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Validation of the AJCC 8th prognostic system for breast cancer in an Asian healthcare setting

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ABSTRACT

Aims: We aim to validate the AJCC 8th edition prognostic staging system for breast cancer in an Asian setting.

Methods: Clinico-pathologic information and cancer-specific survival (CSS) outcomes of 6287 stage I to III patients with invasive breast cancer who underwent upfront surgery at SingHealth institutions in Singapore from 2006 to 2014 were analyzed. Survival distributions for the different staging systems were estimated by the Kaplan-Meier method and compared using the log-rank tests. Multivariable Cox proportional hazards models were used, with Akaike Information Criterion (AIC) and Harrell's Concordance Index (C-index) to compare both staging systems.

Among patients with positive hormone-receptor status, 84.8% received endocrine therapy. Among the cohort, 60.3% of received chemotherapy; 82.1% of node positive patients received chemotherapy and 86.0% of HER2-enriched patients in whom chemotherapy was also indicated received adjuvant HER2-targeted therapy. Ninety-seven percent of patients received anthracyclines and/or taxanes containing chemotherapy regime.

Results: The median follow up was 64 months. 2921 patients (46.5%) were discordant between the anatomic and prognostic systems of which 363 (5.8%) were upstaged and 2558 (40.7%) were downstaged. For all patients, stages in both the prognostic and anatomic systems were discriminating for 5-year CSS. Controlling for age, ethnicity and receipt of chemotherapy, the prognostic staging system model (AIC = 7538.87, C = 0.79) presented slightly better explanation and concordance of survival times than the anatomic staging system model (AIC = 7607.31, C = 0.77).

Conclusion: The prognostic staging system was better than the anatomic staging system in predicting outcomes but the anatomic system remains relevant due to its ease of use.

1. Introduction

The American Joint Committee on Cancer (AJCC) 8th edition staging system [1], which was implemented on 1st January 2018, has included biomarkers to the existing anatomic system as a major change in the new prognostic staging system. As described by Giuliano et al., the multidisciplinary expert panel incorporated biologic factors such as histologic grade, hormone receptor expression, human epidermal growth factor receptor 2 (HER2) over-expression and/or amplification, and genomic information such as oncotype DX recurrence score, whilst still retaining the anatomic system [2,3].

Accurate staging helps to determine the prognosis and guide management.Tumor biology as a treatment indicator has been addressed by the St. Gallen International Expert Consensus, with different systemic therapy recommendations for the different subgroups. For example, node-negative luminal A breast cancer patients would generally require endocrine treatment alone, while luminal B cancers are more likely to benefit from both endocrine and chemotherapy [3,4].

The Oncotype DX assay is based on the expression of a panel of 21 genes to assess the risk of recurrence in hormone receptor positive HER2-negative breast cancer. Although a score of 18 was originally categorized as low risk in the development of the assay,

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the new AJCC prognostic system uses a score of <11 to denote a favourable prognosis. This is based on the prospective TAILORx study [2,5] which reported a five-year distant recurrence-free survival of 99.3% for such patients with score of <11 on endocrine therapy alone. As an example, in the new staging system, T2N0M0 tumors with recurrence score of <11 are re-assigned to stage 1B from anatomic stage 2A.

While AJCC 8th prognostic system has been validated and reported to be superior to the anatomic system [2] [6] [7], the improved discriminatory power of the new staging classification has not been demonstrated in a comprehensive manner beyond the United States population on which it was based. We performed this study to determine if the new prognostic staging from AJCC 8th edition further refines the existing anatomic staging in the setting of an Asian healthcare system, given that it will be implemented worldwide. Our study focuses on stage 1–3 breast carcinoma patients who underwent upfront surgery, as these are the patients who may be affected by the new staging system. Neoadjuvant cases were excluded due to the lack of information on the true pathological stage at initial diagnosis. The prognosis may also be confounded in patients who achieve pathological complete response and better survival outcomes in spite of a more advanced tumor stage at presentation.

2. Material and methods

Information was extracted from the Joint Breast Cancer Registry, a prospectively maintained database of breast cancer patients managed at Singapore General Hospital, National Cancer Centre Singapore and KK Women's and Children's Hospital. Ethics approval was obtained from the Central Institutional Review Board (IRB) prior to study commencement, with waiver of informed consent for this retrospective analysis.

The cohort of patients diagnosed with breast cancer from 1st January 2006 to 31st December 2014 was selected as adjuvant HER2 directed treatment became more widely implemented from 2006, with routine testing of HER2.

Patients with stage 0 and metastatic breast cancer, patients who received neoadjuvant systemic therapies and patients with incomplete clinic-pathologic and follow-up details were excluded.

Oncotype DX scores are not available from our database and hence not used in this study.

The definitions of etrogen receptor (ER), progesterone receptor (PR) and HER2 positivity in this study were based on the recommendations by the American Society of Clinical Oncology and the College of American Pathologists at the time of diagnosis, with the criteria updated in 2010 and 2013 respectively for hormone receptor and HER2 receptor status [8,9].

Estrogen receptor (ER) and Progesterone receptor (PR) expression studies were performed using immunohistochemistry (IHC) and from 2010, considered positive if 1% or greater of the tumor cells stained for the protein [8].

HER2 status, determined either by IHC or Fluorescent In-situ Hybridisation (FISH), was considered positive if immuno-histo chemistry (IHC) 3 + with more than 10% of tumor cells staining intensely according to the updated cutoff from 2013, or amplified on FISH [10].

Patients were classified under the prognostic stage as well as the anatomic stage according to the AJCC eighth edition staging definitions.

Cancer specific survival (CSS) was defined as time from diagnosis to breast cancer death, and censored at death from other causes and at last follow up. We decided to use CSS as an endpoint, in keeping with the original North American data used to generate the new prognostic system [2].

Survival distributions for each staging system were estimated by the Kaplan-Meier product-limit method and compared using the log-rank test.

Multivariable Cox proportional hazards regressions (adjusted for age, ethnicity and receipt of chemotherapy) with the 8th edition prognostic staging system as the primary predictor were compared to those with the 7th edition anatomic staging system as the primary predictor, using Akaike Information Criterion (AIC) and the C-index (Harrell's Concordance Index). Adjustments were made for age and ethnicity as these variables are often associated with survival outcomes [11,12]. A lower AIC value would reflect better explanation of the variation within the data, and a higher C-index value would reflect better concordance of survival times.

Log-rank tests were used to test for statistically significant differences in survival between the patients who were up or down-staged or remained status quo under the new prognostic system in selected anatomic stages.

For all statistical tests, the level of significance was 5%. All analyses were performed using STATA 15.0.

3. Results

A total of 6287 patients diagnosed with breast cancer from 1st January 2006 to 31st December 2014 were analyzed. The clinic-pathologic characteristics and treatment details are listed in Table 1. The median follow-up was 64 months, ranging from 1 to 205 months. The median age at diagnosis was 54 years (range 19–97), with 78.4% of the patients aged between 35 and 65 years. The most common histology was infiltrative ductal carcinoma at 87.3%. Overall, 60.3% received adjuvant chemotherapy. Among node positive patients, 82.1% received chemotherapy. Of those who received chemotherapy, 50.3% had third generation regimen consisting of both anthracycline and taxanes, 16.2% received anthracycline-containing, 31.2% received taxane-containing and 2.0% received other regimens. For histology subtypes, 65.6% of patients were hormone receptor (HR) and HER2 -, 14.8% were HR+ and HER2+ve, 9.0% was HR- and HER2-enriched, and 10.6% were triple negative. For patients with ER and/or PR positive tumors, 84.8% received endocrine therapy. Among HER2 positive patients who received chemotherapy, 86.0% received adjuvant HER2-targeted therapy.

Overall, 2921 (46.5%) patients were up or down-staged; 363 patients (5.8%) were upstaged in prognostic stage groups, while 2558 patients (40.7%) were down-staged. The graphical representation of the migration of patients between the 2 models is illustrated in Fig. 1. The most frequent changes were from anatomic stage IIA to prognostic stage IA in 780 patients (12.4%), followed by anatomic stage IIA to prognostic stage IB in 348 patients (5.5%), and anatomic stage IIB to prognostic stage IB in 283 patients (4.5%) (See Table 1 in the appendix).

3.1. Survival analysis

Under anatomic staging, 2284 cases (36.3%) were stage IA, 110 cases (1.7%) were stage IB, 1759 cases (28.0%) were stage IIA, 871 cases (13.9%) were stage IIB, 720 cases (11.5%) were stage IIIA, 92 cases (1.5%) were stage IIIB, and 451 cases (7.7%) were stage IIIC. There were significant differences in 5-year CSS (log rank test: $p < 0.001$) between anatomic stage groups (Table 2).

Under prognostic staging, 3033 cases (48.2%) were stage IA, 1025 cases (16.3%) were stage IB, 881 cases (14.0%) were stage IIA, 413 cases (6.6%) were stage IIB, 454 cases (7.2%) were stage IIIA, 313 cases (5.0%) were stage IIIB, and 168 cases (2.7%) were stage IIIC. There were significant differences in CSS (log rank test: $p < 0.001$) between prognostic stage groups (Table 2).

Table 1
Patients' characteristics and treatment information.

Characteristic	Number of patients ($n = 6287$)	Percentage (%)
Age		
</= 35	259	4.1
36–50	2241	35.6
51–65	2671	42.8
>/= 65	1116	17.8
Ethnicity		
Chinese	4785	76.1
Malay	610	9.7
Indian	331	5.3
Others	561	8.9
Histological Grade		
G1	942	15.0
G2	2370	37.7
G3	2975	47.3
Histology		
Ductal	5489	87.3
Lobular	301	4.8
Others	497	7.9
Histology Subtypes		
HR + ve, HER2 -ve	4123	65.6
HR + ve, HER2 +ve	930	14.8
HR -ve, HER2 +ve	567	9.0
Triple negative	667	10.6
Surgerys		
Mastectomy	4057	64.5
Breast Conserving Surgery	2230	35.5
Axillary Surgery		
Sentinel lymph node biopsy only	2417	38.4
No	58	0.9
Axillary clearance	3327	52.9
Axillary Sampling	485	7.7
Chemotherapy		
No	2497	39.7
Yes	3790	60.3
Chemotherapy Regimens		
Antracycline-containing	614	16.2
Taxane-containing	1183	31.2
Antracycline and Taxane - containing	1906	50.3
Others	74	2.0
Chemotherapy (for node positive)		
No	465	17.9
Yes	2137	82.1
Endocrine therapy (for receptor positive)		
No	354	7.0
Yes	4287	84.8
Unknown	412	8.2
Targeted Therapy(for HER2-enriched indicated and received chemotherapy)		
No	156	14.0
Yes	960	86.0

Multivariable Cox model for CSS adjusting for age, ethnicity and receipt of chemotherapy was performed. The prognostic staging system model (AIC = 7538.87, C = 0.79) presented slightly better explanation and concordance of survival times than the anatomic staging system model (AIC = 7607.31, C = 0.77) (Table 3). Survival curves are shown in Fig. 2.

Pairwise comparisons in the anatomic system showed stage IB to have a hazard ratio (HR) of 0.39 compared to stage IA, but in the prognostic system the HR was 2.72 (Table 4). All other HR in both systems was greater than 1.0 compared to the sub-stage before.

The new prognostic system predicted significant and relevant changes in its estimation of CSS between patients who were up or down-staged or who have remained status quo. (Fig. 3).

4. Discussion

Our study of 6287 patients treated from 2006 to 2014 showed both anatomic and prognostic models to be individually predictive of CSS. While comparing the 2 models with AIC and HCI and adjusting for age, ethnicity and receipt of chemotherapy, there is a suggestion that the prognostic staging system provides slightly better explanation and concordance. This is one of the first comprehensive validation studies outside the United States of America, and supports the use of the prognostic system beyond the healthcare system upon which it was developed.

Overall, 46.5% of patients were up or down-staged under the new prognostic system, with 5.8% upstaged and 40.7% were down-staged. Other validation studies have similar discordant rates; ranging from 41.6% to 74.0% in other studies with varying study populations and sample size [6,7,13–15].

In coming out with the new prognostic model, the expert panel described the process and rationale for doing so [2]. Data from 3728 patients treated from 1997 to 2006 at the MD Anderson Cancer Centre showed that incorporation of grade and ER status with the pathologic anatomic stage better stratified patients for CSS. A further 26,711 patients from the Surveillance Epidemiology and End Results (SEER) database confirmed the findings. All these data predated the routine use of trastuzumab, hence a further cohort of 3327 patients treated at MD Anderson from 2007 to 2013 which included 9.2% of HER2 subtype, majority of which received trastuzumab, showed that incorporation of HER2 status further refined prognostication with respect to CSS. A further cohort of almost 70 thousand patients from the California Cancer Registry confirmed these findings. Further studies by Dr David J. Winchester using data from National Cancer Database of patients treated in 2010 showed that anatomic staging with grade, ER, PR and HER2 further refined the final AJCC 8th prognostic system.

In the 8th edition prognostic system, triple negative tumors, and tumors with grade 3 that are HER2 negative and either estrogen/progesterone-receptor positive were moved up by at least 1 stage. For T3N1-2M0 hormone receptor positive and HER2 positive tumors are down-staged from IIIA to IB (if grade 2, ER +, PR+), IIA (if grade 1, ER -, PR +) and IIB (if grade 3, ER+, PR+) [2].

As for multigene panel incorporation, the AJCC 8th committee down-staged patients to stage IA if Oncotype DX scores are less than 11. While there is already evidence to show that oncotype DX provides valuable prognostication [5], validation of AJCC 8th edition prognostic staging system based on the Recurrence Score has not been performed in any studies to our knowledge.

The strengths of our study include our prospectively maintained database with comprehensive clinic-pathological and follow-up details. The majority of our patients received standard of care treatment. For node positive patients, 82.1% received chemotherapy. Among patients with hormone receptor positive cancers, 84.8% received endocrine therapy. For patients with HER2 positive tumors who had chemotherapy, 86.0% received targeted therapy. Another strength of our study is that we controlled for age, ethnicity and receipt of chemotherapy in comparing the 2 staging systems. A prior study using results from the same database showed that the Malay ethnicity is an independent risk factor for both screened and clinical presentation groups [11].

Three separate studies in a Chinese population setting were reported in 2017, each focused on a particular histological subtype [13–15]. In the Chinese study on Luminal B HER2 negative tumors (n = 796) 5-year disease free survival (DFS) and OS were significantly different in both the anatomic and prognostic systems, but no comparisons were made between the 2 models [13]. In a separate study on luminal A tumors (n = 421), the authors found significant differences in 5-year DFS but not OS with the anatomic model but significant differences in both 5-year DFS and OS with the prognostic model [14]. In both studies, around 40% of patients were up or down-staged. The third study on patients with HER2

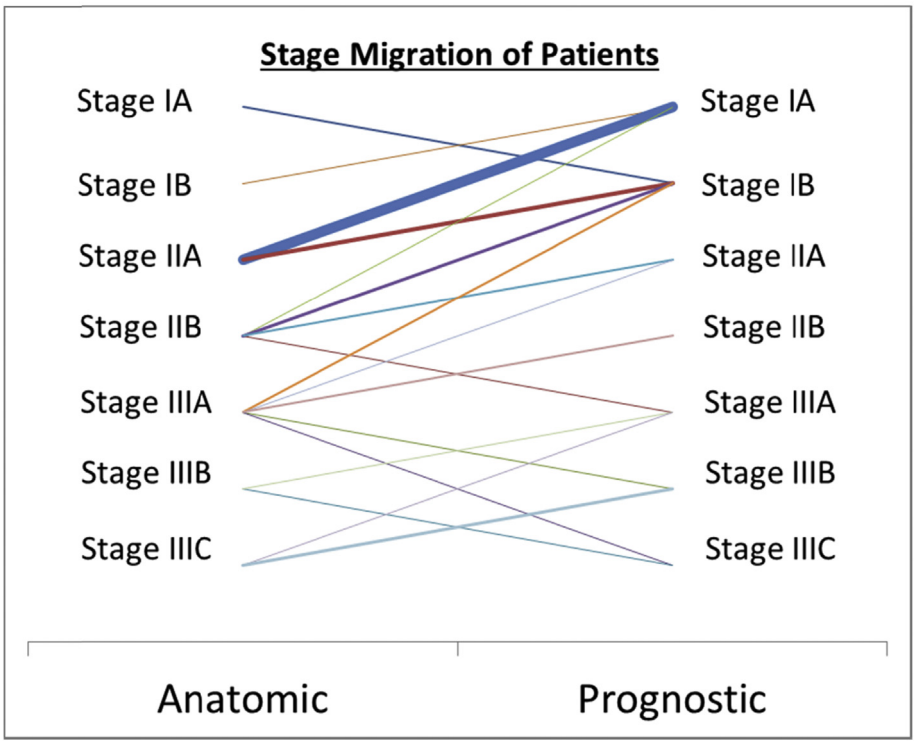

Fig. 1. Migration of patients from anatomic to prognostic system (thickness of lines is proportionate to number of patients).

Table 2
5-year CSS of adjuvant patients using the anatomic and prognostic stage system (n = 6287).

Staging system	Stage	Cases(n)	Events	Percentage	*P*-value from log-rank test
Anatomic	IA	2284	55	98.8	<0.001
	IB	110	1	98.6	
	IIA	1759	103	94.0	
	IIB	871	101	89.0	
	IIIA	720	99	87.1	
	IIIB	92	16	80.4	
	IIIC	451	113	76.2	
Prognostic	IA	3033	73	98.7	<0.001
	IB	1025	67	94.7	
	IIA	881	90	89.1	
	IIB	413	60	85.5	
	IIIA	454	71	83.8	
	IIIB	313	69	79.8	
	IIIC	168	58	62.6	

Table 3
Multivariable Cox models for CSS.

	Anatomic staging model		Prognostic staging model	
	Hazard ratio (95% C.I.)	*p*	Hazard ratio (95% C.I.)	*p*
Staging				
IA	1	–	1	–
IB	0.39 (0.05–2.79)	0.345	2.72 (1.93–3.82)	<0.001
IIA	2.30 (1.64–3.23)	<0.001	4.20 (3.03–5.80)	<0.001
IIB	4.62 (3.27–6.53)	<0.001	6.24 (4.37–8.91)	<0.001
IIIA	5.41 (3.81–7.68)	<0.001	6.91 (4.90–9.74)	<0.001
IIIB	6.12 (3.46–10.83)	<0.001	10.28 (7.23–14.61)	<0.001
IIIC	11.36 (8.02–16.10)	<0.001	19.15 (13.23–27.71)	<0.001
Age at diagnosis (years)				
≤35	1	–	1	–
36–50	0.65 (0.41–1.05)	0.076	0.73 (0.45–1.16)	0.180
51–65	0.74 (0.47–1.17)	0.199	0.74 (0.47–1.17)	0.201
≥66	1.66 (1.02–2.69)	0.042	1.58 (0.98–2.57)	0.063
Ethnicity				
Chinese	1	–	1	–
Malay	1.42 (1.09–1.85)	0.009	1.44 (1.11–1.88)	0.006
Indian	1.24 (0.88–1.76)	0.219	1.25 (0.88–1.77)	0.210
Others	0.36 (0.20–0.66)	0.001	0.38 (0.21–0.69)	0.002
Receipt of chemotherapy				
No	1	–	1	–
Yes	1.37 (1.06–1.78)	0.017	1.18 (0.91–1.53)	0.204
AIC value	7607.31		7538.87	
C-index	0.77		0.79	

enriched breast cancers (n = 170), 68.8% were up or down-staged, and it was reported that both models had significant prognostic impact on DFS and OS, without comparison between the 2 systems [15]. The findings from these studies are limited by the relatively lower proportion of patients who received standard treatment. For instance, the receipt of trastuzumab for HER2 positive cases was less than 50% [15] and for luminal B patients, only about 60% received chemotherapy [13]. Furthermore, these studies included patients who received neoadjuvant chemotherapy further complicating the interpretation of their results.

A Korean study of 7458 patients by Sae Byul Lee et al. found the prognostic system to be more refined; however information on trastuzumab receipt was not included [16].

Another validation study of locally advanced breast cancer patients (AJCC 7th anatomic system IIIA-C) from the SEER 8 database by Wang et al. [6] found the prognostic stage to provide more accurate prognostic information. However, the percentage of patients with HER2 positive tumors who received targeted therapy was again not reported.

Weis et al. published their results using data from MD Anderson and the Californian Cancer registry [7]. However, the Californian Cancer registry data was limited by the lack of information on trastuzumab receipt. The prognostic system was found to be more

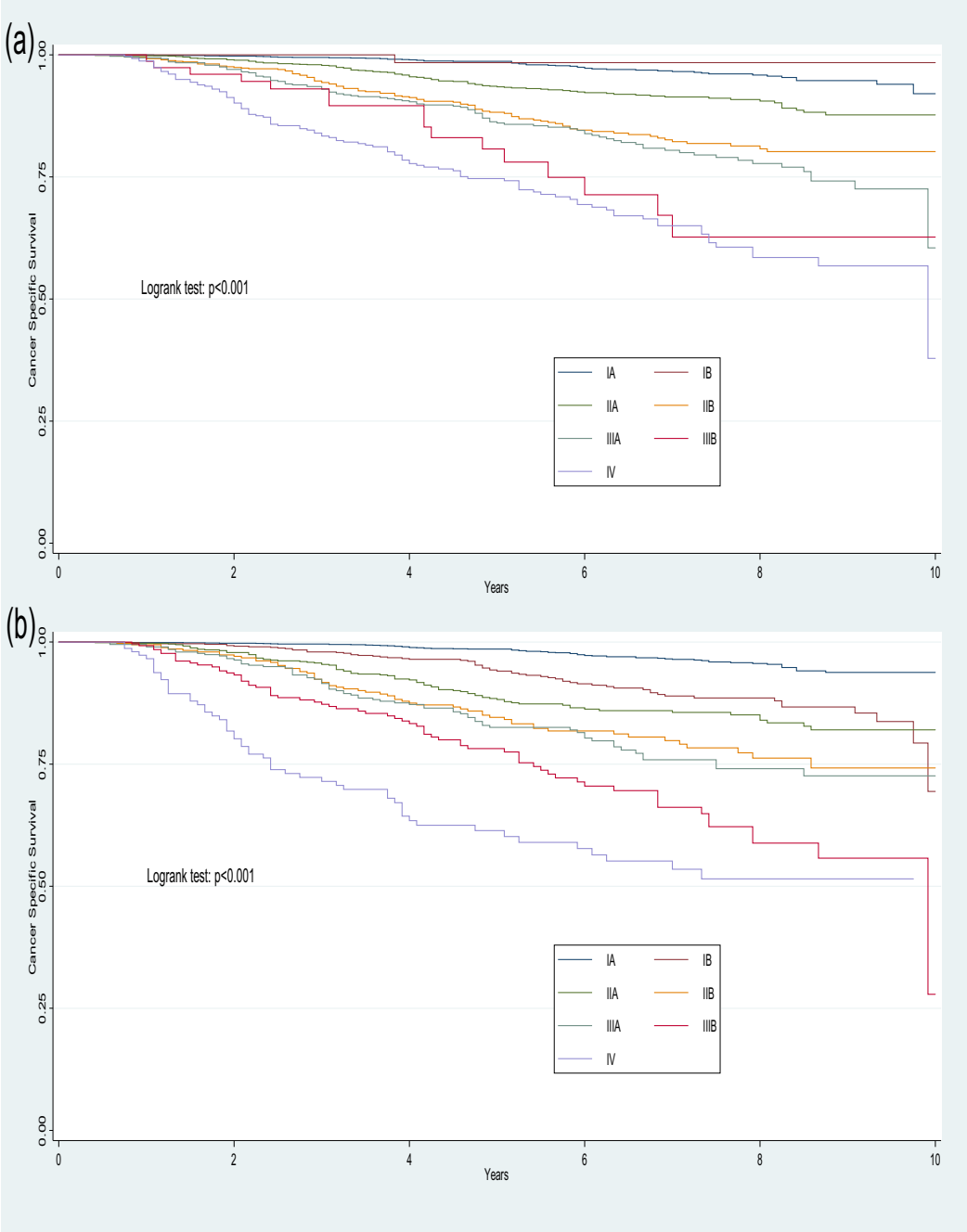

Fig. 2. 10-year CSS according to (a) anatomic staging, and (b) prognostic staging.

Table 4
Pairwise hazard ratio comparisons.

	Anatomic staging model		Prognostic staging model	
	Hazard ratio	95% C.I.	Hazard ratio	95% C.I.
Staging				
IB vs IA	0.39	(0.05–2.79)	2.72	(1.93–3.82)
IIA vs IB	5.97	(0.83–42.81)	1.54	(1.12–2.12)
IIB vs IIA	2.01	(1.53–2.65)	1.49	(1.07–2.06)
IIIA vs IIB	1.17	(0.89–1.54)	1.11	(0.78–1.56)
IIIB vs IIIA	1.13	(0.66–1.93)	1.49	(1.07–2.07)
IIIC vs IIIB	1.86	(1.09–3.16)	1.86	(1.31–2.65)

accurate in both datasets.

Our study is limited by relatively short follow up, mainly due to the selection criteria, as we only included patients treated post 2006 after adjuvant trastuzumab treatment became widespread. Some breast cancers, in particular those of the luminal subtype, are known to relapse after a much longer interval [17–19]. The performance of the prognostic system over a longer period of time needs further assessment. Trastuzumab has only been widely used in the last decade; hence the prognostic model was also built on short-term results, although updated results from the adjuvant trastuzumab trials have shown that the survival benefit of adjuvant

trastuzumab exists even after 10 years [20]. Our study also did not include Oncotype DX scores, similar to the other published studies.

Another limitation relates to the lack of incorporation of Oncotype DX scores in our study, similar to the other published series. In recent times, there has been an increasing trend to use gene expression assays to identify low risk patients who may not benefit much from chemotherapy. Only Oncotype Dx is officially utilised for the current AJCC 8th prognostic system; a score of 11 or less places a patient as stage IA. It is the best validated to predict risk of distant relapse despite tamoxifen. Other studies have also shown that in patients with node-negative and hormone-receptor positive, HER2 negative disease with scores of below 18 can safely omit chemotherapy [21]. For patients with intermediate recurrence score (RS) 19 to 30, a retrospective evaluation of clinical trial specimens in the NSABP B-20 showed that the addition of CMF (cyclophosphamide, methotrexate, 5-FU) chemotherapy did not confer any significant benefit [22]. Currently there is an ongoing RxPONDER trial to investigate the usage of Oncotype Dx RS for limited node positive patients. Other genomic assays such as Endopredict, PAM50 and Breast Cancer Index [23] and Mammaprint (Amsterdam 70-gene profile) may also provide additional prognostic information which can be useful in decision-making on adjuvant therapies. The MINDACT trial evaluated the use of Mammaprint in early stage breast cancer patients, with the majority

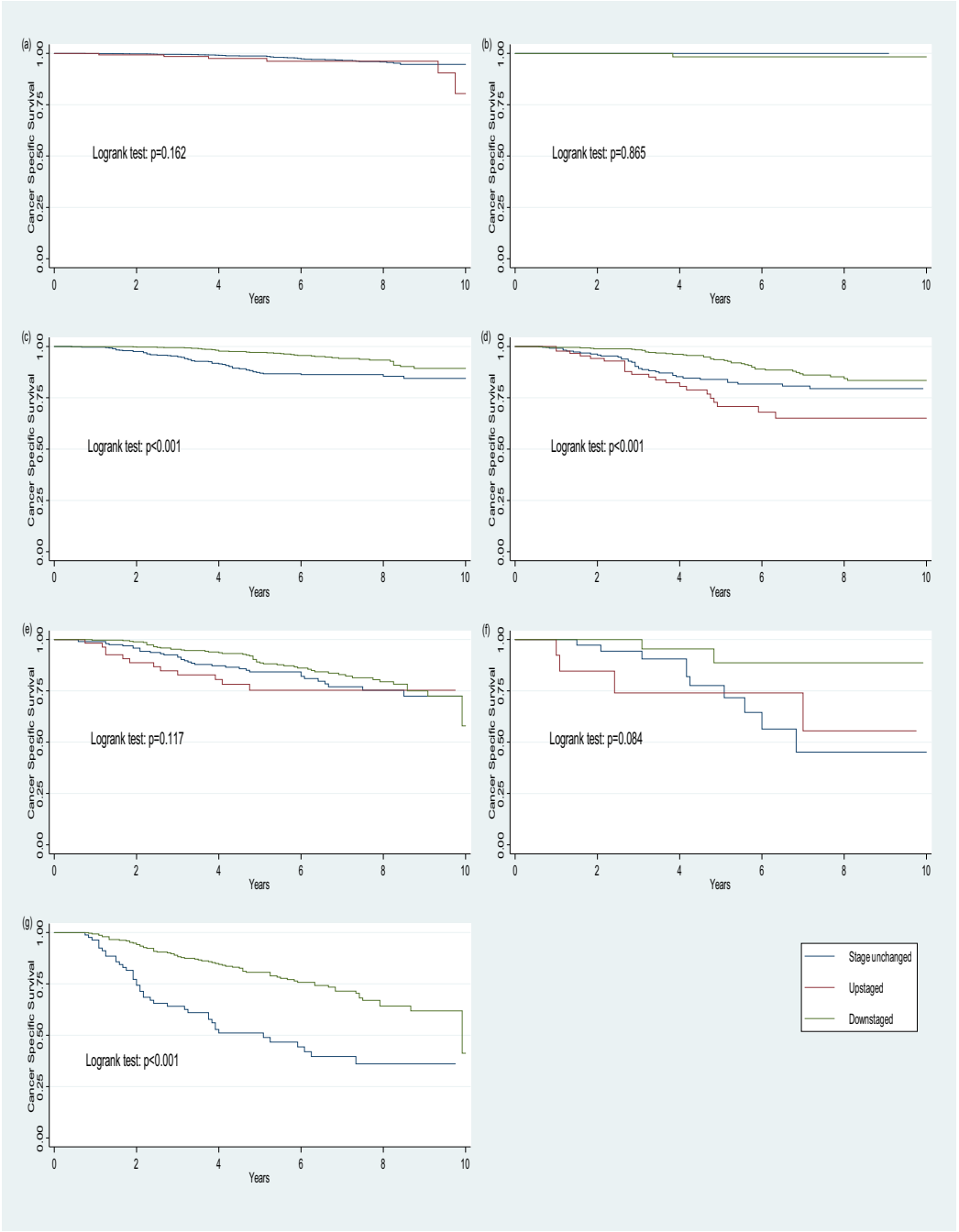

Fig. 3. 10-year CSS according to change of stage for anatomic stage (a) IA, (b) IB, (c) IIA, (d) IIB, (e) IIIA, (f) IIIB, and (g) IIIC.

having hormone receptor-positive, HER2-negative disease and no or limited nodes involved. The trial found no difference in recurrence free survival in 2 groups of patients with high clinical risk by Adjuvant Online profile but low risk by Amsterdam profile, of which 1 group received chemotherapy and the other did not [24]. Going forward, the uptake of such gene expression assays will increase, and may potentially be incorporated into the staging system in future, including for low risk node positive patients. However, most prospective trials on these assays have only reported 5 year results, and luminal A cancers are known to often relapse later. Hence, incorporation of these assays is a complex issue. It is also not clear if patients with low clinical but high genomic risk should be upstaged. And for patients who cannot access such assays, there will be a discrepancy in the staging information available. A good staging system should ideally strive to obtain universal applicability.

Although the new prognostic system may define prognosis, the anatomic system remains relevant in daily clinical practice. We foresee challenges in the day-to-day implementation of the highly complex prognostic model which has more than 100 permutations of the TNM stages, grade and ER, PR, HER2 status to categorize into the different stages. A paper led by Chavez-Macgregor et al. using data from the Californian Cancer Registry reported that using a risk score incorporating grade, ER and HER2 receptor status into the anatomic staging system improves prognostication. The authors concluded that their risk score system should be considered a simpler alternative to the AJCC 8th edition prognostic stage [25].

The improved accuracy of the prognostic system is of utmost importance in guiding and tailoring adjuvant treatment. Patients with what was an 'early' breast cancer may be appropriately recognized as being of higher risks and treated more aggressively. Conversely, the good prognosis conferred by the constellation of biological factors in what was a 'high' anatomic stage patients represent opportunities to deescalate treatment such as the avoidance of chemotherapy and its attendant side effects.

5. Conclusion

The prognostic staging system is better in predicting survival outcomes in our group of Asian women who received standard of care treatment; however the anatomic system will remain relevant due to its ease of use.

Declarations

The authors do not have any conflict of interests or any funding sources. Ethics approval was obtained (Singhealth CIRB ref: **2017/2375**) for this study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2018.04.013.

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