

Validation of the Prognostic Stage from the American Joint Committee on Cancer 8th Staging Manual in Luminal B-Like Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer

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Purpose: The 8th edition American Joint Committee on Cancer (AJCC) prognostic staging system (PS) has been validated numerous times; however, the prognostic value of PS for breast cancer based on molecular subtype has rarely been explored. This study aimed to investigate the prognostic value of PS in Chinese patients with luminal B-like human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

Methods: A total of 407 eligible cases were included in the study. All of the cases were restaged using the 8th edition AJCC Anatomic Staging System (AS) and PS. The Kaplan–Meier method was used to calculate estimated survival and the Log rank test was used to compare the survival differences between groups.

Results: The 5-year disease-specific survival (DSS) and overall survival (OS) rates were 90.3% and 93.5%, respectively, and there were statistically significant differences in the 5-year DSS and 5-year OS rates among the different anatomic and prognostic stage groups. The application of the PS resulted in the assignment of 215 (52.8%) patients to a different group. Different prognostic stage groups restaged from anatomic Stage III had significant differences in both DSS ($\chi^2 = 4.366$, $p = 0.037$) and OS ($\chi^2 = 7.549$, $p = 0.006$); additionally, different prognostic stage groups from the anatomic Stage II group had significant differences in DSS ($\chi^2 = 7.724$, $p = 0.021$) but no significant differences in OS ($\chi^2 = 5.182$, $p = 0.075$). However, different prognostic stage groups from anatomic Stage I had no significant differences in either DSS ($\chi^2 = 0.159$, $p = 0.690$) or OS ($\chi^2 = 0.099$, $p = 0.753$).

Conclusion: The 8th edition AJCC PS refined the anatomic stage grouping in luminal B-like HER2-negative breast cancer and could lead to a more personalized approach to breast cancer treatment.

Keywords: breast cancer, staging system, prognosis, survival outcome, human epidermal growth factor receptor 2

Introduction

Recently, the International Agency for Research on Cancer (IARC) reported the GLOBOCAN 2020 estimates of cancer incidence, and for the first time, breast cancer surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases in 2020, accounting for 11.7% of all newly diagnosed breast cancers.¹ Anatomic factors, including primary tumour (T), regional lymph node involvement (N) and distant metastasis (M), have always been the most important prognostic predictors for patients with cancer, and the anatomic staging system (AS), incorporating the anatomic factors T, N and M, has always been used to guide decisions regarding whether to apply systemic therapy.

However, evolving knowledge about breast cancer biology and the increased validation of biomarkers for prognosis suggest that biomarkers of prognostic attributes such as oestrogen receptor (ER), progesterone receptor (PR), HER2 and histological grade (HG) should also be considered elements of staging in cancer.²⁻⁵ Therefore, the 8th edition AJCC staging system incorporated the prognostic biomarkers ER, PR, HER2 and HG, and multigene assays when available to form the prognostic staging system (PS). Since the publication of the 8th edition AJCC staging system, the PS has repeatedly been validated and proved superior to the AS in Western⁶⁻⁹ and Asian populations.^{10,11} Nevertheless, the prognostic value of PS for breast cancer based on molecular subtype has rarely been explored. Therefore, we conducted this retrospective study and survival analysis to provide further insight into how breast cancer stages changed between AS and PS and to evaluate how restaging affected the prognosis in Chinese luminal B-like HER2-negative breast cancer patients.

Patients and Methods

Patients Selection

The study was approved by the Ethics Committee of Ningbo Medical Center Lihuli Hospital (NMCLH) and conducted in accordance with the Declaration of Helsinki. All of the patients provided written informed consent before they were included in the study. Patients who met the following inclusion criteria were identified as potentially eligible participants: (1) female sex; (2) pathological diagnosis of primary invasive ductal breast cancer (IDC); (3) absence of distant metastasis; (4) and radical mastectomy or breast-conserving surgery (BCS) as a surgical treatment. Adjuvant therapies, including chemotherapy, endocrine therapy and radiation therapy, were appropriately applied according to local guidelines. The exclusion criteria were as follows: (1) inflammatory breast cancer or bilateral breast cancer; (2) incomplete information about clinicopathological characteristics and survival data; (3) and receiving neoadjuvant chemotherapy or neoadjuvant endocrine therapy. Patients were followed up quarterly over the first 2 years, biannually for 2 to 5 years and then annually.

Data Collection and Definitions

Clinicopathological information was collected and reviewed with patient age, menstrual status, educational background, tumour size, axillary lymph node status, tumour laterality, ER, PR, HER2, Ki67 index and HG. According to the 2013 St. Gallen Consensus, luminal B-like HER2-negative tumours were defined as ER positive, HER2 negative, and at least one of the following: (1) Ki67 >14%; (2) PR negative or low PR expression; (3) and high recurrence risk based on multigene-expression assay (if available).¹² The cut-off point of PR expression was 20%, indicating that less than 20% of PR expression was defined as low expression. In addition, multigene expression assay is routinely unavailable in China; therefore, in this study, luminal B-like HER2-negative breast cancer included two categories: (1) ER positive, any PR status, HER2-negative, and Ki-67 >14%; or (2) ER positive, PR positive (<20% expression), HER2-negative, and any Ki-67 index.

ER and PR assays were considered positive if immunostaining was seen in more than 1% of tumour nuclei.¹³ Additionally, less than 20% PR expression was defined as low expression.¹² HER2 positivity was defined as either IHC3+ or gene amplification by fluorescence in situ hybridization (FISH) if IHC2+.¹⁴ Thus, in our study, IHC1+ or IHC (-) or no gene amplification by FISH was defined as HER2 negativity. The Nottingham combined histological grade¹⁵ was adopted in our study. The grade was determined by assessing three morphologic features (nuclear pleomorphism, tubule formation, and number of mitotic figures). A score of 1 (favourable) to 3 (unfavourable) was given for each feature, and the scores were totalled. A combined score of 3 to 5 was designated as grade 1 (G1); 6 to 7 as grade 2 (G2); and 8 to 9 as grade 3 (G3).

Restaging and Survival Analysis

All of the included cases were restaged using the 8th edition AJCC PS.¹⁶ The AS was based on the anatomic extent of cancer as defined by the tumour (T), node (N), and metastasis (M) categories; while with the PS, any prognostic stage should be comprehensively assessed by using anatomic T, N, and M and status (positive or negative) of the biomarkers ER, PR, HER2 and tumour grade.

Disease-specific survival (DSS) was calculated from the time of diagnosis to the time of recurrence, metastasis from breast cancer or death or to the last date of follow-up. The overall survival (OS) was calculated from the time of diagnosis to the time of death from any cause. Patients who had a follow-up time of less than 24 months were excluded from the study unless there was a clinical event.

Statistical Analysis

The survival outcomes (5-year DSS and 5-year OS) were estimated by the Kaplan–Meier method and were compared by the Log rank test. Statistical significance was defined as $p < 0.05$, and hazard ratios (HRs) and 95% confidence intervals (CIs) were also calculated. Statistical tests were two-sided, and analysis was performed using SPSS software, version 19.0 (SPSS, Chicago, IL, USA, <http://www.spss.com>).

Results

Patient Characteristics

Between January 2012 and November 2015, 1138 patients with primary breast cancer were treated at NMCLH, and 425 patients were diagnosed with luminal B-like HER2-negative breast cancer. Due to the incomplete clinicopathological data or a lack of follow-up in 18 patients, 407 patients were included in the final analysis. The median age was 54 (range: 24–80) years old, all of the patients were ER positive and HER2 negative, 70 patients (17.2%) were PR negative and 245 patients (60.2%) had low PR expressin. The median follow-up time was 79 (range: 8–115) months, and as many as 82.8% of patients had a follow-up time of 60 months or more. Among 407 patients, the 5-year DSS and OS were 90.3% and 93.5%, respectively. The other clinicopathological characteristics are shown in [Table 1](#).

Patients Staged by the 8th Edition AJCC PS

According to the 8th edition AJCC PS, 223 (54.8%) patients had stage I cancer, including 116 (28.5%) stage IA and 107 (26.3%) stage IB; 107 (26.3%) patients had stage II cancer, including 39 (9.6%) stage IIA and 68 (16.7%) stage IIB; 77 (18.9%) patients had stage III cancer, including 29 (7.1%) stage IIIA, 28 (6.9%) stage IIIB, and 20 (4.9%) stage IIIC.

Analysis by the Log rank test showed that there were statistically significant differences in 5-year DSS (log-rank=29.827, $p < 0.001$) and 5-year OS (log-rank=38.849, $p < 0.001$) between different anatomic stage groups, and statistically significant differences in 5-year DSS (log-rank=40.646, $p < 0.001$) and 5-year OS (log-rank=47.885, $p < 0.001$) between different prognostic stage groups. [Table 2](#) and [Figure 1](#) show the differences in 5-year DSS and 5-year OS in different stage groups among patients staged by the AS and the PS.

Changes from Anatomic Stage Groups to Prognostic Stage Groups

Compared to the anatomic stage groups, the application of the PS resulted in the assignment of 215 (52.8%) patients to a different group, including 39 (25.5%) patients in the anatomic IA group, 1 (33.3%) in the anatomic IB group, 99 (75.0%) in the anatomic IIA group, 25 (47.2%) in the anatomic IIB group, 42 (100.0%) in the anatomic IIIA group, and 9 (37.5%) in the anatomic IIIC group. Among them, 102 (25.1%) patients were downstaged, and 113 (27.8%) patients were upstaged. [Table 3](#) shows the detailed changes from anatomic to prognostic stage groups.

Survival Analysis of Different Prognostic Stage Groups in the Same Anatomic Stage Group

In the anatomic Stage III group, 21 and 45 patients were assigned to the prognostic Stage II and III groups, and the 5-year DSS rates were 87.5% and 59.0%, respectively; and there was a statistically significant difference ($\chi^2 = 4.366$, $p = 0.037$). The 5-year OS rates in the prognostic Stage II and III groups were 100.0% and 70.3%, respectively, and there were statistically significant differences ($\chi^2 = 7.549$, $p = 0.006$). [Figure 2](#) shows the Kaplan–Meier curves of prognostic Stages II and III from the anatomic Stage III group.

In the anatomic Stage II group, 71, 82 and 32 patients were restaged to the prognostic Stage I, II and III groups, and the 5-year DSS rates were 97.1%, 90.7% and 84.1%, respectively, and there was a statistically significant difference ($\chi^2 =$

Table 1 5-Year DSS and 5-Year OS Rates Based on the Clinicopathological Characteristics

Variables	Cases (n,%)	Events (n)	5-Year DSS			Cases of Death(n)	5-Year OS		
			(%)*	χ^2	p**		(%)*	χ^2	p**
Age									
<35 years	13 (3.2)	3	84.6	1.139	0.566	3	83.9	2.337	0.311
35–60 years	277 (68.1)	33	91.0			23	93.1		
>60 years	117 (28.7)	16	89.3			13	95.5		
Menstrual status									
Perimenopause	173 (42.5)	21	92.8	0.274	0.601	13	94.6	1.691	0.193
Postmenopause	234 (57.5)	31	88.3			26	92.1		
Education									
Primary education	191 (46.9)	27	89.2	0.606	0.739	20	92.8	0.599	0.741
High school education	193 (47.4)	22	91.2			16	93.9		
College education	23 (5.7)	3	91.3			3	90.9		
Tumor laterality									
Left	201 (49.4)	24	91.2	0.354	0.552	19	93.2	0.044	0.833
Right	206 (50.6)	28	89.3			20	93.2		
Tumor size									
T1	228 (56.0)	17	94.1	14.938	0.001	13	96.8	9.999	0.007
T2	163 (40.1)	33	85.2			24	88.7		
T3	16 (3.9)	2	87.5			2	84.8		
Lymph nodes									
N0	228 (56.0)	13	96.8	107.549	0.000	8	97.3	117.853	0.000
N1	114 (28.0)	19	89.7			14	89.7		
N2	41 (10.1)	5	86.3			3	91.2		
N3	24 (5.9)	15	40.9			14	40.9		
Histological grade									
I	48 (11.8)	2	95.6	4.005	0.135	2	95.6	3.505	0.173
II	267 (65.6)	35	90.1			24	94.0		
III	92 (22.6)	15	87.8			13	89.7		

Notes: *DSS and OS are analyzed by Kaplan-Meier survival analysis; **Univariate analysis by Log rank test.

Abbreviations: DSS, disease specific survival; OS, overall survival.

7.724, $p = 0.021$). The 5-year OS rates in the prognostic Stage I, II and III groups were 98.5%, 93.3% and 87.3%, respectively, and there was no significant difference ($\chi^2 = 5.182$, $p = 0.075$). Figure 3 demonstrates the Kaplan–Meier curves of the prognostic Stages I, II and III from the anatomic Stage II group.

In the anatomic Stage I group, 152 and 4 patients were restaged to the prognostic Stage I and II groups, and the 5-year DSS rates were 97.3% and 100.0%, respectively, and there was no significant difference ($\chi^2 = 0.159$, $p = 0.690$). The 5-year OS rates in the prognostic Stage I and II groups were 98.0% and 100.0%, respectively, and there was no significant difference ($\chi^2 = 0.099$, $p = 0.753$). Figure 4 shows the Kaplan–Meier curves of the prognostic Stages I and II from the anatomic Stage I group.

Discussion

The first edition of the AJCC staging manual was published in 1977,¹⁷ and since then, the manual has been periodically revised and updated to improve its predictive accuracy in stratifying patient outcomes. These editions (from the first to the seventh editions) of the AJCC staging system were solely based on the anatomic extent of primary breast tumour, lymph nodes, and metastasis (TNM); however, the evolving knowledge of breast cancer biology has made AS alone less sufficient to show the differences in the molecular characteristics of breast cancer.^{2–5,18–20} In 2018, the 8th edition AJCC

Table 2 Differences in the 5-Year DSS and 5-Year OS in Different Stage Groups Among Patients Staged by the AS and the PS

Stage	Anatomic Stage Groups					Prognostic Stage Groups				
	n	5-Year DSS(%)*	p**	5-Year OS(%)*	p**	n	5-Year DSS(%)*	p**	5-Year OS(%)*	p**
I	156	96.7	<0.001	98.0	<0.001	223	97.2	<0.001	98.6	<0.001
II	185	92.6		94.2		107	90.9		93.6	
III	66	69.0		77.9		77	69.5		77.4	

Notes: *DFS and OS are analyzed by Kaplan-Meier survival analysis; **Log rank test.

Abbreviations: DSS, disease-specific survival; OS, overall survival.

began to incorporate prognostic factors including ER, PR, HER2, tumour grade and multigene expression assay for AS to form the PS.¹⁶ In our study, 215 (52.8%) patients changed their pathological stages when the 8th edition AJCC PS was used, which was in line with that in our previous study.²¹

In this study, the 5-year DSS rates in the anatomic stage I, II, and III groups were 96.7%, 92.6%, 69.0%, and 97.2%, 90.9%, and 69.5% in the prognostic stage I, II, and III groups, respectively, and there were statistically significant differences between the different staging groups regardless of the staging system. Similarly, the 5-year OS rates in the anatomic stage I, II, and III groups were 98.0%, 94.2% and 77.9%, and 98.6%, 93.6% and 77.4% in the prognostic stage I, II, and III groups, respectively, and there were statistically significant differences between the different staging groups regardless of staging system. These results indicated that both PS and AS had sufficient ability to differentiate the prognoses of patients with different pathological stages.

In the anatomic stage III group, 21 and 45 cases were restaged to the prognostic Stage II and III groups, and the 5-year DSS rates were 87.5% and 59.0%, respectively, and there was a statistically significant difference ($\chi^2 = 4.366$, $p = 0.037$). Correspondingly, the 5-year OS rates were 100.0% and 70.3%, and the difference was also statistically significant ($\chi^2 = 7.549$, $p = 0.006$). Similar results were seen in the patients who had anatomic stage II disease. All of these results suggested that PS not only can differentiate the prognoses of patients with different prognostic stages, but also can differentiate the prognoses of patients with the same anatomical staging but different prognostic staging. This finding was the most important one regarding PS, herein, the Breast Cancer Expert Panel recommends prioritizing the use of the PS in patients with breast cancer.

Since the 8th edition AJCC PS manual has been published for more than three years, most studies have validated its superiority over AS.⁶⁻¹¹ To the best of our knowledge, only a few studies have investigated the value of PS in different molecular subtypes. In a retrospective study of 170 HER2-enriched breast cancers, Zhou et al found that both AS and PS had prognostic value in this subtype of breast cancer.²² In another retrospective analysis of triple-negative breast cancer (TNBC), the anatomic stage and prognostic stage were restaged according to the 8th edition AJCC staging system, and no significant difference in C-index between AS and PS models for DSS, progression-free survival (PFS) or OS was found.²³

Ye et al²⁴ conducted a retrospective study of 796 patients with luminal B-like HER2-negative breast cancer, and found that the prognostic stage II and III groups restaged from the anatomic stage III group had significant differences in 5-year DSS ($\chi^2 = 11.319$, $p = 0.001$) and 5-year OS ($\chi^2 = 5.225$, $p = 0.022$). In addition, prognostic Stage I, II, or III groups restaged from the anatomic Stage II group had statistically significant differences in 5-year DFS ($\chi^2 = 6.510$, $P = 0.039$) but not in 5-year OS ($\chi^2 = 5.087$, $P = 0.079$). These results were consistent with those in our study. All of these results indicated that PS had sufficient ability to differentiate the prognoses of patients with the same anatomical staging but different prognostic staging. However, when compared to our study, the shortcomings of that study were obvious. First, the category and definition of HER2-negative luminal B-like tumours were not accurate in that study. The surrogate definition of intrinsic subtype was updated in the 2013 St. Gallen Consensus; however, the study, which was published in 2017 did not adopt the updated definition. Second, the time of follow-up in that study was too short. The median follow-up time was 38 months in the study by Ye et al and for luminal-like breast cancer, there was a steady and long-term recurrence risk. Herein, over a short follow-up time, most cases of recurrence or metastasis could not be observed, and results based on short follow-up are likely to be inaccurate.

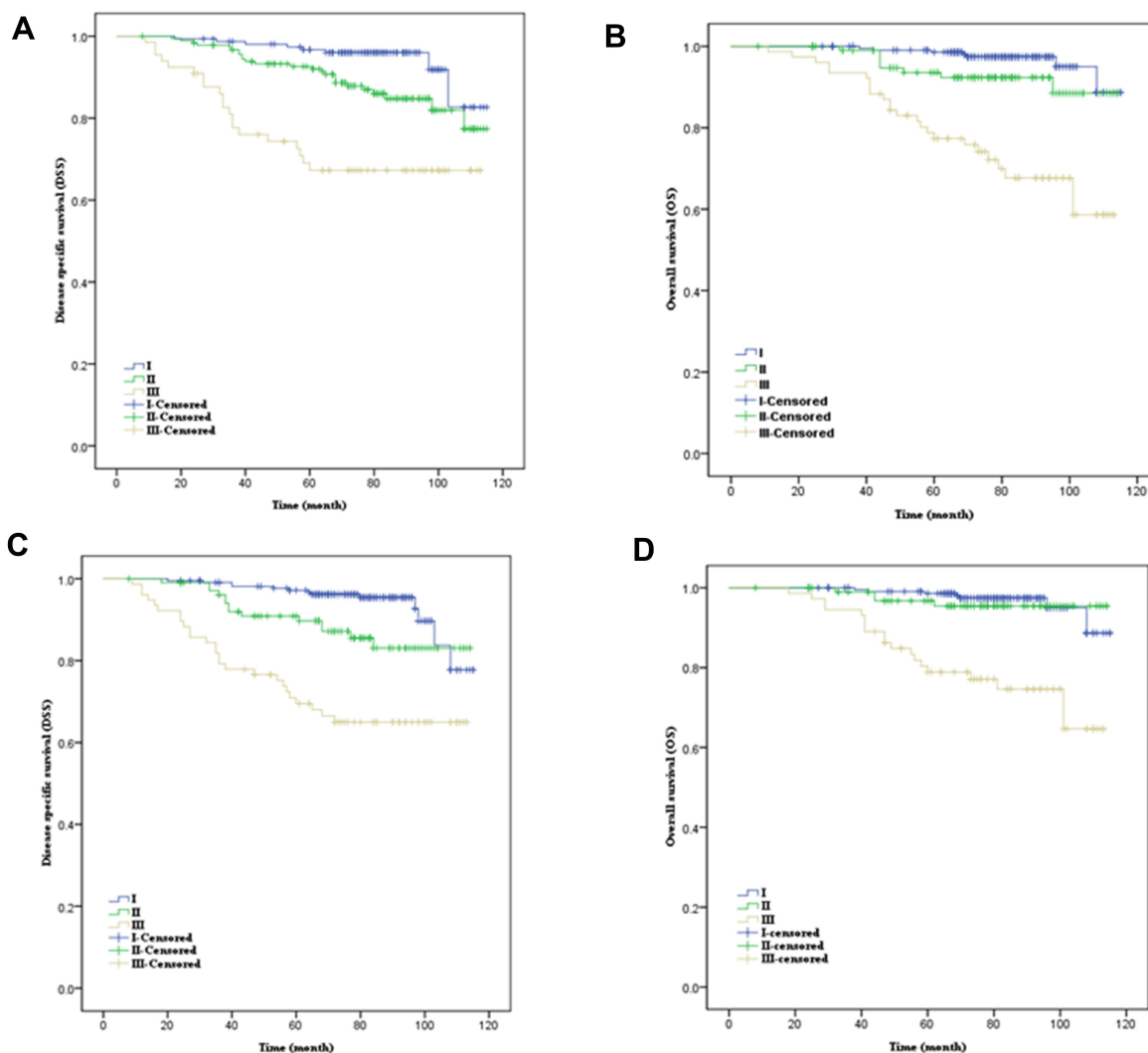


Figure 1 (A–D) Kaplan–Meier curves of 5-year DSS and 5-year OS in different stage groups; **(A)** Kaplan–Meier curve of 5-year DSS in different stage groups staged by the AS; **(B)** Kaplan–Meier curve of 5-year OS in different stage groups staged by the AS; **(C)** Kaplan–Meier curve of 5-year DSS in different stage groups staged by the PS; **(D)** Kaplan–Meier curve of 5-year OS in different stage groups staged by the PS.

The strengths of our study should be acknowledged. First, the population included in the study was from mainland China, which accounted for 18.1% of newly diagnosed breast cancers in 2020.¹ The results of our study and those of the study by Ye et al²⁴ showed that the PS not only can differentiate the prognoses of patients with different prognostic stages, but also can differentiate the prognoses of patients with the same anatomical staging but different prognostic staging. Thus, the treatment decisions for individuals should be made mostly based on the PS. Second, in our study, the median follow-up time was 79 months, and 82.8% of patients were followed up for 60 months or more time enabling us to observe the majority of cases of recurrence in luminal B-like HER2-negative breast cancer; thus, the analysis was based on long-term follow-up and thus should be more reliable.

Of course, limitations of this study were also present. One limitation lay in the lack of Oncotype DX recurrence score (RS) data in the present study. The PS incorporated RS into the staging system and downstaged patients with T1-2N0M0, ER-positive, and HER2-negative tumours into stage IA when $RS < 11$ because these patients had a good survival outcome in the TAILORx trial.²⁵ Second, it was a single-centre, retrospective study with a relatively small number of patients, which might have resulted in some selection bias. Therefore, more multicentre, prospective studies with large samples should be performed to fully determine the prognostic value of the PS in luminal B-like HER2-negative breast cancer patients.

Table 3 Detailed Changes from Anatomic to Prognostic Stage Groups

Anatomic Stage Groups		Alteration	Prognostic Stage Groups	
Stage	n		Stage	n
IA	153	(a) IA→(p) IA (a) IA→(p) IB (a) IA→(p) IIA	IA IB IIA	114 35 4
IB	3	(a) IB→(p) IA (a) IB→(p) IB	IA IB	1 2
IIA	132	(a) IIA→(p) IB (a) IIA→(p) IIA (a) IIA→(p) IIB (a) IIA→(p) IIIA	IB IIA IIB IIIA	69 33 21 9
IIB	53	(a) IIB→(p) IB (a) IIB→(p) IIB (a) IIB→(p) IIIA (a) IIB→(p) IIIB	IB IIB IIIA IIIB	2 28 20 3
IIIA	42	(a) IIIA→(p) IIA (a) IIIA→(p) IIB (a) IIIA→(p) IIIB (a) IIIA→(p) IIIC	IIA IIB IIIB IIIC	2 19 16 5
IIIC	24	(a) IIIC→(p) IIIB (a) IIIC→(p) IIIC	IIIB IIIC	9 15

Conclusion

The eighth edition AJCC PS restaged 52.8% of patients with luminal B-like HER2-negative breast cancer and could provide more accurate predictions of survival outcomes than the AS. Thus, the treatment decisions for individuals should be made mostly based on the PS.

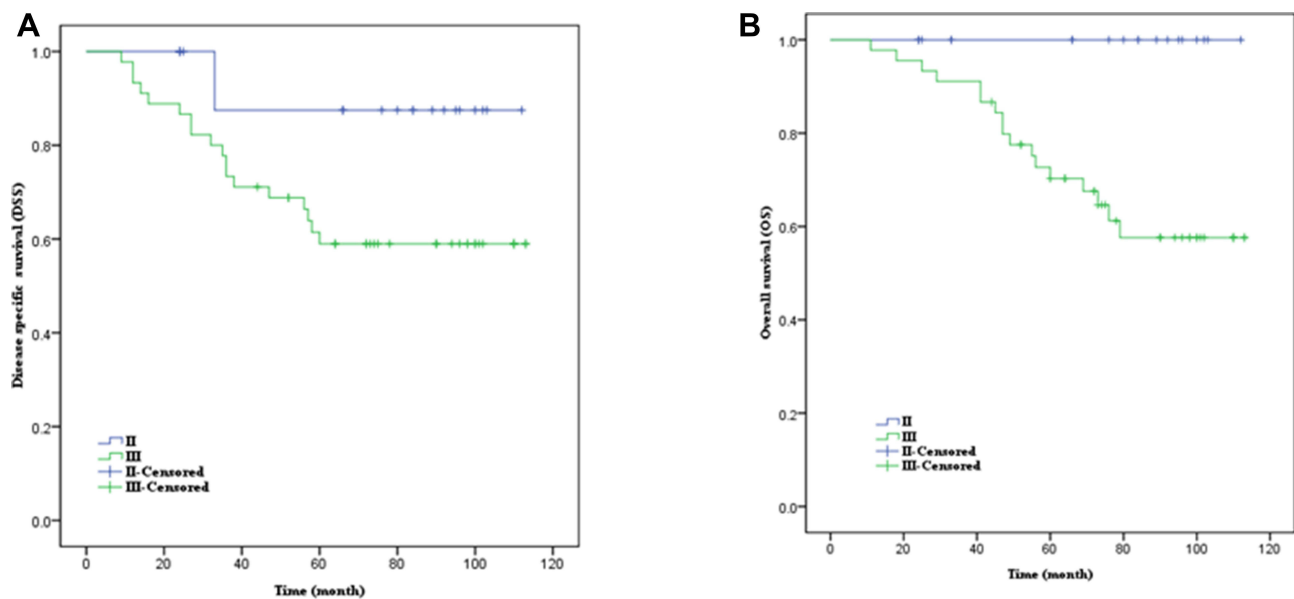


Figure 2 (A and B) Kaplan–Meier curves of prognostic Stages II and III from the anatomic Stage III group; **(A)** Kaplan–Meier curve of 5-year DSS for the patients in prognostic Stages II and III groups; **(B)** Kaplan–Meier curve of 5-year OS for the patients in prognostic Stages II and III groups.

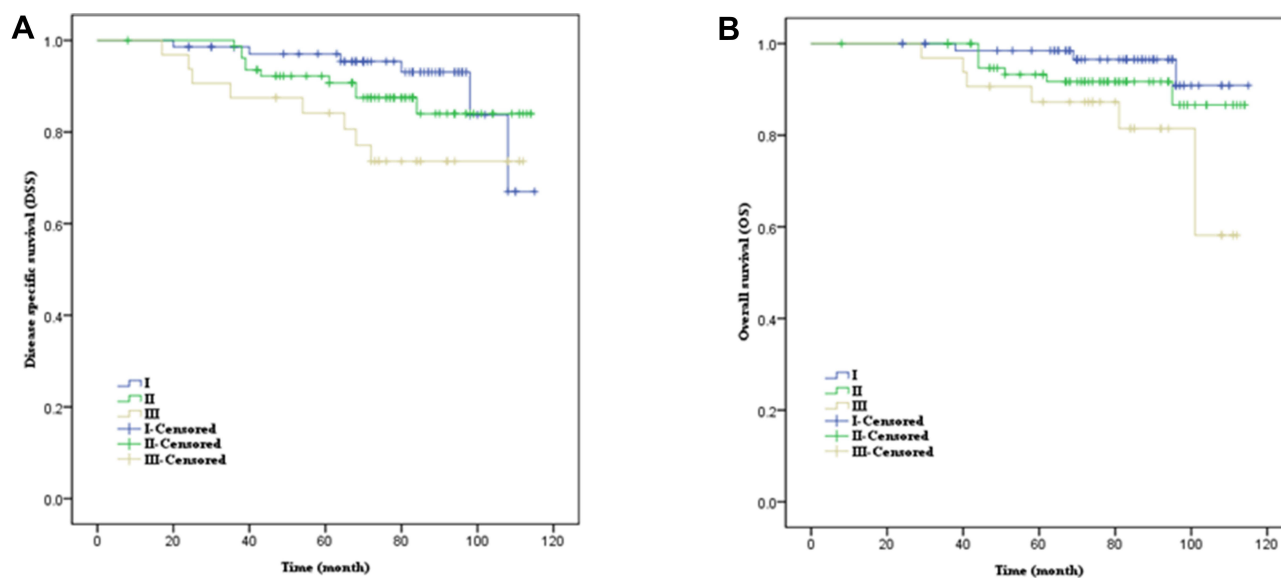


Figure 3 (A and B) Kaplan–Meier curves of the prognostic Stages I, II and III from the anatomic Stage II group; **(A)** Kaplan–Meier curve of 5-year DSS for the patients in prognostic Stages I, II and III groups; **(B)** Kaplan–Meier curve of 5-year OS for the patients in prognostic Stages I, II and III groups.

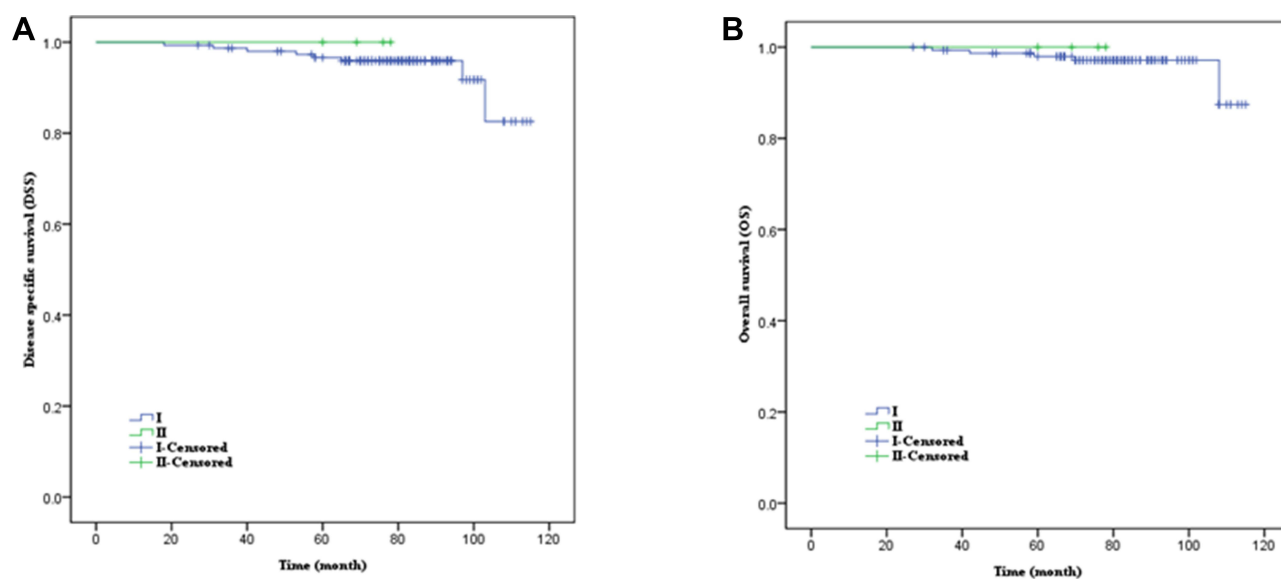


Figure 4 (A and B) Kaplan–Meier curves of the prognostic Stages I and II from the anatomic Stage I group; **(A)** Kaplan–Meier curve of 5-year DSS for the patients in prognostic Stages I and II groups; **(B)** Kaplan–Meier curve of 5-year OS for the patients in prognostic Stages I and II groups.

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Disclosure

The authors declare no competing financial and non-financial interests in this work.

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