Validation of a Novel Staging System for Disease-Specific Survival in Patients With Breast Cancer Treated With Neoadjuvant Chemotherapy

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ABSTRACT

Purpose

We previously described a novel breast cancer staging system for assessing prognosis after neoadjuvant chemotherapy on the basis of pretreatment clinical stage (CS), estrogen receptor status (E), grade (G), and post-treatment pathologic stage (PS). This clinical-pathologic stage (CPS) + EG staging system assigned and summed points for each factor, allowing for better determination of breast cancer–specific survival than CS or PS alone. The current study was undertaken to validate this staging system using internal and external cohorts.

Methods

We identified an internal cohort of 804 patients treated with neoadjuvant chemotherapy at our institution from 2003 to 2005 and an external cohort of 165 patients treated at another institution. Clinicopathologic characteristics, treatment regimens, and patient outcomes were assessed. Outcomes were stratified by CPS + EG score.

Results

Five-year disease-specific survival (DSS) for the internal cohort was 77% (95% CI, 72 to 82) at a median follow-up of 3.4 years (range, 0.3 to 5.9 years). Five-year DSS for the external cohort was 86% (95% CI, 79 to 91) at a median follow-up of 4.7 years (range, 0.5 to 10.5 years). The ability of the CPS + EG score to stratify outcomes was confirmed in both the internal and external cohorts. Application of the CPS + EG staging system facilitated more refined categorization of patients into prognostic subgroups by outcome than presenting CS or final PS as defined by the American Joint Committee on Cancer (AJCC) staging system.

Conclusion

The current study validates the CPS + EG staging system in two independent cohorts. We recommend that biologic markers and response to treatment be incorporated into revised versions of the AJCC staging system for patients receiving neoadjuvant chemotherapy.

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INTRODUCTION

Neoadjuvant chemotherapy has long been considered the standard of care for treatment of patients with locally advanced or inoperable breast cancer. As this approach has facilitated improved surgical options and allowed for assessment of clinical and pathologic response rates, it has been increasingly used in patients with operable breast cancer. As the indications for neoadjuvant chemotherapy have expanded, interest has grown in using treatment response as a prognostic tool.

Clinical and pathologic response to neoadjuvant chemotherapy have been shown to correlate with patient outcomes, with significant improve-

ment in both disease-free¹⁻³ and overall survival (OS) noted in patients achieving pathologic complete response (pCR).¹ For patients with residual tumor in the breast and axilla, assignment of pathologic stage according to the American Joint Committee on Cancer (AJCC) breast cancer staging system has been shown to stratify patients by both distant disease-free survival and OS.⁴ This strategy relies solely on final pathologic stage for stratifying patients. Our group hypothesized that incorporating initial clinical stage and biologic markers from the primary tumor along with the final pathologic stage could more accurately stratify patients according to prognosis after administration of neoadjuvant chemotherapy. We developed two novel

staging systems using pretreatment clinical stage (CS), estrogen receptor (ER) status (E), grade (G), and post-treatment pathologic stage (PS) and demonstrated their utility in a large cohort of patients treated with neoadjuvant chemotherapy at our institution.⁵ We used a Cox proportional hazards model to create the clinical-pathologic staging (CPS) system using all clinical and pathologic substages. A second analysis was performed to test the added significance of ER and progesterone receptor status, nuclear grade, human epidermal growth factor receptor 2 (HER2)/*neu* status, presence of lymphovascular invasion, age at presentation, and number of chemotherapy cycles administered (three ν $\geq$ four). ER-negative disease and nuclear grade 3 tumor pathology were found to be independent risk factors for poor prognosis, and these variables were added to the CPS system to create a second staging system, the CPS + EG system.^{5,6} Application of the CPS + EG staging system allowed for stratification of patients into seven groups with significantly different 5-year distant metastasis-free and disease-specific survival (DSS).

The increased ability to discriminate among subgroups of patients using the CPS + EG staging system was demonstrated by the variation in 5-year DSS, which ranged from 22% to 100%. On the basis of these data, we concluded that the CPS + EG staging system could provide more precise information regarding prognosis and facilitate decision making regarding adjuvant treatment strategies.^{5,6} The current study was undertaken to validate the CPS + EG staging system using a more contemporary cohort of patients from our institution as well as an external cohort of patients treated at The University of Michigan (Ann Arbor, MI).

METHODS

A prospectively maintained database of patients with breast cancer treated at The University of Texas MD Anderson Cancer Center (Houston, TX) was used to identify 804 patients with nonmetastatic breast cancer who received neoadjuvant chemotherapy from January 2003 through December 2005. A second cohort of 165 patients treated with neoadjuvant chemotherapy at The University of Michigan from July 1997 through November 2006 was identified. All patients received a neoadjuvant chemotherapy regimen with a backbone of anthracycline or taxane or a combination of the two. These cohorts were compared with the initial cohort used to develop the CPS + EG system. The initial cohort included 932 patients receiving neoadjuvant chemotherapy at the MD Anderson Cancer Center from January 1997 through December 2002.⁵ Because determination of the CPS + EG staging system predated the use of neoadjuvant trastuzumab therapy, patients receiving neoadjuvant trastuzumab were excluded from the initial and validation cohorts.

Table 1 summarizes the point assignment for each variable used to calculate the CPS + EG score. For both cohorts, CS at presentation, ER status, nuclear grade, and final PS were identified to develop the CPS + EG score. Consistent with our initial cohort, CS and PS were both determined using the sixth edition of the AJCC staging system. Additional clinical and pathologic data, including patient age, clinical tumor size as measured by mammogram or ultrasound, chemotherapy regimen, type of surgery, use of adjuvant radiation therapy, pathologic tumor size, and HER2 status, were recorded. ER, progesterone receptor, and HER2 status and nuclear grade were determined on the patient's diagnostic biopsy specimen. pCR was defined as no residual invasive disease in the breast or axilla.

Differences in clinicopathologic factors between the groups were assessed using the Mann Whitney test for continuous variables and the χ^2 test for categorical variables. The CPS + EG score was determined for each patient according to the previously published staging system.⁵ DSS was calculated from date of diagnosis to date of death as a result of breast cancer or censored at date of last follow-up. Five-year DSS was calculated using the Kaplan-Meier

Table 1. Point Assignments for the CPS + EG Staging System

Stage	Points
Clinical stage	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic stage	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Tumor marker	
ER negative	1
Nuclear grade 3	1

Abbreviations: CPS + EG, clinical-pathologic staging system incorporating ER-negative disease and nuclear grade 3 tumor pathology; ER, estrogen receptor.

method, and differences were compared using the log-rank test.⁷ The Greenwood method was used to calculate 95% CIs.⁸ The institutional review boards at the MD Anderson Cancer Center and University of Michigan approved this study.

RESULTS

Clinicopathologic Characteristics of the Initial and Validation Cohorts

Clinicopathologic characteristics for the initial as well as the internal and external validation cohorts are listed in Table 2. As demonstrated in the table, there were significant differences between the initial cohort and internal validation cohort with respect to several factors, including nuclear grade ($P = .029$), with a greater percentage of patients in the validation cohort having grade 3 disease. When patients with nuclear grade 1 or 2 tumor pathology were grouped together and compared with patients with grade 3 tumors, the difference in distribution between the groups persisted ($P = .028$). In the validation cohort, a greater percentage of HER2-negative patients was identified (85% in validation cohort ν 68% in initial cohort), in part because of the fact that HER2 status was not routinely reported during the initial time period (HER2 unknown in 12.4% of patients in initial cohort ν 1% in validation cohort). There was also a difference with respect to chemotherapy regimens administered ($P < .001$) and receipt of adjuvant radiation therapy (83% [validation cohort] ν 76% [initial cohort]; $P < .001$). The difference in adjuvant radiation therapy was attributable to a higher percentage of mastectomy patients receiving postmastectomy radiation in the validation cohort (75% ν 65% in initial cohort; $P < .001$). There was no difference with respect to adjuvant radiation therapy in the two cohorts for patients undergoing breast-conserving therapy ($P = .232$).

There were also a number of differences between the initial cohort and external validation cohort (Table 2). Important for the

Table 2. Clinicopathologic Factors for Validation Cohorts

Factor	Initial Cohort (n = 932)		Internal Cohort (n = 804)			External Cohort (n = 165)		
	No.	%	No.	%	P*	No.	%	P*
Age, years					.808			.032
Median	50		50			48		
Range	22-83		24-79			26-95		
Clinical tumor size, cm					< .001			.238
Median	4		3.5			3.5		
Range						1-15.5		
Clinical stage at presentation					< .001			< .001
I	49	5	25	3		4	2	
IIA	330	35	243	30		48	29	
IIB	267	29	208	26		66	40	
IIIA	130	14	90	11		36	22	
IIIB	119	13	103	13		5	3	
IIIC	37	4	135	17		6	4	
Pathologic tumor size, cm					.828			.004
Median	1.5		1.5			1.1		
Range	0-18		0-15			0-11.7		
Pathologic stage					.018			.616
0	130	14	128	16		23	14	
I	209	22	156	19		36	22	
IIA	256	27	180	22		42	25	
IIB	83	9	74	9		16	10	
IIIA	147	16	136	17		29	18	
IIIB	35	4	37	5		2	1	
IIIC	72	8	93	12		17	10	
ER status					.194†			.003†
Positive	573	61	474	59		82	50	
Negative	351	38	330	41		83	50	
Unknown	8	1	0	0		0	0	
HER2 status					< .001†			.891†
Positive	187	20	115	14		37	22	
Negative	629	68	679	85		128	78	
Unknown	116	12	10	1		0	0	
Nuclear grade					.029†			.001†
1	29	3	32	4		14	9	
2	339	36	249	31		70	42	
3	550	59	523	65		81	49	
Unknown	14	2	0	0		0	0	
Neoadjuvant therapy					< .001			< .001
Anthracycline based	262	28	135	17		17	10	
Taxane based	63	7	40	5		9	6	
Combination	607	65	629	78		139	84	
Surgical therapy					.869			.057
Mastectomy	576	62	500	62		89	54	
Lumpectomy	356	38	304	38		76	46	
Adjuvant radiation therapy					< .001†			< .001†
Yes	710	76	670	83		144	87	
No	221	24	134	17		14	9	
Unknown	1	< 1	0	0		7	4	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

*P values reflect comparison of each validation cohort with the initial cohort.

†Unknown values excluded.

CPS + EG system, there was a greater percentage of patients presenting with clinical stage IIB disease (40% v 29% in initial cohort) and fewer patients with clinical stage IIIB disease (3% v 13%). Similar to what was seen with the internal validation cohort, there were differences with respect to chemotherapy regimen used ($P < .001$) and use of adjuvant radiation therapy ($P < .001$).

Survival

For the internal cohort, median follow-up was 3.4 years (range, 0.3 to 5.9 years), and 5-year DSS was 77% (95% CI, 72 to 82). Median follow-up was 4.7 years (range, 0.5 to 10.5 years) in the external cohort, and 5-year DSS was 86% (95% CI, 79 to 91). Table 3 summarizes 5-year DSS for the initial and validation cohorts

Table 3. Disease-Specific Survival Outcomes Determined Based on CPS + EG Staging System for Initial and Validation Cohorts

CPS + EG Score	Initial Cohort			Internal Validation Cohort				External Validation Cohort			
	No. of Patients	5-Year DSS (%)	95% CI	No. of Patients	5-Year DSS (%)	95% CI	<i>P</i> *	No. of Patients	5-Year DSS (%)	95% CI	<i>P</i> *
0	73	100		32	97	80 to 100	NS	10	100		NS
1	155	98	94 to 100	108	98	86 to 100	NS	17	94	63 to 99	NS
2	245	96	91 to 98	223	88	79 to 93	NS	60	93	80 to 98	NS
3	226	88	83 to 92	186	72	51 to 85	.046	45	74	56 to 86	NS
4	151	72	64 to 79	169	73	62 to 81	NS	27	88	61 to 97	NS
5	51	57	42 to 70	64	52	33 to 68	NS	5†	33	1 to 77	NS
6	9	22	3 to 51	22	17	4 to 40	NS				

Abbreviations: CPS + EG, clinical-pathologic staging system incorporating estrogen receptor–negative disease and nuclear grade 3 tumor pathology; DSS, disease-specific survival; NS, not significant.

**P* values reflect comparison of each validation cohort with the initial cohort.

†Patients with a CPS + EG score of 5 or 6 were analyzed together because of the small number of patients in this group.

stratified according to CPS + EG score. A survival difference was noted between the initial and internal validation cohorts for patients with a CPS + EG score of 3. In the initial cohort, there were 226 patients with a CPS + EG score of 3 with a 5-year DSS of 88% (95% CI, 83 to 92), whereas those in the internal validation cohort (186 patients) with a CPS + EG score of 3 had a DSS rate of 72% (95% CI, 51 to 85).

To investigate further the differences between patients with a CPS + EG score of 3 in the initial and internal validation cohorts, we compared the two groups with respect to each component. No difference was found between patients from the initial and internal validation cohorts with respect to pathologic stage ($P = .891$), ER status ($P = .205$), or grade ($P = .208$). However, there was a significant difference in the distribution of clinical stages ($P = .003$), with a smaller percentage of patients presenting with stage IIIB or higher disease in the initial (15.9%) compared with the validation cohort (29%; $P = .001$).

For both validation cohorts, CPS + EG staging facilitated categorization of patients into more refined subgroups than presenting clinical stage or final pathologic stage, with a pattern of prediction for DSS similar to that demonstrated in the initial cohort (Fig 1). Furthermore, when all three cohorts were combined, 5-year DSS determined by the CPS + EG system ranged from 23% to 99% (Fig 2) versus 61% to 92% for clinical stage alone and 58% to 95% for pathologic stage alone.

To determine if the CPS + EG staging system might have broader clinical utility, we looked at the ability of the score to categorize patients from the initial and internal validation cohorts with respect to recurrence-free survival (RFS). As shown in Figure 3, the CPS + EG score did stratify patients with respect to RFS, with 5-year RFS rates ranging from 15% to 95% ($P < .001$).

DISCUSSION

The CPS + EG staging system was previously developed by our group to provide a more precise assessment of patient prognosis after neoadjuvant chemotherapy. This staging system is unique in that it was developed on the basis of both traditional anatomic staging pretreatment (CS) and post-treatment (PS) and factors determining tumor biology (ER status and grade).⁵ We found that application of the CPS + EG staging system facilitated more refined stratification by DSS than did CS or PS alone. In addition, the CPS + EG system was able to

stratify further patients with a pCR on the basis of presenting clinical stage and biologic tumor markers. In the current study, we used internal and external patient cohorts to validate this novel staging system and confirmed that the CPS + EG score has the ability to separate patients into more refined subgroups by outcome than either pathologic response rate or clinical or pathologic AJCC staging.

We first validated the CPS + EG staging system with a cohort of more than 800 patients who were treated with neoadjuvant chemotherapy at our institution during the 2 years after the time period used for the initial development of the staging system. In this analysis, we noted several differences in the clinicopathologic features of the initial and internal validation cohorts, the majority of which are explained by differences in treatment strategies. Median presenting clinical tumor size was smaller in the validation cohort, consistent with expanding indications for the use of neoadjuvant chemotherapy in patients with earlier-stage disease.^{2,9} There was also a difference between the cohorts with respect to chemotherapy regimens, with a greater percentage of women in the internal validation cohort receiving both an anthracycline and taxane. This is consistent with a change in treatment regimens in response to clinical trials suggesting that treatment with both an anthracycline and taxane is superior to that with an anthracycline alone.^{2,9-12} Also, a greater percentage of patients in the internal validation cohort received adjuvant radiation therapy as a result of an increase in adjuvant postmastectomy radiation therapy.

Despite differences in treatment strategies used during the time periods from which the initial and internal validation cohorts were identified, when applied to the internal cohort, the CPS + EG scoring system again stratified patients into more refined prognostic subgroups than the AJCC staging system applied to either the presenting CS or final PS. These findings were confirmed using an additional cohort of patients treated at The University of Michigan. Application of the CPS + EG staging system to a cohort of patients from that institution demonstrated a similar pattern of stratification on the basis of outcomes. The CIs of the survival estimates were not as precise for this cohort because there were fewer patients in this group. Together, these findings suggest that the CPS + EG staging system has excellent discrimination and broad applicability and can be generalized to other institutions where patient populations and/or practice patterns may not be identical to those implemented at the MD Anderson Cancer Center.

Fig 1. Disease-specific survival for (A to C) internal and (D to F) external validation cohorts on the basis of (A and D) presenting clinical stage, (B and E) final pathologic stage, and (C and F) clinical-pathologic stage + estrogen receptor status and grade score.

Although the validation cohorts demonstrated the ability of the CPS + EG staging system to identify prognostic subgroups similar to the initial cohort, there was one CPS + EG score that was discrepant between the groups. In the initial cohort, 5-year DSS for patients with a CPS + EG score of 3 was 88% (95% CI, 83 to 92), whereas 5-year DSS for patients with a CPS + EG score of 3 was 72% (95% CI, 51 to 85) in the internal validation cohort and 74% (95% CI, 56 to 86) in the

external cohort. To investigate this finding, we identified differences between the initial cohort and the internal validation cohort with respect to the components of the score. The only difference between the groups was in clinical stage, with patients in the internal validation cohort having higher-stage disease at presentation. This finding supports the idea that the burden of disease at presentation is important in determining overall prognosis. Consistent with the findings from our

Fig 2. Disease-specific survival as determined by the clinical-pathologic stage + estrogen receptor status and grade staging system using combined data from the initial, internal validation, and external validation cohorts (N = 1,901).

previous study, we noted that using the CPS + EG staging system in patients achieving pCR, we could stratify patients' DSS by presenting clinical stage and biologic markers. Patients who achieved pCR after presenting with stage I or IIA disease without adverse biologic markers had a better predicted DSS than patients who achieved pCR after presenting with stage IIIC, grade 3, or ER-negative disease (100% v 72%).⁵

Other investigators have proposed methods for determining how response to neoadjuvant chemotherapy affects prognosis. Initial studies examining the impact of response emphasized the association between pCR and improved OS.^{1-3,4} Carey et al⁴ reported that assignment of pathologic stage, defined by the sixth edition of the AJCC staging system, after treatment with neoadjuvant chemotherapy facilitated stratification of subgroups according to survival in patients with breast cancer. Symmans et al¹³ demonstrated that determining the extent of residual disease in the breast and axilla as well as the degree of residual cellularity in the primary tumor (ie, the residual cancer burden [RCB]) was a significant predictor of distant relapse-free survival. Patients were stratified according to RCB score, which reflected the

Fig 3. Recurrence-free survival as determined by the clinical-pathologic stage + estrogen receptor status and grade staging system using data from the initial and internal validation cohorts.

extent of residual disease. Applying the RCB group to each post-therapy AJCC stage group, the authors found that the RCB classified stage II patients into three subgroups and stage III patients into two subgroups with significantly different prognoses. The CPS + EG staging system combines the standard of anatomic staging as determined at initial clinical presentation with the PS after chemotherapy and includes strong indicators of tumor biology, ER status, and grade. Incorporating these biologic markers allows us to better stratify patient prognosis and may additionally enhance our understanding of the need for additional therapy.

It is important to acknowledge that the CPS + EG staging system was developed before the routine use of trastuzumab therapy in the neoadjuvant or adjuvant setting. When the CPS + EG staging system was devised, HER2 status was not found to be significant with respect to DSS either as a univariate factor or when added to an initial model stratified by CS and PS. In the initial cohort, HER2 status was unknown in more than 10% of patients because HER2 status was not routinely assessed in that timeframe. In the internal validation cohort, HER2 status was unknown in 1% of patients. Because the validation cohort provided a more complete data set with respect to HER2 status, this factor was reassessed and still was not significant either as a univariate factor ($P = .797$) or when added to a model stratified by CPS + EG ($P = .15$). We hypothesize that HER2 status would be a significant factor in the current era because patients with HER2-positive tumors are routinely treated with trastuzumab, which has been shown to improve survival in the adjuvant setting.^{14,15} Trastuzumab-based neoadjuvant chemotherapy has also been shown to be efficacious, with pCR rates as high as 65% in patients with both early and locally advanced breast cancer.¹⁶⁻¹⁸ Our group recently published data regarding RFS in patients with HER2-positive disease treated with trastuzumab-based neoadjuvant chemotherapy and noted that patients who achieved pCR had a 3-year RFS of 96% (95% CI, 91 to 100) compared with a 3-year RFS of 80% (95% CI, 71 to 91) in patients who did not achieve pCR ($P = .018$).¹⁷ Recognizing the importance of biologic factors in the prognosis of patients with breast cancer, future work will focus on developing a staging system that can be applied to patients with HER2-positive disease receiving HER2-directed therapies as part of their treatment. Ideally, a staging system would be devised with the capacity to be refined by the addition of new molecular markers as they are identified.

In conclusion, the current study confirms that the CPS + EG staging system can discriminate among patient subgroups with respect to survival after neoadjuvant chemotherapy. In addition to providing more refined assessment of prognosis, this staging system may help identify patients for clinical trials investigating novel therapies after completion of standard neoadjuvant chemotherapy. Importantly, the CPS + EG score can be readily determined using data routinely available in clinical and pathologic records. To assist with determination of the CPS + EG score, we created a Web site (<http://www.mdanderson.org/postchemotherapy staging>) that allows access to this staging system through a prognostic calculator.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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