatic and/or vascular spaces in the breast (lymphatic vascular invasion – LVI) with or without other residual invasive cancer precludes classification as a complete pathological response. Patients with isolated tumor foci in lymph nodes are not classified as having a complete pathological response. The presence of axillary nodal tumor deposits of any size, including cell clusters 0.2 mm or smaller, excludes a complete pathological response. These cancers are categorized as ypN0(i+).
Partial Response (cPR and pCR)	A Partial Response (cPR or pPR) is a decrease in either or both the T or N category compared to the clinical (pretreatment) assignment, and with no increase in either T or N. Clinical partial response (cPR) is determined by clinically assessing the tumor and regional lymph nodes compared to the pretreatment clinical tumor and lymph node information. This comparison should be based on the clinical method that most clearly defined tumor dimensions before treatment. Objective measurement of the degree of pathological response that is less than a complete response is based on the pathological assessment of the extent of residual cancer (size of areas of involvement, cellularity, presence of LVI, and other features). This provides useful information to the clinician, but there is no pretreatment pathological categorization for comparison. The finding of positive nodes is determined by physical examination and/or radiologic evaluation before chemotherapy. If prechemotherapy microscopic lymph node involvement is demonstrated by FNA, core needle biopsy, or sentinel node biopsy, it should be recorded as such using cN. Nodal response should be evaluated by physical examination and imaging for ycN. Evaluation by microscopically examining resected nodes after chemotherapy allows pathological categorization (ypN). Absence of posttreatment pathological nodal involvement should be used to document pathological complete response, and should be recorded, but does not necessarily represent a true "response" since the pre-therapy status of resected nodes is not necessarily known.
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 pathological evaluation indicates no response to treatment. Clinical (pretreatment) T and N is defined by clinical and radiographic findings. Posttreatment T is determined by pathological size (ypT) in resectable tumors and by clinical exam and imaging in unresectable tumors (ycT). For resectable tumors, the response category is appended to the y stage description. For example: ypTis ypN0 cM0 CR; ypT1 ypN0 cM0 PR; ypT2 ypN1c M0 NR. Rarely the cancer grows or progresses during therapy. There is no specific notation for this circumstance. In these situations, the code for "No Response" should be used for the registry.

assignment in this setting should be based only on the largest tumor; the sum of the sizes should not be used. However, the presence and sizes of the smaller tumor(s) should be recorded and the "(m)" modifier, as defined by the staging rules in Chap. 1, should be appended to the T category.

Invasive cancers that are in close proximity, but are apparently separate grossly, may represent truly separate tumors, or one tumor with a complex shape, or intramammary spread of disease. Distinguishing these situations may require judgment and close correlation between pathological 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 apparent distinct tumors are very close (e.g., less than 5 mm apart from each other), especially if they are similar histologically, they are most likely one tumor with a complex shape, and their T category—after consideration of imaging, macroscopic, and microscopic findings—may 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 tissue is needed to justify summing the size of two grossly distinct masses to define the T-category. These criteria apply to multiple macroscopically identified and measurable tumors. These criteria do not apply to one macroscopic carcinoma associated with multiple separate microscopic (satellite) foci. For these tumors the T-category is assigned by the size and extent of the macroscopic carcinoma. If the two tumors appear to be separate, then the T-category should be determined by the characteristics of the larger or higher T-category cancer.

Simultaneous Bilateral Primary Carcinomas

Each carcinoma is classified and staged as a separate primary carcinoma in a separate organ based on its own characteristics, including T category as specified in the staging rules (see Chap. 1). Each tumor should have a separate biomarker determination (ER, PR, HER2, and grade).

Biomarkers and Prognostic Breast Cancer Staging

From the start of the planning phase of the 8th Edition, the Breast Expert Panel discussed the importance of integrating biomarkers into TNM staging for this edition. In view of the challenges identified during the development of the 7th Edition, many of them persisting to date, a Methodology Task Force was created to advise the Breast Panel on how to accomplish the goal of integrating biomarkers into staging without compromising the ability of using the staging system if biomarker information was not available. The Methodology Task Force also reviewed appropriately validated multigene prognostic and predictive panels for consideration of integration into staging.

This issue was discussed in some detail in preparation of the 7th Edition. However it was determined that there were insufficient validated data to take that step. The discussion remains relevant for the 8th Edition. If anything, the incorporation of biomarkers is a more pressing need now than at the time of the previous edition.

For the 8th Edition, a great deal of uncertainty remained about how to accurately integrate biomarkers and prognostic and predictive multigene panel results into the AJCC staging system. The large majority of the relevant data is retrospective in nature, with little prospective data available. Nonetheless, the clinical value of multigene panels for selecting treatment for certain subsets of patients has been demonstrated in a reproducible and convincing fashion. The value of multigene panels for managing patients has now progressed to the point where such panels are routinely incorporated into national guidelines and recommendations for treatment (e.g., NCCN and ASCO tumor marker guidelines).

Maintaining Anatomic Stage

The Expert Panel reached a strong consensus that each patient should be able to be assigned a purely anatomic stage even if prognostic staging is possible. It is recognized that prognostic staging is not appropriate for all subsets of patients and that in many situations and parts of the world where biomarker determination and/or multigene panels are not routinely performed or available. This occurs most often in regions of the world with limited resources to pay for such testing. Furthermore, anatomic staging remains a valuable aspect of the staging process because it is a link to the past for comparison of studies and patient populations, as well as a common terminology for providers, researchers, and others, regardless of country or available resources.

Breast Biomarkers

It is clear that in addition to the traditional tumor size, lymph node status, and presence of metastasis, tumor biology is vitally important in prognosis and response to therapy. The AJCC staging system has always applied to treated patients. Initially, the treatment was surgical, with or without radiation therapy. Over time the system has adapted from a classic tumor size, nodal status and the presence or absence of metastasis to include evaluation of sentinel lymph nodes only, post systemic therapy, and even findings at autopsy. There never was a group of "totally untreated" patients. To remain clinically relevant, it is critically important to alter staging as new advances in the understanding and treatment of cancer develop.

Grade A key proxy for the biologic character of a cancer is tumor differentiation. Tumor differentiation is reflected and assessed in many ways, including proliferative index, grade, hormone receptor status, expression of oncogenes, and gene expression profiles. The earliest attempts at evaluating tumor differentiation and prognosis were characterizing tumors by histologic or nuclear grade.[57–61] Different systems have been used, but the most reliable and widely used is the histologic grading system of Scarff, Bloom, and Richardson, as updated and standardized by the Nottingham group.[62–64] Tumors of high histologic grade or poorly differentiated tumors have a worse prognosis than low-grade or well-differentiated tumors without regard to hormonal or chemotherapy.

An analysis of data from the SEER Program of the National Cancer Institute has shown that histologic grade is an important prognostic factor, independent of the tumor size or number of positive lymph nodes.[65] Although the reproducibility of histologic grade among pathologists has been called into question,[66] the work of Elston and Ellis gives guidelines on how to reproducibly grade breast cancers.[63, 64] They modified the Scarff–Bloom–Richardson (SBR) system with semiquantitative evaluations for tubules (glands), nuclear pleomorphism, and mitotic counts. Gland or tubule formation is judged over the entire tumor, as is nuclear pleomorphism. Mitotic counts are done in the most mitotic active area of carcinoma in 10 consecutive high-powered fields. The high-powered fields are standardized by measuring the diameter (and area) of the microscopic field and converting the mitotic counts in comparison to a standardized area.[63] This system has been endorsed by the Royal College of Pathologists' Working Group for the National Health Service Breast Screening Program, on Pathological Reporting. In

addition, it has been adopted by the Cancer Committee of CAP and is required by the Commission on Cancer (CoC) and the National Accreditation Program for Breast Centers (NAPBC). The guidelines for grading of breast cancers are available on the CAP website (www.cap.org).

High-grade and rapidly dividing tumor cells are more likely to respond to nontargeted chemotherapy. In the traditional histopathologic sense, the measure of dividing cells is the mitotic count. To attempt a more accurate picture of percent dividing cells, many pathologists use expression of Ki-67 measured by IHC.[67] Although there are no universally agreed-upon cut points for low, intermediate, or high Ki-67 values, and no standardized methodology is applied, it is clear that high Ki-67 levels reflect rapidly dividing tumor cells and predict response to anthracycline chemotherapy.[68]

Hormone Receptors It has been recognized since the late 1800s that hormonal manipulation can affect the growth of breast cancer.[69] More recently, ER assays have been standardized.[70] It has been shown that selective ER modulators, such as tamoxifen and other endocrine therapies, slow or stop progression of ER- and PR-positive tumors. The higher the level of expression of ER and PR, the greater the benefit.[71, 72] The response rate is lower for tumors that are ER-positive and PR-negative, and lower still for ER-negative, PR-positive tumors. ER-negative, PR-negative tumors are very unlikely to respond to endocrine therapy.[71–73]

HER2 A number of oncogenes also have been linked to prognosis in breast cancer. The most studied is HER2.[74] The presence of HER2 positivity in untreated patients, either by gene amplification or protein overexpression, has been associated with a worse prognosis in both node-negative and node-positive patients.[75–77] HER2 positivity in breast cancers is associated with poor differentiation and, therefore, is very rarely seen with low-grade invasive ductal carcinomas or traditional invasive lobular carcinoma.[77] HER2 positivity, in addition to being associated with high-grade tumors, also is associated with high cell proliferation rates, DNA aneuploidy, and hormone receptor negativity.[78–80] ASCO and CAP have together issued guidelines for performing and evaluating HER2 testing.[81, 82]

The development of HER2-targeting agents for the treatment of HER2-positive breast cancer has dramatically improved outcomes for patients with this disease. The monoclonal antibody trastuzumab and related agents, given in conjunction with various chemotherapeutic regimens, have been shown to be particularly effective in improving prognosis of HER2-positive patients.[83, 84] There appear to be complex relationships between hormone receptor status and HER2 expression. It has been reported that patients with tumors that are HER2- and ER-positive are less responsive or resistant to single-agent tamoxifen.[85–87] Even in hormone receptor–positive tumors, the expression of HER2 appears to be inversely related to the expression of ER and PR.[88]

Breast cancer biologic subtypes It is clear that breast cancer, like other cancers, is not a single disease; the cancers vary tremendously, not only in histologic appearance, grade, hormone receptor, and HER2 status, but also on a molecular/genetic basis. Genomic analysis of breast cancers identifies four groups,[89] similar to the intrinsic subtypes defined by gene expression profiling.[90–93] These subtypes—Luminal A, Luminal B, HER2 and Basal—have widely different gene expressions, natural histories, metastatic patterns, and sensitivity to existing therapies.[90, 94, 95]

Although gene expression profiling has become a more commonly used laboratory technique, and its cost has decreased significantly, it is still not broadly available as a validated diagnostic technique in most health care situations. Therefore, instead of gene expression-based molecular subtypes of breast cancer, clinically defined subtypes have been used to estimate prognosis and guide therapeutic decisions. These subtypes are based on the expression of ER, PR, and HER2, with the additional measurement of grade or a measure of proliferation, such as Ki-67 or mitotic count. The characteristics of each subtype are shown in Table 48.2.

Luminal A-type tumors are usually low-grade invasive ductal carcinomas (NOS type) or special types of carcinoma—such as tubular, cribriform, or mucinous—and have an excellent prognosis. These tumors generally have a poor response to traditional chemotherapy but have an excellent response to endocrine therapies. Luminal B tumors tend to be poorly differentiated, less likely to respond to endocrine therapy and more likely to respond to traditional chemotherapy. The HER2-like (or HER2-enriched) tumors, prior to the introduction of anti-HER2 therapy, were the most aggressive subtype and had the highest mortality rate and shortest survival. However, in current practice, when appropriately managed with anti-HER2 therapy, patients with these tumors have a much better prognosis. The basal-like tumors, which are thought to arise from myoepithelial cells, have the highest mortality and are most difficult to treat with adjuvant therapy.

Multigene Panels, Genomic Profiles, Signature Scores

Another consideration for adding biologic factors into breast cancer staging is to incorporate the findings from multigene panel testing. The multigene panels test for the levels of expression of multiple genes in the breast cancer tissue, most often by some measure of the levels of message

Table 48.2 Clinically defined subtypes of breast cancer (Modified with permission from Konecny et al. 2003[88] and Eiermann et al. 2013[94])

Clinically Defined – Treatment Oriented Subtypes of Breast Cancer	
LUMINAL LIKE Hormone receptor-positive and HER2-negative luminal disease as a spectrum:	**LUMINAL LIKE** Hormone receptor-positive and HER2-negative luminal disease as a spectrum:
(Luminal A-like) High receptor, low proliferation	Multiparameter molecular marker "favorable prognosis," if available; high ER/PR and clearly low proliferation rate (low Ki-67, low mitotic count); generally histological grade 1 or 2
(Luminal B-like) Low receptor, high proliferation	Multiparameter molecular marker "unfavorable prognosis," if available; lower ER/PR with high proliferation rate (high Ki-67, high mitotic count); generally histological grade 3
HER2 LIKE HER2-positive	HER2-positive and hormone receptor-negative *or* HER2-positive and hormone receptor-positive; generally histological grade 3
BASAL LIKE Triple-negative	Negative ER, PR, and HER2; generally histological grade 3

(RNA) present in the tumor. Several such panels are in clinical use because of studies demonstrating their value in providing more specific prognostic information and in predicting sensitivity to classes of systemic agents, especially chemotherapy.

One issue in assessing the use of multigene panels is that the panels currently in clinical use may simply represent a substitute for measuring proliferation. These panels often include significant numbers of proliferation genes and track closely with proliferation. The most widely used single marker of proliferation is Ki-67. As a single factor, Ki-67 was not considered a reliable factor for implementation in clinical practice, both because of the known lack of reproducibility (especially between different laboratories) as well as the lack of agreement on an optimal cut-point. Multigene panels have the advantage of being reproducible and reliable, but the disadvantage of substantial cost, at least at the present time.

As a consideration for integrating multigene marker panels into staging, the Expert Panel felt that a prerequisite to obtaining a multigene panel was to perform the required individual tumor markers, including at a minimum, ER, PR, and HER2. The strong recommendation was that prognostic and predictive models should not be part of the staging system without knowledge of ER, PR, and HER2, and, in part because their use may be limited only to patients with specific breast cancer subtypes (e.g., hormone receptor–positive, HER2 negative). A second recommendation was that multigene panels should only be incorporated into the staging system for certain subsets of breast cancer. For example, multigene panels might be considered for smaller node-negative hormone receptor–positive, HER2-negative subgroup. There was agreement that multigene panels would not be incorporated into staging for triple-negative or HER2-positive tumors at this time because they have no demonstrated clinical value for these patients. Third, it was recognized that most data on multigene marker panels do not include prospective cohorts of patients; rather they were derived from retrospective analyses of databases and tumor collections.

A number of recent publications and abstracts provide relevant data for integrating multigene panels into clinical staging. Specifically in relation to the Oncotype Dx® assay, the TAILORx study enrolled patients on a low-risk arm (Arm A; not randomized) based on the following criteria: hormone receptor–positive, HER2-negative, node-negative, invasive breast carcinoma, tumor size 1.1–5.0 cm (or 0.6 cm–1.0 cm with intermediate or high histologic or nuclear grade), and Oncotype Dx® Recurrence Score less than 11.[10] Systemic treatment was hormone therapy alone, without chemotherapy. At 5 years, the rate of invasive disease-free survival was 93.8%, the rate of freedom from recurrence of breast cancer at a distant site was 99.3%, the rate of freedom from recurrence was 98.7%, and the rate of overall survival was 98.0%.

Similar excellent results based on favorable Oncotype Dx® Recurrence Score results have been presented in three other studies. First, a population-based study from Israel of 930 patients treated according to Recurrence Score has been reported as an abstract.[11] Of the 930 patients, 479 were classified as low risk based on the standard definition of Recurrence Score less than 18. Only 1% of this low-risk group received chemotherapy. At 5 years, the rate of breast cancer-specific survival was 99.8%, and the rate of distant recurrence was 0.5%. The analysis by Stemmer et al. was updated in abstract form with a larger cohort of patients at the 2015 San Antonio Breast Cancer Symposium.[96] This updated analysis was based on 1594 patients with a 5.9-year median follow-up. The 5-year estimates for distant recurrence rate in patients with low and intermediate Recurrence Score results were 0.5% and 1.2%, respectively. Second, in a prospective German study of 3198 patients, 348 were classified as low risk defined by the authors as a Recurrence Score less than 11 and were treated with endocrine therapy alone, without chemotherapy.[12] In this low-risk subgroup, the 3-year event-free survival was 98.3%. Real-life analysis evaluating 1594 N0 or N1mi breast cancer patients for whom treatment decisions incorporated the 21-gene recurrence score result showed 5-year Kaplan-Meier estimates for

breast cancer–specific survival with recurrence to be greater than 98% when score results were 30 or lower.

A third group including investigators from Genomic Health, Inc., the company that developed the Oncotype Dx® assay, and investigators at SEER combined the data of patients who had the Oncotype Dx® recurrence score with clinical-pathological data available from the SEER database. The analysis based on 38,568 patients showed that 5-year breast cancer–specific survival for patients with a recurrence score less than 18 was 99.6%; for those with a recurrence score of 18–30, it was 98.6%.[26]

There are similar though more limited data on other genomic profiles. The data supporting the use of the 70-gene signature assay (Mammaprint®) are presented earlier in this chapter. Drukker et al. reported results from 427 patients enrolled in the RASTER (microarRAy-prognoSTics-in-breast-cancER) from the Netherlands, which prospectively defined treatment based on the 70-gene signature (Mammaprint®), in addition to clinical and pathological features. In the subset of 95 patients with low-risk clinical and molecular features (defined by Adjuvant! Online and the 70-gene signature, respectively), systemic therapy (chemotherapy and/or hormonal therapy) was given to less than 10% of these patients. At 5 years, the rate of distant disease-free survival was 94.3%, and the rate of distant recurrence-free survival was 95.3%.[97]

As a result of these recent publications and an exhaustive review of the literature, the ASCO Clinical Practice Guideline Committee updated its guideline regarding the use of biomarkers to guide decisions on adjuvant systemic therapy for patients with early-stage breast cancer.[3] This guideline was published online on February 8, 2016, and incorporates specific recommendations about the single biomarkers and multigene panels.[98] The ASCO Panel further updated its recommendations in June 2017.[9]

In summary, comparison of the results from these studies demonstrates a consistently very low risk of recurrence of disease at 3–5 years in the low-risk subgroup of patients, as selected by low-risk molecular profiling in the context of clinically defined low-risk features. It is not clear that any of these profile assays is superior to the others. Caveats include that follow-up is short in these studies, with only 3- to 5-year results reported, differing clinical selection criteria, differing treatments used, differing molecular profiling tools used, and differing cut points used for selecting the low-risk subgroup of patients. Nonetheless, on balance, low-risk biology as identified by multigene molecular testing in reported studies to date is associated with a very favorable prognosis at 3–5 years.

Expert Panel Decisions Based on the best available evidence at the time of this writing, the Expert Panel determined that it was appropriate to include multigene molecular profiling and incorporate the Oncotype Dx® score into staging for the subgroup of patients defined by Arm A of the TAILORx study (including Oncotype Dx® Recurrence Score less than or equal to 10). These patients should be staged according to the AJCC Prognostic Stage Groups. The findings for the Oncotype Dx® assay are supported by Level I Evidence (large-scale prospective clinical trial data).

Other multigene panels provide similar information that could allow them to be used to assign Prognostic Stage Group I.[99] One assay that generated extensive discussion among the Expert Panel was the 70-gene signature score (Mammaprint®). There are substantial data that could support its incorporation in a similar fashion as the OncotypeDx® recurrence score. The MINDACT study, reported in 2016, showed that for women with a Mammaprint® low genomic risk of recurrence but a high clinical risk with ER-positive and HER2-negative cancers might be spared chemotherapy.[8] Its use is limited in that the Mammaprint® result does not predict benefit of chemotherapy. However, even if the Task Force determined the MINDACT study provided sufficient Level I evidence for use in prognostic staging, incorporating it into Pathological Prognostic Stage table would be difficult. The clinical risk of recurrence used in MINDACT cannot currently be determined as it was based on survival estimates from the Adjuvant!OnLine system that as of July 2017 has not been available online for use while it is being changed and updated, a process that according to the website is taking longer than expected. For these reasons the panel decided not to incorporate Mammaprint® into the Pathological Prognostic Stage table. Similarly there are other genomic assays, including those cited in this chapter, with varying degrees of evidence to improve prognostication that the Expert Panel decided not to use for assigning prognostic stage in the absence of published, level I evidence demonstrating that an assay improved prognostication in discrete TNM stages.

Despite inclusion of one multigene panel, the Expert Panel makes no representation that one or another of the genomic profiles and assays should or should not be used in defining prognosis and making treatment decisions. It is likely that additional evidence will become available in the near- and mid-term about the profiles named in this chapter, and potentially other prognostic and treatment predictive genomic assays. Clinicians and patients should make decisions about the use of any genomic profile (including OncotypeDx®) based on the evidence available at the time of treatment, and the expected value of the results of the assay in making treatment decisions. In doing so, clinicians are cautioned to recognize that while all the listed genomic profile assays stratify patients into a low risk and high risk (and in some cases an intermediate risk) group, these assays are not interchangeable. They do not necessarily identify the same patients as having low or high risk of recurrence/relapse. Direct comparisons of various genomic profiles are

just starting at the time of this writing. Additional information will be needed to determine which of these profiles is best for prognostication and determination of responsiveness to therapy.[27]

For all patients, providers and registries should continue to collect and record ER, PR, HER2, and Ki-67 and should continue to collect and record multigene panel results in appropriate cases, if the markers and panels are performed.

Incorporating Biomarkers into TNM – Prognostic Stage Groups

Heretofore, large databases that have complete data on all biomarkers and sufficient follow-up have not been available, largely because HER2 was not routinely captured in population registries until 2010. However, with these biologic factors in mind, two members of the Breast Expert Panel for the 8th Edition analyzed large cohorts of patients to determine whether the incorporation of biologic markers would improve discrimination over the classic anatomic TNM system.

The first group conducting data analyses to demonstrate the value of biomarkers on prognosis and stage group assignment, led by Drs. Kelly K. Hunt and Elizabeth A. Mittendorf, used a large database from the University of Texas MD Anderson Cancer Center.[20] Invasive breast cancer patients treated at MD Anderson between January 1997 and December 2006 were included in the analysis if they had no known distant metastasis; had information about grade, ER, and PR status; had not received neoadjuvant chemotherapy; and had follow-up longer than 2 years: 3728 patients fulfilled these criteria. Disease-specific survival (DSS) was calculated from the time of diagnosis to death due to breast cancer. Patients not experiencing this endpoint were censored at last follow-up. Pathological stage was then used to derive a prognostic model for DSS. Univariate and multivariate analyses were performed to identify factors associated with DSS. Factors evaluated included ER, PR, grade, and lymphovascular invasion. Independent predictors of DSS were assigned a prognostic score of 0 to 2, based on the hazard ratio (HR). For binary variables, the comparison group with a significant impact on DSS was assigned 1 point. For ordinal variables, comparison groups with a significant impact and an HR between 1.1 and 3 were assigned 1 point, and those between 3.1 and 6 were assigned 2 points. Six staging systems that included various combinations of biologic factors with pathological stage were evaluated, and the staging system that incorporated grade and ER status with pathological stage was determined to be the most precise, with a high C-index and low Akaike's information criterion (AIC). When compared to pathological stage alone, this novel staging system resulted in improved discrimination between stages with respect to DSS. These results were subsequently validated using the SEER data.

One limitation of this staging system is that its development predated the routine use of trastuzumab for patients with HER2-positive breast cancer. Recognizing this, the MD Anderson group updated the model using a cohort of 3327 patients, including 306 patients with HER2-positive breast cancer, treated at their institution between January 2007 and December 2013.[100] With this update, a multivariate analysis was again performed to identify factors associated with DSS. Factors evaluated included pathological stage, grade, ER status, PR status, and HER2 status. A score of 0 to 4 was assigned to each factor based on the HR. Factors with an HR of 1.1–3 were assigned 1 point, factors with a HR of 3.1–6 were assigned 2 points; those with an HR of 6.1–10 were assigned 3 points, and those with an HR greater than 10 were assigned 4 points (Table 48.3). An overall staging score, the Bioscore, was calculated by summing the scores for the individual independent predictors of DSS. The staging system that included pathological stage, grade, ER, and HER2 had the highest C-index and lowest AIC. These results were validated using a cohort of 67,944 patients identified from the California Cancer Registry diagnosed between 2005 and 2010 with a first primary non-metastatic breast cancer who underwent surgery as initial intervention with known grade, ER status and HER2 status.

The analyses performed on these large databases from MD Anderson assumed proper multidisciplinary treatment with appropriate adjuvant chemotherapy and hormonal therapy. The data confirmed the prognostic significance of biologic factors to include grade, ER, and HER2 status and led to the development of a risk profile that can be used to further refine the prognostic information provided by the pathological stage. The risk profile is determined by assigning points as shown in Table 48.4.

The estimated 5-year DSS and overall survival for the MD Anderson cohort of patients treated from January 2007 to December 2013 (n = 3327), based on the addition of the risk profile to the pathological stage, are shown in Table 48.5.

The risk score has been validated using a cohort of 43,938 patients identified in the California Cancer Registry diagnosed with primary breast cancer between 2005 and 2008.[101]

The other group, led by Dr. David J. Winchester and colleagues, studied the impact of prognostic factors on staging using the National Cancer Data Base (NCDB). The study used the conventional variables (TNM categories based upon 7th Edition stage groups), as well as tumor grade (Nottingham modification of the SBR system), ER status, PR status, and HER2 status. All patients had a complete set of variables. Survival calculations were performed for each prognostic subgroup based on 7th Edition stage group, grade, HER2, ER and PR status combination. Patients with triple-negative tumors (all grades) and patients with grade 3 tumors that did

Table 48.3 Univariate and multivariate analyses of prognostic factors and their influence on Disease-Specific Survival (DSS). The last column shows the assignment of points based on the magnitude of the Hazard Ratios (HR). MD Anderson Analysis

	5-year DSS	Univariate Analysis		Multivariate Analysis 2		
	(%)	HR	*p*	HR	*p*	Assigned Points
Pathological Stage (7th Edition)						
I	99.1	Referent		Referent		0
IIA	98.0	2.8	0.002	2.3	0.01	1
IIB	95.6	4.8	< 0.0001	4.0	< 0.0001	2
IIIA	95.4	6.8	< 0.0001	7.2	< 0.0001	3
IIIC	79.5	26.6	< 0.0001	19.9	< 0.0001	4
Nuclear grade						
I	99.8	Referent		Referent		0
II	98.9	5.0	0.1	4.0	0.2	0
III	95.3	25.0	0.001	13.1	0.01	1
ER status						
Positive	98.8	Referent		Referent		0
Negative	92.9	4.9	< 0.0001	2.5	0.001	1
PR status						
Positive	98.8	Referent		Referent		
Negative	95.2	4.0	< 0.0001		NS	
HER2 status						
Positive	97.5	Referent		Referent		0
Negative	98.0	0.8	0.5	2.2	0.04	1

Note: There were insufficient numbers of cases with Stage IIIB cancer for analysis

Table 48.4 Determination of the risk profile. MD Anderson Analysis

Factor	0 points	1 point
Grade	Grade 1/2	Grade 3
ER status	ER positive	ER negative
HER2 status	HER2 positive	HER2 negative

not overexpress HER2 and did not express either ER or PR had decreased survival, comparable to patients at least one stage higher with 7th Edition criteria. Conversely, many subgroups with tumors expressing both ER and PR with or without HER2 overexpression had better survival than others with the same 7th Edition stage group. These findings were consistent with the point score developed in the MD Anderson model. Survival ranges of stage groups were defined using 7th Edition staging criteria to maintain consistency with previous stage survival expectations. Prognostic subgroups were assigned to a respective stage according to the calculated mean survival.

Two analyses were performed. The first used clinical information that includes all patients to provide Clinical Prognostic Stage. The analysis included 334,243 patients diagnosed with invasive breast cancer in 2010–2012 with a median follow up of 41.7 months.[102] This included all patients regardless of the type of subsequent therapy, though most received stage and biomarker appropriate local and systemic therapy. Clinical Prognostic Stage should be assigned on all patients.

The second analysis was restricted to patients from among those with clinical stage who received surgical resection as the initial treatment. It excludes those who received presurgical systemic or radiation therapy (neoadjuvant therapy). It includes all such patients regardless of subsequent therapy, though most received stage and biomarker appropriate local and systemic therapy. Therefore, these patients had pathological information to allow assignment of a Pathological Prognostic Stage. The analysis included 305,519 patients diagnosed in 2010–2012 with a median follow-up of 42.3 months. Pathological Prognostic Stage should be calculated on those patients who receive surgical resection as initial treatment.

During the same time frame, the NCDB data included 44,189 patients who received neoadjuvant therapy (cytotoxic chemotherapy, immunotherapy and endocrine therapy) prior to surgical resection. Because of the relatively small numbers of patients, and the exponential increase in the number of variables generated with degree of neoadjuvant therapy response, meaningful stage assignments for this group of patients could not be generated. As has been the case for the 7th Edition, these patients should all have T and N categorization of clinical or pathological post therapy tumor and node (ycT and ycN or ypT and ypN) status and degree of response (complete, partial, no response) recorded in addition to the Clinical Prognostic Stage. Collection of this information will be critical to generate useful data to inform the Expert Panel for future staging modifications.

Table 48.5 Overall Survival (OS) and disease-specific survival, determined by adding the risk profile to the AJCC TNM pathological stage. MD Anderson Analysis

Stage (7th Edition)	Risk Profile	N	5-yr. DSS	95% CI	5-yr. OS	95% CI
I (IA and IB)	0	36	100%		97%	80.4%–99.6%
	1	1173	99.4%	98.7%–99.7%	96.7%	95.4%–97.0%
	2	274	98.8%	96.4%–99.6%	94.6%	91.0%–96.8%
	3	119	96.6%	91.1%–98.7%	93.8%	87.5%–97.0%
IIA	0	31	100%		96.8%	79.2%–99.5%
	1	634	99.4%	97.5%–99.8%	97.1%	94.7%–98.4%
	2	236	97.5%	93.2%–99.1%	94.1%	88.7%–97.0%
	3	98	91.0%	81.8%–95.7%	88.2%	78.5%–93.8%
IIB	0	11	100%		100%	
	1	309	96.9%	92.6%–98.8%	94.6%	89.6%–97.2%
	2	107	92.9%	83.6%–97.1%	89.3%	80.1%–94.4%
	3	40	91.5%	75.6%–97.2%	91.5%	75.6%–97.2%
IIIA	0	3	100%		100%	
	1	134	98.3%	88.2%–99.8%	91.5%	82.6–96.0%
	2	50	92.2%	77.2%–97.5%	90.3%	75.7%–96.3%
	3	7	68.6%	21.3%–91.2%	68.6%	21.3%–91.2%
IIIC	0	0				
	1	39	92.2%	72.1%–98.0%	84.4%	63.7%–93.9%
	2	16	80.8%	51.4%–93.4%	80.8%	51.4%–93.4%
	3	10	33.3%	6.3%–64.6%	33.3%	6.3%–64.6%

Note: There were insufficient numbers of cases with Stage IIIB cancer for analysis

Prognostic stage groups were defined by combining the anatomic stage group with grade, HER2, ER and PR. Stage IA and IB and Stage IIIB and IIIC were combined. This created 120 different categories of patients. For each Prognostic Stage group, 3-year overall survival was computed. Using the same data, 7th Edition staging criteria were used to generate survival benchmarks and ranges for new stage assignments. If the calculated survival of a Prognostic Stage group fell above or below the 95% confidence interval of the derived 7th Edition stage, the subgroup was downstaged or upstaged, respectively. To maintain consistency with previous breast stage groups, Stage I patients were then divided into Stage IA and IB according to survival. Stage IIIB/C patients were separated in a similar fashion to create Stage IIIB and IIIC. This reestablished 8 stage groups for invasive cancer (IA, IB, IIA, IIB, IIIA, IIIB, IIIC) in addition to Stage Groups 0 and IV for ductal carcinoma *in situ* and metastatic cancer, respectively. For those with pT1 or pT2, pN0, M0, ER positive and HER negative cancers on whom OncotypeDx® was performed, Pathological Prognostic Stage Group IA was assigned if the recurrence score was <11.

The NCDB analyses were used to establish Clinical and Pathological Prognostic Stage Groups for the 8th Edition that are included in this chapter. The inclusion of grade, HER2 and hormone receptor status for both Clinical and Pathological Prognostic Stage resulted in stage reassignment for more than 35% of patients to a stage group higher or lower than would otherwise be assigned using 7th Edition anatomic stage. It is important to note that in applying this stage grouping, survival and stage were derived from patients treated in approximately 1500 Commission on Cancer accredited hospitals, capturing over 70% of breast cancers diagnosed in the United States. The majority of the women in the NCDB were offered and treated with appropriate adjuvant endocrine and/or systemic chemotherapy (including anti-HER2 therapy). Prognostic stage and survival should be considered only in the context of appropriate therapy.

The use of these prognostic groups provides a marked improvement in defining prognosis. The prognostic stage groups contain patients with similar survival. Anatomic stage groups without the biomarker information include patients with widely disparate outcomes. Though the prognostic stage groupings are based on data with relatively short follow-up, the data are robust and reflect outcomes with modern-era therapy. Analyses show that when these biomarker are included in the prognostic evaluation of groups of patients, the survival at the short follow-up time correlates highly with the findings of longer term follow-up. Further, there is excellent correlation of the NCDB and the MD Anderson Cancer Center analyses. In addition, it is important to recognize that the outcomes of patients relate to utilization of appropriate therapy. Survival calculations of patients treated more than a decade ago are not reflective of current therapy for many patients, arguing for survival calculations to be derived from patients treated only with contemporary therapy.

While the application of these prognostic stage groups in practice and cancer registries will be more complicated than the anatomic stage groups, the prognostic stage more accurately predicts outcome. The Expert Panel believes this added clinical value outweighs the added complexity. It is expected that electronic health record and cancer registry software systems in the near future will offer tools to generate the Clinical and Pathological Prognostic Stage Groups from the data entered for T, N, M, grade and prognostic factors. Regardless, the Expert Panel and AJCC believe this is a necessary and positive step forward in breast cancer staging as it provides information more relevant to clinical practice that will better serve our patients.

It is recognized that in coming years, and potentially as soon as the next 2–3 years after publication of this Manual, additional data from the NCDB and other large populations of patients with full prognostic factor information and increasingly longer follow-up will become available. Based on analyses of these data, the Prognostic Stage Groups may require revision. In addition, as outcome data on patients treated with modern era neoadjuvant therapy mature and become increasingly available, a post neoadjuvant therapy prognostic staging system may also evolve. Further, it is likely that additional high level evidence related to multi-gene prognostic and predictive assays will also become available. The AJCC Breast Expert Panel will regularly review new data as they become available and make necessary revisions as needed in a more rapid fashion than the standard 6–8 year cycle for staging revision.

PROGNOSTIC FACTORS

Prognostic Factors Required for Stage Grouping

Estrogen receptor (ER) expression

ER expression is measured primarily by IHC. Any staining of 1% of cells or more is considered positive for ER.[72] AJCC Level of Evidence: I.

Progesterone receptor (PR) expression

PR expression is measured primarily by IHC. Any staining of 1% of cells or more is considered positive for PR. AJCC Level of Evidence: I.

Human Epidermal Growth Factor Receptor-2 (HER2)

The measurement of HER2 is primarily by either IHC to assess expression of the HER2 protein or by *in situ* hybridization (ISH) – most commonly by fluorescent labeled probes (FISH) or chromogenic labeled probes (CISH) to assess gene copy number. The 2013 American Society of Clinical Oncology/College of American Pathologists Guidelines provide standards for sequential performance of tests to accurately and efficiently determine HER2 status, most commonly starting with IHC and progressing to ISH testing if IHC is equivocal (2+ pattern). Below the standards are summarized. Users are referred to the full guideline for detailed information on HER2 testing and reporting.[81] AJCC Level of Evidence: I.

IHC: Negative: 0 or 1+ staining
Equivocal: 2+ staining
Positive: 3+ staining

ISH: Possible negative results:
- HER2/CEP17 ratio < 2.0 **AND** HER2 copy number < 4

Possible equivocal results: (requires performing alternative ISH test to confirm equivocal or IHC if not previously performed)
- HER2/CEP17 ratio < 2.0 **AND** HER2 copy number ≥ 4 but <6

Possible positive results:
- HER2/CEP17 ratio ≥ 2.0 by ISH
- HER2 copy number ≥ 6 regardless of ratio by ISH

The above summary is for dual probe ISH. Some laboratories may still use single probe. In that case, the thresholds are:

Negative: < 4 HER2 copies.
Equivocal: ≥ 4 HER2 copies but <6 HER2 copies.
Positive: 6 or more HER2 copies.

Histologic Grade

Invasive Cancer: Scarff–Bloom–Richardson (SBR) Grading System, Nottingham Modification

All invasive breast carcinomas should be assigned a histologic grade. The Nottingham combined histologic grade (Nottingham modification of the SBR grading system) is recommended and is stipulated for use by the College of American Pathologists (www.cap.org).[59, 62, 63] The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and calibrated mitotic count), assigning a value from 1 (favorable) to 3 (unfavorable) for each feature, and totaling 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. The use of subjective grading alone is discouraged.

G	G Definition
GX	Grade cannot be assessed
G1	Low combined histologic grade (favorable), SBR score of 3–5 points
G2	Intermediate combined histologic grade (moderately favorable); SBR score of 6–7 points
G3	High combined histologic grade (unfavorable); SBR score of 8–9 points

Ductal Carcinoma *in situ*: Nuclear Grade

The grade that should be used for ductal carcinoma *in situ* is nuclear grade (www.cap.org).

G	G Definition
GX	Grade cannot be assessed
G1	Low nuclear grade
G2	Intermediate nuclear grade
G3	High nuclear grade

Additional Factors Recommended for Clinical Care

Circulating Tumor Cells (CTC) and Method of Detection

(RT-PCR, immunomagnetic separation, other)

CTCs are cancer cells that detach from solid tumors and enter the blood stream. The presence of CTCs is an adverse prognostic factor for patients with primary and metastatic breast cancer. Multiple methods are available to identify and measure CTCs, but the only FDA-approved method is the CellSearch assay. A 7.5-mL sample of blood is centrifuged to separate solid blood components from plasma, then placed in the CELLTRACKS® AUTOPREP® system. Using ferrofluid nanoparticles with antibodies that target epithelial cell adhesion molecules, CTCs are magnetically separated from the bulk of other cells in the blood. CTCs are then stained with cytokeratin monoclonal antibodies, which are specific to epithelial cells. A monoclonal antibody stain is used to identify CD45, a marker specific to leukocytes, which identifies any leukocytes that may have contaminated the sample. A DNA stain called DAPI is added to highlight the nuclei of both CTCs and leukocytes. Cells are put in a magnet cartridge that applies a magnetic force that pulls the cells to a single focal depth. The cartridge containing stained CTCs is scanned by the CELLTRACKS ANALYZER II®, and the system displays tumor cell candidates that are positive for cytokeratin and DAPI. These candidate cells are presented to an operator for final review. For metastatic breast cancer, the cutoff for unfavorable prognosis is ≥5 cells/7.5 mL. For primary breast cancer, a cutoff of ≥1 cell/7.5 mL has been used. AJCC Level of Evidence: II

Disseminated Tumor Cells (DTC; Bone Marrow Micrometastases) and Method of Detection

(RT-PCR, IHC, other)

DTCs in bone marrow (BM) might be used as a "liquid biopsy" to obtain information helpful to steer therapies in individual patients. There is an association between the presence of DTCs in BM at the time of initial tumor resection and postoperative metastatic relapse in patients with cancers of the breast. Cytokeratins are currently the standard markers for detecting epithelial tumor cells in mesenchymal organs, such as BM, blood, or lymph nodes. They are detected by IHC, and the pertinent cutoff value is ≥1 cell. AJCC Level of Evidence: I.

Ki-67

Ki-67 is a nuclear protein associated with cellular proliferation.[66, 103] The most prevalent analysis method of Ki-67 antigen is IHC; to date, however, no standard operating procedure or generally accepted cutoff definition for Ki-67 exists. AJCC Level of Evidence: III.

Multigene Panels, Genomic Profiles, Signature Scores

Breast Cancer Index

Breast Cancer Index is measured and reported in gene expression profiling as a numerical result on a continuous curve (delineated by HIGH/LOW risk categories).[104] AJCC Level of Evidence: II.

EndoPredict

EndoPredict is measured and reported in gene expression profiling as a numerical result on a continuous curve (from 0 to 15), with a score of 5 separating low risk from high risk.[105] AJCC Level of Evidence: II.

IHC4

IHC4 combines the IHC assessment of ER, PR, HER2, and Ki-67.[93, 104] The developers presented evidence to suggest that it has prognostic value similar to the Oncotype Dx® assay. The results are based on a multivariate model that uses semi-quantitative information from IHC assessment of ER, PR, HER2, and Ki-67. IHC4 uses a mathematical formula that weighs the semi-quantitative expression values and combines these into a single risk score. AJCC Level of Evidence: II.

Mammaprint®

Mammaprint® is a genomic test based on the level of expression of 70 genes associated with breast cancer recurrence.[6, 7] It is measured and reported by gene expression profiling, with the pertinent cutoff value yielding binary results: low risk (< 10%) versus high risk of recurrence within 10 years. AJCC Level of Evidence: II.

Oncotype Dx®

Oncotype Dx® is a genomic test based on the assessment of 21 genes; the result is the outcome of a mathematical formula of the weighted expression of each gene combined into a single score. It is measured by RT-PCR on sections of paraffin-fixed tissue and reported as a numerical score. Prospective trial data show very low recurrence rates with recurrence score of <11.[16] If performed, Oncotype Dx® is used to assign prognostic stage group IA to patients with T1–2 N0 M0, ER-positive, HER2-negative cancers and recurrence score less than 11. AJCC Level of Evidence: I.

PAM50 (ProSigna®)

PAM50 (ProSigna) is measured and reported in expression profiling as a single numerical score on a 0-to-100 scale that correlates with the probability of distant recurrence within 10 years.[91, 93, 103] AJCC Level of Evidence: II.

EMERGING FACTORS FOR CLINICAL CARE

The authors have not noted any emerging factors for clinical care.

RISK ASSESSMENT MODELS

Prognostic models will continue to play an important role in twenty-first century medicine for several reasons.[106] First, by identifying which factors predict outcomes, clinicians gain insight into the biology and natural history of the disease. Second, treatment strategies may be optimized based on the outcome risks of the individual patient. Third, because of the heterogeneity of disease in most cancers, prognostic models will play a critical role in the design, conduct, and analysis of clinical trials in oncology.[106] If developed and validated appropriately, these models will become part of routine patient care, decision-making trial design, and conduct.

The AJCC Precision Medicine Core (PMC) developed and published criteria for critical evaluation of prognostic tool quality,[107] which are presented and discussed in Chap. 4. Although developed independently by the PMC, the AJCC quality criteria correspond fully with the recently developed Cochrane CHARMS CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies.[108]

Existing prognostic models for breast cancer meeting all of the AJCC inclusion/exclusion criteria and meriting AJCC endorsement are presented in this section. A full list of the evaluated models and their adherence to the quality criteria is available on www.cancerstaging.org.

The PMC performed a systematic search of literature for prognostic models/tools in breast cancer published from January 2011 to December 2015. The search strategy is provided in Chap. 4. The PMC defined "prognostic model" as a multivariable model where factors predict a clinical outcome that will occur in the future. Each tool identified was compared against the quality criteria developed by the PMC as guidelines for AJCC commendation for prognostication models (see Chap. 4).

Thirty prognostication tools for breast cancer were identified and reviewed against a checklist derived from the PMC guidelines. Only two tools, Adjuvant! Online[109, 110] and PREDICT-Plus[111, 112] were found to have met all predefined AJCC inclusion and none of the exclusion criteria. Table 48.6 presents information about these two models. One tool, CancerMath, looked promising, but not all the criteria could be evaluated with the available information in the scientific article and on the author's website.

Adjuvant! Online[109] is primarily a tool to assist in making decisions about adjuvant therapy for women with early-stage breast cancer. Outcome estimates are made from projections based on U.S. population-based SEER data, and adjuvant therapy efficacy estimates are from randomized trial overviews. These probability estimates are combined according to a proprietary system. Input data used to predict outcomes are periodically updated. PREDICT-Plus[112] was developed to predict outcome in women treated for early breast cancer in the United Kingdom. Estimates are based on a Cox proportional hazards regression model fit to data from a population-based registry. Both tools were externally validated with good calibration and acceptable levels of predictive accuracy.

Table 48.6 Prognostic tools for breast cancer that met all AJCC quality criteria

Approved Prognostic Tool	Web Address	Factors Included in the Model
Adjuvant! Online	www.adjuvantonline.com	Tumor size, number of positive lymph nodes, ER status, age, menopausal status, comorbidity, adjuvant therapy
PREDICT-Plus	www.predict.nhs.uk/predict.html	Age, number of positive lymph nodes, tumor size, tumor grade, mode of detection, chemotherapy, hormone therapy; separate models for ER-negative and ER-positive; HER2 added in PREDICT-Plus

DEFINITIONS OF AJCC TNM

Definition of Primary Tumor (T) – Clinical and Pathological

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

**Note:* Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the *AJCC Cancer Staging Manual, 8th Edition.*

Definition of Regional Lymph Nodes – Clinical (cN)

cN Category	cN Criteria
cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axillary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with 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
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Definition of Regional Lymph Nodes – Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)

pN Category	pN Criteria
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (Level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes;
	or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

*Note that imaging studies are not required to assign the cM0 category

AJCC ANATOMIC AND PROGNOSTIC STAGE GROUPS

There are three stage group tables: The Anatomic Stage Group table, the Clinical Prognostic Stage Group table and the Pathological Prognostic Stage Group table. Cancer registries and clinicians in the United States must use the Clinical and Pathological Prognostic Stage Group tables for reporting. It is expected that grade, HER2, ER and PR are performed and reported on all cases of invasive cancer in the United States.

Clinical prognostic stage should be recorded on all patients. Pathological prognostic stage should be recorded for patients who have surgery as initial treatment and therefore have pathological T and N information. Patients treated with neoadjuvant therapy should have clnical prognostic stage and the observed degree of response to treatment recorded, but are not assigned pathological prognostic stage.

The Anatomic Stage Group table should only be used in regions of the world where tumor grading and/or biomarker testing for HER2, ER and PR are not routinely available. For worldwide comparison, the Anatomic Stage Group can be back-calculated from U.S. registries from the recorded T, N, and M categories.

AJCC Anatomic Stage Groups

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available.

Cancer registries in the U.S. must use the Clinical and Pathological Prognostic Stage Group tables for case reporting.

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

Notes:

1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are staged using the N1 category.
4. M0 includes M0(i+).
5. The designation pM0 is not valid; any M0 is clinical.
6. If a patient presents with M1 disease prior to neoadjuvant systemic therapy, the stage is Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
7. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression, and provided the patient has not received neoadjuvant therapy.
8. Staging following neoadjuvant therapy is denoted with a "yc" or "yp" prefix to the T and N classification. There is no anatomic stage group assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

AJCC PROGNOSTIC STAGE GROUPS

The Prognostic Stage Group tables should be used as the primary staging system in countries where these biomarker tests are routinely performed for patient care (U.S., Canada, etc.). Cancer registries in the U.S. must use the Prognostic Stage Group tables for case reporting. If biomarkers are not available, the cancer should be reported as unstaged.

Patients should be counseled to receive appropriate adjuvant therapies as per the applicable clinical practice standards. However, both clinical and pathological prognostic stage should be assigned according to the T, N, M, and biomarker status in the tables below irrespective of whether the patient receives adjuvant therapies.

The tables included in this chapter are sorted by T, N, M, and then grade, HER2, ER and PR. For each combination there is an assigned Clinical Prognostic Stage Group or Pathological Prognostic Stage Group (separate tables). For space considerations, the T, N, and M are collapsed. A complete "look up" table format will be available on the AJCC website (www.cancerstaging.org). This format may prove more valuable to cancer registrars until such time as computerized applications are available to generate stage from the primary data on T, N, M, and biomarkers.

Clinical Prognostic Stage

Clinical Prognostic Stage applies to ALL patients with breast cancer for clinical classification and staging. It uses clinical tumor (T), node (N) and metastases (M) information based on history, physical examination, any imaging performed (not necessary for clinical staging) and relevant biopsies. Genomic profile information is not included in Clinical Prognostic Stage as pathologic information from surgery is necessary to ascertain the prognosis using these tools.

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Any T Any N M1	Any	Any	Any	Any	IV

*T1 Includes T1mi.
**N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.
***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.
Notes:

1. Because N1mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with Clinical Prognostic Staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.
2. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
3. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the Clinical Prognostic Stage Group table.[81, 82]
4. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Pathological Prognostic Stage

Pathological Prognostic Stage applies to patients with breast cancer treated with surgery as the initial treatment. It includes all information used for clinical staging plus findings at surgery and pathological findings from surgical resection. Pathological Prognostic Stage does not apply to patients treated with systemic or radiation prior to surgical resection (neoadjuvant therapy).

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
	G2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
Any T Any N M1	Any	Any	Any	Any	IV

*T1 includes T1mi.
**N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.
***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

Notes:

1. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER and PR information from the tumor in the lymph node should be used for assigning stage group.
2. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, HER2 "negative" category should be used for staging in the Pathological Prognostic Stage Group Table.[81, 82]
3. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Genomic Profile for Pathologic Prognostic Staging

When Oncotype Dx Score is Less than 11…

And TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Pathological Prognostic Stage Group is…
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Notes:

1. Obtaining genomic profiles is NOT required for assigning Pathological Prognostic Stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx® test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned Pathological Prognostic Stage Group IA.
2. If OncotypeDx® is not performed, or if it is performed and the OncotypeDx® score is not available, or is 11 or greater for patients with T1–2 N0 M0 HER2–negative, ER-positive cancer, then the Prognostic Stage Group is assigned based on the anatomic and biomarker categories shown above.
3. OncotypeDx® is the only multigene panel included to classify Pathologic Prognostic Stage because prospective Level I data supports this use for patients with a score less than 11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to Prognostic Stage Groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

REGISTRY DATA COLLECTION VARIABLES

1. ER: positive versus negative; percent positive; Allred score, if available
2. PR: positive versus negative; percent positive; Allred score, if available
3. HER2—IHC: 0, 1+, 2+, 3+; or unknown or not performed
4. HER2—FISH: negative, positive; HER2:CEP17 ratio; and HER2 copy number, if available; or unknown or not performed
5. HER2: Overall result, negative, positive, unknown if done; not performed
6. Nottingham histologic grade: low (1), intermediate (2), high (3)
7. Ki-67, if available: percent positive
8. Oncotype Dx® recurrence score (numeric score preferred over risk level)
9. Oncotype Dx® DCIS recurrence score (numeric score preferred over risk level)
10. Mammaprint® (numeric score preferred over risk level)
11. ProSigna® PAM50 intrinsic subtypes and Risk of Recurrence score (numeric score preferred over risk level)
12. Breast Cancer Index (numeric score preferred over risk level)
13. EndoPredict (numeric score preferred over risk level)
14. IHC4 (numeric score preferred over risk level)
15. Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1)[113]
16. Response to treatment: CR, PR, NR

HISTOLOGIC GRADE (G)

Invasive Cancer: Scarff–Bloom–Richardson (SBR) Grading System, Nottingham Modification

All invasive breast carcinomas should be assigned a histologic grade. The Nottingham combined histologic grade (Nottingham modification of the SBR grading system) is recommended and is stipulated for use by the College of American Pathologists (see www.cap.org).[59, 62, 63] The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and calibrated mitotic count), assigning a value from 1 (favorable) to 3 (unfavorable) for each feature, and totaling 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. The use of subjective grading alone is discouraged.

G	G Definition
GX	Grade cannot be assessed
G1	Low combined histologic grade (favorable), SBR score of 3–5 points
G2	Intermediate combined histologic grade (moderately favorable); SBR score of 6–7 points
G3	High combined histologic grade (unfavorable); SBR score of 8–9 points

Ductal Carcinoma *in situ*: Nuclear Grade

The grade that should be used for ductal carcinoma *in situ* is nuclear grade (see www.cap.org).

G	G Definition
GX	Grade cannot be assessed
G1	Low nuclear grade
G2	Intermediate nuclear grade
G3	High nuclear grade

HISTOPATHOLOGIC TYPE

In situ Carcinomas
- Ductal carcinoma *in situ*
- Paget disease

Invasive Carcinomas
- Not otherwise specified (NOS)
- Ductal
- Inflammatory
- Medullary, NOS
- Medullary with lymphoid stroma
- Mucinous
- Papillary (predominantly micropapillary pattern)
- Tubular
- Lobular
- Paget disease and infiltrating
- Undifferentiated
- Squamous cell
- Adenoid cystic
- Secretory
- Cribriform

Bibliography

1. Edge SB, Compton CC. *The AJCC Cancer Staging Manual.* 7th ed: Springer; 2009.
2. Prat A, Pineda E, Adamo B, et al. Clinical implications of the intrinsic molecular subtypes of breast cancer. *Breast.* 2015;24 Suppl 2:S26–35.
3. Van Poznak C, Somerfield MR, Bast RC, et al. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology.* 2015:JCO. 2015.2061. 1459.
4. Selz J, Stevens D, Jouanneau L, Labib A, Le Scodan R. Prognostic value of molecular subtypes, ki67 expression and impact of post-mastectomy radiation therapy in breast cancer patients with negative lymph nodes after mastectomy. *International journal of radiation oncology, biology, physics.* 2012;84(5):1123–1132.
5. Carlson RW, Allred DC, Anderson BO, et al. Breast cancer. Clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2009;7(2):122–192.
6. van't Veer LJ, Paik S, Hayes DF. Gene expression profiling of breast cancer: a new tumor marker. *J Clin Oncol.* 2005;23(8):1631–1635.
7. Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *Journal of the National Cancer Institute.* 2006;98(17):1183–1192.
8. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med.* 2016;375(8):717–729.
9. Krop I, Ismaila N, Andre F, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *J Clin Oncol.* 2017:JCO2017740472.
10. Sparano JA, Gray RJ, Makower DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med.* 2015;373(21):2005–2014.
11. Stemmer S, Steiner M, Rizel S, et al. 1963 First prospective outcome data in 930 patients with more than 5 year median follow up in whom treatment decisions in clinical practice have been made incorporating the 21-Gene Recurrence Score. *European journal of cancer.* 2015(51):S321.
12. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. *J Clin Oncol.* 2016;34(20):2341–2349.
13. Van De Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *New England Journal of Medicine.* 2002;347(25):1999–2009.

14. Wang Y, Klijn JG, Zhang Y, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. *Lancet.* 2005;365(9460):671–679.
15. Tang G, Cuzick J, Costantino JP, et al. Risk of recurrence and chemotherapy benefit for patients with node-negative, estrogen receptor-positive breast cancer: recurrence score alone and integrated with pathologic and clinical factors. *J Clin Oncol.* 2011;29(33):4365–4372.
16. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004;351(27):2817–2826.
17. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *Journal of Clinical Oncology.* 2010;28(11):1829–1834.
18. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* 2006;24(23):3726–3734.
19. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *The lancet oncology.* 2010;11(1):55–65.
20. Yi M, Mittendorf EA, Cormier JN, et al. Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: time to modify the current American Joint Committee on Cancer staging system. *Journal of Clinical Oncology.* 2011;29(35):4654–4661.
21. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast Cancer Version 2.2015. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2015;13(4):448–475.
22. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol.* 2007;18(7):1133–1144.
23. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, et al. The Global Burden of Cancer 2013. *JAMA oncology.* 2015;1(4):505–527.
24. Anderson BO, Yip CH, Smith RA, et al. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer.* 2008;113(8 Suppl):2221–2243.
25. Gluz O, Nitz U, Kreipe H, et al. 1937 Clinical impact of risk classification by central/local grade or luminal-like subtype vs. Oncotype DX®: First prospective survival results from the WSG phase III planB trial. *European journal of cancer.* 2015(51):S311.
26. Petkov VI, Miller DP, Howlader N, et al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. *NPJ Breast Cancer.* 2016;2:16017.
27. Bartlett JM, Bayani J, Marshall A, et al. Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others. *Journal of the National Cancer Institute.* 2016;108(9).
28. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet.* 2010;375(9714):563–571.
29. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. *Annals of surgery.* 2013;257(2):249–255.
30. Arnaout A, Catley C, Booth CM, et al. Use of Preoperative Magnetic Resonance Imaging for Breast Cancer: A Canadian Population-Based Study. *JAMA oncology.* 2015;1(9):1238–1250.
31. Vos EL, Voogd AC, Verhoef C, Siesling S, Obdeijn IM, Koppert LB. Benefits of preoperative MRI in breast cancer surgery studied in a large population-based cancer registry. *The British journal of surgery.* 2015;102(13):1649–1657.
32. Houssami N, Turner R, Macaskill P, et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. *J Clin Oncol.* 2014;32(5):392–401.
33. Yi A, Cho N, Yang K-S, Han W, Noh D-Y, Moon WK. Breast cancer recurrence in patients with newly diagnosed breast cancer without and with preoperative MR Imaging: A matched cohort study. *Radiology.* 2015;276(3):695–705.
34. D'Orsi CJ, Radiology ACo, Committee B-R. ACR BI-RADS Atlas: Breast Imaging Reporting and Data System. 2013.
35. Morris EA, Schwartz LH, Drotman MB, et al. Evaluation of pectoralis major muscle in patients with posterior breast tumors on breast MR images: early experience. *Radiology.* 2000;214(1):67–72.
36. Dawood S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann Oncol.* 2011;22(3):515–523.
37. Houssami N, Diepstraten SC, Cody HS, 3rd, Turner RM, Sever AR. Clinical utility of ultrasound-needle biopsy for preoperative staging of the axilla in invasive breast cancer. *Anticancer research.* 2014;34(3):1087–1097.
38. Diepstraten SC, Sever AR, Buckens CF, et al. Value of preoperative ultrasound-guided axillary lymph node biopsy for preventing completion axillary lymph node dissection in breast cancer: a systematic review and meta-analysis. *Annals of surgical oncology.* 2014;21(1):51–59.
39. Dogan BE, Dryden MJ, Wei W, et al. Sonography and Sonographically Guided Needle Biopsy of Internal Mammary Nodes in Staging of Patients With Breast Cancer. *AJR. American journal of roentgenology.* 2015;205(4):905–911.
40. Gradishar W, Anderson B, Blair S, Burstein H, Cyr A, Elias A. National comprehensive cancer network breast cancer panel. *Breast cancer version.*3:542–590.
41. Aebi S, Davidson T, Gruber G, Castiglione M, Group EGW. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010;21 Suppl 5(suppl 5):v9–14.
42. Moy L, Newell MS, Mahoney MC, et al. ACR Appropriateness Criteria stage I breast cancer: initial workup and surveillance for local recurrence and distant metastases in asymptomatic women. *Journal of the American College of Radiology : JACR.* 2014;11(12 Pt A):1160–1168.
43. Schwartz GF, Hortobagyi GN. Proceedings of the consensus conference on neoadjuvant chemotherapy in carcinoma of the breast, April 26–28, 2003, Philadelphia, Pennsylvania. *Cancer.* 2004;100(12):2512–2532.
44. Tavassoli FA. Ductal carcinoma in situ: introduction of the concept of ductal intraepithelial neoplasia. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 1998;11(2):140-154.
45. Tavassoli FA. Breast pathology: rationale for adopting the ductal intraepithelial neoplasia (DIN) classification. *Nat Clin Pract Oncol.* 2005;2(3):116–117.
46. Lester SC, Bose S, Chen YY, et al. Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast. *Arch Pathol Lab Med.* 2009;133(1):15–25.
47. Chen CY, Sun LM, Anderson BO. Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the US. *Cancer.* 2006;107(7):1448–1458.
48. Hortobagyi GN, Ames FC, Buzdar AU, et al. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. *Cancer.* 1988;62(12):2507–2516.
49. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol.* 1998;16(8):2672–2685.

50. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384(9938):164–172.
51. Symmans WF, Wei C, Gould R, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. *J Clin Oncol.* 2017;35(10):1049–1060.
52. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol.* 2007;25(28):4414–4422.
53. Ogston KN, Miller ID, Payne S, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *Breast.* 2003;12(5):320–327.
54. Chevallier B, Roche H, Olivier JP, Chollet P, Hurteloup P. Inflammatory breast cancer. Pilot study of intensive induction chemotherapy (FEC-HD) results in a high histologic response rate. *Am J Clin Oncol.* 1993;16(3):223–228.
55. Sataloff DM, Mason BA, Prestipino AJ, Seinige UL, Lieber CP, Baloch Z. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: a determinant of outcome. *J Am Coll Surg.* 1995;180(3):297–306.
56. Provenzano E, Bossuyt V, Viale G, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol.* 2015;28(9):1185–1201.
57. Greenough RB. Varying degrees of malignancy in cancer of the breast. *The Journal of Cancer Research.* 1925;9(4):453–463.
58. Patey D, Scarff R. The position of histology in the prognosis of carcinoma of the breast. *The Lancet.* 1928;211(5460): 801–804.
59. Scarff R, Handley R. Prognosis in carcinoma of the breast. *The Lancet.* 1938;232(6001):582–583.
60. Bloom H, Richardson W. Histological grading and prognosis in breast cancer: a study of 1409 cases of which 359 have been followed for 15 years. *British journal of cancer.* 1957;11(3):359.
61. Scarff R, Torloni H. *Histological typing of breast tumors.* Geneva: WHO; 1968.
62. Black MM. Survival in breast cancer cases in relation to the structure of the primary tumor and regional lymphnodes. *Surg Gynecol Obstet.* 1955;100:543–551.
63. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology.* 1991;19(5):403–410.
64. Elston EW, Ellis IO. Method for grading breast cancer. *Journal of clinical pathology.* 1993;46(2):189–190.
65. Schwartz AM, Henson DE, Chen D, Rajamarthandan S. Histologic grade remains a prognostic factor for breast cancer regardless of the number of positive lymph nodes and tumor size: a study of 161 708 cases of breast cancer from the SEER Program. *Arch Pathol Lab Med.* 2014;138(8):1048–1052.
66. Gilchrist KW, Kalish L, Gould VE, et al. Interobserver reproducibility of histopathological features in stage II breast cancer. An ECOG study. *Breast cancer research and treatment.* 1985;5(1):3–10.
67. Gerdes J, Schwab U, Lemke H, Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. *Int J Cancer.* 1983;31(1):13–20.
68. Coates AS, Winer EP, Goldhirsch A, et al. -Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* 2015;26(8):1533–1546.
69. Beatson G. On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases. 1. *The Lancet.* 1896;148(3802):104–107.
70. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol.* 2010;28(16):2784–2795.
71. Group EBCTC. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *The lancet.* 2011;378(9793):771–784.
72. Barnes DM, Harris WH, Smith P, Millis RR, Rubens RD. Immunohistochemical determination of oestrogen receptor: comparison of different methods of assessment of staining and correlation with clinical outcome of breast cancer patients. *Br J Cancer.* 1996;74(9):1445–1451.
73. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med.* 2010;134(7):e48–72.
74. Schechter AL, Stern DF, Vaidyanathan L, et al. The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumour antigen. *Nature.* 1984;312(5994):513–516.
75. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987;235(4785):177–182.
76. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *The oncologist.* 2009;14(4):320–368.
77. Rosenthal SI, Depowski PL, Sheehan CE, Ross JS. Comparison of HER-2/neu oncogene amplification detected by fluorescence in situ hybridization in lobular and ductal breast cancer. *Appl Immunohistochem Mol Morphol.* 2002;10(1):40–46.
78. Eccles SA. The role of c-erbB-2/HER2/neu in breast cancer progression and metastasis. *Journal of mammary gland biology and neoplasia.* 2001;6(4):393–406.
79. Piccart M, Lohrisch C, Di Leo A, Larsimont D. The predictive value of HER2 in breast cancer. *Oncology.* 2001;61 Suppl 2(Suppl. 2):73–82.
80. Yarden Y. Biology of HER2 and its importance in breast cancer. *Oncology.* 2001;61 Suppl 2(Suppl. 2):1–13.
81. Wolff A, Hammond M, Hicks D, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2013;31(31):3997–4013.
82. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *Archives of Pathology and Laboratory Medicine.* 2013;138(2):241–256.
83. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011;365(14):1273–1283.
84. Moasser MM, Krop IE. The Evolving Landscape of HER2 Targeting in Breast Cancer. *JAMA oncology.* 2015;1(8):1154–1161.
85. Dowsett M. Overexpression of HER-2 as a resistance mechanism to hormonal therapy for breast cancer. *Endocrine-related cancer.* 2001;8(3):191–195.
86. Muss HB. Role of adjuvant endocrine therapy in early-stage breast cancer. Paper presented at: Seminars in oncology2001.
87. Schmid P, Wischnewsky MB, Sezer O, Bohm R, Possinger K. Prediction of response to hormonal treatment in metastatic breast cancer. *Oncology.* 2002;63(4):309–316.

88. Konecny G, Pauletti G, Pegram M, et al. Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer. *Journal of the National Cancer Institute.* 2003;95(2):142–153.
89. Network CGA. Comprehensive molecular portraits of human breast tumours. *Nature.* 2012;490(7418):61–70.
90. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A.* 2001;98(19):10869–10874.
91. Bastien RR, Rodriguez-Lescure A, Ebbert MT, et al. PAM50 breast cancer subtyping by RT-qPCR and concordance with standard clinical molecular markers. *BMC medical genomics.* 2012;5(1):44.
92. Bayraktar S, Royce M, Stork-Sloots L, de Snoo F, Glück S. Molecular subtyping predicts pathologic tumor response in early-stage breast cancer treated with neoadjuvant docetaxel plus capecitabine with or without trastuzumab chemotherapy. *Medical oncology.* 2014;31(10):1–7.
93. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol.* 2013;31(22):2783–2790.
94. Eiermann W, Rezai M, Kümmel S, et al. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. *Annals of Oncology.* 2013;24(3):618–624.
95. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* 2015;26(8):1533–1546.
96. Stemmer S, Steiner M, Rizel S, et al. Real-life analysis evaluating 1594 N0/Nmic breast cancer patients for whom treatment decisions incorporated the 21-gene recurrence score result: 5-year KM estimate for breast cancer specific survival with recurrence score results≤ 30 is> 98%. *Cancer Research.* 2016;76(4 Supplement):P5–08-02-P05–08-02.
97. Drukker CA, Bueno-de-Mesquita JM, Retel VP, et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. *Int J Cancer.* 2013;133(4):929–936.
98. Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology.* 2016:JCO652289.
99. Wuerstlein R, Sotlar K, Gluz O, et al. The West German Study Group Breast Cancer Intrinsic Subtype study: a prospective multicenter decision impact study utilizing the Prosigna assay for adjuvant treatment decision-making in estrogen-receptor-positive, HER2-negative early-stage breast cancer. *Curr Med Res Opin.* 2016;32(7):1217–1224.
100. Mittendorf EA, Chavez-MacGregor M, Vila J, et al. Bioscore: A Staging System for Breast Cancer Patients that Reflects the Prognostic Significance of Underlying Tumor Biology. *Annals of surgical oncology.* 2017.
101. Chavez-MacGregor M, Mittendorf EA, Clarke CA, Lichtensztajn DY, Hunt KK, Giordano SH. Incorporating Tumor Characteristics to the American Joint Committee on Cancer Breast Cancer Staging System. *The oncologist.* 2017.
102. Winchester DJ. Personal communication. In: Hortobagyi GN, ed2015.
103. Wallden B, Storhoff J, Nielsen T, et al. Development and verification of the PAM50-based Prosigna breast cancer gene signature assay. *BMC medical genomics.* 2015;8(1):54.
104. Sgroi DC, Sestak I, Cuzick J, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *The lancet oncology.* 2013;14(11):1067–1076.
105. Fitzal F, Filipits M, Rudas M, et al. The genomic expression test EndoPredict is a prognostic tool for identifying risk of local recurrence in postmenopausal endocrine receptor-positive, her2neu-negative breast cancer patients randomised within the prospective ABCSG 8 trial. *British journal of cancer.* 2015;112(8):1405–1410.
106. Halabi S, Owzar K. The importance of identifying and validating prognostic factors in oncology. Paper presented at: Seminars in oncology2010.
107. Kattan MW, Hess KR, Amin MB, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA: a cancer journal for clinicians.* 2016.
108. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS medicine.* 2014;11(10):e1001744.
109. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol.* 2001;19(4):980–991.
110. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. *J Clin Oncol.* 2005;23(12):2716–2725.
111. Wishart GC, Azzato EM, Greenberg DC, et al. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. *Breast cancer research : BCR.* 2010;12(1):R1.
112. Wishart GC, Bajdik CD, Dicks E, et al. PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2. *Br J Cancer.* 2012;107(5):800–807.
113. Harbeck N, Schmitt M, Meisner C, et al. Ten-year analysis of the prospective multicentre Chemo-N0 trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. *European journal of cancer.* 2013;49(8):1825–1835.