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Bioscore: A Staging System for Breast Cancer Patients that Reflects the Prognostic Significance of Underlying Tumor Biology

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ABSTRACT

Background. Biologic factors guide treatment decisions and have a significant impact on prognosis for breast cancer patients. This study was undertaken to develop a staging system incorporating biologic factors in addition to standard anatomic factors in the American Joint Committee on Cancer (AJCC) pathologic stage (PS) to assess disease-specific survival (DSS).

Methods. Overall, 3327 patients treated with surgery as an initial intervention at MD Anderson Cancer Center from 2007 to 2013 were identified. Multivariate analyses of factors, including PS, T stage (T), nodal stage (N), grade (G), estrogen receptor (ER) status (E) and human epidermal growth factor receptor (HER2) status (H) were performed to identify associations with DSS. A score of 0–4 was assigned for each factor by considering the hazard ratio magnitude. Multiple staging system models were then constructed: PS, PS + G, PS + G + E, PS + G + E + H, T + N, T + N + G, T + N + G + E, and T + N + G + E + H. Model performance was quantified using Harrell's concordance index, and the Akaike Information Criterion (AIC) was used to compare model fits. Comparable cases from California ($n = 67{,}944$) were used for validation.

Results. Median follow-up was 5.0 years (range 0.1–8.8) and 5-year DSS was 97.9% (95% confidence interval 97.3–98.4). Models incorporating grade, ER status, and HER2 status were most precise with identical C-index (0.81) and comparable AIC (994.9 for PS + G + E + H and 987.8 for T + N + G + E + H). Both models were externally validated.

Conclusions. These results confirm the importance of biologic factors in determining prognosis for breast cancer patients. We propose the Bioscore, which incorporates grade, ER and HER2 status with AJCC PS, to provide more refined stratification of breast cancer patients undergoing surgery as an initial intervention with respect to DSS.

The goal of cancer staging systems is to inform prognosis and guide clinicians in designing an individual patient's treatment plan. One staging system used for breast cancer patients is the American Joint Committee on Cancer (AJCC) system, which is based on tumor size, the presence or absence of lymph node involvement, and the presence or absence of distant metastasis. The TNM status for a patient is determined and this corresponds with a specific disease stage.[1] Breast cancer patients are assigned a clinical stage at the time of diagnosis, then after surgery, the pathologic stage (PS) is determined by evaluation of the resected tumor and regional lymph nodes.

It is well accepted that tumor biologic features, including grade, hormone receptor (HR) status, and human

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epidermal growth factor receptor 2 (HER2) status have predictive and prognostic value in breast cancer patients. Treatment recommendations are made largely based on HR and HER2 expression.[2–5] Patient outcomes within each TNM stage therefore have wide variation with respect to survival based on biologic features. Recognizing this, the expert panel that was convened to develop the 8th edition of the AJCC staging system sought to incorporate biologic factors. The expert panel, which included one author of the current study (EAM), found that there are limited published data quantifying the impact of biologic factors on prognosis, making it difficult to incorporate biologic factors into the staging system based on a lack of evidence.

Our group had previously recognized the limitations of a staging system based only on anatomy, and had reported a novel staging system for predicting disease-specific survival (DSS) for patients treated with surgery as the initial intervention. This staging system incorporated grade and estrogen receptor (ER) status with PS to facilitate improved stratification with respect to DSS when compared with PS alone.[6] The development of this staging system pre-dated the routine use of trastuzumab in the adjuvant setting for HER2-positive patients, which began in 2006. Because this staging system does not account for the favorable response of HER2-positive tumors to trastuzumab, it cannot be used to provide prognostic information for patients with HER2-positive breast cancer. The current study was therefore undertaken to update the staging system with a more contemporary cohort of patients treated at the MD Anderson Cancer Center to include those with HER2-positive disease receiving trastuzumab, and to validate this staging system using a large cohort of patients reported to the population-based California Cancer Registry (CCR).

PATIENTS AND METHODS

Patient Population

A prospectively maintained database was used to identify 3327 patients with non-metastatic invasive breast cancer who underwent surgery as a first intervention at MD Anderson from January 2007 through December 2013. None of these patients had been included in the development of the initial staging system incorporating biologic factors. Clinicopathologic data were recorded, including age, modified Black's nuclear grade, ER status, HER2 status, and PS determined according to the 7th edition of the AJCC staging guidelines. Patients with incomplete data were excluded. Prior to 2010, tumors were classified as ER-positive if there was >10% staining. A cut-off of 1% was used for patients treated after 2010, consistent with the change in American Society of Clinical Oncology (ASCO) guidelines.[7] HER2 status was defined as positive if 3+ on immunohistochemistry, or gene amplification was shown on fluorescence in situ hybridization. An external cohort was identified from the CCR, including 67,944 patients diagnosed between 2005 and 2010 with a first primary non-metastatic breast cancer who underwent surgery as a first intervention with known grade, ER status, and HER2 status. CCR patients were followed for vital status through 31 December 2013.

Model Building

The clinical endpoint was DSS, calculated from the date of diagnosis to the date of death from breast cancer. Patients not experiencing this endpoint were censored at last follow-up. Univariate and two multivariate analyses were performed to identify factors associated with DSS. The first multivariate analysis included pathologic T stage and pathologic N stage as separate variables, while the second analysis used the AJCC PS, which takes into account the combined T and N stage, as a variable. A prognostic score of 0–4 was then assigned to each factor by considering the magnitude of the hazard ratio (HR) and defining cut-offs. Only independent predictors of DSS ($p < 0.05$) were assigned a score. For binary variables, the comparison group with a significant impact on DSS was assigned one point. For ordinal variables, the comparison groups that were determined to have a significant impact on DSS with an HR between 1.1 and 3 were assigned one point, variables determined to have an HR between 3.1 and 6 were assigned two points, variables with an HR between 6.1 and 10 were assigned three points, and variables with an HR more than 10 were assigned four points. An overall staging score was calculated by summing scores for the individual predictors of DSS.

Models were built to determine the utility of combining variables, including T stage (T), N stage (N), PS, grade (G), ER status (E), and HER2 status (H), in determining DSS. The first set of models used pathologic T and N stage as the backbone and included T + N, T + N + G, T + N + G + E, and T + N + G + E + H, while the second set used PS as the backbone and included PS, PS + G, PS + G + E, and PS + G + E + H. Model performance was quantified using Harrell's concordance index (C-index), which can range from perfect discordance (0.0) to perfect concordance (1.0).[8] Akaike Information Criterion (AIC) was determined.[9] AIC takes into account how well the model fits the data and the complexity of the model, thereby decreasing the risk of overfitting.

Applying the point values described above, prognostic scores and an overall staging score were calculated for the

CCR data. DSS was then modeled in the CCR validation data using the same combinations of prognostic variables.

Statistical analyses were performed using R 3.2.1 (http://www.r-project.org/). The Institutional Review Boards at the MDACC and the Cancer Prevention Institute of California approved this study.

RESULTS

Clinicopathologic characteristics of the MD Anderson cohort are shown in Table 1. Median follow-up time for the cohort was 5.0 years (range 0.1–8.8 years), and the estimated 5-year DSS rate for the entire cohort was 97.9% (95% confidence interval [CI] 97.3–98.4). The results of univariate and multivariate analyses for clinicopathologic factors associated with DSS, as well as points assigned for each predictor, are shown in Table 2. DSS, the C-index, and AIC for each proposed staging system are shown in Fig. 1. The two staging systems that included grade, ER status, and HER2 status had the highest C-indexes (0.813 for PS + G + E + H and 0.811 for T + N G + E + H) and the lowest AIC (993.9 for PS + G + E + H and 986.6 for T + N + G + E + H), indicating that the addition of the biologic factors of grade, ER status, and HER2 status to anatomic factors facilitates improved stratification with respect to DSS. The estimated 5-year DSS determined using the AJCC PS ranged from 79.5 to 99.1%. In comparison, the estimated 5-year DSS rates determined using the PS + G + E + H system (Bioscore) ranged from 33.3 to 100%. The 5-year DSS outcomes by PS and Bioscore are shown in Table 3.

Electronic Supplementary Table 1 shows the clinicopathologic characteristics of the California breast cancer patient cohort. The median follow-up time for this cohort was 5.3 years (range 0.0–9.0 years) and the estimated 5-year DSS was 94.9% (95% CI 94.7–95.1). In this external cohort, the addition of biologic tumor characteristics again facilitated stratification with respect to DSS compared with PS alone (Fig. 2; Electronic Supplementary Table 2).

TABLE 1 Clinicopathologic factors for the MD Anderson Cancer Center cohort ($N = 3327$)

Variable	No. of patients (%)
Age (years)	
Mean	58
Median (range)	57 (25–99)
Pathologic T stage	
T1	2013 (60.5)
T2	1125 (33.8)
T3	189 (5.7)
Pathologic N stage	
N0	2230 (67.1)
N1mic	180 (5.4)
N1	726 (21.8)
N2	123 (3.7)
N3	65 (2.0)
Pathologic stage	
I (A and B)	1602 (48.1)
IIA	999 (30.0)
IIB	467 (14.1)
IIIA	194 (5.8)
IIIC	65 (2.0)
ER status	
Positive	2901 (87.2)
Negative	426 (12.8)
PR status	
Positive	2491 (74.9)
Negative	836 (25.1)
HER2 status	
Positive	306 (9.2)
Negative	3021 (90.8)
Nuclear grade	
1	482 (14.5)
2	1815 (54.5)
3	1030 (31.0)
Adjuvant chemotherapy	
No	1651 (50.4)
Yes	1624 (49.6)
Adjuvant hormonal therapy	
No	612 (18.8)
Yes	2648 (81.2)

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

DISCUSSION

The goals of the AJCC staging system include providing prognostic information for patients and facilitating a common language for physicians to communicate regarding a patient's disease. The 7th edition of the AJCC system relied only on anatomic factors, including primary tumor size and the presence or absence of lymph node or distant metastases. While anatomic factors are important in informing prognosis and guiding treatment options for breast cancer patients, biologic factors are routinely assessed and used to guide treatment decisions. Despite the widespread acceptance that biologic factors therefore impact prognosis, the expert panel convened to develop the AJCC 8th edition found limited published data quantifying that impact, thus making it difficult to incorporate biologic factors into the staging system based on a lack of evidence. To address that, in this study we have shown that incorporation of the biologic factors of grade, ER status, and

TABLE 2 Univariate and multivariate analyses for clinicopathologic factors associated with DSS in the MD Anderson Cancer Center cohort

Factor	5-year DSS (%)	Univariate analysis		Multivariate analysis 1		Multivariate analysis 2		Points assigned
		HR	*p* value	HR	*p* value	HR	*p*-value	
Pathologic T stage								
T1	98.9	Referent		Referent				0
T2	95.9	4.3	<0.0001	2.5	0.001			1
T3	95.5	4.3	0.001	2.5	0.04			1
Pathologic N stage								
N0	98.7	Referent		Referent				0
N1mic	98.9	0.4	0.4	0.4	0.3			0
N1	97.1	1.9	0.03	1.4	0.3			0
N2	93.7	5.8	<0.0001	4.6	<0.0001			2
N3	79.5	16.2	<0.0001	8.6	<0.0001			3
Pathologic stage								
I (A and B)	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
ER status								
Positive	98.8	Referent		Referent		Referent		0
Negative	92.9	4.9	<0.0001	2.5	0.001	2.5	0.001	1
PR status								
Positive	98.8	Referent		Referent		Referent		
Negative	95.2	4.0	<0.0001		NS		NS	
HER2 status								
Positive	97.5	Referent		Referent		Referent		0
Negative	98.0	0.8	0.5	2.2	0.03	2.2	0.04	1
Nuclear grade								
1	99.8	Referent		Referent		Referent		0
2	98.9	5.0	0.1	4.2	0.2	4.0	0.2	0
3	95.3	25.0	0.001	13.8	0.01	13.0	0.01	1

DSS disease-specific survival, *HR* hazard ratio, *ER* estrogen receptor, *PR* progesterone receptor, *NS* non-significant, *HER2* human epidermal growth factor receptor

HER2 status allows for refined stratification with respect to DSS for breast cancer patients treated with surgery as an initial intervention. Although the 8th edition of the AJCC staging did not formally incorporate the Bioscore, based on these and other data, the 8th edition of the breast cancer staging system, published in October 2016, includes an unchanged anatomic stage, as well as a prognostic stage that incorporates biologic factors.[1,10]

In a previous study defining a staging system incorporating biologic factors in patients who underwent surgery as the initial intervention, we evaluated 3728 patients treated between 1997 and 2006, and showed that incorporating grade and ER status, along with PS, defined a staging system that was more precise with respect to determining DSS than PS alone.[6] A limitation of this previous work was that it pre-dated the routine use of trastuzumab in patients with HER2-positive breast cancer. Multiple studies have shown that overexpression or amplification of HER2 in the primary tumor is associated with a worse prognosis in untreated patients,[11,12] and that treatment with trastuzumab improves outcomes in the metastatic, adjuvant and neoadjuvant settings.[13–21] The Bioscore can range from 0 to 7 points, with points assigned based on AJCC PS, grade, ER status, and HER2 status. A lower score is associated with improved DSS. Patients with HER2-positive tumors do not receive any points assigned for that variable, whereas patients with HER2-negative disease have one point assigned, reflecting that they are not expected to

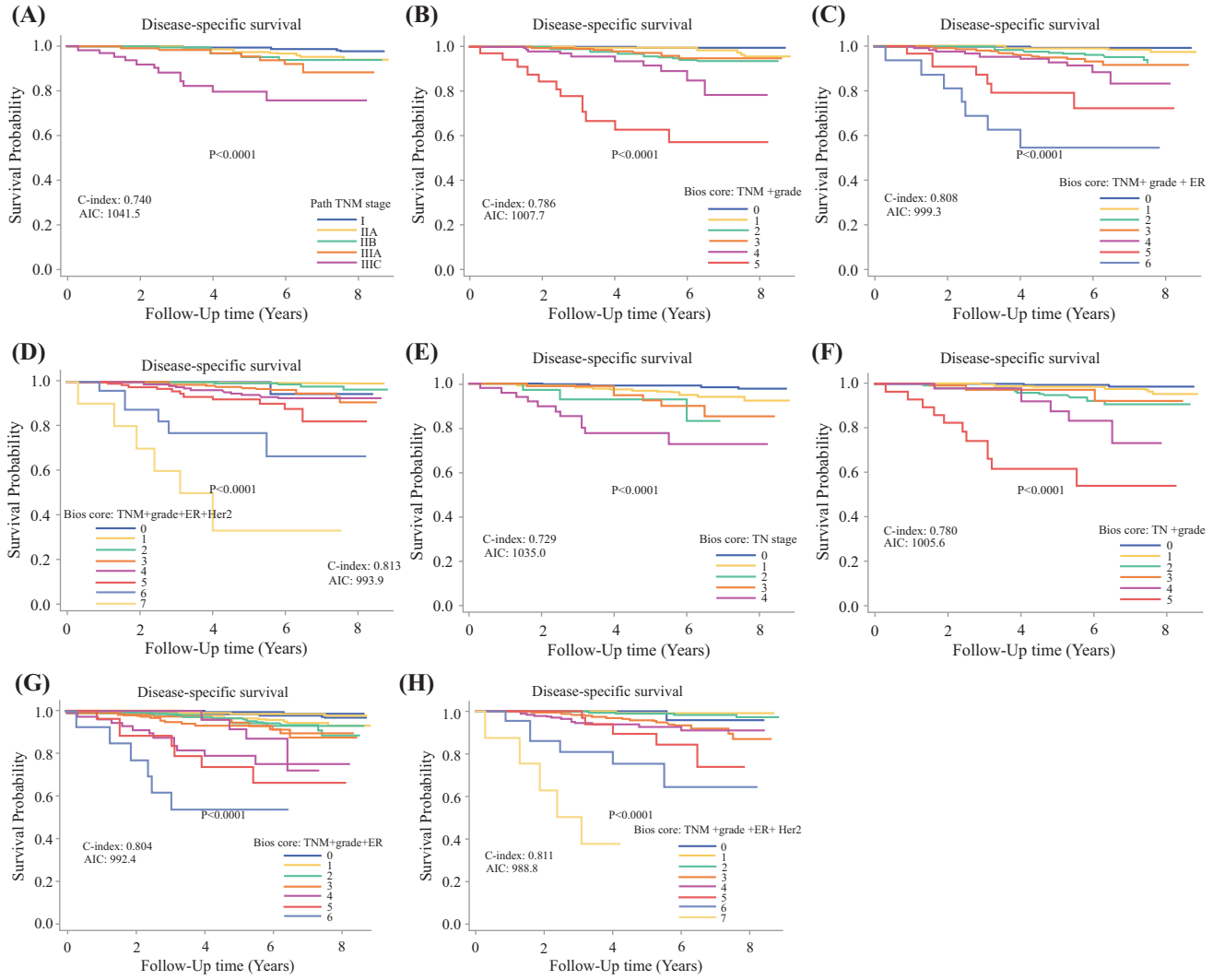

FIG. 1 Kaplan–Meier survival plots with risk tables showing the association between different staging systems and disease-specific survival in breast cancer patients treated at the MD Anderson Cancer Center, with surgery as the first intervention. **a** American Joint Committee on Cancer pathologic stage (PS); **b** pathologic stage plus grade (PS + G); **c** pathologic stage plus grade plus estrogen receptor status (PS + G + E); **d** pathologic stage plus grade plus estrogen receptor status plus HER2 status (PS + E + G + H); **e** T (T stage) + N (N stage); **f** T stage plus N stage plus grade (T + N + G); **g** T stage plus N stage plus grade plus estrogen receptor status (T + N + G + E); **h** T stage plus N stage plus grade plus estrogen receptor status plus HER2 status (T + N + G + E + H). The log-rank test is shown for each comparison. *C-index* Harrell's concordance index, *AIC* Akaike Information Criterion, *PS* pathologic stage, *G* grade, *E* ER status, *H* HER2 status, *T* T stage, *N* N stage, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor

TABLE 3 Five-year DSS outcomes by pathologic stage and Bioscore

Pathologic stage	DSS, % (95% CI)	Bioscore	DSS, % (95% CI)
I (A and B) ($n = 1602$)	99.1 (98.5–99.5)	0 ($n = 36$)	100
IIA ($n = 999$)	98.0 (96.5–98.8)	1 ($n = 1204$)	99.4 (98.8–99.8)
IIB ($n = 467$)	95.6 (92.3–97.5)	2 ($n = 919$)	99.2 (98.0–99.7)
IIIA ($n = 194$)	95.4 (89.7–98.0)	3 ($n = 667$)	97.2 (95.2–98.4)
IIIC ($n = 65$)	79.5 (65.6–88.2)	4 ($n = 339$)	94.2 (90.1–96.7)
		5 ($n = 129$)	92.0 (84.5–96.0)
		6 ($n = 23$)	77.3 (53.6–89.9)
		7 ($n = 10$)	33.3 (6.3–64.6)

DSS disease-specific survival, *CI* confidence interval

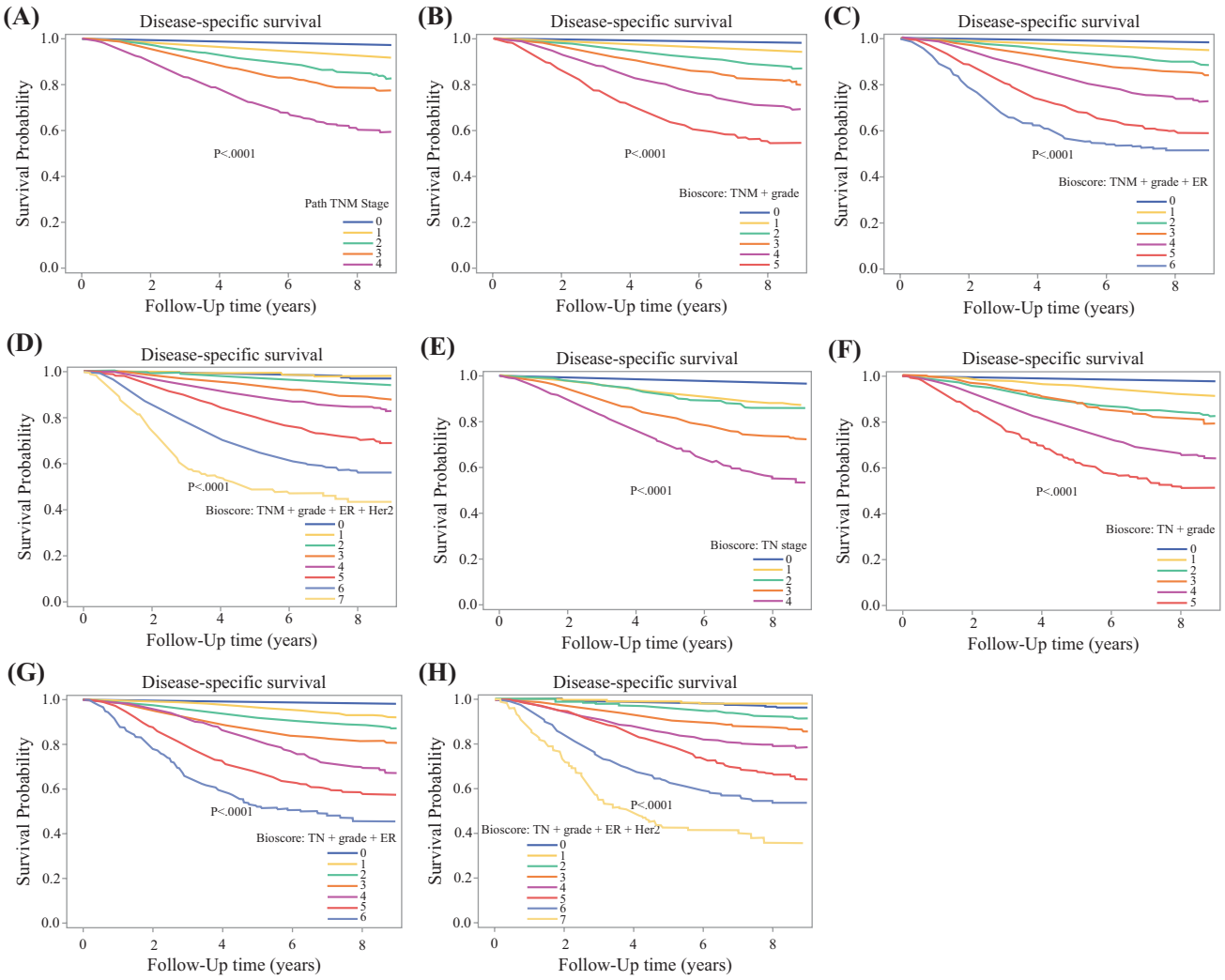

FIG. 2 Kaplan–Meier survival plots with risk tables of disease-specific survival for patients in the external validation cohort from the California Cancer Registry. **a** American Joint Committee on Cancer pathologic stage (PS); **b** pathologic stage plus grade (PS + G); **c** pathologic stage plus grade plus estrogen receptor status (PS + G + E); **d** pathologic stage plus grade plus estrogen receptor status plus HER2 status (PS + E + G + H); **e** T stage (T) + N stage (N); **f** T stage plus N stage plus grade (T + N + G); **g** T stage plus N stage plus grade plus estrogen receptor status (T + N + G + E); **h** T stage plus N stage plus grade plus estrogen receptor status plus HER2 status (T + N + G + E + H). The log-rank test is shown for each comparison. *PS* pathologic stage, *G* grade, *E* ER status, *H* HER2, *T* T stage, *N* N stage, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2

benefit from trastuzumab therapy. Similarly, patients with ER-negative tumors receive one point, reflecting that they are not expected to benefit from administration of adjuvant endocrine therapy. Current ASCO guidelines recommend using biomarkers, specifically ER and HER2, to guide adjuvant therapy decisions.[4] The Bioscore accounts for this clinical management of breast cancer to provide accurate prognostic information for patients treated with regimens targeting the underlying biology of their breast cancer.

The cohort used to define the Bioscore was from a single academic center and, although not all patients adhered to treatment recommendations, all patients with HER2-positive breast cancer received trastuzumab, and all patients with HR-positive disease were advised to take endocrine therapy, with over 90% accepting that recommendation. However, the fact that the Bioscore was developed at a single center represents one limitation of this study. Specifically, the majority of patients seen at MD Anderson during the study period with higher stage (stage III) disease, triple-negative breast cancer, or HER2-positive breast cancer received neoadjuvant chemotherapy and are therefore not included in the current cohort. This is reflected in the very favorable 5-year DSS rate of 98% for the entire cohort. In addition, 85% of patients in the MD Anderson cohort had a Bioscore of 0–3, with a corresponding 5-year DSS of >97%, and 65% had a Bioscore ranging from 0 to

2, with a corresponding 5-year DSS of >99%. Fewer patients had higher-stage disease or triple-negative tumors. However those patients did have higher Bioscores with worse prognosis, further supporting the concept of biologic factors providing additional, important information with respect to prognosis. Our group has also published a staging system, the Neo-Bioscore, which incorporates presenting clinical stage, final PS, grade, ER status, and HER2 status to provide prognostic information for patients receiving neoadjuvant chemotherapy.[22]

Importantly, the Bioscore was validated with a cohort of 67,944 patients from the CCR, suggesting broad applicability. When compared with the MD Anderson cohort, the CCR cohort had a higher percentage of patients with ER-positive and HER2-negative tumors. These patients would be more likely to have a lower Bioscore. Therefore, in addition to confirming excellent separation of the curves for high-risk patients with Bioscores of 5, 6, or 7, as was seen in the MD Anderson cohort, the data from the CCR also showed excellent separation of the curves for Bioscores of 0–4, suggesting utility in also stratifying these lower-risk patients.

While the Bioscore represents a significant improvement over PS alone with respect to providing prognostic information, it too has limitations. In patients with the most favorable tumor biology, ER-positive tumors, and HER2-negative tumors, which are node negative, the most recent ASCO guidelines state that there is sufficient evidence of clinical utility for biomarker assays, including Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1.[4] Using Oncotype DX as an example, studies performed on archival tumor samples showed that this assay provides prognostic information independent of other clinicopathologic features, and that the Oncotype DX recurrence score predicts benefit from chemotherapy.[23,24] More recently, an initial report from a prospective trial evaluating the assay in HR-positive, HER2-negative, node-negative patients, showed that in patients with a recurrence score of < 11 who received endocrine therapy alone, the 5-year invasive DFS rate was 93.8%, thereby providing additional evidence of the clinical utility of the assay.[25] Based on these data, the 8th edition prognostic stage categorizes any patient with a T1-2N0, ER-positive, HER2-negative tumor and a recurrence score <11 as stage IA disease. With respect to the Bioscore, it is possible that two patients with ER-positive tumors that are the same grade and PS could have different Oncotype DX recurrence scores, and could suggest different treatment recommendations as well as a different prognosis, despite the same Bioscore. Data regarding the Oncotype DX score for patients included in the current study were not available for analysis, therefore it is uncertain whether that data were used to inform adjuvant chemotherapy decisions. Future work could address the use of Oncotype DX, or other genomic assays, to further refine the Bioscore for patients with ER-positive, HER2-negative, node-negative breast cancer.

CONCLUSIONS

We would suggest that data from the current study support the recent modification of the AJCC staging system for breast cancer to include biologic features. The addition of grade, ER status, and HER2 status as biologic modifiers to the AJCC staging system for breast cancer will facilitate more refined information regarding prognosis, therefore allowing the staging system to retain its utility in clinical practice. A staging system based on anatomic factors alone limits the ability to fully understand prognosis or make treatment decisions, therefore failure to modify by incorporating biologic factors risks would have rendered the AJCC staging system obsolete.

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