Ann Surg Oncol (2018) 25:1783–1785
https://doi.org/10.1245/s10434-018-6486-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – BREAST ONCOLOGY

Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer

Armando E. Giuliano, MD[1], Stephen B. Edge, MD[2,3], and Gabriel N. Hortobagyi, MD[4]

[1]Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [3]Jacobs School of Medicine, University at Buffalo, Buffalo, NY; [4]Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Since its inception in 1977, the American Joint Committee on Cancer (AJCC) has published a staging system based on anatomic findings: tumor size (T), nodal status (N), and metastases (M). This staging system has evolved, not only encompassing a wide spectrum of tumors but also including multiple updates that enable physicians to utilize new information and outcomes for management strategies in different malignancies. The breast cancer staging system has always been based similarly on TNM classification despite the fact that, for several years, clinicians in practice have used a number of biologic factors to describe the patient's disease, outcomes, and appropriate therapy.

The eighth edition of the AJCC staging for breast cancer is conceptually a radical departure from prior editions, because it incorporates contemporary biologic factors (biomarkers) into the traditional anatomic staging system. These biomarkers result in a modification of the TNM stage. These factors—estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), grade, and multigene assays—are widely used in practice to define prognosis and determine therapy. The eighth edition also maintains a firm footing in the past, enabling comparisons of outcomes to prior studies using the traditional TNM system as the basis, especially important in parts of the world where biologic markers are not routinely available. In the *AJCC Staging Manual*, biomarkers have previously been incorporated into other tumor systems, such as thyroid and prostate cancer; however, until recently, there have been insufficient data to permit incorporation of biomarkers into the staging system for breast cancer. The expert panel for the eighth edition felt that the peer-reviewed literature was now sufficient to permit inclusion of several of the most well-studied biomarkers. These biomarkers, especially hormone-receptor and HER2, have a great impact on treatment and outcomes.

Gene expression profiling has identified several molecular subtypes of breast cancer.[1] While gene expression profiling is the defining feature of breast cancer subtypes, it is not often used clinically. Biomarker assays for ER, PR, and HER2 are used as surrogates for gene expression profiling and are measured with immunohistochemical methods or in situ hybridization. These clinically identifiable and well-studied biomarkers as well as histologic grade have been evaluated in prospective, controlled trials and display sufficient prognostic information to justify incorporation into the AJCC staging system. Measures of proliferation, such as Ki67, were also considered. Because of concerns about interobserver reproducibility, the expert panel elected not to incorporate Ki67 until technical issues were resolved. In the United States, virtually all patients' primary tumors are evaluated for ER, PR, HER2, and grade. The Nottingham grading system is the most commonly used to report tumor grade. The expert panel felt that, when possible, evaluation of these four biomarkers should adhere to guidelines of the American Society of Clinical Oncology and the College of American Pathology.[2,3]

In the AJCC 8th edition, patients are clinically staged using the traditional TNM anatomic information modified by the expression of these four biomarkers, creating a Clinical Prognostic Stage Group. This stage should be used for all patients whose tumors are evaluated for expression

First Received: 5 April 2018;
Published Online: 18 April 2018

A. E. Giuliano, MD
e-mail: armando.giuliano@cshs.org

of these biomarkers, which should encompass virtually all patients treated in the United States. The Clinical Prognostic Stage should be based on initial evaluation before any systemic therapy. The TNM evaluation uses the traditional clinical assessment by physical examination and imaging of size, lymph node evaluation, and evidence of metastatic disease. When patients undergo resection of their primary tumor, pathologic staging is then determined. Pathologic staging includes information from clinical staging plus evaluation of T and N status from surgical resection. The post-resection anatomic information coupled with the pretreatment biomarker findings result in the final Pathologic Prognostic Stage Group.

As initially published in late 2016, the large and complex tables were found to have several discrepancies. These were corrected in the updated Breast Chapter of the AJCC Cancer Staging Manual provided online in November 2017 (see https://cancerstaging.org/About/news/Pages/Updated-Breast-Chapter-for-8th-Edition.aspx). The AJCC 8th edition staging is effective for cancer diagnosed beginning January 1, 2018. Calculation of stage has been made less complicated and easier to interpret and soon will be available as an app for mobile phones. Examining the tables starting on the left, the T, N, and M categories are determined. Grade is the next modification followed by HER2, ER, and PR status, resulting in the Pathologic Prognostic Stage Group (Table 1). The panel felt strongly supported by literature that this Pathologic Prognostic Stage Group is the most accurate predictor of outcome.

The introduction of neoadjuvant systemic therapy has added a confounding dimension to staging evaluation. For a number of reasons, including limited complete pre- and post-therapy data on patients treated with neoadjuvant therapy, the expert panel determined that a separate post-neoadjuvant prognostic stage grouping was not possible at this time. However, post-neoadjuvant categorization of T and N indicated by "ypT" and "ypN" should be used and the degree of tumor response recorded. Biomarkers cannot be used to modify the post-neoadjuvant "y" stage. However, all patients should have clinical prognostic stage group determined and recorded that includes these biomarkers.

In addition to biomarkers, the expert panel felt that the use of multigene assays, which are commercially available, provide additional prognostic information suitable for incorporation in the AJCC 8th edition. Many panels have been developed and are available commercially. Most were developed for hormone receptor-positive, HER2-negative tumors, although some now are available for evaluation of hormone receptor-negative tumors as well. In addition, most of the data available are for lymph node-negative breast cancer, although information also is accumulating for women who are node-positive. At the time of evaluation of data for the 8th edition, the 21-gene assay Oncotype DX® was felt to be the only multigene assay sufficiently evaluated prospectively for inclusion in the staging system. This assay was evaluated prospectively in the TAILORx clinical trial. Women with hormone receptor-positive, HER2-negative breast cancer, pathologically node-negative with a recurrence score less than 11 were treated with endocrine therapy without chemotherapy. Women whose recurrence score was $\geq$ 25 were assigned to chemotherapy as well as subsequent endocrine therapy. Women with intermediate recurrence scores (11–24) were randomly assigned to either endocrine therapy or endocrine therapy plus chemotherapy. Only outcomes for the low recurrence score group have been reported.[4] Patients with recurrence scores less than 11 had excellent disease-free survival at 6.9 years of 98.6% with endocrine therapy alone, suggesting that chemotherapy is not likely to improve outcome and is not warranted in this low recurrence score group. Other databases have been prospectively evaluated using a number of different assays and support the observation that women with a low-risk multigene assay can safely omit adjuvant systemic chemotherapy.[5–7] The 8th edition utilizes the Oncotype DX® low recurrence score to lower the AJCC stage, such that patients with a low recurrence score ($<$ 11) are staged as 1A (Table 2). Other assays have not yet been included in staging, but this does not preclude their use in clinical care as determined by the patient and physician using data existing at the time of treatment. The panel is committed to reevaluating and updating the staging system to include other multigene panels that are being evaluated prospectively in studies, such as MINDACT using the Mammaprint test.[8]

Several studies have recently been published utilizing the new AJCC 8th edition staging system to reexamine stages from known databases, such as that of MD Anderson Cancer Center and the California Cancer Registry.[9,10] Among this large number of patients, the AJCC 8th edition

TABLE 1 Example of 8th edition AJCC pathological prognostic staging with biomarkers

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 N2 M0	G1	Positive	Positive	Positive	IB

TABLE 2 Example of 8th edition AJCC Pathological Prognostic Staging with biomarkers when Oncotype DX® score is <11

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 N0 M0	G2	Negative	Positive	Negative	1A

more accurately predicted outcome than did the prior staging editions based solely on anatomic extent of disease, supporting the Expert Panel's opinion to incorporate biomarkers. As in all prior editions, the 8th edition reports the prognosis of patients offered appropriate treatment.

While the AJCC 8th edition staging system for breast cancer remains based on TNM staging, permitting comparisons with prior years, it incorporates changes in the understanding of the biological diversity of breast cancer appropriate for contemporary and future management.

REFERENCES

1. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747–52.
2. 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):2784-95. https://doi.org/10.1200/jco.2009.25.6529.
3. Wolff AC, Hammond ME, Hicks DG, et al., American Society of Clinical Oncology; College of American Pathologists. 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. *J Clin Oncol*. 2013;31(31):3997–4013. https://doi.org/10.1200/jco.2013.50.9984.
4. 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):2005–14. https://doi.org/10.1056/nejmoa1510764.
5. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat*. 2017;165(3):573–83. https://doi.org/10.1007/s10549-017-4358-6.
6. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in patients with node-negative breast cancer treated based on the recurrence score results: evidence from a large prospectively designed registry. *NPJ Breast Cancer*. 2017;3:33. https://doi.org/10.1038/s41523-017-0034-6.
7. 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. *Lancet Oncol*. 2013;14(11):1067–76. https://doi.org/10.1016/s1470-2045(13)70387-5.
8. Cardoso F, van Veer LJ, Bogaerts J, et al.; MINDACT Investigators 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717–29. https://doi.org/10.1056/nejmoa1602253.
9. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation study of the American Joint Committee on cancer eighth edition prognostic stage compared with the anatomic stage in breast cancer. *JAMA Oncol*. 2018;4(2):203–9. https://doi.org/10.1001/jamaoncol.2017.4298.
10. Abdel-Rahman O. Validation of the 8th AJCC prognostic staging system for breast cancer in a population-based setting. *Breast Cancer Res Treat*. 2018;168(1):269–75. https://doi.org/10.1007/s10549-017-4577-x.