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The effect of the American Joint Committee on Cancer eighth edition on breast cancer staging and prognostication

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ABSTRACT

Introduction: Breast cancer staging has been developed to quantify prognosis and guide treatment. The American Joint Committee on Cancer eighth edition manual (AJCC8) departed from traditional anatomic staging by incorporating biological factors such as grade, hormone and HER2 receptor status into a novel prognostic staging model. The aim of this study was to externally validate AJCC8 prognostic staging.
Methods: This retrospective cohort investigated patients diagnosed between 2010 and 2013 at the McGill University Health Center. Patients were classified using both anatomic and prognostic staging systems according AJCC8. Overall survival analysis using a multivariate Cox-proportional hazard model was performed and model accuracy was evaluated using the Harrell concordance index (C-index) and Akaike Information Criterion (AIC).
Results: The cohort included 1703 women. Anatomic and prognostic stage assignments displayed discrepancies for 46.2% of patients, where 38.8% were downstaged and 7.5% were upstaged with prognostic staging. Patients with anatomic stages IB, IIA, IIB, IIIA and IIIC had high rates of downstaging (64.6–96.5%), as opposed to anatomic stages IA and IIIB where 93.1% and 75.0% of patients stage remained unchanged, respectively. The prognostic stage displayed increased prognostic accuracy with respect to overall survival, where the C-index was significantly higher compared to anatomic staging (0.810 vs 0.799, $p < 0.05$). In addition, prognostic staging displayed an improved model fit with a lower AIC (983.9) compared to anatomic staging (995.2).
Conclusion: Prognostic and anatomic staging differ in their classification of patients, where prognostic staging displays improved accuracy, supporting its use in informing patient prognosis and guiding treatment decisions.

Introduction

Breast cancer staging has been developed to quantify prognosis and guide treatment. The American Joint Committee on Cancer (AJCC) has established criteria which have traditionally assigned stage based on the anatomic extent of disease, including tumor size (T), nodal (N), and distant metastasis (M) [1]. Since its inception in 1977 through the seventh edition of the AJCC manual published in 2009, the TNM framework has served as the global standard for comparing epidemiological cohorts, used for inclusion criteria in clinical trials and more routinely as a cohesive language to succinctly convey disease status among clinicians.

The value of anatomical staging remains an integral component of planning of local and systemic therapies. An increasing understanding of breast cancer heterogeneity, however, has demonstrated the significant prognostic and predictive value of tumor

Abbreviations: AIC, Akaike information criterion; AJCC, American Joint Committee on Cancer; AJCC8, American Joint Committee on Cancer staging eighth edition; ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, Hazard ratio; PR, Progesterone receptor; MUHC, McGill University Health Centre; OS, Overall survival; TNM, Tumor, node, metastasis staging.

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intrinsic features, such as grade, hormone and human epidermal growth factor receptor 2/Neu (HER2) receptor status [2–4]. These markers are now routinely evaluated to select systemic therapy, yet are not accounted for in the anatomy-based TNM staging. More recently, further improvements in prognostication have been made possible with the use of gene expression signatures as readouts for more complex biological processes, particularly for axillary node-negative, estrogen receptor (ER)-positive, HER2-negative breast cancers [5]. These expression profiles have translated into clinical decision-making tools, such as OncotypeDx, which can identify a subset of women who can be spared chemotherapy. To remain relevant to contemporary practice, the eighth edition of AJCC staging manual (AJCC8) outlines a novel prognostic staging system which incorporates these biological factors and genomic assays [6]. Although the anatomic staging system remains for areas of the world where access to molecular testing and corresponding therapies are limited, effective January 1, 2018, the prognostic staging system has become standard-of-care where resources are available.

Although prognostic staging had been founded on a well-studied Bioscore staging system, there was little published data to support the prognostic staging model at the time of its initial release [7]. While the analysis of the National Cancer Database which was used in the actual development of the prognostic staging system by the AJCC has yet to be published, subsequent external validation studies have demonstrated improved performance of the prognostic model compared to anatomic staging [8,9]. In these early studies, however, 7–14% of patients could not be staged because of uncategorized combinations of TNM, grade, hormone and HER2 receptor parameters. Since the initial publication of the staging tables in 2016, the AJCC manual was updated in November 2017 to account for all possible combinations [10]. Here, we aim to externally validate the prognostic staging model with the most recent version of the AJCC8 in a single-institution breast cancer population (see Fig. 1).

Materials and methods

Study population

This study was approved by the McGill University Health Centre (MUHC) Research Ethics Board (2018–4382). Informed consent was waved for this retrospective analysis. After obtaining institutional review board approval, clinicopathologic data was extracted from a prospectively-maintained clinical database of breast cancer patients treated at a university cancer center between January 1, 2010 and December 31, 2013. Data collected included age at diagnosis, gender, TNM stage, histological subtype, grade, estrogen receptor (ER), progesterone receptor (PR) and HER2 status, surgical treatment, receipt of radiation therapy, chemotherapy, hormone therapy as well as follow-up time and vital status. ER, PR and HER2 classification was performed according to the most recent ASCO/CAP guidelines [11,12]. A consecutive series of 2242 cases of invasive breast carcinomas treated within the study period was initially identified for inclusion in the study. Exclusion criteria included incomplete clinicopathological data (424 cases), stage IV disease (78 cases), no follow-up data (20 cases) and male breast cancer (17 cases), yielding a final study population of 1703 patients. No cases of mesenchymal tumors or lymphomas were included in the study. The majority of patients (1382, 81.2%) had data for pathological staging, while clinical staging was used for 321 (18.8%) patients with incomplete pathological information.

Statistical analyses

The prognostic stage and anatomic stage were ascertained for all patients according to the AJCC8 [6]. Overall survival (OS) was analyzed using a multivariate Cox proportional-hazards model to compare differences between anatomic and prognostic groups. Age, grade, surgical treatment, receipt of radiotherapy, and hormone therapy were included in the model. The results were expressed as hazard ratios with 95% confidence intervals (CI). The Harrell concordance index (C-index) was calculated for each model using the survival package in the R Project for Statistical Computing (The R Foundation) [13,14]. The C-index can be interpreted as a measure of the model's predictive performance, where a higher C-index indicates a better predictive performance. The C-index of the two staging models were compared and statistical significance was determined using the compare C package in R. To compare model fits, a generalized linear model with a binomial distribution was built, generating an Akaike Information Criterion (AIC), where a lower AIC supports a better model fit [15]. All statistical analyses were completed using R with p-values $\leq$0.05 being considered significant.

Results

We identified 1703 women diagnosed with stage IA to IIIC breast cancer who underwent evaluation at the MUHC between 2010 and 2013 for inclusion in this study. The clinicopathological data for this population is shown in Table 1. The median age at diagnosis was 59 (range 24–97). Histological subtypes were predominantly invasive ductal carcinoma of no special type (IDC-NST, 76.2%) and invasive lobular carcinomas (ILC, 9.0%), with the remaining 14.7% comprised of other histologies. The majority of cases were ER+/HER2- (74.5%), followed by ER+/HER2+ (10.7%), ER-/HER2- (10.3%), and ER-/HER2+ (4.5%). Most patients received local therapies, with 96.8% undergoing surgery and 81.7% undergoing radiation therapy. Regarding systemic therapy, 86.8% of patients with ER + tumors received hormonal therapy while 50.4% of the overall cohort received chemotherapy.

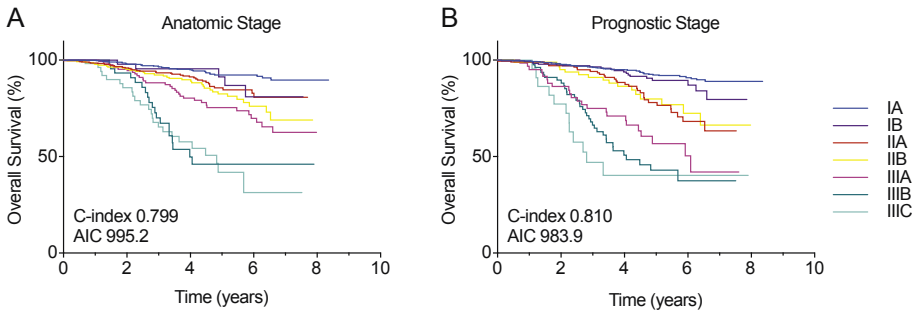

Fig. 1. Overall survival. Kaplan-Meier curves for overall survival using (A) anatomic and (B) prognostic staging. AIC, Akaike information criterion.

Table 1
Clinicopathologic characteristics of patients (n = 1703).

Clinicopathologic feature	n (%)
Gender	
Female	1703 (100)
Male	0 (0)
Age (years)	
<40	89 (5.2)
40-69	1236 (72.6)
>69	378 (22.2)
Median (range)	59 (24–97)
Histology	
IDC-NST	1299 (76.2)
ILC	154 (9.0)
Other	250 (14.7)
Grade	
1	292 (17.1)
2	855 (50.2)
3	556 (32.6)
ER	
Positive	1450 (85.1)
Negative	253 (14.9)
PR	
Positive	1341 (78.7)
Negative	362 (21.3)
HER2	
Positive	259 (15.2)
Negative	1444 (84.8)
T Stage	
1	949 (55.7)
2	581 (34.1)
3	110 (6.5)
4	63 (3.7)
N stage	
0	1077 (63.2)
1mi	85 (5.0)
1	396 (23.3)
2	89 (5.2)
3	56 (3.3)
M stage	
0	1703 (100)
1	0 (0)
Surgery	
Yes	1649 (96.8)
No	54 (3.2)
Radiation	
Yes	1392 (81.7)
No	311 (18.3)
Hormone	
Yes	1281 (75.2)
No	422 (24.8)
Chemotherapy	
Yes	859 (50.4)
No	844 (49.6)

Patients were staged according to the AJCC8 anatomic and prognostic staging systems (Table 2). By anatomic staging, 47.3% of patients were stage I (44.0% IA and 3.3% IB), 37.6% were stage II (23.7% IIA and 13.9% IIB), and 15.0% were stage III (8.4% IIIA, 3.3% IIIB, 3.3% IIIC). In contrast to studies using the first release of the eighth edition staging tables, all patients could be assigned to a prognostic stage group in this analysis using the updated versions. Compared to anatomic staging, there were more patients with prognostic stage I disease, with 72.2% patients in this group (56.3% IA and 15.9% IB), while 17.2% were stage II (11.5% IIA and 5.7% IIB), and 10.6% were stage III (3.9% IIIA, 5.2% IIIB, 1.5% IIIC).

Table 2
Anatomic and prognostic stage distribution.

Stage	Anatomic, n (%)	Prognostic, n (%)
IA	750 (44.0)	959 (56.3)
IB	57 (3.3)	271 (15.9)
IIA	404 (23.7)	196 (11.5)
IIB	236 (13.9)	96 (5.6)
IIIA	144 (8.4)	66 (3.9)
IIIB	56 (3.3)	89 (5.2)
IIIC	56 (3.3)	26 (1.5)

To further delineate the differences between anatomic and prognostic staging, the frequency of stage discrepancies for individual patients was evaluated (Table 3). When prognostic staging was applied, 46.2% of patients were assigned a different stage compared to anatomic staging. Of the 38.8% patients who were downstaged, 16.3%, 19.4% and 3.0% were downstaged by one, two or three stage categories, respectively. Anatomic stages IB, IIA, IIB, IIIA and IIIC had high rates of downstaging, ranging from 64.6% to 96.5%. In contrast, in anatomic stages IA and IIIB, 93.1% and 75.0% of patients' stage remained unchanged, respectively. Only 7.5% of patients were upstaged, with 6.5%, 1.0% and 0.0% being upstaged by one, two or three categories, respectively. These data highlight marked differences in the staging of patients, with an increased tendency for downstaging when using the prognostic system.

To validate the prognostic staging system in a survival analysis, a multivariable Cox proportional hazards regression model, including age, grade, surgical treatment, radiation, and hormone therapy was developed. The median follow-up for OS analysis was 44.4 months. Hazard ratios (HR) for OS for each of the anatomic and prognostic stages with stage IA as the reference are shown in Table 4. For both anatomic and prognostic staging, all stages with the exception of stage IB showed significantly worse survival compared to stage IA. The C-index, a measure of concordance between predicted and observed outcomes, was significantly higher for the prognostic model (0.810) when compared to the anatomic model (0.799)($p < 0.05$). Further supporting its improved performance, the prognostic model demonstrated a lower AIC (983.9) compared to the anatomic model (995.2), indicating better model fit and accuracy. Together, this validates the improved prognostic value of the prognostic staging system in patients diagnosed with breast cancer.

Discussion

Because of the overwhelming data supporting the additional prognostic value of biological markers in breast cancer, the AJCC has made a radical departure away from traditional anatomic staging and implemented a novel prognostic staging system that has become the new standard for staging. This aligns with a broader movement by breast cancer expert panels and guideline committees which have supported the use of tumor biological factors in clinical decision-making for breast cancer care [11,12,16,17]. Although there was no level-one evidence to support the use of the AJCC8 breast cancer staging system prior to its implementation, our study on a single-institution population supports the growing body of data externally validating the increased accuracy of the

Table 3
Anatomic and prognostic stage discrepancies.

	Prognostic							*Total*
Anatomic	IA	IB	IIA	IIB	IIIA	IIIB	IIIC	
IA	698	52	0	0	0	0	0	*750*
IB	55	2	0	0	0	0	0	*57*
IIA	195	84	95	30	0	0	0	*404*
IIB	11	93	76	38	10	8	0	*236*
IIIA	0	40	25	28	33	9	9	*144*
IIIB	0	0	0	0	5	42	9	*56*
IIIC	0	0	0	0	18	30	8	*56*
Total	*959*	*271*	*196*	*96*	*66*	*89*	*26*	*1703*

Table 4
Hazard ratios for anatomic and prognostic stages.

	Anatomic		Prognostic	
Stage	HR (95% CI)	p-value	HR (95% CI)	p-value
IA	1.00 [Reference]		1.00 [Reference]	
IB	1.82 (0.71–4.66)	0.21	1.26 (0.74–2.15)	0.39
IIA	1.66 (1.04–2.64)	0.03	2.63 (1.62–4.26)	8.76×10^{-5}
IIB	2.99 (1.83–4.88)	1.10×10^{-5}	2.32 (1.25–4.32)	8.01×10^{-3}
IIIA	3.94 (2.41–6.44)	4.12×10^{-8}	6.26 (3.70–10.58)	7.87×10^{-12}
IIIB	5.08 (2.81–9.15)	6.30×10^{-8}	7.19 (4.43–11.67)	1.44×10^{-15}
IIIC	11.37 (6.58–19.64)	2.00×10^{-16}	9.30 (4.59–18.82)	5.79×10^{-10}

prognostic staging compared to traditional anatomic staging.

Using the first published version of the AJCC8 staging tables, early validation studies found that 7–14% of patients could not be categorized using prognostic staging [8,9]. Here we used the most up-to-date tables released in November 2017 where we found that all TNM, grade, ER, PR, and HER2 combinations are accounted for and all patients can be classified into a single prognostic stage group. In this study, 46.2% of patients have discrepancies between anatomic and prognostic stages, similar to the 46.5–57.6% previously reported [8,18]. Downstaging was much more common than upstaging (38.8% versus 7.5%) in the population reported here, a distribution similar to that observed by Wong et al. (40.7% versus 5.8%) [18]. These findings contrast with earlier studies where down- and upstaging were equally distributed, though it should be noted that the majority (349/451, 77.4%) of patients from the MD Anderson cohort who could not be classified were in fact downstaged with the updated prognostic stage tables [8]. It remains unclear whether this fully accounts for the differences in up/downstaging rates, which is why application of the updated AJCC8 staging on further breast cancer study populations is warranted.

The immediate clinical implications of the AJCC updates lie in the improved prognostic accuracy of prognostic staging (C-index 0.810, AIC 983.9) compared to anatomic staging (C-index 0.799, AIC 995.2) identified in this study. While prognostic stage alone does not guide current treatment decisions which continue to rely on tumor size, nodal involvement, receptor status and genomic assays, prognostic stage is valuable in counselling patients with regards to prognosis. Prospective studies evaluating benefits of chemotherapy in patients who were down- or upstaged are warranted. The addition of biological parameters has increased the complexity of staging tables by an order of magnitude, where the possible stage combinations have gone from tens to hundreds. Although this could represent a challenge in the adoption and implementation of the new staging system, online calculators and mobile applications have been developed to facilitate the transition.

Our study is not without limitations. While the data were collected prospectively in a single center, the analysis was performed retrospectively, possibly inducing a selection bias. Moreover, our study did not include gene expression data, as use of Oncotype Dx at our institution was limited during the study period and results were not readily accessible in the medical record. Of the 807 women with T1-2, N0, ER+/HER2-disease in our study who would be candidates for OncotypeDx, only 83 (10.3%, or 4.9% of overall population) had a prognostic stage greater than IA and could potentially be downstaged with OncotypeDx scores of less than 11. As genomic assays rapidly expand to larger subsets of breast cancer patients, future iterations of staging guidelines will need to keep pace with these rapid advances and will likely require revisions more frequently than the current 5–7 year interval. Moreover, a study like ours represent a real-life scenario validation given that OncotypeDx might not be available in developing countries due to its costs while the presence of hormone receptors is routinely ascertained.

Disclosures

None.

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