Evolution of the Staging System in Breast Cancer

Cory A. Donovan, MD and Armando E. Giuliano, MD

Department of Surgical Oncology, Cedars-Sinai Medical Center, Los Angeles, CA

Tumor biology strongly influences the prognosis and treatment of breast cancer. Hormone receptor status and HER2/Neu (HER2) receptor overexpression guide treatment and are related to disease recurrence and survival. Anatomic staging based solely on tumor size, nodal status and the presence or absence of metastatic disease (TNM staging) fails to accurately capture the behavior of some tumors, patient prognosis, and tumor response to targeted therapy. This limitation of anatomic staging has been acknowledged by the American Joint Committee on Cancer (AJCC) Expert Panels in past editions of the staging system, and has resulted in the incorporation of estrogen receptor (ER) status, HER2 status, grade, and molecular tumor characteristics into the 8th Edition Revision published in November 2016 and set for adoption in 2018.¹ Unfortunately, since there are no robust data to support the prognostic value of a more complex staging system, the Expert Panel writing the 8th edition extensively debated the incorporation of biologic factors into the AJCC staging system.

The Bioscore and the Neo-Bioscore are two scoring systems that incorporate aspects of tumor biology into staging to produce a more nuanced understanding of individual prognosis and to address modern treatment strategies. By including ER status and overexpression of HER2 alongside anatomic factors, these systems more accurately mirror how we understand and treat contemporary breast cancer patients. Mittendorf et al. used pathologic tumor size, nodal status, grade, ER and HER2 to stratify untreated patients into seven distinct subgroups.² Each tumor characteristic was given a numeric score based

on the hazard ratio for disease-specific survival derived from multivariable analysis of a baseline group of 3327 patients treated at MD Anderson Cancer Center from 2007 to 2013. A final ‘Bioscore’ from 1 to 7 is calculated by summing the scores of individual predictors. Once developed, this system was applied to a large cohort (67,944 patients) from the California Cancer Registry and compared favorably with the traditional 7th edition AJCC staging system. While the AJCC 7th edition stage groups estimated 5-year disease-specific survival ranging from 79.5 to 99.1, the Bioscore staging system better separated outcomes and had cohorts spanning a broader range, from 33.3–100%. The Bioscore model had a higher concordance index than anatomical staging alone. The improved stratification was most pronounced in patients with higher Bioscores, although in the larger cohort from the California Cancer Registry there was also clear stratification of the cohorts with lower Bioscores. The Bioscore of Mittendorf and colleagues was considered by the Expert Panel for the 8th edition as evidence of the importance of biomarkers.

Bergquist et al. applied similar principles to patients following treatment with neoadjuvant chemotherapy.³ Staging after neoadjuvant treatment is not included in the 8th edition of the AJCC staging manual. The Neo-Bioscore allocates numerical points for pretreatment clinical stage and pathologic stage after neoadjuvant chemotherapy, as well as tumor grade, ER status, and HER2 status. This 7-point scale was validated in a single institutional dataset involving 2377 patients treated with neoadjuvant chemotherapy.⁴ The authors applied this Neo-Bioscore to a much broader cohort of 43,320 patients obtained through the National Cancer Data Base (NCDB). Of these, only 12,002 (27.7%) had HER2 data available since the NCDB did not begin the collection of HER2 status until 2010. Neo-Bioscore outperformed the anatomic AJCC pathologic and clinical staging systems, providing improved stage discrimination and quality of staging. This was most significant when staging systems were compared at shorter follow-up times.

Both Bioscore and Neo-Bioscore are part of an overall movement towards more individualized cancer care that accompanies an improved understanding of the complexity of tumor biology. They support the transition of the AJCC 8th edition from a purely anatomic staging system to one that incorporates biologic factors. In patients treated with and without neoadjuvant chemotherapy, the inclusion of tumor biologic features is superior to the use of anatomic stage alone. Staging is improved when tumor biology is considered.

There are some limitations to the above two studies and longer-term follow-up is required. In these studies, the median follow-up was 5 years and 35.8 months, respectively. This is likely not sufficient to capture all mortality events in ER+ patients, given the long disease-free survival and late recurrences for patients with this tumor subtype. Longer-term follow-up is also needed for the patients treated with neoadjuvant HER2-targeted therapy as HER2-positive status was only recorded in NCDB patients after 2010, and the resultant median follow-up time was only 36 months.

Additionally, the Bioscore staging system treated patients with ER + tumors as a monolithic group, while, in clinical practice, ER+ patients can have different prognoses based on genomic profiles. Incorporating genomic risk evaluation into a staging system might help to better stratify tumors with lower Bioscores. The authors were unable to include genomic information as the data were not widely available. As this information is routinely collected, it will add to current knowledge and may help distinguish among some ER+ tumors. The 8th edition of the AJCC staging system incorporates Oncotype DX[®] low-risk score to lower stage for some ER+ tumors.

The staging system is adapting to reflect a better understanding of the heterogeneity of breast cancers and the implications of individual tumor factors on prognosis and treatment. As treatment approaches change, staging must adapt to reflect current clinical practice. As genomic and molecular assays are better understood, they may become further incorporated into the staging system. The result will be a richer understanding of treatment and prognosis for the individual patient and the clinician. The unintended consequence may be an increasingly complex and perhaps more difficult-to-manage staging system. It remains to be seen how these complex algorithms will be incorporated into clinical practice to improve care, but it is clear that anatomic staging alone is inadequate to fully explain tumor behavior.

REFERENCES

1. Hortobagyi GN, Connolly JL, D'Orsi CJ, Edge SB, Mittendorf EA, Rugo HS et al. Breast. In: Amin MB, editor. AJCC cancer staging manual. 8th Ed. New York: Springer; 2017. p. 589–628.
2. Mittendorf E, Chavez-MacGregor M, Vila J, Yi M, Lichtensztajn D, Clarke C, et al. Bioscore: a staging system for breast cancer patients that reflects the prognostic significance of underlying tumor biology. *Ann Surg Oncol*. doi:[10.1245/s10434-017-6009-x](https://doi.org/10.1245/s10434-017-6009-x).
3. Bergquist J, Murphy B, Storlie C, Habermann E, Boughey J. Incorporation of tumor grade and receptor status improves staging quality in breast cancer patients treated with neoadjuvant chemotherapy. *Ann Surg Oncol*. 2017. doi:[10.1245/s10434-017-6010-4](https://doi.org/10.1245/s10434-017-6010-4).
4. Mittendorf EA, Vila J, Tucker SL, Chavez-MacGregor M, Smith BD, Symmans WF, et al. The neo-bioscore update for staging breast cancer treated with neoadjuvant chemotherapy: incorporation of prognostic biologic factors into staging after treatment. *JAMA Oncol*. 2016;2(7):929–36.