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Breast Cancer

Evaluation of the Incorporation of Recurrence Score into the American Joint Committee on Cancer Eighth Edition Staging System in Patients with T1-2N0M0, Estrogen Receptor-Positive, Human Epidermal Growth Receptor 2-Negative Invasive Breast Cancer: A Population-Based Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast malignancy • Tumor staging • Prognosis • Multigene assay

Abstract

Background. The current study aimed to evaluate the predictive performance of the American Joint Committee on Cancer eighth edition staging system in patients with invasive breast cancer based on the Surveillance, Epidemiology, and End Results database.

Subjects, Materials, and Methods. Patients diagnosed with T1-2N0M0, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer from 2010 to 2014 were retrospectively recruited in this analysis. Patients were reassigned to different stages according to the anatomic staging system (AS), prognostic staging system (PS), and prognostic and genomic staging criteria downstaging patients with recurrence score (RS) lower than 11 (PGS_RS11). Cox models were conducted for multivariate analyses, and likelihood ratio (LR) χ^2, Akaike information criterion (AIC), and Harrell's concordance index (C-index) were calculated for the comparison of different staging systems. Additionally, adjustments were made to generate prognostic and genomic staging criteria downstaging patients with RS lower than 18 (PGS_RS18) and RS lower than 25 (PGS_RS25).

Results. PGS_RS11 was an independent predictor for breast cancer-specific survival, as were PS and AS. Adjusted for age and ethnicity, PGS_RS11 (AIC = 2,322.763, C-index = 0.7482, LR χ^2 = 113.17) showed superiority in predicting survival outcomes and discriminating patients compared with AS (AIC = 2,369.132, C-index = 0.6986, LR χ^2 = 60.80) but didn't outperform PS (AIC = 2,320.992, C-index = 0.7487, LR χ^2 = 114.94). The predictive and discriminative ability of PGS_RS18 was the best (AIC = 2297.434, C-index = 0.7828, LR χ^2 = 138.50) when compared with PS and PGS_RS11.

Conclusion. PGS_RS11 was superior to AS but comparable with PS in predicting prognosis. Further validations and refinements are needed for the better incorporation of RS into staging systems. ***The Oncologist*** 2019;24:e1014–e1023

Implications for Practice: Staging systems are of critical importance in informing prognosis and guiding treatment. This study's objective was to evaluate the newly proposed staging system in the American Joint Committee on Cancer eighth edition staging manual, which combined biological and genomic information with the traditional TNM classification for the first time to determine tumor stages of breast cancer. The superiority of the prognostic and genomic staging system was validated in our cohort and possibly could encourage the utility of genomic assays in clinical practice for staging assessment and prognosis prediction.

Introduction

Cancer staging systems are of critical importance in precisely defining prognosis and effectively guiding management. With regard to breast cancer, the American Joint Committee on Cancer (AJCC) system is the most widely used classification

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system. To predict disease prognosis and treatment response with more accuracy, regular revisions have been made to the existing staging system with the constant evolution of knowledge in tumor biology [1]. Most recently, the eighth edition of the AJCC Cancer Staging Manual was released and implemented in all newly diagnosed cases after January 2018 [2].

The major change in the eighth edition AJCC staging system for breast cancer was the introduction of a "prognostic staging system" incorporating biological features such as estrogen receptor (ER) and progesterone receptor (PR) expression, human epidermal growth receptor 2 (HER2) status, and tumor grade to the classic staging system based on the primary tumor size (T), the lymph node status (N), and the presence or absence of distant metastasis (M) [3, 4]. Over the past decades, tumor biology has been proved to have a dramatic impact on the disease prognosis, recurrence patterns, and therapeutic plans [5–10]. However, the historical TNM staging system was restricted to the anatomic characteristics of the disease without accounting for the prognostic value of biomarkers. Accordingly, this update integrated both anatomic and biological factors into one staging system to refine the prognostic information and help the decision-making of the stage-specific therapeutic strategy.

The eighth edition AJCC staging system also included the genomic prognostic panel, namely, 21-gene assay (Oncotype DX Recurrence Score; Genomic Health, Redwood City, CA), into the new classification system. The prognostic and predictive value of the 21-gene recurrence score (RS) has been constantly validated and refined over the past years [11–14]. Based on the currently reported results of the Trial Assigning Individualized Options for Treatment (TAILORx), an RS of 0 to 10 was recognized as a low-risk RS [14]. The eighth edition AJCC staging system recommended the combination of 21-gene RS, if available, into the prognostic staging system for patients with T1-2N0M0, ER-positive, and HER2-negative tumors, and the major impact of the introduction of RS lay in downstaging these biologically low-risk patients into stage IA if the RS was less than 11 [4].

To the best of our knowledge, the prognostic staging system in conjunction with RS has not yet been validated in any study. The prognostic staging system has been validated in prior series, but those studies did not focus on the incorporation of RS [15–20]. Moreover, few studies performed the validation and comparison among the three staging systems to determine the most useful classification criteria for patients. Therefore, the objective of our study is to validate the prognostic significance of the AJCC eighth edition prognostic system incorporating RS, named the prognostic and genomic staging system (PGS) for conciseness, and to evaluate the incorporation of RS in the staging system by comparisons with anatomic staging (AS) and prognostic staging system (PS) in patients with T1-2N0M0 ER-positive and HER2-negative diseases.

Subjects, Materials, and Methods

Data Source and Study Cohort

This retrospective study reviewed data from the Surveillance, Epidemiology, and End Results (SEER) database, which represents 28% of the U.S. population. The selection of study cohort used SEER data from 2010 to 2014, owing to that the HER2 status was not routinely recorded until 2010 in the database.

Patients fitting the following inclusion criteria were included in the analysis: (a) female patients with microscopically confirmed diagnosis of primary invasive breast cancer, identified based on International Classification of Diseases for Oncology, Third Revision category of "breast" and (b) surgically treated patients diagnosed with T1-2N0M0, ER-positive, and HER2-negative diseases from 2010 through 2014.

Patients without complete information of biomarkers including tumor grade, ER, PR, HER2 status, and RS were excluded. Patients with a history of prior malignancy or those diagnosed by death certificate or autopsy only were further excluded from the analysis. A total of 31,575 patients were included in the final study cohort.

Data obtained from SEER for each patient included the following: age at diagnosis, race, pathological characteristics including tumor size, lymph node involvement, and histological subtype, biological features including status of hormone receptor and HER2, tumor grade, and basic treatment information such as surgery type, radiation therapy, and chemotherapy. The RS was also obtained on our request.

The definitions of ER, PR, and HER2 positivity were defined as recommended by American Society of Clinical Oncology/College of American Pathologists guidelines [21, 22]. ER and PR expression were determined by immunohistochemistry and were defined as positive if more than 1% of cells were stained [21]. The HER2 status was considered to be positive if 3+ on immunohistochemistry or gene amplification confirmed by in situ hybridization [22]. Patients were stratified into risk groups according to traditional RS cutoffs (<18 [low], 18–30 [intermediate], >30 [high]) as well as TAILORx RS cutoffs (<11 [low], 11–25 [intermediate], >25 [high]).

Patients were restaged according to a different classification system proposed in the eighth edition of the AJCC staging manual. AS was solely based on TNM. PS incorporated biological factors including tumor grade, ER, PR, and HER2 status beyond classical anatomic factors. PGS further incorporated genomic assays. With regard to PGS with RS <11 (PGS_RS11), patients with low-risk RS (RS <11) were downstaged to stage IA on the basis of prognostic stage.

Two other modified PGSs were proposed and analyzed to explore the refinements of PGS. Eighteen and twenty-five were determined as the RS cutoffs to filter patients who needed to be downstaged to stage IA according to the traditional RS cutoffs from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 [23, 24] as well as the recent released findings of TAILORx [13, 14]. PGS with RS <18 (PGS_RS18) reassigned patients with a traditional low-risk RS (RS <18), instead of TAILORx low-risk (RS <11), to stage IA. Prognostic and genomic stage with RS ≤25 (PGS_RS25) was generated by redistributing patients with a TAILORx low- or intermediate-risk RS (RS ≤25) to stage IA.

Statistical Analysis

Breast cancer-specific survival (BCSS) was computed from the time of diagnosis of breast cancer to the time of death from breast cancer, and patients who died of other causes or who were still alive at last follow-up were censored.

Overall survival (OS) was computed from the time of diagnosis of breast cancer to the time of death of any cause, and patients who were still alive at last follow-up were censored.

Survival was estimated by Kaplan-Meier method and compared using the log-rank test. A univariate Cox proportional hazards model was used to identify factors related to BCSS, and corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A multivariate Cox proportional hazards model adjusted for age and race was used to calculate Akaike information criterion (AIC) and Harrell's concordance index (C-index) to assess the predictive ability of each staging model. A lower AIC value would reflect a better model for predicting outcomes, and a higher C-index value would indicate better concordance of survival times [25, 26]. Additionally, the likelihood ratio (LR) test was used to compare the LR values (LR χ^2) of different Cox models when necessary. Two-tailed $p < .05$ was considered statistically significant. All the statistical analysis was performed using STATA (version 14.0; College Station, TX).

Results

Patient and Tumor Characteristics

A total of 31,575 female patients with ER-positive, HER2-negative, T1-2N0M0 invasive breast cancer diagnosed from 2010 to 2014 were included in this study. The median age of the cohort was 58 (range 18–91). Demographic and clinicopathological characteristics were summarized in Table 1. The majority of patients were of white race (82.2%). A total of 69.5% of the included patients underwent breast-conserving surgery, and 30.5% underwent mastectomy. The most common histological type was invasive ductal carcinoma (74.8%), followed by invasive lobular carcinoma (10.4%). Most patients (76.8%) presented with T1 tumors, and only 8.5% of patients had PR-negative tumors. The percentage of patients with low-, intermediate-, and high-risk RS was 58.7%, 36.7%, and 6.6%, respectively, according to the traditional RS cutoffs, whereas the percentage was 21.8%, 64.5%, and 13.7%, respectively, according to the TAILORx RS cutoffs. According to traditional RS risk groups, the percentage of patients receiving chemotherapy in low-, intermediate-, and high-risk groups was 3.5%, 32.5%, and 73.8%, respectively. According to TAILORx RS risk groups, the percentage of patients receiving chemotherapy in low-, intermediate-, and high-risk groups was 1.9%, 14.0%, and 63.8%, respectively. The rate of chemotherapy use in patients varied according to different RS risk groups ($p < .001$). Univariate analyses indicated that age at diagnosis, race, tumor size, PR status, grade, RS risk group, and the receipt of radiation and chemotherapy were associated with BCSS ($p < .05$). Details of HR and 95% CI are presented in Table 1.

Survival Outcomes in Different Staging Systems

The distribution and alternation of stage regarding different classification systems are outlined in Table 2 and supplemental online Table 1. Under AS, most patients presented with stage IA tumors (76.8%), and 23.2% of the patients had stage IIA tumors. Under PS, stage IA tumors were found to be the most common type (64.3%), followed by stage IB (27.4%), stage IIA (6.6%), stage IIB (1.1%), and stage IIIA (0.6%) tumors, as shown in Table 2. Compared with AS, 14.2% of patients were redistributed into a higher stage after applying AJCC eighth edition PS criteria. Conversely, 16.2% of patients were downstaged. Under PGS_RS11, the most frequent type were stage IA tumors (70%), followed by stage IB (22.2%), stage IIA (6.1%), stage IIB (1.1%), and stage IIIA (0.6%) tumors. Compared with AS, 13.1% of patients were redistributed into a higher stage after applying AJCC eighth edition PSG_RS11 criteria. Conversely, 16.7% of patients were downstaged. Moreover, downstaging from PS to PGS_RS11 was observed in 5.7% of patients.

With a median follow-up of 32 months (ranging 0–60), 405 cases (1.28%) were dead, with 125 cases (0.4%) having died of breast cancer. BCSS was assessed for different stages, and survival curves are illustrated in Figure 1. As listed in Table 2, there were significant differences in BCSS among different stages according to the three grouping systems ($p < .001$). In terms of AS, the 3-year BCSS and 5-year BCSS was 99.71% and 99.29% for stage IA tumors and 99.12% and 97.97% for stage IIA tumors, respectively. Under PS, the 3-year BCSS rates were 99.79% of stage IA, 99.47% of stage IB, 98.36% of stage IIA, 98.43% of stage IIB, and 97.20% of stage IIIA; the 5-year BCSS rates were 99.63% of stage IA, 98.67% of stage IB, 94.59% of stage IIA, 96.55% of stage IIB, and 86.64% of stage IIIA. According to PGS_RS11, the 3-year BCSS rates were 99.78% of stage IA, 99.40% of stage IB, 98.28% of stage IIA, 98.39% of stage IIB, and 97.20% of stage IIIA; the 5-year BCSS rates were 99.57% of stage IA, 99.02% of stage IB, 94.30% of stage IIA, 96.47% of stage IIB, and 86.64% of stage IIIA. Similar results were generated in the survival analyses conducted in patients diagnosed in 2010–2011 (supplemental online Table 2). Significant differences were observed in BCSS among different stages according to AS (log-rank χ^2 40.20, $p < .001$), PS (log-rank χ^2 145.41, $p < .001$), and PGS (log-rank χ^2 150.03, $p < .001$).

OS was also assessed for different stages, and survival curves are illustrated in Figure 2. There were significant differences among stages with respect to OS according to AS (log-rank χ^2 47.89, $p < .001$), PS (log-rank χ^2 99.93, $p < .001$), and PGS (log-rank χ^2 88.32, $p < .001$; supplemental online Table 3).

Comparisons of Different Staging Systems

Because all of three staging systems were significantly associated with both BCSS and OS in univariate analyses, multivariable Cox proportional hazards models for both BCSS and OS adjusting for age and ethnicity were performed to compare the discriminatory ability of different staging criteria. The LR χ^2, AIC, and C-index were also calculated to evaluate the performance of separate staging systems.

As described in Table 3, AS, PS, and PGS_RS11 were all independent prognostic factors for BCSS ($p < .001$). The PGS_RS11 had a higher C-index compared with AS (0.7237 vs. 0.6658, $p < .001$), indicating the superiority in predictive accuracy of survival outcome. Additionally, a lower AIC value was exhibited by PGS_RS11 (AIC = 2,335.539) compared with AS (AIC = 2,381.569), demonstrating optimistic prognostic stratification. Moreover, a larger LR χ^2 was observed in PGS_RS11 compared with AS (100.37 vs. 48.34, $p < .001$),

Table 1. Baseline characteristics of patients (*n* = 31,575) and univariate analysis for factors associated with breast cancer-specific survival

Characteristics	*n* (%)	HR (95% CI)	*p* value
Age at diagnosis, years			
≤50	8,569	ref	<.032
>50	23,005	1.63 (1.04–2.54)	
Race			
White	25,949 (82.2)	ref	
Black	2,504 (7.9)	1.99 (1.21–3.30)	.007
Other[a]	3,122 (9.9)	0.87 (0.455–1.67)	.681
Histology			
IDC	23,617 (74.8)	ref	
ILC	3,275 (10.4)	1.18 (0.73–1.90)	.437
Other	4,683 (14.8)	1.24 (0.72–3.15)	.492
Surgery			
BCS	21,933 (69.5)	ref	
Mastectomy	9,643 (30.5)	1.35 (0.94–1.94)	.104
Tumor size, cm			
≤2	24,256 (76.8)	ref	
>2	7,319 (23.2)	3.10 (2.18–4.39)	<.001
PR status			
Positive	28,882 (91.5)	ref	
Negative	2,693 (8.5)	2.17 (1.37–3.45)	.001
Grade			
1	9,370 (29.7)	ref	
2	17,085 (54.1)	1.56 (0.90–2.71)	.117
3	5,120 (16.2)	6.45 (3.76–11.06)	<.001
Anatomic stage			
IA	24,256 (76.8)	ref	
IIA	7,319 (23.2)	1.76 (1.48–2.10)	<.001
Traditional RS risk group			
Low (<18)	18,532 (58.7)	ref	
Intermediate (18–30)	10,942 (34.7)	2.39 (1.55–3.69)	<.001
High (>30)	2,101 (6.6)	9.71 (6.15–15.34)	<.001
TAILORx RS risk group			
Low (<11)	6,885 (21.8)	ref	
Intermediate (11–25)	20,353 (64.5)	0.62 (0.37–1.04)	.070
High (>25)	4,337 (13.7)	3.87 (2.37–6.30)	<.001
Radiation			
No	12,349 (39.1)	ref	
Yes	19,226 (60.9)	0.52 (0.37–0.74)	<.001
Chemotherapy			
No/unknown	25,816 (81.8)	ref	
Yes	5,759 (18.2)	2.86 (2.01–4.09)	<.001

[a]Including American Indian, Alaskan Native, Asian, and Pacific Islander.
Abbreviations: BCS, breast-conserving surgery; CI, confidence interval; HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PR, progesterone receptor; ref, reference; RS, recurrence score; TAILORx, Trial Assigning Individualized Options for Treatment.

showing better homogeneity. The PS model was comparable to the PGS_RS11 model in terms of C-index (0.7254 vs. 0.7237, $p = .873$), AIC value (2,332.555 vs. 2,335.539), and LR χ^2 (103.36 vs. 100.37). Overall, the statistical assessment of the predictive performance of the PGS_RS11 revealed that PGS_RS11 was superior to AS, whereas PGS_RS11 did not outperform PS.

After excluding 5,759 (18.2%) patients receiving chemotherapy, the predictive performances were compared again. The results showed that PGS_RS11 outperformed AS with a

Table 2. The distribution and BCSS outcomes by stage according to different staging systems

Staging system	Stage	Cases, *n* (%)	Events	3-year BCSS, %	5-year BCSS, %	Log-rank χ^2	*p* value
AS						44.20	<.001
	IA	24,256 (76.8)	65	99.71	99.29		
	IIA	7,319 (23.2)	60	99.12	97.97		
PS						154.92	<.001
	IA	203,069 (64.3)	37	99.79	99.63		
	IB	8,644 (27.4)	44	99.47	98.97		
	IIA	2,083 (6.6)	31	98.36	94.59		
	IIB	344 (1.1)	6	98.43	96.55		
	IIIA	198 (0.6)	7	97.20	86.64		
PGS_RS11						155.14	<.001
	IA	22,111 (70.0)	45	99.78	99.57		
	IB	7,000 (22.2)	37	99.40	99.02		
	IIA	1,931 (6.1)	30	98.28	94.30		
	IIB	335 (1.1)	6	98.39	96.47		
	IIIA	198 (0.6)	7	97.20	86.64		

Abbreviations: AS, anatomic staging system; BCSS, breast cancer-specific survival; PGS_RS11, prognostic and genomic staging system with RS <11; PS prognostic staging system.

larger LR χ^2 (53.40 vs. 28.62, $p < .001$) and a lower AIC (1,358.059 vs. 1,376.837; supplemental online Table 4).

According to analyses in the subgroup of patients diagnosed in 2010–2011, PGS_RS11 was superior to AS with a larger LR χ^2 (87.00 vs. 42.46, $p < .001$), a higher C-index (0.7228 vs. 0.6648, $p < .001$), and a lower AIC (1,771.559 vs. 1,810.103).

PGS_RS11 was comparable to PS with similar LR χ^2 (87.00 vs. 87.33), C-index (0.7228 vs. 0.7221, $p = .928$), and AIC (0.7228 vs. 0.7221; supplemental online Table 5).

With respect to multivariate analyses using OS as an endpoint, AS, PS, and PGS_RS11 remained independent prognostic factors ($p < .001$). PGS_RS11 showed its superiority to AS in prognosis with a higher LR χ^2 (144.68 vs. 126.14, $p < .001$) and a lower AIC (7,807.055 vs. 7,819.589; supplemental online Table 6).

PGS with Different RS Cutoffs

To explore the better incorporation of RS into the staging model, slight modifications were made to the existing prognostic and genomic staging system to propose two new systems, namely, PGS_RS18 and PGS_RS25. PGS_RS18 was generated by reclassifying patients with RS <18 into stage IA, and PGS_RS25 was generated by reclassifying patients with RS ≤25 into stage IA.

As outlined in Table 4, both newly proposed staging systems were independent prognostic factors for BCSS. Figure 3 presented the predictive performances of different staging systems. PGS_RS18 presented better concordance of survival times with the highest C-index compared with PS (0.7579 vs. 0.7254, $p = .009$) and PGS_RS11 (0.7579 vs. 0.7237, $p < .001$. Also, the lowest AIC of the PGS_RS18 reflected a slightly more accurate model predictive of BCSS than the PS and PGS_RS11 (PS, 2,332.555; PGS_RS11, 2,335.539; PGS_RS18, 2,310.541). However, the overall discrimination of the PGS_RS25 was comparable to that of the PS and the PGS_RS11 with a C-index of 0.7080 and AIC value of 2,335.379. In patients not receiving chemotherapy or without chemotherapy information, PGS_RS18 remained superior in predictive performances (Fig. 3; supplemental online Table 4).

According to analyses in the subgroup of patients diagnosed in 2010–2011, similar results were observed. Compared with PS and PGS_RS11, PGS_RS18 had the best predictive performance with the highest C-index (PGS_RS18 vs. PS, 0.7503 vs. 0.7221, $p = .012$; PGS_RS18 vs. PGS_RS11, 0.7503 vs. 0.7228, $p = .001$) and the lowest AIC ((PGS_RS18 vs. PGS_RS11 vs. PS, 1,754.956 vs. 1,771.559 vs. 1,771.238). In line with the results in the overall population, PGS_RS25 did not outperform PS and PGS_RS11 (supplemental online Table 5).

In the Cox model using OS as an endpoint, any PGS with RS cutoff of 11, 18, or 25 failed to outperform PS (supplemental online Table 6).

Discussion

With the evolving knowledge of tumor biology and multigene assays, biological features and genomic panels were validated to have prognostic and predictive values for breast cancer [7, 8, 13, 14]. Thus, the traditional TNM classification has limited value in assessing prognosis and determining therapeutic options in the era of individualized care. To address this, the eighth edition AJCC staging system recommends the incorporation of biomarkers and multigene assay into the staging system. In this population-based study, the newly proposed PGS was validated for stratifying patients with T1-2, N0 and ER-positive, HER2-negative breast cancer, and its discriminatory value was evaluated compared with AS and PS.

In our analysis including 31,575 female patients with ER-positive, HER2-negative, T1-2N0M0 invasive breast cancer diagnosed from 2010 to 2014 in the SEER database, patients with stage IA and IIA tumors under AS were reassigned to

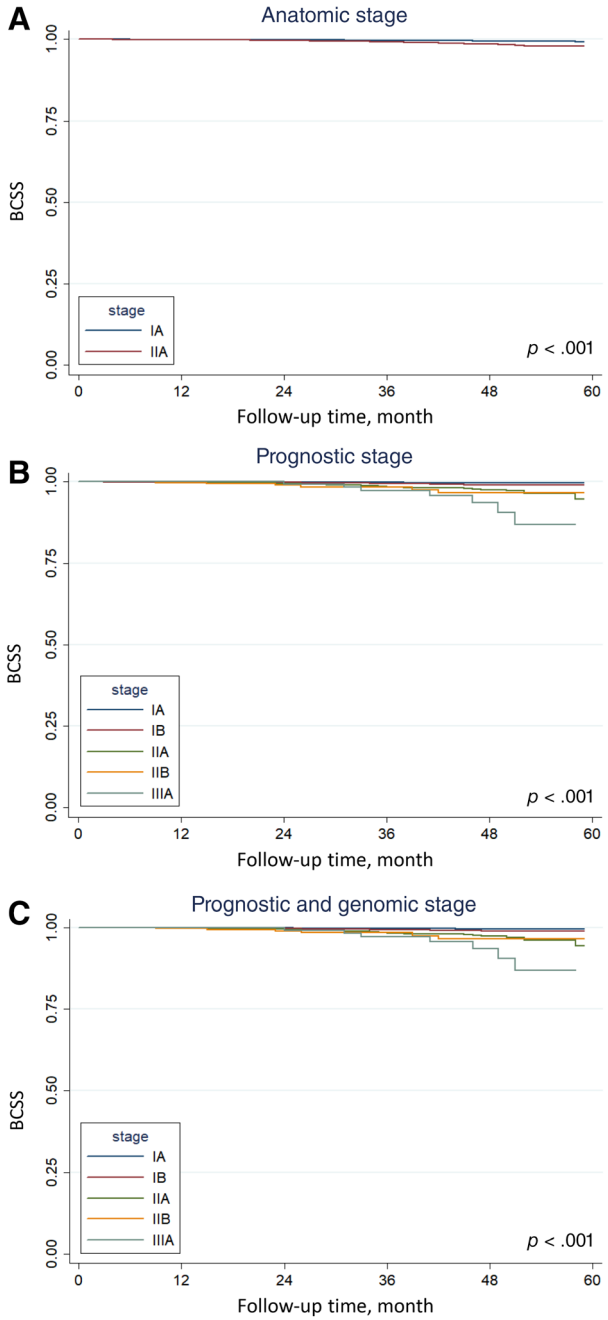

Figure 1. BCSS curves according to three staging systems. **(A):** BCSS according to the anatomic staging system. **(B):** BCSS according to the prognostic staging system. **(C):** BCSS according to the prognostic and genomic staging system with RS <11.
Abbreviation: BCSS, breast cancer-specific survival.

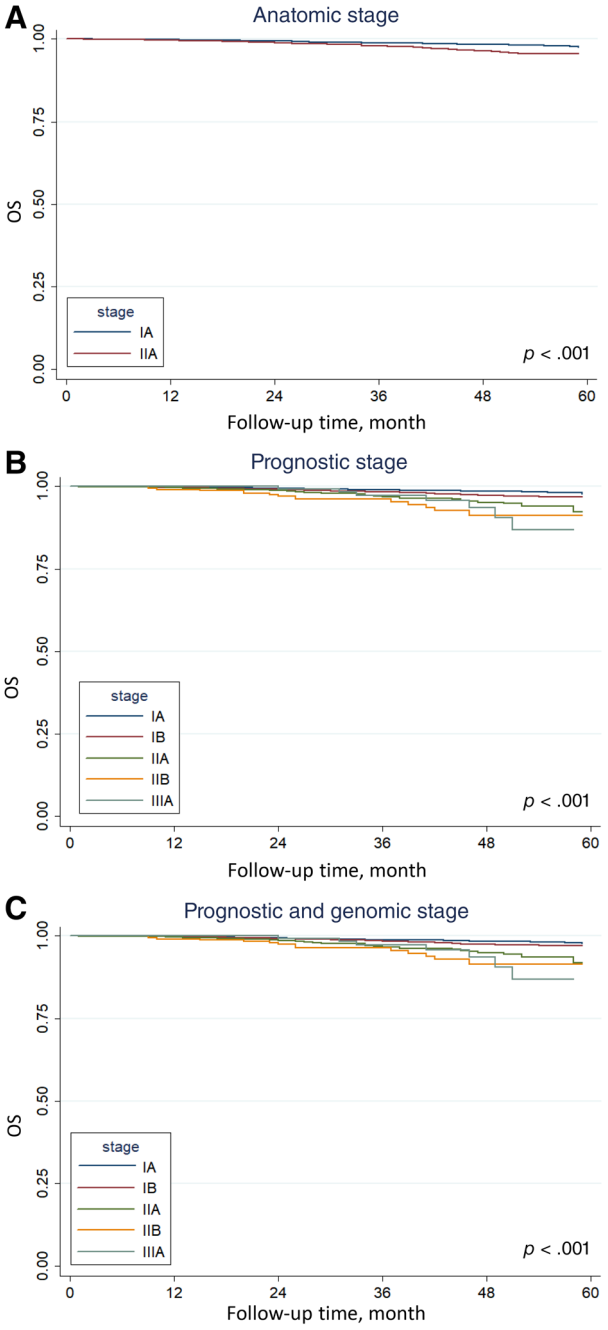

Figure 2. OS curves according to three staging systems. **(A):** OS according to the anatomic staging system. **(B):** OS according to the prognostic staging system. **(C):** OS according to the prognostic and genomic staging system with RS <11.
Abbreviation: OS, overall survival.

five different stages from stage IA to IIIA after applying PGS criteria, with 13.1% of patients upstaged and 16.7% of patients downstaged. A total of 9,398 patients (29.8%) were precisely restaged into different PGS stages. Both univariate and multivariate analysis showed that PGS could significantly predict BCSS and OS. Compared with AS, PGS also showed superiority in predicting outcomes with its lower AIC as well as higher LR χ^2 and C-index.

Several retrospective studies were undertaken to validate the AJCC eighth edition PS and had present concrete evidence of the advantages of PS in refining stratification and prognostic information [15, 16, 19, 20, 27]. For instance, Weis et al. reviewed a total of 3,327 patients with stage I to IIIC breast cancer treated between 2007 and 2013 at MD Anderson Cancer Center and identified a total of 54,727 patients with stage I to IV breast cancer treated between 2005 and 2009 in the California Cancer Registry [19]. The PS was found to be more precise in both databases [19]. Another study focused on locally advanced breast cancer (LABC) found that the PS could provide more accurate prognostic information based on the data of 10,053 LABCs diagnosed between 2010 and 2013 from the SEER database [16]. The PS also yielded

Table 3. Multivariate Cox models for breast cancer-specific survival under different staging systems

	AS model		PS model		PGS_RS11 model	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Stage						
IA	1	—	1	—	1	—
IB	/		2.76 (1.78–4.27)	<.001	2.54 (1.645–3.93)	<.001
IIA	1.75(1.47–2.09)	<.001	7.81 (4.84–12.61)	<.001	7.29 (4.59–11.58)	<.001
IIB	/		9.43 (3.96–22.44)	<.001	8.62 (3.66–20.27)	<.001
IIIA	/		18.65 (8.29–41.98)	<.001	16.59 (7.45–36.90)	<.001
Race						
White	1	—	1	—	1	—
Black	1.94 (1.17–3.21)	.010	1.75 (1.06–2.90)	.030	1.79 (1.08–2.97)	.024
Other[a]	0.82 (0.42–1.58)	.552	0.75 (0.39–1.44)	.385	0.77 (0.40–1.49)	.441
Age, years						
≤50	1	—	1	—	1	—
>50	1.60 (1.03–2.51)	.038	1.45 (0.93–2.28)	.102	1.50 (0.96–2.34)	.078
LR χ^2	48.34		103.36		100.37	
C-index	0.6658		0.7254		0.7237	
AIC	2,381.569		2,332.555		2,335.539	

[a]Including American Indian, Alaskan Native, Asian, and Pacific Islander.
Abbreviations: —, no *p* value; /, no hazard ratio; AIC, Akaike's information criterion; AS, anatomic staging system; CI, confidence interval; C-index, Harrell's concordance index; HR, hazard ratio; LR, likelihood ratio; PGS_RS11, prognostic and genomic staging system with RS <11; PS prognostic staging system.

Table 4. Multivariate Cox models for breast cancer-specific survival in newly proposed staging systems

	PGS_RS25 model		PGS_RS18 model	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Stage				
IA	1	—	1	—
IB	4.00 (2.57–6.20)	<.001	4.01 (2.37–6.80)	<.001
IIA	9.39 (5.97–14.77)	<.001	8.28 (5.15–13.32)	<.001
IIB	8.80 (3.49–22.14)	<.001	10.45 (3.81–28.67)	<.001
IIIA	17.67 (7.99–39.10)	<.001	12.28 (5.33–28.28)	<.001
Race				
White	1	—	1	—
Black	1.77 (1.07–2.94)	.026	1.84 (1.11–3.06)	.018
Other[a]	0.77 (0.40–1.47)	.425	0.78 (0.40–1.49)	.447
Age				
≤50	1		1	
>50	1.51 (0.97–2.37)	.079	1.55 (0.99–2.42)	.055
LR χ^2	125.37		100.51	
AIC value	0.7597		0.7080	
C-index	2,310.541		2,335.379	

[a]Including American Indian, Alaskan Native, Asian, and Pacific Islander.
Abbreviations: —, no *p* value; AIC, Akaike's information criterion; CI, confidence interval; C-index, Harrell's concordance index; HR, hazard ratio; LR, likelihood ratio; PGS_RS18, prognostic and genomic staging system with RS <18; PGS_RS25, prognostic and genomic staging system with RS ≤25.

improved prognostic discrimination in comparison with AS in our analyses in line with previous reports. However, previous studies did not lay much emphasis on the PGS. The current study focused on the integration of RS into the staging system and evaluated the performance of PGS for the first time. Moreover, the proposal of PS was based on the unpublished data from 238,253 patients diagnosed with breast cancer between 2010 and 2011 in the National Cancer Database, whereas the incorporation of RS into the staging system was merely supported by the low 5-year risk of recurrence of patients defined as low-risk group [4, 13]. Our findings added to the growing body of evidence that genomic assays contributed to the precise staging.

It was supposed that the superiority of PGS was due to that genomic assays provided valuable information beyond clinicopathological and pathological factors. Patients with

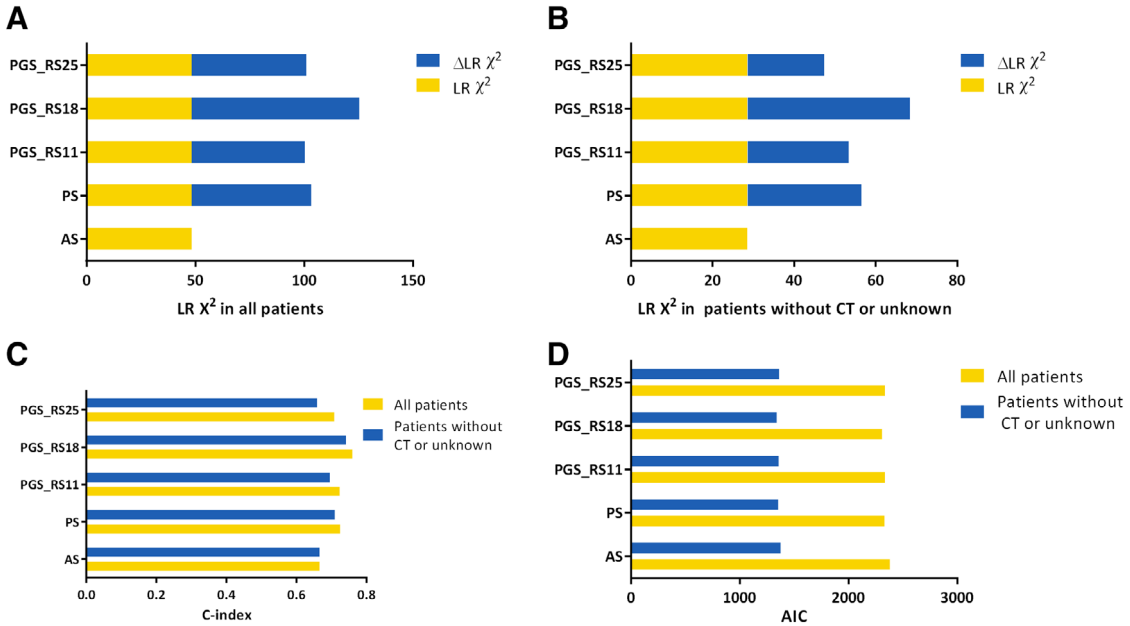

Figure 3. LR χ^2, C-indices, and AIC for different staging models. **(A):** Change in LR χ^2 of different staging models in all patients. **(B):** Change in LR χ^2 of different staging models in patients not receiving chemotherapy or without chemotherapy information. **(C):** Comparison of C-index for different staging models. **(D):** Comparison of AIC for different staging models.
Abbreviations: AIC, Akaike's information criterion; AS, anatomic staging system; C-index, Harrell's concordance index; CT, chemotherapy; LR, likelihood ratio; PGS_RS11, prognostic and genomic staging system with RS <11; PGS_RS18, prognostic and genomic staging system with RS <18; PGS_RS25, prognostic and genomic staging system with RS ≤25; PS, prognostic staging system.

genomic low risk may have good prognosis regardless of risk level evaluated by clinical risk-assignment methods. Results from the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (EORTC 10041/BIG 3-04 MINDACT) study backed up this idea. For patients enrolled in MINDACT study, the clinical risk was assessed by Adjuvant! Online, whereas the genomic risk was evaluated by 70-gene signature profile (MammaPrint). Patients deemed to have high clinical risk but low genomic risk (23.2%) were randomly assigned to the chemotherapy group and nonchemotherapy group. At 5 years, the rate of survival without distant metastasis in the nonchemotherapy group was 94.7% (1.5 percentage points lower than the rate in the chemotherapy group), indicating relatively good prognosis in these patients [28]. The results implied that genomic assay was more able to select patients with low recurrence risk who can safely omit chemotherapy. Similarly, by grading patients with low-risk RS as IA, the PGS uses the genomic tool to select patients with low genomic risk but high clinical risk and further downgrades these patients to provide the staging system with better prognostic value.

Although the statistical assessment of predictive performances revealed that PGS_RS11 is superior to AS, it failed to outperform PS. Therefore, further analyses were conducted to find out a better RS cutoff to integrate into PGS to improve its stratification accuracy. The results suggested that PGS_RS18 had better predictive performance compared with PGS_RS11 and PGS_RS25. The possible reasons may lie in the following aspects.

First, traditional RS category (low risk: RS <18) has been proved in many large retrospective analyses of prospective randomized controlled trials, and consistent results were documented that low-risk patients with RS <18 had favorable prognosis [11, 12, 23, 24, 29–31]. Second, although the previous results of TAILORx proved that patients with RS <11 had good prognosis and can omit chemotherapy safely [13], according to the latest reported results of TAILORx [14], patients with an RS score of 11 to 25 also had good prognosis with endocrine therapy alone, which was noninferior to the chemotherapy group in terms of invasive disease-free survival (iDFS). However, not all patients with an RS of 25 or lower can omit chemotherapy safely because exploration analyses of TAILORx indicated that women 50 years of age or younger with an RS of 16 to 25 would benefit from chemotherapy. In addition, for the reason that the 5-year rates of iDFS were different between patients with RS <11 (94.0%) and RS of 11–25 (92.8%), it was inappropriate to downstage patients with RS of 25 or lower into the same stage IA. Accordingly, both 11 and 25 as RS cutoffs in PGS have their imperfections in identifying patients who need to be downgraded, which may confer an explanation to the nonsuperiority in predictive performance of PGS_RS11 and PGS_RS25 found in the current study. Moreover, RS <18 had served as a low-risk RS for a long time to guide therapeutic decision making, until the results from TAILORx were reported in 2015 [13]. Patients were diagnosed with breast cancer from 2010 to 2014 in our analyses; therefore, the chemotherapy treatment decision may be mostly influenced by traditional low-risk RS, rather than TAILORx low-risk RS. In brief, questions need to be addressed on how to incorporate RS values in staging, and the utility of RS in the staging system needs further validations and refinements.

In multivariate analyses using OS as an endpoint, the results supported the main conclusion according to the analyses using BCSS that PGS was more accurate than AS in prognosis. However, the results were slightly different in the

evaluation of the modified PGS with different RS cutoffs. Neither PGS with 18 nor PGS with 25 as RS cutoff outperformed PS. We postulated that the possible reason could be that RS was not so strongly associated with OS as with BCSS. In the validation study of RS conducted in patients enrolled in NSABP B14 and B20 trial, the primary endpoint was freedom from distant recurrence [23, 24]. Additionally, the results in TAILORx showed that between patients with RS <11 and patients with RS of 11–25, the rate of iDFS at 5 years varied (94.0% vs. 92.8%) whereas the rates of OS at 5 years are similar (98.0% vs. 98.0%) [14]. Possibly, RS was not so sensitive to predict OS. Furthermore, the previous study indicated that RS was more related to early recurrence in years 0–5 but was only weakly prognostic in the late follow-up period [32].

In the era of individualized treatment, the combination of multigene panels to staging systems is of vital importance but is a complex issue. First, the AJCC eighth edition only mentioned the downstaging of low-risk patients to stage IA. It remains unknown whether upstaging is necessary for patients with low clinical risk but high genomic risk. Second, the downstaging was restricted in node-negative patients in this update. The data of ongoing clinical trials, which aimed to investigate the use of Oncotype Dx RS for limited node-positive patients, may support the integrating of RS in patients with node involvements. Finally, other genomic assays may be incorporated into the staging system in the future. To summarize, with the evolving knowledge of multigene assays, the prognostic and genomic staging required continuous improvements.

Limitations of our study were as follows. First, this study was conducted on the basis of retrospective analysis, and despite the large number of patients that were included, intrinsic defects exist in any retrospective study. Another limitation lay in the lack of detailed treatment information. The prognostic staging system was proposed on the patient populations who received appropriate treatment, including endocrine therapy, systemic chemotherapy, and targeted therapy. Our study focused on ER-positive, HER2-negative, and node-negative patients, whereas the endocrine therapy information was unavailable and the chemotherapy information was inadequate in the SEER database. In addition, patients having systemic therapy before surgery cannot be excluded because of the limited neoadjuvant treatment information. But the influence was assumed to be slight and acceptable for the reason that patients included in our analyses with luminal-like breast cancer and RS scores were less likely to receive neoadjuvant therapy. Furthermore, it has been acknowledged that women with HR-positive breast cancer remain at risk even after 5-year initial endocrine treatment [8, 33, 34]. Because the majority of tumors in our study population were considered to be "luminal," long-term follow-up and outcome data will be essential. HER2 status was not routinely recorded in the SEER database until 2010, so only patients diagnosed between 2010 and 2014 were identified in our study, leading to a relatively short follow-up.

Conclusion

This population-based retrospective analysis showed the obvious superiority of the AJCC eighth edition prognostic and genomic staging system compared with the anatomic staging system. But the discriminatory ability of PGS was comparable to that of the prognostic staging system. The prognostic and genomic staging system needs further improvements and validations.

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Disclosures

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