Novel Postneoadjuvant Prognostic Breast Cancer Staging System

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ABSTRACT

PURPOSE Prognostic staging after neoadjuvant chemotherapy (NACT) is not included in American Joint Commission on Cancer (AJCC) staging. This study addressed this deficiency by including responses to therapy with standardized staging variables in a validated prognostic staging system for patients treated with NACT.

METHODS The National Cancer Database was queried to identify 140,605 patients treated with NACT between 2010 and 2018. Three response categories (no response, partial response, and complete response [pCR]) were created on the basis of comparison of clinical and post-NACT pathologic staging. Univariate and multivariate analyses of clinical stage, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and grade were analyzed for each category. Predictive models for each response category were validated using the bootstrap technique. Calibration plots compared predicted and observed 3-year survival probabilities in the training and validation data sets.

RESULTS Each validated model demonstrated statistically significant survival differences in the postneoadjuvant prognostic stage assignment. Of all patients with a pCR, 94.2% were assigned to postneoadjuvant ypStage I compared with 35.5% of patients with no response. Advancing clinical stage had a progressive but small impact on overall survival (OS) with pCR (high-grade, triple-negative breast cancer [TNBC]: cStage I, 97% *v* cStage IIIB/IIIC, 91%; grade 2 luminal A: 97% *v* 91%) but was associated with a profound decrease in OS with no response for TNBC or HER2+ disease (high-grade TNBC 89% *v* 50%) and less profound for grade 2 luminal A disease with no response (97% *v* 81%).

CONCLUSION We present a novel, validated prognostic staging system that predicts OS according to the response to NACT. These data will provide AJCC stage assignments for a growing proportion of patients treated with NACT.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

The Eighth Edition of the American Joint Commission on Cancer (AJCC) introduced a novel prognostic staging system for breast cancer that incorporated estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and histologic grade in conjunction with the anatomic extent of the disease.[1] This allowed more accurate staging of patients with breast cancer. Traditionally, stage assignments have only included information on the anatomic extent of the primary tumor (T), regional lymph node involvement (N), and the presence of metastases (M) combined to provide a TNM stage group. Clinical stage was assigned on the basis of clinical information only, and pathologic stage was defined by clinical criteria supplemented by the pathologic extent of cancer identified by upfront surgical resection with the exclusion of patients treated with neoadjuvant chemotherapy (NACT). Until the eighth edition, pathologic staging was applicable for all patients, regardless of the use of chemotherapy in the adjuvant or neoadjuvant setting.[2-8]

In recent years, NACT has become the initial treatment of choice for many patients with operable breast cancer, especially those with HER2-amplified tumors and triple-negative disease, as well as an increasing number of

CONTEXT

Key Objective

Postneoadjuvant pathologic prognostic staging has not been a component of American Joint Commission on Cancer breast cancer staging because of insufficient data assessing response to therapy.

Knowledge Generated

Three different validated models derived from the National Cancer Database, created for each response category (no response, partial response, and complete response) after neoadjuvant chemotherapy, predict survival and postneoadjuvant prognostic stage assignment according to clinical stage, grade, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status. Response to therapy and clinical stage at presentation are important variables to predict outcome.

Relevance *(G.F. Fleming)*

This standardized postneoadjuvant staging should help clinicians prognosticate for individual patients and will inform future neoadjuvant or postneoadjuvant breast cancer studies.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD.

patients with luminal B-type breast cancer. One of the benefits of neoadjuvant therapy is that the response provides significant prognostic information. This variable has not been previously incorporated into staging.

At the time of the creation of the AJCC eighth edition, sufficient data were not available to create a staging system for women treated with NACT; therefore, postneoadjuvant therapy pathologic staging could not be assigned. This analysis provides data to address this deficiency in the current AJCC staging system with a postneoadjuvant prognostic staging system.

METHODS

Data Source

The 2021 Participant User File (PUF) of the National Cancer Database (NCDB) was used. The NCDB is a facility-based nationwide data set containing information on nearly 70% of newly diagnosed breast cancer cases in the United States, operated by the American College of Surgeons Commission on Cancer in collaboration with the American Cancer Society.[9]

Study Population

This study included female patients with breast cancer, age 18-89 years, diagnosed with clinical stage I, II, or III invasive breast cancer diagnosed from 2010 to 2018. Those who received NACT, had baseline (or pre-NACT) clinical and postneoadjuvant pathologic TNM variables, and vital status were included in the analysis. Pre-NACT ER, PR, HER2, and grade were analyzed according to the treating hospital pathology report, without a central review. Patients were excluded if their last contact or death was <6 months after the start of NACT or if they were diagnosed with stage 0 or stage IV disease at presentation. Overall survival (OS) was calculated using landmark time to allow for response evaluation, set to 6 months after diagnosis to the time of last follow-up or death, as reported by the facility registry to the NCDB. Patients were censored at last follow-up, allowing the inclusion of all available survival data in the analysis.

Response Category

The pathologic response to therapy was determined by comparing the clinical (cT and cN) categories at diagnosis and pathologic (ypT and ypN) categories after NACT and definitive surgery. Three categories (no response, partial response, and complete response [pCR]) were defined using these comparisons. No response was defined as having the same or higher T and/or N categories after the NACT (Data Supplement, Table S1, online only). Patients with disease progression during NACT were included in the no-response category. Partial response was defined as downstaging (lower category) of one or both T and N categories with no upstaging (higher category) of either but with residual invasive cancer in one or both locations. pCR was defined as any presenting clinical stage (I-IIIC) with no invasive cancer after NACT (ypT0ypN0cM0 or ypTisypN0cM0). The data were divided into these three separate groups for analysis.

Stage Assignment

Survival was computed using each response model according to the clinicopathologic variables defined above. To maintain consistency of survival ranges with previous AJCC staging editions, postneoadjuvant pathologic prognostic stage assignments were defined by the 3-year OS ranges used in the

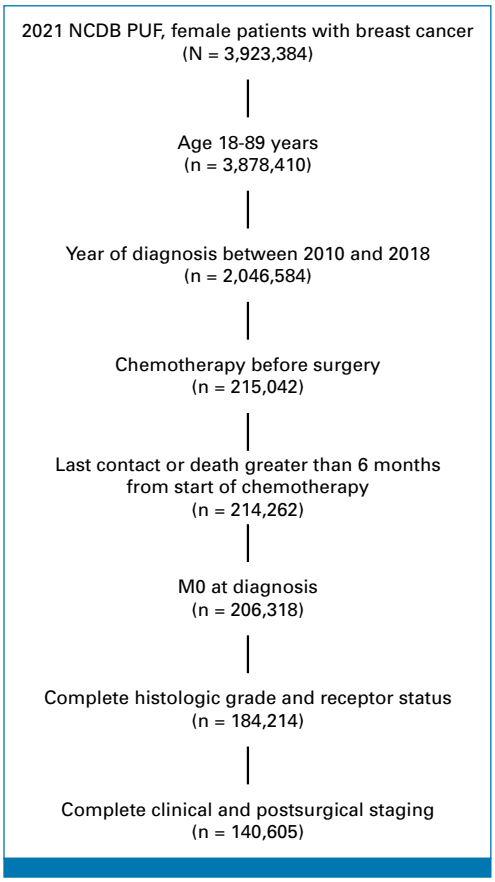

FIG 1. Patient selection map (National Cancer Data Base [NCDB] 2021 participant user file [PUF]).

AJCC Eighth Edition Staging Manual (Data Supplement, Table S2; stage IA >94.0%, stage IB 92.0 to <94.0%, stage IIA 88.0 to <92.0%, stage IIB 85.0 to <88.0%, IIIA 80.0 to <85.0%, IIIB 70% to <80%, IIIC <70%).[1] See the Data Supplement for detailed statistical methods.

RESULTS

A total of 3,956,621 women diagnosed with breast cancer between 2010 and 2018 were identified in the 2021 NCDB PUF. Complete data were identified for 140,605 patients who underwent NACT (Fig 1). The median follow-up period for patients who did not die was 73.7 months (range, 6.4-158.2). Among the 140,605 women, 34,572 had a pCR (96.0% survival), 59,764 had a partial response (87.6% survival), and 46,269 had no response (85.5% survival; log-rank $P < .0001$).

Patients With No Response

Advanced clinical stage, higher grade, ER-negative status, PR-negative status, and HER2-negative status were all predictive of increased hazard of death in the univariable analysis of the training data set ($P < .0001$; Data Supplement, Table S3). There was no difference between the training (n = 37,016) and testing (n = 9,253) data sets in the frequency of variable subsets or survival (log-rank $P = .49$). Multivariable Cox regression analysis showed that advanced clinical stage, higher grade, ER-negative, PR-negative, and HER2-negative remained predictive of worsened OS. Within this response category, patients with clinical stage IIIB/IIIC breast cancer had an OS hazard ratio (HR) of 5.89 relative to those with clinical stage I (Data Supplement, Table S4). The Data Supplement (Fig S1) displays the model calibration curves and receiver operating characteristic (ROC) association statistics for the training and testing sets (AUC of 0.79 and 0.79, respectively). Table 1 lists the predicted survival and assigned postneoadjuvant prognostic stage according to the clinical stage, receptor and grade category, and response. Not all the clinical stage/receptor/grade combinations are included in this table. Statistically significant differences were noted between the postneoadjuvant prognostic stages IA, IB, IIA, IIB, IIIA, IIIB, and IIIC for patients with no response (log-rank $P < .0001$; Fig 2).

Patients With a Partial Pathologic Response

Advanced clinical stage, higher grade, ER-negative, PR-negative, and HER2-negative status were all predictive of increased hazard of death in the univariable analysis of the training data set ($P < .0001$; Data Supplement, Table S5). There was no difference between the training (n = 47,812) and testing (n = 11,952) data sets in terms of the frequency of variable subsets or survival (log-rank $P = .65$). Multivariable Cox regression analysis showed that advanced clinical stage (except for stage IIA [HR, 0.67]), higher grade, ER-negative, PR-negative, and HER2-negative status remained predictive of worsened OS. The Data Supplement (Fig S2) displays the model calibration curves and ROC association statistics for the training and testing sets (AUC of 0.75 and 0.74, respectively). Table 1 lists the predicted survival and postneoadjuvant prognostic stage according to the clinical stage, receptor and grade category, and response. Not all the clinical stage/receptor/grade combinations are included in this table. Statistically significant differences were noted between the postneoadjuvant prognostic stages IA, IB, IIA, IIB, IIIA, and IIIB (log-rank $P < .0001$; Fig 3).

Patients With a Complete Pathologic Response

Advanced clinical stage, lower grade, ER-negative, PR-negative, and HER2-negative status were all predictive of an increased hazard of death in the univariable analysis of the training data set ($P < .0001$; Data Supplement, Table S7). There was no difference between the training (n = 27,658) and testing (n = 6,914) data sets in terms of the frequency of variable subsets or survival (log-rank $P = .07$). Multivariable Cox regression analysis showed that advanced clinical stage, lower grade, ER-negative, and HER2-negative were predictive of decreased OS (Data Supplement, Table S8). Unlike the other two response categories, PR was not significant (HR, 1.03 for PR-negative), and grade 3 predicted improved survival (HR, 0.55) relative to grade 1 and grade 2 (HR, 0.70).

TABLE 1. Three-Year Predicted Survival and Stage Assignments

TNM Clinical Stage	Grade	HER2 Status	ER Status	PR Status	No Response			Partial Response			Complete Response		
					No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage
I	1	+	+	+	223	0.977	IA	10	0.967	IA	37	0.963	IA
				−	33	0.963	IA	[a]	0.954	IA	15	0.962	IA
			−	+	1	0.969	IA	[a]	0.957	IA	2	0.958	IA
				−	13	0.951	IA	[a]	0.940	IA	8	0.956	IA
		−	+	+	890	0.963	IA	24	0.949	IA	97	0.944	IA
				−	111	0.941	IA	1	0.929	IB	10	0.942	IA
			−	+	[a]	0.951	IA	[a]	0.933	IB	1	0.936	IA
				−	62	0.922	IB	2	0.907	IIA	12	0.934	IB
	2	+	+	+	1,368	0.973	IA	113	0.952	IA	422	0.974	IA
				−	271	0.957	IA	4	0.934	IB	163	0.974	IA
			−	+	24	0.964	IA	[a]	0.937	IA	23	0.971	IA
				−	236	0.943	IA	9	0.914	IIA	256	0.970	IA
		−	+	+	2,286	0.957	IA	69	0.926	IB	142	0.961	IA
				−	318	0.931	IB	4	0.898	IIA	37	0.960	IA
			−	+	22	0.943	IA	[a]	0.903	IIA	6	0.955	IA
				−	744	0.909	IIA	19	0.868	IIB	212	0.954	IA
	3	+	+	+	1,013	0.962	IA	98	0.944	IA	531	0.980	IA
				−	255	0.938	IA	5	0.923	IB	209	0.979	IA
			−	+	57	0.949	IA	1	0.927	IB	48	0.977	IA
				−	555	0.919	IB	22	0.899	IIA	595	0.976	IA
		−	+	+	1,003	0.939	IA	41	0.913	IIA	124	0.969	IA
				−	437	0.902	IIA	12	0.881	IIA	142	0.968	IA
			−	+	137	0.919	IB	5	0.887	IIA	74	0.964	IA
				−	2,788	0.872	IIB	65	0.846	IIB	1,400	0.963	IA

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TABLE 1. Three-Year Predicted Survival and Stage Assignments (continued)

TNM Clinical Stage	Grade	HER2 Status	ER Status	PR Status	No Response			Partial Response			Complete Response		
					No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage
IIA	1	+	+	+	125	0.958	IA	218	0.978	IA	72	0.964	IA
				−	19	0.933	IB	31	0.969	IA	26	0.963	IA
			−	+	1	0.945	IA	[a]	0.971	IA	2	0.958	IA
				−	8	0.911	IIA	19	0.959	IA	22	0.957	IA
		−	+	+	849	0.933	IB	475	0.965	IA	31	0.945	IA
				−	79	0.893	IIA	38	0.952	IA	9	0.943	IA
			−	+	2	0.912	IIA	1	0.954	IA	[a]	0.937	IA
				−	39	0.860	IIB	60	0.937	IA	15	0.935	IA
	2	+	+	+	1,119	0.951	IA	1,718	0.968	IA	870	0.975	IA
				−	176	0.922	IB	366	0.955	IA	460	0.974	IA
			−	+	20	0.935	IA	31	0.958	IA	53	0.971	IA
				−	164	0.897	IIA	314	0.941	IA	730	0.970	IA
		−	+	+	3,696	0.922	IB	1,933	0.950	IA	210	0.961	IA
				−	416	0.876	IIA	293	0.931	IB	82	0.960	IA
			−	+	28	0.897	IIA	44	0.934	IB	21	0.956	IA
				−	631	0.839	IIIA	913	0.909	IIA	429	0.955	IA
	3	+	+	+	975	0.931	IB	1,535	0.962	IA	1,406	0.980	IA
				−	259	0.890	IIA	431	0.947	IA	751	0.979	IA
			−	+	50	0.909	IIA	77	0.950	IA	138	0.977	IA
				−	632	0.856	IIB	984	0.931	IB	2,106	0.976	IA
		−	+	+	1,878	0.890	IIA	1,475	0.941	IA	486	0.970	IA
				−	704	0.828	IIIA	716	0.919	IB	598	0.969	IA
			−	+	181	0.856	IIB	198	0.923	IB	214	0.965	IA
				−	3,231	0.777	IIIB	4,268	0.894	IIA	4,314	0.964	IA

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TABLE 1. Three-Year Predicted Survival and Stage Assignments (continued)

TNM Clinical Stage	Grade	HER2 Status	ER Status	PR Status	No Response			Partial Response			Complete Response		
					No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage
IIB	1	+	+	+	51	0.934	IB	125	0.965	IA	26	0.952	IA
				−	9	0.895	IIA	25	0.952	IA	14	0.951	IA
			−	+	[a]	0.913	IIA	[a]	0.954	IA	1	0.945	IA
				−	4	0.863	IIB	15	0.937	IA	21	0.943	IA
		−	+	+	608	0.896	IIA	652	0.946	IA	20	0.927	IB
				−	55	0.836	IIIA	57	0.926	IB	8	0.925	IB
			−	+	[a]	0.863	IIB	6	0.929	IB	1	0.917	IB
				−	16	0.787	IIIB	42	0.903	IIA	6	0.915	IIA
	2	+	+	+	538	0.923	IB	1,366	0.950	IA	515	0.967	IA
				−	94	0.878	IIA	315	0.931	IB	307	0.966	IA
			−	+	2	0.899	IIA	20	0.934	IB	48	0.962	IA
				−	76	0.841	IIIA	338	0.909	IIA	528	0.961	IA
		−	+	+	3,041	0.879	IIA	3,500	0.922	IB	213	0.949	IA
				−	368	0.811	IIIA	490	0.893	IIA	60	0.948	IA
			−	+	10	0.842	IIIA	33	0.899	IIA	20	0.942	IA
				−	289	0.756	IIIB	688	0.861	IIB	254	0.940	IA
	3	+	+	+	521	0.892	IIA	1,539	0.941	IA	941	0.974	IA
				−	138	0.830	IIIA	494	0.919	IB	593	0.973	IA
			−	+	24	0.859	IIB	85	0.923	IB	112	0.970	IA
				−	371	0.781	IIIB	1,231	0.894	IIA	1,614	0.969	IA
		−	+	+	1,484	0.831	IIIA	2,428	0.909	IIA	437	0.960	IA
				−	462	0.740	IIIB	931	0.876	IIA	505	0.958	IA
			−	+	85	0.781	IIIB	234	0.882	IIA	130	0.954	IA
				−	1,604	0.669	IIIC	3,986	0.839	IIIA	2,559	0.952	IA

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TABLE 1. Three-Year Predicted Survival and Stage Assignments (continued)

TNM Clinical Stage	Grade	HER2 Status	ER Status	PR Status	No Response			Partial Response			Complete Response		
					No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage
IIIA	1	+	+	+	19	0.903	IIA	67	0.947	IA	12	0.935	IB
				−	4	0.847	IIB	15	0.926	IB	9	0.933	IB
			−	+	[a]	0.873	IIB	1	0.930	IB	1	0.925	IB
				−	2	0.801	IIIA	10	0.904	IIA	15	0.923	IB
		−	+	+	283	0.847	IIB	454	0.918	IB	6	0.902	IIA
				−	39	0.764	IIIB	57	0.887	IIA	4	0.899	IIA
			−	+	1	0.802	IIIA	[a]	0.893	IIA	[a]	0.888	IIA
				−	14	0.698	IIIB	26	0.853	IIB	6	0.885	IIA
	2	+	+	+	220	0.887	IIA	754	0.923	IB	245	0.954	IA
				−	51	0.823	IIIA	208	0.894	IIA	166	0.953	IA
			−	+	3	0.853	IIB	21	0.900	IIA	15	0.948	IA
				−	52	0.772	IIIB	211	0.863	IIB	317	0.946	IA
		−	+	+	1,386	0.824	IIIA	2,566	0.882	IIA	79	0.931	IB
				−	209	0.730	IIIB	382	0.840	IIIA	42	0.929	IB
			−	+	10	0.772	IIIB	25	0.847	IIB	10	0.921	IB
				−	132	0.657	IIIC	384	0.794	IIIB	133	0.919	IB
	3	+	+	+	206	0.842	IIIA	894	0.910	IIA	400	0.964	IA
				−	82	0.757	IIIB	320	0.877	IIA	305	0.963	IA
			−	+	13	0.796	IIIA	57	0.883	IIA	53	0.959	IA
				−	168	0.689	IIIC	866	0.840	IIIA	875	0.957	IA
		−	+	+	756	0.757	IIIB	1,693	0.863	IIB	194	0.945	IA
				−	256	0.636	IIIC	724	0.814	IIIA	214	0.943	IA
			−	+	39	0.690	IIIC	114	0.823	IIIA	54	0.937	IA
				−	821	0.547	IIIC	2,441	0.762	IIIB	1,025	0.935	IA

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TABLE 1. Three-Year Predicted Survival and Stage Assignments (continued)

TNM Clinical Stage	Grade	HER2 Status	ER Status	PR Status	No Response			Partial Response			Complete Response		
					No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage	No.	3-Year Predicted Survival	Assigned Stage
IIIB/IIIC	1	+	+	+	16	0.872	IIB	53	0.920	IB	8	0.890	IIA
				−	1	0.800	IIIA	8	0.890	IIA	3	0.887	IIA
			−	+	[a]	0.833	IIIA	1	0.896	IIA	[a]	0.875	IIB
				−	4	0.743	IIIB	13	0.857	IIB	11	0.872	IIB
		−	+	+	137	0.801	IIIA	381	0.877	IIA	7	0.837	IIIA
				−	19	0.697	IIIB	38	0.833	IIIA	2	0.832	IIIA
			−	+	[a]	0.744	IIIB	1	0.841	IIIA	[a]	0.815	IIIA
				−	5	0.618	IIIC	15	0.786	IIIB	5	0.810	IIIA
	2	+	+	+	117	0.852	IIB	567	0.885	IIA	159	0.923	IB
				−	28	0.771	IIIB	154	0.844	IIIA	138	0.920	IB
			−	+	2	0.808	IIIA	13	0.851	IIB	25	0.912	IIA
				−	56	0.706	IIIB	250	0.799	IIIA	271	0.909	IIA
		−	+	+	726	0.771	IIIB	2,410	0.826	IIIA	77	0.884	IIA
				−	113	0.656	IIIC	378	0.766	IIIB	37	0.881	IIA
			−	+	8	0.708	IIIB	28	0.777	IIIB	7	0.868	IIB
				−	131	0.570	IIIC	459	0.703	IIIB	107	0.864	IIB
	3	+	+	+	180	0.795	IIIB	804	0.866	IIB	335	0.939	IA
				−	68	0.688	IIIC	343	0.819	IIIA	234	0.937	IA
			−	+	7	0.736	IIIB	61	0.827	IIIA	79	0.930	IB
				−	218	0.608	IIIC	845	0.768	IIIB	912	0.928	IB
		−	+	+	566	0.689	IIIC	1,792	0.799	IIIA	162	0.907	IIA
				−	242	0.546	IIIC	677	0.731	IIIB	182	0.905	IIA
			−	+	35	0.609	IIIC	142	0.743	IIIB	46	0.894	IIA
				−	845	0.446	IIIC	2,799	0.661	IIIC	1,041	0.891	IIA

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
[a]There are no patients with this variable combination within the data set.

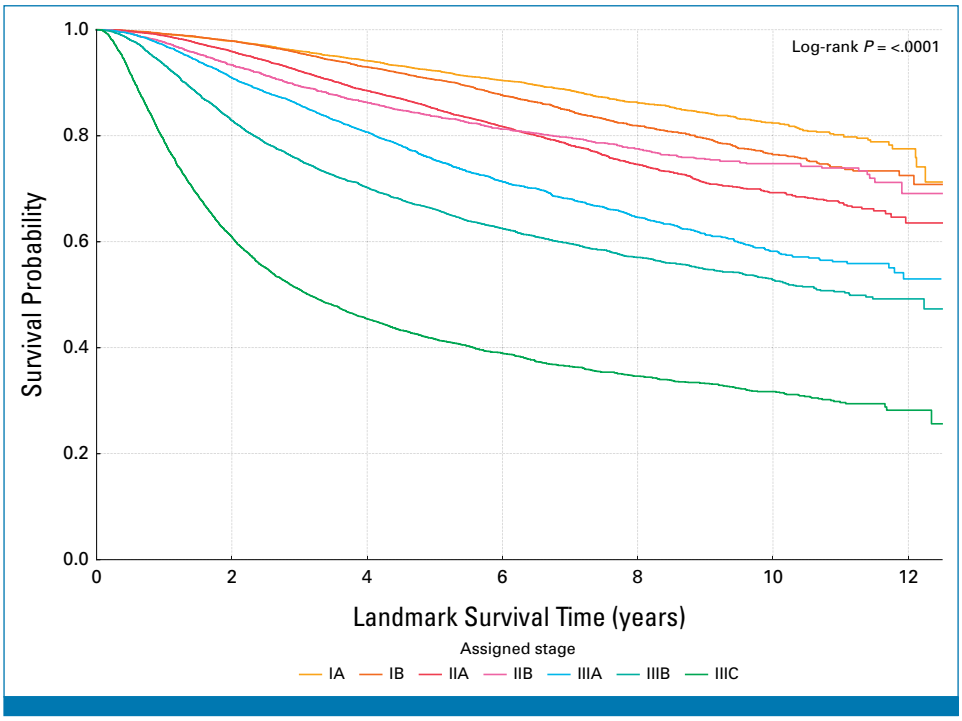

FIG 2. Survival according to assigned postneoadjuvant prognostic stage for patients with no response.

The loss of statistical significance for PR in the multivariable model suggests that its prognostic impact is not independent but mediated through related factors. ER was most likely to account for this (Cramer's $V = 0.60$, strong association), followed by HER2 (Cramer's $V = 0.21$, weak association), PR (Cramer's $V = 0.19$, weak association), and TNM stage (Cramer's $V = 0.06$, very weak association). Clinical stages IIIB/IIIC had a hazard ratio of 3.09 relative to clinical stage I with pCR. The Data Supplement (Fig S3) displays the model calibration curves and ROC association

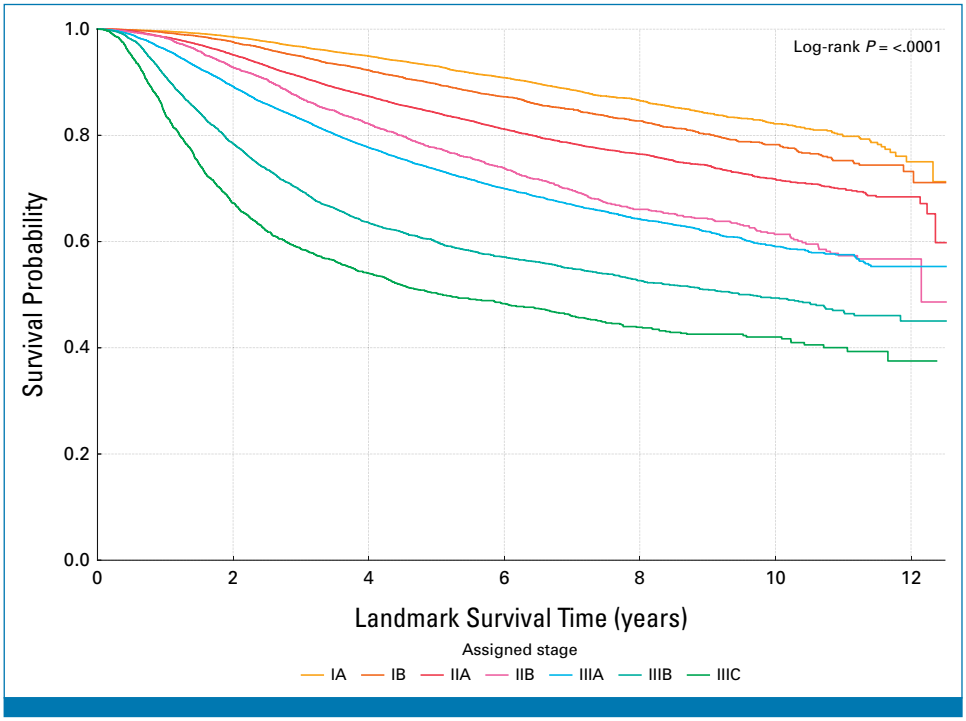

FIG 3. Survival according to assigned postneoadjuvant prognostic stage for patients with partial response.

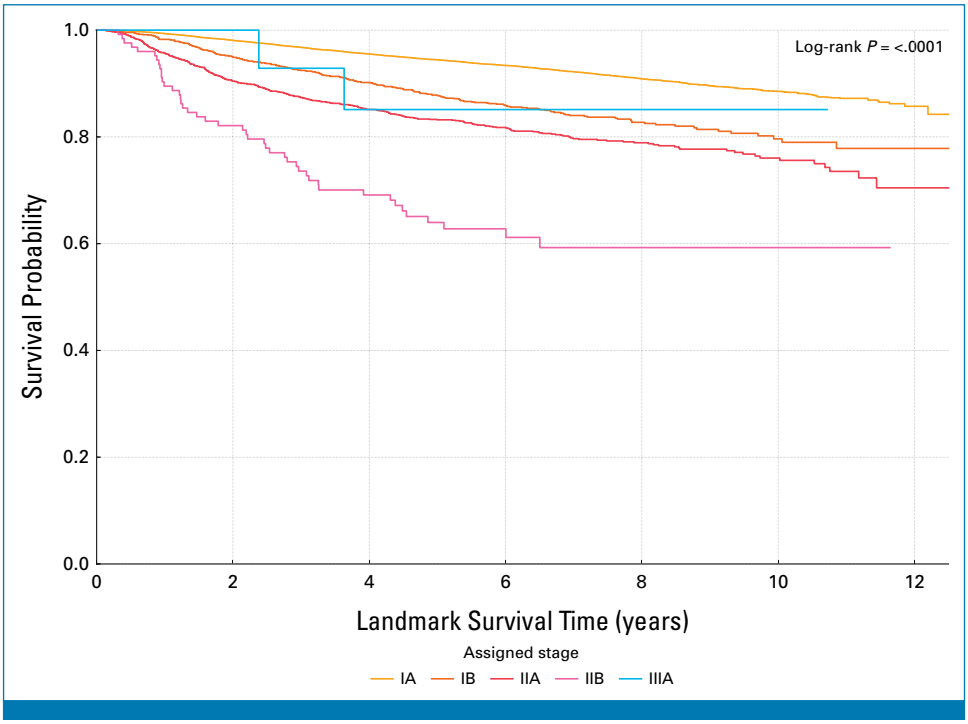

FIG 4. Survival according to assigned postneoadjuvant prognostic stage for patients with complete response.

statistics for the training and testing sets (AUC of 0.68 and 0.71, respectively). Table 1 lists the number of patients, predicted survival, and assigned postneoadjuvant prognostic stage according to the clinical stage, receptor, grade category, and response. Not all the clinical stage/receptor/grade combinations are included in this table. Statistically significant differences were noted between the postneoadjuvant prognostic stages IA, IB, IIA, and IIB (log-rank $P < .0001$, Fig 4).

Summary of Findings

Response to therapy is one of the most important variables for predicting OS after NACT. Over 94% of patients achieving pCR in this study were assigned to postneoadjuvant prognostic stage ypI, regardless of breast cancer subtype. As reflected by the hazard ratios in each of the three response group models, clinical stage has an important impact on OS, showing a progressive decrease with advancing clinical stage (Table 1). The increased hazard of death is greatest for patients with no response and most pronounced for those with high-grade triple-negative breast cancer (TNBC) or high-grade HER2+ disease. The reduction in mortality is less pronounced in patients with intermediate-grade luminal A-like disease, likely reflective of adjuvant endocrine therapy. In patients with a pCR, a progressive increase in the hazard of death was noted with advancing clinical stage for each breast cancer subtype, but with less than a 6% difference between clinical stage I and clinical stage IIIB/IIIC for each of the examples listed above, in contrast to a 39% difference for high-grade TNBC with no response (Table 1). Patients with a pCR had two unique findings. Grade had a paradoxical effect on patients with pCR, with low-grade tumors having a greater risk of death. Second, PR was not predictive of an increased risk of death in patients with a pCR.

DISCUSSION

AJCC breast staging systems have historically been defined solely on the basis of anatomic criteria (TNM) to predict survival at diagnosis (clinical stage) and with more refined metrics after surgery (pathologic stage).[2] In the eighth edition, additional prognostic factors (grade, ER, PR, and HER2 status) were used to supplement TNM to define stage groups. This has improved the precision of outcome prediction and the relevance of staging for clinicians and patients. With the eighth edition, the postsurgical staging of patients undergoing NACT was specifically excluded. A top priority for the next version of the AJCC breast cancer staging system is to comprehensively address this deficiency.

Subsequently, many studies have validated the eighth edition clinical and pathologic prognostic staging. In addition, some studies have also applied the pathologic prognostic stage to patients treated with NACT with relative success, despite the lack of response analysis.[10-21]

The current study provides statistically valid models for staging patients treated with NACT on the basis of anatomic and biological factors within response categories. The data elements necessary to assign the response category and

postneoadjuvant prognostic stage are currently collected in cancer registries in North America and are in place within the NCDB. Thus, this postneoadjuvant staging system can be implemented without any additional variables.

Breast cancer is a heterogeneous disease that is treated according to different criteria, including stage, primary molecular/clinical subtype (luminal A, luminal B, HER2+, and basal), and identifiable mutations or receptor targets.

In the analysis that led to the changes introduced in the eighth edition, as well as this study to expand prognostic staging to postneoadjuvant therapy staging, an attempt was made to recognize specific subtypes for analysis. This strategy was also explored by evaluating eight different models (data not shown), but ultimately relied upon one construct consisting of T, N, M, grade, ER, PR, HER2, and response to provide a system that prioritized efficiency and simplicity for clinicians and patients.

The most striking finding in the models presented here for those treated with neoadjuvant therapy was the commonality of an excellent prognosis for those with a complete pathologic response, spanning across a very wide range of clinical stages, and each breast cancer subtype. These data confirm that pCR is a very important prognosticator, regardless of stage, histology, grade, and subtype, as reported in many previous studies.[22-27] In addition, these models showed that clinical staging remains an important prognostic factor in all three response groups.

In a meta-analysis of 27,895 patients undergoing NACT between 1999 and 2016, pCR, event-free status, and OS were uniformly improved regardless of the receptor profile.[28] Survival advantages with pCR were more pronounced in HER2+ and TNBC than in hormone receptor–positive breast cancer. Patients with TNBC and pCR had an 84% 5-year OS compared with 47% for those without a pCR; patients with HER2+ breast cancer with a pCR had a 95% 5-year OS compared with 76% for those without a pCR; patients with hormone receptor–positive breast cancer with a pCR had a 98% 5-year OS compared with 82% without a pCR. Although significant, the survival of patients with TNBC and pCR was not as favorable in the meta-analysis as in the current study (94%), likely reflecting improved therapy in a more recent period of analysis and 3-year follow-up versus 5-year follow-up. It should be emphasized that a pCR has a much greater OS impact for specific subtypes of breast cancer, particularly in patients diagnosed with TNBC.

The finding of an increase in breast cancer mortality with low-grade tumors and pCR was unexpected. One explanation is the expected low response rates to NACT.[29,30] Mortality from breast cancer after a pCR implies that unrecognized residual disease leads to eventual progression. It may be possible that incorrect categorization of a pCR is less common for higher-grade disease.

Future refinements of AJCC staging may include more quantified assessments of treatment response, such as the residual cancer burden (RCB) index.[31] RCB has been validated in a multi-institutional pooled analysis that, like our study, confirmed the importance of receptor subtype in predicting the response to NACT.[32] However, there are insufficient data to allow the inclusion of RCB in staging at this time and it is not yet routinely reported in the United States.

This study has several limitations. In this retrospective study, it was not possible to determine why a specific patient was administered NACT, leading to a selection bias created by institutional, physician, and/or patient preferences. However, the large number of patients included in the analysis should reduce the possibility of major bias. For the same reason, only a limited number of patients with clinical stage I cancer treated with NACT are in the database, reflecting infrequent NACT for that patient population. It is not possible to determine from the NCDB specific drug treatments as NACT or as postsurgery adjuvant therapy or the duration of treatment for individual patients. Given the 9-year study period, it is highly likely that survival has improved as therapy continues to evolve through better adjuvant regimens and advances in treating recurrent cancer. The survival of patients with triple-negative and HER2-positive breast cancer is very likely underestimated in this patient population diagnosed from 2010 to 2018, which straddles the introduction of adjuvant trastuzumab, pertuzumab, emtansine, and pembrolizumab. Although not used during this study period, CDK4/6 inhibitors and neoadjuvant endocrine therapy will likely increase the survival and pCR compliments for patients treated with neoadjuvant therapy.

The absence of recurrence data and breast cancer–specific survival are recognized limitations of NCDB. These data are very important end points, particularly in clinical trials, for understanding the effectiveness of new therapies. The purpose of this study was to address an obvious deficiency in staging of patients undergoing NACT. In line with all previous AJCC staging editions, OS has been the sole end point used in staging and is arguably the most accurate and measurable. The median follow-up in the NCDB for the patients included in this analysis was relatively short, especially for patients with hormone receptor–positive breast cancer, where late recurrences are more common. In addition to the lack of specific NACT regimens, including trastuzumab and pertuzumab, NCDB does not record specific adjuvant endocrine therapy, cytotoxic chemotherapy, or HER2-targeted therapy for patients with residual disease after surgery. Key studies demonstrating the value of additional adjuvant therapy were reported in 2017 and 2018 and may have led to improved outcomes in the last 2 years of this study and to overestimate the hazard of death of patients with a partial response and no response.[33,34] The same holds true for patients who progress to develop metastatic disease. Treatment for this

circumstance has also improved, possibly leading to increased OS but not reported in the NCDB and not included in the models.

Because of patient, biomarker, and treatment heterogeneity, some combinations of stages and biomarkers are underrepresented. Such heterogeneity also reflects the current patterns of practice that routinely use NACT for patients with HER2-amplified breast cancer and TNBC but more selectively in patients with luminal breast cancer. Improved therapy is likely to increase the percentage of patients who achieve a complete pathologic response.

In conclusion, breast cancer is a heterogeneous disease, and the prognosis of patients treated with NACT varies significantly according to the treatment response and clinical stage. These validated models, created for each of the three pathologic response categories, provided OS predictions after NACT. These data set forth a new postneoadjuvant prognostic staging system that we recommend for inclusion in upcoming versions of AJCC breast cancer staging.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Novel Postneoadjuvant Prognostic Breast Cancer Staging System

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