Anatomy and Breast Cancer Staging: Is It Still Relevant?

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KEYWORDS

• Breast cancer • Staging • Prognosis • Biomarkers

KEY POINTS

- Anatomic staging for breast cancer continues to provide prognostic information relevant to patients and clinicians.
- Prognostic staging for breast cancer now includes both anatomic factors and tumor-specific factors, such as receptor status and genomic profiles.
- By incorporating tumor biology, the new staging system will likely improve the future discrimination of prognosis between tumor stages.

WHY CLINICIANS STAGE PATIENTS

A patient's breast cancer stage provides a concise summary of the disease at the time of diagnosis and/or surgery. It conveys how much cancer is present, where it is located, and highlights important tumor characteristics. It also allows for efficient communication between clinicians and provides a framework for assessing and relaying prognostic information based on the sum of the tumor and disease features. By providing this prognostic framework, staging can be used to determine the best treatment approach for individual patients. In addition to its patient-specific purpose, it also forms the foundation on which changes in population-level cancer incidences can be more thoroughly and accurately evaluated, by allowing assessment of the overall impact of novel or changing breast cancer treatments. Staging information is also frequently used to define groups for inclusion in clinical trials, facilitating screening and evaluation of large groups of patients for research purposes.

To achieve these goals, the American Joint Committee on Cancer (AJCC) was organized in 1959 to develop a system of cancer staging using standardized language

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acceptable to the American medical profession.[1] During this era, aggressive local treatments were standard (usually a radical mastectomy and postoperative radiation to the chest wall for most patients with breast cancer), and effective systemic therapies had not yet been established. Thus, the primary objective was to provide standard nomenclature for breast cancer prognostication to prevent futile care for those likely to die from the disease. The guiding philosophy was to develop a classification system that would convey the progression of the usual events that created the life history of a cancer, including tumor growth (size) and spread (to regional lymph nodes and/or distant organs).[1] The AJCC used the principles of the TNM system (T, tumor; N, nodes; M, metastasis), as described by the International Union Against Cancer (UICC)[2] to serve as the basis for categorizing the extent of disease. The aim was to create a staging system that would allow physicians to determine treatment more appropriately, to evaluate results of management more reliably, and to compare statistics from diverse institutions more confidently.[1]

Today, staging continues to be a critical tool used to communicate and understand a patient's breast cancer diagnosis, thus allowing for more accurate treatment discussions and decisions. In today's era of personalized medicine, breast cancer treatment is leading the charge to incorporate more patient-specific and tumor-specific data into determining a patient's prognosis and thus customizing treatment decisions. As treatments continue to evolve and improve, the staging system is also continuously being refined.

Despite significant changes in breast cancer treatment, traditional anatomic TNM staging remains relevant for several reasons. First, it allows investigators to continue to study historic groups of patients and relate them to contemporary patients. Second, it provides consistency in the way clinicians communicate with each other worldwide. Last, it is often the only source of staging classification available in low-income and middle-income countries and will likely remain the cornerstone on which evaluation and treatment decisions are made.[3] Moreover, early detection programs may be the most effective tools for improving outcomes in these countries and TNM staging directly reflects the success of such programs. However, in this modern era, many treatment decisions for patients with breast cancer are not based solely on the TNM stage. For example, local-regional treatments (eg, surgery and radiation) are often influenced by multicentricity and tumor margins, in addition to tumor size and nodal status. Similarly, endocrine therapy is routinely recommended for hormone receptor–positive disease and targeted therapies are frequently recommended for human epidermal growth factor receptor 2 (HER2)-positive tumors. Thus, modern staging systems have moved toward incorporating molecular markers into the staging classification system.

HOW CLINICIANS STAGE PATIENTS

Breast cancer staging is continually evolving, and it has been defined and updated by the AJCC for over 4 decades; the AJCC *Cancer Staging Manual*, 1st edition, was published in 1977.[1] Grouping cancer cases into stages was derived from survival rates being higher for localized disease compared with those in which the disease had spread beyond the original site, initially referred to as early and late cases. The AJCC *Cancer Staging Manual* was created to facilitate improved consistency in describing the extent of the neoplastic disease present, and thus allow clinicians to better determine appropriate treatments, more reliably evaluate the results of management strategies, and more accurately compare statistics or research outcomes.[1] Although it will not be fully adopted until January 2018, the most recent edition (8th)

of the AJCC *Cancer Staging Manual*, was published in 2016 and includes 2 staging systems: the anatomic stage and the prognostic stage.[4] The anatomic stage includes the traditional anatomic factors, the primary tumor size (T), nodal status (N), and distant metastasis (M) based on clinical and/or pathologic assessments. However, additional tumor characteristics have recently been added to the AJCC prognostic staging system to more accurately determine the stage of a cancer, such as tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, and (when available) tumor multigene panel testing (ie, Oncotype DX, Genomic Health, Redwood City, CA). Taken together, staging provides the most reliable source for accurately predicting a patient's outcome and, although anatomic staging may be predominantly used in some countries, prognostic staging is preferred for patients diagnosed and treated in the United States.

Determining a patient's breast cancer stage typically starts with a physical examination to provide an initial evaluation of the extent of the cancer, such as the tumor location, tumor size, and presence of regional and/or distant metastases. Imaging tests are then used to confirm physical examination findings. This may include a mammogram; breast or axillary ultrasound; breast MRI; computed tomography (CT) scan of the chest, abdomen, or pelvis; nuclear medicine bone scan; and/or PET scan. Depending on the examination and imaging findings, laboratory tests may be sent to make additional assessments, such as blood tests and/or tissue biopsies. When breast biopsies are performed, the pathologic assessment report routinely provides information on the tumor histology, grade, and receptor status (ER, PR, and HER2). If axillary lymph nodes or suspicious lesions of distant organs are biopsied, metastases may be identified.

The National Comprehensive Cancer Network guidelines for an invasive breast cancer staging workup include[5]

- History and physical examination
- Diagnostic bilateral mammogram
- Pathologic assessment review
- Determination of ER, PR, and HER2 status
- Breast MRI (optional).

Although many surgeons obtain a breast MRI with each new breast cancer diagnosis to more fully evaluate the extent of disease and rule out mammographically occult disease, wide variation in MRI use is observed and misconceptions about MRI benefits persist.[6] In general, breast MRIs have not been clearly shown to improve the surgeon's ability to obtain negative margins[7,8] or to improve recurrence or survival rates.[9,10] Similarly, routine axillary ultrasound to determine clinical nodal status is also frequently used but remains controversial.[11,12] The benefit of axillary staging by imaging is to avoid 2-stage axillary surgery; however, the main disadvantage is for those women who may have limited axillary disease managed via sentinel lymph node biopsy with or without axillary radiation. Thus, no consensus currently exists on routine use of breast MRI or staging axillary ultrasound.

For patients with early-stage breast cancer, consideration of additional studies is directed by signs or symptoms, and systemic imaging is not routinely indicated.[13] For patients with more advanced disease, additional studies to consider may include[14]

- Complete blood count
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase

- CT abdomen or pelvis with contrast or MRI with contrast
- CT chest with contrast
- Bone scan or sodium fluoride PET-CT
- Fluorodeoxyglucose (FDG) PET-CT (optional).

Depending on when staging is assessed, breast cancer staging can be divided into 4 types:

1. Clinical staging relies on the physical examination, imaging tests, and biopsies of affected areas. This designation is recorded with a lower case "c" before the TNM staging categories.
2. Pathologic staging can only be determined after a patient has had surgery to remove the primary tumor and regional lymph nodes. These results are then combined with the clinical stage to determine the final pathologic stage. This designation is recorded with a lower case "p" before the TNM staging categories.
3. Post-therapy or postneoadjuvant therapy staging determines how much cancer remains after a patient completes preoperative systemic therapy and/or radiation therapy before surgery. This is often assessed after surgery, but it may incorporate both clinical and pathologic staging information. This designation is recorded with a lower case "y" before the TNM staging categories.
4. Restaging is performed if a cancer returns after treatment and is used to determine the extent of disease recurrence. However, importantly, the formal stage of a cancer does not change over time, even if the cancer returns or progresses. Rarely, a cancer may be restaged after a significant disease-free interval, which would include the same assessments performed at the time of the initial diagnosis (ie, examinations, imaging, biopsies, and possibly surgery), and the new stage is recorded with a lower case "r" before the restaged TNM designation. A contralateral cancer is staged as a new episode of cancer, with the exception of direct tumor extension or dissemination via lymphatic spread.

When determining the anatomic stage, the categories for the primary tumor are the same for both clinical and pathologic assessments[4] (**Fig. 1**A; **Table 1**). The T stage should include the prefix "c" for clinical stage or "p" for pathologic stage, as appropriate. Tumor size should be rounded up to the nearest millimeter and, when multifocal, the largest tumor focus is used for T categorization (multiple foci are not added together). The additional suffix "m" can be used when the tumor is multifocal and the prefix "y" can be used when the patient has received preoperative (neoadjuvant) systemic therapy.

The categories for the regional lymph nodes vary between clinical and pathologic[4] assessments (see **Fig. 1**B; see **Table 1**). Similar to the T category, the N category should include the prefix "c" for clinical stage or "p" for pathologic stage, as appropriate. The additional suffix "sn" can be used when the lymph nodes have been evaluated by sentinel lymph node biopsy or "f" when the lymph nodes have been evaluated by fine-needle aspiration (FNA) or core needle biopsy without further resection of the nodes. Category cNX is considered invalid for most patients and, if a patient's clinical examination (and/or imaging) is negative, it should be more accurately listed as cN0; the exception to this being patients who have had prior axillary nodal clearance and cannot be evaluated by clinical examination or imaging.

To assess the M stage, clinical examination is used to classify patients as cM0 or cM1 (see **Table 1**), and the designation pM0 is considered invalid.[4] Patients who are microscopically confirmed to have metastatic disease can be categorized as pM1. Notably, M0 includes M0(i+). If a patient is deemed to have M1 disease before

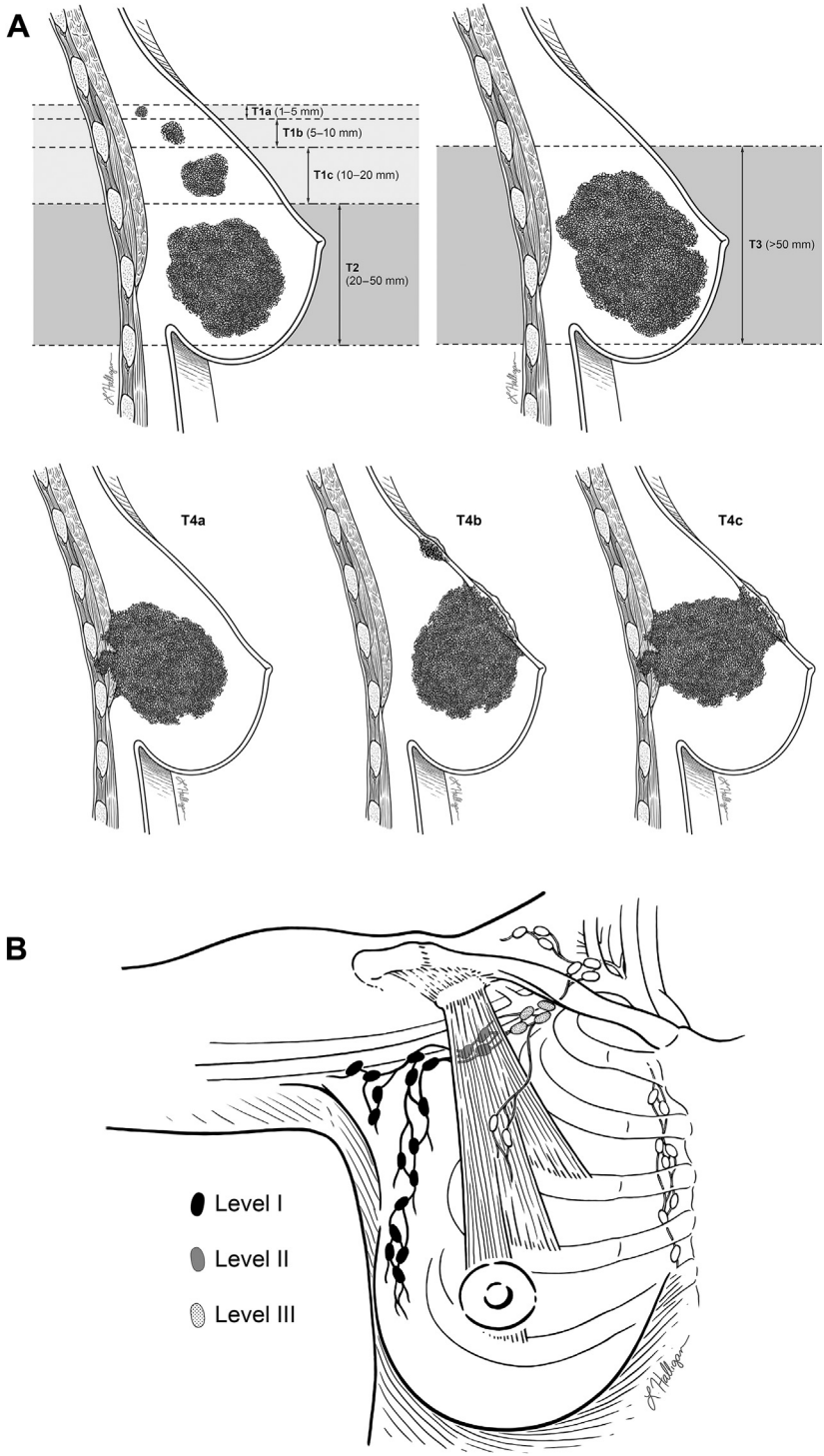


Fig. 1. Clinical staging categories for the (*A*) primary breast tumor and (*B*) regional axillary lymph nodes.[4] For the primary breast tumor (*A*), tumor size is used for delineating

preoperative systemic therapy, the patient is categorized as having stage IV disease and remains stage IV regardless of response to therapy. However, the stage designation should be updated if postsurgical imaging (within 4 months of diagnosis) reveals distant metastases, provided the patient has not received preoperative therapy.

For patients undergoing preoperative therapy, no pathologic stage group is assigned if there is a complete pathologic response (pCR), although these patients have been shown to have a significantly improved disease-free and overall survival, as confirmed in a recent meta-analysis.[15] However, when documenting staging for patients who received preoperative systemic therapy and experienced a pCR, one should continue to list the initial clinical staging information, as well as the pCR status.

Histopathologic tumor types include in situ carcinomas (ductal carcinoma in situ, Paget disease) and invasive carcinomas (ductal, inflammatory, medullary, medullary with lymphoid stroma, mucinous, papillary, tubular, lobular, Paget with infiltrating, undifferentiated, squamous cell, adenoid cystic, secretory, cribriform, and not otherwise specified). For histologic grading, all invasive breast cancers should be assigned a grade using the Nottingham modification of the Scarff-Bloom-Richardson grading system. Tumor grade is determined by scoring 3 morphologic features: tubule formation, nuclear pleomorphism, and mitotic count. Each feature is assigned a score from 1 (favorable) to 3 (unfavorable), and the summation of the 3 scores determines the category as follows:

- Grade 1 (low): 3 to 5 points
- Grade 2 (intermediate): 6 to 7 points
- Grade 3 (high): 8 to 9 points.

ANATOMIC STAGING, TUMOR GRADING, AND OUTCOMES

Although the anatomic extent of disease alone may not define the entire prognosis, it has remained a key prognostic factor in breast cancer (**Table 2**). In 1969, Fisher and colleagues[16] evaluated more than 2000 subjects with operative breast cancer entered into the National Breast Project by 45 institutions and reported that a larger tumor size was associated with a decreased survival, increased recurrence rates, and an increased likelihood of positive axillary lymph nodes. As such, tumor size was considered a key factor in breast cancer staging. Subsequently, a review of 24,136 female subjects with breast cancer from a Breast Cancer Survey was carried out by the American College of Surgeons in 1978.[17] Disease-free survival (cure rates) at 5 years were 60.5% for clinically localized disease and 33.9% for regional disease. Overall survival rates at 5 years were 72.8% for localized disease and 49.1% for regional disease. These findings confirmed that reduced cure and survival rates were associated with an increase in the number of positive nodes; a correlation with tumor size and

T categories 1 to 3; however, chest wall involvement results in categorization as T4a disease, whereas skin involvement via satellite nodules or ulceration is considered T4b disease and, when both are present, the tumor is categorized as T4c. Inflammatory breast cancer is categorized as T4d disease (not shown). For the regional axillary lymph nodes (*B*), patients are categorized as cN1 with metastases to movable ipsilateral level I to II nodes, whereas clinically fixed or matted nodes in the ipsilateral level I to II axilla are considered cN2. For cN3 disease, patients have metastases to ipsilateral infraclavicular (level III axillary) nodes, or to ipsilateral internal mammary nodes with level I to II axillary nodal metastases, or to ipsilateral supraclavicular nodes. (*Courtesy of* Duke University. Illustrated by Lauren Halligan, MSMI; copyright Duke University; with permission under a CC BY-ND 4.0 license.)

Table 1
The American Joint Committee *Cancer Staging Manual*, 8th edition, breast cancer definitions of anatomic and pathologic staging guidelines

T Category	T criteria (clinical and pathologic)
Tis	Only ductal carcinoma in situ identified (no invasive component)
T1	Tumor size ≤2 cm in greatest dimension (using the largest tumor foci, if multifocal) • T1mi: tumor size ≤1 mm • T1a: tumor size >1 mm but ≤5 mm • T1b: tumor size >5 mm but ≤10 mm • T1c: tumor size >10 mm but ≤20 mm
T2	Tumor size >2 cm but ≤5 cm in greatest dimension
T3	Tumor size >5 cm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4 • T4a: tumor extension to the chest wall; invasion or adherence to the pectoralis muscle without chest wall invasion does not qualify as T4 • T4b: ulceration and/or ipsilateral macroscopic satellite nodules and/or skin edema (eg, peau d'orange) that does not meet criteria for inflammatory carcinoma • T4c: both T4a and T4b are present • T4d: inflammatory carcinoma
N Category	**N criteria (clinical)**
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I–II axillary lymph nodes
cN2	Metastases to ipsilateral level I–II axillary lymph nodes that are clinically fixed or matted, or to ipsilateral internal mammary nodes without axillary lymph node involvement • cN2a: metastases to ipsilateral level I–II axillary nodes that are clinically fixed or matted • cN2b: metastases to ipsilateral internal mammary nodes without axillary nodal involvement
cN3	Metastases to ipsilateral infraclavicular (level III axillary) lymph nodes, to ipsilateral internal mammary lymph nodes with level I–II axillary lymph node metastases, or to ipsilateral supraclavicular lymph nodes • cN3a: metastases to ipsilateral infraclavicular (level III axillary) nodes with or without level I–II axillary nodal involvement • cN3b: metastases to ipsilateral internal mammary nodes with level I–II axillary nodal metastases • cN3c: metastases to ipsilateral supraclavicular nodes with or without axillary or internal mammary nodal involvement
N Category	**N criteria (pathologic)**
pN0	No regional lymph node metastases identified or ITCs only • pN0(i+): regional lymph nodes with ITCs only (malignant cell clusters ≤0.2 mm)
pN1	Micrometastases, metastases to 1–3 axillary lymph nodes and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy • pN1mi: micrometastases (>0.2 mm but ≤2 mm) • pN1a: metastases to 1–3 axillary nodes, at least 1 metastasis > 2 mm • pN1b: metastases to ipsilateral internal mammary sentinel nodes, excluding ITCs • pN1c: pN1a and pN1b combined

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Table 1 (*continued*)

pN2	Metastases to 4–9 axillary lymph nodes or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases • pN2a: metastases to 4–9 axillary nodes, at least 1 metastasis > 2 mm • pN2b: metastases in clinically detected internal mammary nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases to ≥10 axillary lymph nodes, to infraclavicular level III axillary nodes, to positive ipsilateral internal mammary nodes by imaging in the presence of ≥1 positive level I–II axillary nodes, to >3 axillary nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary nodes, or to ipsilateral supraclavicular nodes • pN3a: metastases to ≥10 axillary nodes or to infraclavicular level III axillary nodes • pN3b: positive ipsilateral internal mammary nodes by imaging in the presence of ≥1 positive level I–II axillary nodes, or to >3 axillary nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary nodes • pN3c: metastases to ipsilateral supraclavicular nodes
M Category	M criteria (clinical and pathologic)
M0	No clinical or radiographic evidence of distant metastases (designated cM0, never pM0); imaging studies are not required to assign the cM0 category • cM0(i+): no clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits ≤ 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
M1	Distant metastases detected by clinical and/or radiographic means (cM1), or histologically proven metastases with at least 1 tumor deposit >0.2 mm (pM1)

Abbreviation: ITC, isolated tumor cells.

From AJCC Cancer Staging Manual. 8th edition. New York: Springer International Publishing; 2016.

prognosis was also noted.[17] Similarly, review of 24,740 cases in the Surveillance, Epidemiology, and End Results (SEER) program from 1977 to 1982 found that tumor diameter and lymph node status were independent but additive prognostic indicators: as tumor size increased, survival decreased regardless of nodal status; as nodal involvement increased, survival decreased regardless of tumor size.[18] Of note, the study also suggested that lymph node status indicates a tumor's ability to spread but that lymph node involvement was not mandatory for distant disease progression.[18]

Of 50,834 patients diagnosed between 1983 to 1987 in the SEER program, relative survival data clearly demonstrated separation of the stages with an expected progression from the best (stage I) to the worst (stage IV) using the AJCC *Cancer Staging Manual*, 4th edition, TNM staging system.[19] This separation of stages was again confirmed in the AJCC *Cancer Staging Manual*, 5th edition, in which survival rates for 50,383 patients with breast carcinoma were classified by the AJCC staging system. Clearly separate 5-year observed and relative survival rates were noted for each stage with an expected progression from the best (stage I: 5-year observed survival rate 87%, 5-year relative survival rate 98%) to the worst (stage IV: 5-year observed survival rate 13%, 5-year relative survival 16%).[20] At that time, numerous prognostic parameters for breast cancer had been postulated with well-supported literature for tumor size, regional lymph node involvement, metastasis, tumor

Table 2
Key references and findings in the history of breast cancer staging

Author, Y of Publication	Select Highlights
Fisher et al,[16] 1969	• Larger tumor size is associated with decreased survival, increased recurrence rates, and increased likelihood of positive axillary nodes
McGuire,[38] 1975	• Between 50%–60% of ER positive breast cancers will respond to endocrine therapy, whereas only 8%–16% of ER negative cancers will respond
Knight et al,[26] 1977	• ER absence is associated with earlier recurrence, independent of tumor size and lymph node status
AJCC guidelines, 1st edition,[1] 1977	• Lower stage cancers have higher recovery rates and greater survival time • Tumor size (T), spread to local lymph nodes (N) and distant metastases (M) are important staging factors; tumor grade was recorded but not included in the TNM classification
Nemoto et al,[17] 1980	• Expected survival decreases linearly with increasing number of histologically positive axillary nodes, up to 21 positive nodes
Clark et al,[27] 1983	• PR and ER positivity are both associated with increased time to recurrence and improved overall survival
AJCC guidelines, 2nd edition,[39] 1983	• Detection of cancers before direction extension or metastatic spread generally leads to improved survival
Slamon et al,[28] 1987	• HER2 gene amplification was a significant predictor of recurrence and overall survival, independent of other prognostic factors • For node positive disease, HER2 gene amplification had greater prognostic value than hormonal receptor status
AJCC guidelines, 3rd edition,[40] 1988	• T3N0M0 5-y survival (76%) most closely matches stage II (75%) rather than stage III (56%), thus reclassified as stage II
Carter et al,[18] 1989	• Both tumor size and number of positive lymph nodes are independent, additive prognostic indicators • Women with 1–3 positive lymph nodes have improved 5-y survival compared with those with 4 + positive nodes
Tandon et al,[41] 1989	• HER2 oncogene amplification is associated with significantly decreased DFS and 5-y OS • Axillary lymph node status is the most important prognostic indicator
Henson et al,[23] 1991	• Observed positive correlation between grade and stage • Both stage and grade are useful prognostic indicators, and provide the best prediction of outcome when used in combination
AJCC guidelines, 4th edition (SEER data),[19] 1992	• Relative survival is directly correlated with AJCC stage (best survival for stages 0-I and incrementally worse through stage IV)
Gusterson et al,[31] 1992	• Expression of c-erbB-2 is prognostically significant for node-positive breast cancer
Press et al,[30] 1993	• In node-negative women, HER2 overexpression is an independent risk factor for disease recurrence • Subgroup analysis confirmed a persistent increased risk in premenopausal and postmenopausal women, as well as ER negative and small (T1a) tumors

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Table 2
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Author, Y of Publication	Select Highlights
Press et al,[29] 1997	• HER2 gene amplification is an independent predictor of poor clinical outcome (in the absence of adjuvant therapy) • HER2 gene amplification is a stronger discriminant than tumor size in this population
AJCC guidelines, 5th edition,[20] 1997	• 5-y observed survival decreases as stage increases (stage 0: 92%; stage I: 87%; stage IIA: 78%; stage IIB: 68%; stage IIIA: 51%; stage IIIB: 42%; stage IV: 13%) • 5-y relative survival decreases as stage increases (stage 0: 100%; stage I: 98%: stage IIA: 88%; stage IIB: 76%; stage IIIA: 56%; stage IIIB: 49%; stage IV: 16%) • Prognostic factors reviewed and literature support noted for: tumor size, regional lymph node involvement, metastasis, tumor histology, tumor grade, chromatin, tumor necrosis, mitotic counts, thymidine labeling index, S-phase flow cytometry, Ki-67, angiogenesis, and peritumoral LVI
Fitzgibbons et al,[32] 2000	• Axillary lymph node status is among the most important prognostic indicators for surviving breast cancer • Increasing tumor size, number of positive axillary lymph nodes, and grade are poor prognostic indicators in breast cancer
AJCC guidelines, 6th edition,[42] 2002	• Though data are not yet sufficient to incorporate histologic grade into TNM stage, it remains an important prognostic indicator
AJCC guidelines, 7th edition (NCDB data),[21] 2009	• Increasing tumor size and number of positive nodes demonstrate progressively worse 5-y survivals • 5-y observed survival decreases as stage increases (stage 0: 93%; stage I: 88%; stage IIA: 81%; stage IIB: 74%; stage IIIA: 67%; stage IIIB: 41%; stage IIIC: 49%; stage IV: 15%)
Elston & Ellis (in UICC 7th Edition),[43,44] 2010	• Revised grading criteria (Bloom-Richardson-Elston criteria) provided more objective and reproducible grading results • Using these criteria, grade was directly correlated with prognosis: grade I tumors had significantly better survival than grades II–III
Yi et al,[22] 2011	• Pathologic (anatomic) staging still associated with progressively worse 5-y disease-specific survival • Stage I: 98.8%, stage IIA: 96.3%, stage IIB: 94.5%, and stage IIIA: 88.6% • Staging that included pathologic stage, nuclear grade, and ER status was the most precise in predicting survival
Sparano et al. (TailorX Study),[34] 2015	• Women with T1-2, hormone receptor–positive, HER2 negative, axillary node-negative breast cancer that had a 21-gene recurrence score of 0–10 had a 98.7% DFS rate and 98% overall survival rate
Mittendorf et al,[33] 2016	• The Neo-Bioscore incorporates biomarkers and treatment response to determine prognosis in patients undergoing systemic chemotherapy before definitive surgery • Scoring included the previously defined CPS + EG staging system (clinical-pathologic stage, estrogen receptor status, tumor grade) and added ERBB2 status, which improved prognostic stratification

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Table 2
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Author, Y of Publication	Select Highlights
Harris et al,[35] 2016	• Of breast tumor biomarker assays, evidence supports use of Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in select subgroups • Only ER, PR, and HER2 biomarkers should guide specific treatment regimen decisions, although disease stage, comorbidities, and patient preference should also be considered
Cardoso et al,(MINDACT Study)[36] 2016	• Assessed clinical risk (using Adjuvant! Online) and genomic risk (using 70-gene signature) in women with early-stage breast cancer • Women with discordant disease (low clinical risk and high genomic risk, or high clinical risk and low genomic risk) had similar 5-y survival rates regardless of chemotherapy receipt
AJCC guidelines, 8th edition,[4] 2016	• Prognostic factors (nuclear grade, ER status, and HER2 status) create a risk profile (sum of scores = 0–3) combined with pathologic stage to create a new staging system • 5-y DSS and OS decreased as pathologic stage + risk profile score increased (ie, path stage IIA + risk profile 0 = 100% DSS and 96.8% OS vs path stage IIA = risk profile 3 = 91% DSS and 88.2% OS)

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; LVI, lymphovascular invasion; NCDB, National Cancer Database; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

histology, tumor grade, chromatin, tumor necrosis, mitotic counts, thymidine labeling index, S-phase flow cytometry, Ki-67, angiogenesis, and peritumoral lymphatic vessel invasion.

Recent studies confirm the continued importance of anatomic staging. Review of 211,645 breast cancer cases diagnosed between 2001 and 2002, and reported in the National Cancer Database (NCDB), again demonstrated the significance of increasing tumor size and nodal burden because both correlated with progressively worse survival.[21] With regard to overall survival and disease stage (as classified by the AJCC *Cancer Staging Manual*, 7th edition), the 5-year observed survival rates were 93% for stage 0 disease and only 15% for stage IV disease.[21] Using a more contemporary database of 3728 patients with invasive breast cancer treated at MD Anderson from 1997 to 2006, pathologic (anatomic) staging was still associated with a progressively worse 5-year disease-specific survival on univariate and multivariate analyses: stage I, 98.8%; stage IIA, 96.3%; stage IIB, 94.5%; and stage IIIA, 88.6%.[22] Importantly, the combination of pathologic stage, nuclear grade, and ER status were the most precise in predicting survival, assuming proper multidisciplinary treatment with appropriate use of chemotherapy and endocrine therapy.[22]

Although tumor grade was not officially incorporated into the breast cancer staging system until the 8th edition, it has been recommended for reporting since the 1st edition in 1977.[1] In 1991, survival rates for 22,616 breast cancer cases in the SEER database were reviewed using both stage and tumor grade.[23] Survival rates for those with stage II, grade 1 disease were similar to those assigned stage I, grade 3 and were better than those assigned stage I, grade 4 (which would now be included with grade 3 tumors). These results suggested that combining histologic grade and

breast cancer stage may improve the prediction of outcomes.[23] This was again confirmed in a more recent analysis of 161,708 patients in the SEER database.[24] Schwartz and colleagues[24] demonstrated that a higher histologic grade was associated with a progressive decrease in 10-year survival, independent of tumor size or nodal status, thus confirming grade as a prognostic factor. Although some investigators have questioned the reproducibility of histologic grading, specific methodology has been developed to address these concerns.[25]

EVIDENCE TO SUPPORT INCORPORATION OF BIOMARKERS AND IMPLEMENTATION

Tumor biomarkers have long been recognized as important prognostic factors in breast cancer and, for the first time, the AJCC *Cancer Staging Manual*, 8th edition, incorporates tumor biology. The first biomarkers to be recognized as having prognostic significance for breast cancer were the ERs and PRs. McGuire and colleagues[26] demonstrated as early as 1977 that the ER was an important prognostic factor in early-stage breast cancer, independent of anatomic staging factors. In 1983, both the ER and PR were examined in 189 subjects receiving adjuvant therapy for stage II breast cancer and it was found that the presence of either ER or PR was positively correlated with disease-free survival.[27] Studies such as these led to the recommendation that hormone receptor status should be routinely examined, to improve survival predictions. In 1987, the *HER-2/neu* oncogene was recognized to confer a worse prognosis in patients with early-stage breast cancer.[28] These findings were later confirmed in larger datasets of both node-negative[29,30] and as node-positive patients in the Ludwig Breast Cancer Study Group.[31]

In 2000, Fitzgibbons and colleagues[32] published the College of American Pathologists Consensus Statement 1999, which ranked factors as follows: category I, factors with prognostic value and useful in clinical patient management; category II, factors extensively studied biologically and clinically, but its value remained unvalidated; and category III, all other factors not sufficiently studied to demonstrate their prognostic value. Category I factors included TNM staging information, histologic grade, histologic type, mitotic figure counts, and hormone receptor status. Category II factors included HER2-neu, proliferation markers, lymphatic and vascular channel invasion, and p53. Following this publication, subsequent revisions of the AJCC guidelines continued to evaluate the potential incorporation of many of these category I and II factors. These efforts have resulted in the addition of new prognostic staging categories, which for the first time includes a select group of molecular markers.[4]

Evidence has now accumulated to support the combination of tumor biology and anatomic extent of disease demonstrating significant predictive synergy for breast cancer prognosis, beyond anatomic staging alone. Investigators at MD Anderson evaluated the performance of a risk profile, which included pathologic stage, tumor grade, lymphovascular invasion, hormone receptor status, and HER2 receptor status.[22] The incorporation of biomarkers yielded superior stratification of breast cancer specific survivals compared with TNM staging alone. These findings were confirmed by Winchester and colleagues,[4] who evaluated 238,265 women diagnosed with invasive breast cancer in 2010 to 2011 with a median follow-up of 37.6 months. Notably, patients with triple-negative cancer (all grades) had a worse survival, which was comparable to those at least 1 stage higher in the AJCC *Cancer Staging Manual*, 7th edition. Furthermore, several ER-positive or PR-positive subgroups (regardless of HER2 status) had a better survival than those with the same 7th edition stage group.[4] Recently, the MD Anderson group has built on their previous experience to develop the Neo-Bioscore, which incorporates biomarkers, as well as treatment

response, to determine prognosis in patients who undergo systemic chemotherapy before definitive surgery.[33] Thus, there is evidence to propose that future staging systems should incorporate treatment response, as well as staging at diagnosis.

The breast cancer field has been replete with studies to support multigene panel testing for prediction of both prognosis and response to therapy. To date, the Oncotype DX assay has been tested in the largest prospective validation cohort. Among 10,253 women enrolled in a prospective study, 1626 women had a recurrence score of 0 to 10 and received endocrine therapy alone (without chemotherapy). At 5-year follow-up, this group had a distant disease-free survival of 99.3% (95% CI, 98.7–99.6), confirming the ability of this test to identify with high accuracy a group of patients who had an excellent outcome with endocrine therapy alone.[34]

More recently, an American Society of Clinical Oncology panel convened to provide guideline recommendations on the use of biomarkers for decision-making regarding systemic therapy for women with early-stage breast cancer.[35] After extensive review of published evidence, the panel concluded that in addition to ER, PR, and HER2 receptors, additional assays, including Oncotype DX, EndoPredict (Myriad Genetics, Salt Lake City, UT), PAM50 (Nanostring Technologies, Inc, Seattle, WA), Breast Cancer Index (Biotheranostics, San Diego, CA), and urokinase plasminogen activator and plasminogen activator inhibitor type 1, had clinical utility for making adjuvant treatment recommendations. Based on these and other recommendations, the AJCC *Cancer Staging Manual*, 8th edition, includes the Oncotype DX score (level I evidence) and the MammaPrint (Agendia Inc, Irvine, CA), EndoPredict, PAM50, and EndoPredict scores (level II evidence) as part of the staging for newly diagnosed breast cancers.

Following publication of the AJCC 8th edition guidelines, the MINDACT (Microarray in Node-Negative and 1–3 Positive Lymph Node Disease May Avoid Chemotherapy) trial reported that women with early-stage breast cancer and a low genomic risk (based on a 70-gene signature, MammaPrint) but high clinical risk (as determined by Adjuvant! Online) had similar 5-year survival rates regardless of chemotherapy receipt.[36] Survival rates were also similar for women with a high genomic risk and low clinical risk. These findings suggest that chemotherapy may not be significantly beneficial for women with discordant clinical and genomic risks (ie, high clinical risk and low genomic risk, or low clinical risk and high genomic risk).[36] Thus, in a summary of the changes to the AJCC *Cancer Staging Manual*, 8th edition, Giuliano and colleagues[37] reported that these findings are consistent with downstaging selected tumors with low-risk genomic profiling and would likely be incorporated in future updates to the manual.

For the of the AJCC *Cancer Staging Manual*, 8th edition, the new prognostic stage groups were determined based on breast cancer populations from the NCDB that were offered and mostly treated with appropriate endocrine and/or systemic therapy.[4] This highlights not only the importance of tumor and disease characteristics but also the critical need for appropriate multidisciplinary treatment. The authors recently performed an analysis comparing the 7th edition to the revised 8th edition AJCC staging system in 501,451 women in the NCDB diagnosed in 2004 to 2014, excluding patients undergoing neoadjuvant chemotherapy (**Table 3**). In this analysis, we found that 19.3% of women stages I to III will be upstaged and 23.8% will be downstaged, with the largest proportion of downstaged patients seen in the stage IB group becoming stage IA (9175, 76.7%). By providing a staging system that better reflects the current understanding of tumor biology and targeted therapy, this restaging is expected to provide a more accurate prediction of patient outcome. Work is ongoing to determine whether this expectation can be validated in large population-based datasets treated with contemporary systemic therapy regimens.

Table 3
Implications of the American Joint Committee on Cancer 8th edition staging guidelines, comparing 7th edition and 8th edition in patients in the National Cancer Database from 2004 to 2014

		AJCC Guidelines 8th Edition Prognostic Stage									
		0 (%)	IA (%)	IB (%)	IIA (%)	IIB (%)	IIIA (%)	IIIB (%)	IIIC (%)	IV (%)	*Total (N)*
AJCC Guidelines, 7th Edition, Pathologic or Anatomic Stage	**0**	100	0	0	0	0	0	0	0	0	*6955*
	IA	0	86.5	3.9	9.6	0	0	0	0	0	*304279*
	IB	0	76.7	15.2	8.1	0	0	0	0	0	*11,970*
	IIA	0	44.8	27.1	5.3	6.5	16.3	0	0	0	*115819*
	IIB	0	0	27.8	0	1	25.7	14.4	31.2	0	*16,982*
	IIIA	0	0	3.5	8.4	39.8	3.1	29.3	15.9	0	*27,845*
	IIIB	0	0	0	0	0	5.8	35	59.2	0	*3360*
	IIIC	0	0	0	0	0	6.1	39.7	54.2	0	*11,458*
	IV	0	0	0	0	0	0	0	0	100	*2783*
Total (N)		*6955*	*324249*	*50,885*	*38,628*	*18,739*	*24,967*	*16,328*	*17,917*	*2783*	*501451*

Black shading represents patients with no change in their stage, light grey represents patients that were downstaged, and dark grey represents patients that were upstaged. Each percent is per row total for each stage using the AJCC 7th edition, then restaged based on the 8th edition (each cell contains row percent). Total from each column or row contains patient sample sizes for each stage. Overall N 5 501,451. Patients who did not have a corresponding prognostic stage in the 8th edition were excluded.

(*Data from* Plichta and colleagues, unpublished data, 2017.)

SUMMARY

The AJCC staging system continues to provide a universal, efficient, and consistent basis on which to communicate those factors that influence patient prognosis and treatment recommendations. The 8th edition of the AJCC staging system incorporates, for the first time, molecular biomarkers that have been validated to have critical prognostic significance. With these recent updates to the AJCC staging manual, clinicians are strongly encouraged to use the prognostic stage groups, including these additional variables whenever possible. These advancements in the understanding of the biology of breast cancer will undoubtedly continue to serve critical roles in the ongoing refinement of breast cancer staging and to advance both patient care and research.

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