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Clinical and pathological stage discordance among 433,514 breast cancer patients

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ABSTRACT

Background: We aim to determine clinical and pathological stage discordance rates and to evaluate factors associated with discordance.
Methods: Adults with clinical stages I-III breast cancer were identified from the National Cancer Data Base. Concordance was defined as cTN = pTN (discordance: cTN ≠ pTN). Multivariate logistic regression was used to identify factors associated with discordance.
Results: Comparing clinical and pathological stage, 23.1% were downstaged and 8.7% were upstaged. After adjustment, factors associated with downstaging (vs concordance) included grade 3 (OR 10.56, vs grade 1) and HER2-negative (OR 3.79). Factors associated with upstaging (vs concordance) were grade 3 (OR 10.56, vs grade 1), HER2-negative (OR 1.25), and lobular histology (OR 2.47, vs ductal). ER-negative status was associated with stage concordance (vs downstaged or upstaged, OR 0.52 and 0.87).
Conclusions: Among breast cancer patients, nearly one-third exhibit clinical-pathological stage discordance. This high likelihood of discordance is important to consider for counseling and treatment planning.

Introduction

Breast cancer staging provides a universal framework that enables providers to concisely relay diagnostic and prognostic information among both patients and providers. The American Joint Committee on Cancer's (AJCC) Cancer Staging Manual was recently updated (January 2018) and now combines tumor biology with anatomic staging, which has been shown to improve the prognostic accuracy of staging.[1] The traditional anatomic stage continues to include the primary tumor size (T), nodal status (N), and distant metastases (M). Although anatomic staging remains especially important for local-regional treatments,[2] tumor phenotyping has resulted in an increased use of targeted therapies. Thus, the new prognostic stages now incorporate both anatomic factors (TNM) and tumor biology, including tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, human-epidermal-growth-factor-receptor-2 (HER2) status, and tumor multigene panel testing.[1]

Within this new system, prognostic staging can be assessed at the time of diagnosis (clinical staging) and/or after surgery (pathological staging). Clinical staging typically occurs prior to surgery, based on physical examination, imaging, and percutaneous needle biopsies. The clinical stage is often used as the basis for treatment planning and discussing prognosis with patients embarking on therapy but may often change with the final pathological stage. The final pathological stage is considered the gold standard for staging and is only determined after surgery, thus combining the histopathological findings and clinical staging information. Once assessed, the final prognostic stage can be determined and provide patients with a more accurate estimate of their prognosis.

Discordance between clinical and pathological stage has been reported to potentially portend a worse prognosis for other malignancies[3,4] and to have certain demographic and histopathological associations.[4,5] However, the concordance rate of clinical and

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pathological staging for breast cancer is largely unknown, and the populations with greatest likelihood of discordance are not well defined. Furthermore, the potential prognostic effect of stage concordance or discordance is also unknown. Here, we sought to compare clinical and pathological staging and to explore what factors may be associated with stage discordance.

Methods

Individuals ≥18 years old, diagnosed with clinical stages I-III invasive breast cancer and histology codes defined by the World Health Organization (WHO) Classification of Tumors[6] from 2004 to 2014 in the National Cancer Data Base (NCDB) were identified. Patients that underwent local tumor destruction, had no surgery, or had missing/unknown surgery were excluded, as were those with inflammatory breast cancer and those who received neoadjuvant therapy. Clinical and pathological stages were defined using the 8th edition of the AJCC Cancer Staging Manual, which is based on tumor size (T stage), nodal status (N stage), distant metastasis (M stage), tumor grade, ER, PR, and HER2 status.[1] Patients with unknown or missing staging variables (T/N, ER, PR, HER2 status, grade) and AJCC stage 0 or IV were excluded. The Oncotype Dx (Genomic Health; Redwood, CA) recurrence score was included when available, for pathological staging.

Stage concordance was defined as being assigned to the same clinical and pathological stages. Stage discordance was defined as being assigned to different clinical and pathological stages. Patients were categorized as upstaged if the pathological stage was greater than the clinical stage, or downstaged if the pathological stage was lower than the clinical stage. Patient characteristics were summarized by N (%) for categorical variables, and median (interquartile range, IQR) for continuous variables. Hospital volume was defined as low (<148 breast cases/year), moderate (148–298 breast cases/year), and high (>298 breast cases/year) based on previously published thresholds. The full Breast NCDB 2004–2014 dataset was used to assign volume group to each hospital.[7] Analysis of variance (ANOVA) and chi-square tests were used to test for differences between groups for continuous and categorical variables, respectively.

A multivariate logistic regression model was used to identify factors associated with discordance. Variables included in the model were: patient age, race/ethnicity, distance traveled to treating institution, income level, insurance status, education level, Charlson/Deyo comorbidity score,[8,9] facility type and location, hospital volume, tumor grade, ER/PR/HER2 status, triple negative status, clinical T/N stage, tumor histology, and surgery type. This model was built in the generalized estimating equations framework[10] and accounted for the correlation of patients treated at the same hospital. An independent correlation structure was selected based on the lowest quasi-likelihood information criteria (QIC) of all tested correlation structures.[11] A multivariate generalized logistic model was used to identify factors associated with upstage vs. concordance and downstage vs. concordance, after adjustment for covariates. Odds Ratios (OR) and 95% Confidence Intervals (CI) are reported for all logistic models.

Overall survival (OS) was defined as the time from diagnosis to death or last follow-up. The Kaplan-Meier method was used to estimate the 5-year and 10-year survival rates. A Cox proportional hazards model was used to estimate the effect of concordance on OS after adjustment for known covariates, and hazard ratios (HR) and 95% CIs are reported. In order to account for the correlation of patients treated at the same facility, a robust sandwich covariance estimator was used.[12] Patients diagnosed in 2014 were excluded from all survival models, according to NCDB requirements.

Only patients with available data for all covariates were included in each model, and effective sample sizes are reported for each table/figure. A p-value <0.05 was considered significant; no adjustments were made for multiple comparisons. All statistical analyses were conducted with SAS, version 9.4 (SAS Institute; Cary, North Carolina, USA). This study was exempt from Institutional Review Board review.

Results

Patient and tumor characteristics

Starting with the initial NCDB population of 2,246,363 patients diagnosed with breast cancer from 2004 to 2014, application of the defined inclusion and exclusion criteria resulted in the final study population of 433,514 patients (Supplemental Fig. 1). The median patient age was 62 years (IQR 53–71 years). The median follow-up time was 38.2 months (95% confidence interval [CI] 38.1–38.3 months). The majority of patients were women (99%) with invasive ductal carcinoma (88.4%), ER-positive (84.2%), PR-positive (74.4%), HER2-negative (87.4%), and grade 2 (48%) disease. Of those with a known Oncotype Dx recurrence score (N = 94,048), 23.8% had a score of 0–10. The most common clinical and pathological stage was IA (59% and 68.2%, respectively). More patients underwent lumpectomy than mastectomy (60% vs 40%, respectively). (Table 1).

Concordance between clinical and pathological stage

Concordant clinical and pathological stage was observed for 68.2% of patients, while 23.1% were downstaged and 8.7% were upstaged (31.8% changed stage overall). This varied widely by the initial clinical stage, with concordance being the highest for clinical stage IA (94.4%) and lowest for clinical stage IIB (13.6%) patients (Table 2). Excluding cT0 breast disease, stage concordance was high for T stage overall (86.9% concordant T stage, 4.6% downstaged, 8.5% upstaged), which varied from 70.4% for cT3 (lowest) to 90% for cT1 (highest) tumors. Stage concordance for N stage was similarly high overall (80.3% concordant N stage, 1.2% downstaged, 18.5% upstaged), but extended over a wider range from 62.2% for cN1 (lowest) to 88.5% for cN3 (highest) tumors. For patients with cN0 disease, 17.9% were upstaged to pN1-3 (pN1mi 3.6%, pN1 11.4%, pN2 2.1%, pN3 0.8%).

Patient, tumor, and staging variables differed significantly based on stage concordance (Table 1). Stage concordance was more prevalent among older (70% concordance if age >50y vs 61.3% if ≤ 50y, $p < 0.001$) and non-Hispanic white patients (69.9% concordance vs 58.5% for non-Hispanic black and 62% for Hispanic, $p < 0.001$). Stage discordance was most prevalent among the uninsured (57.5% concordance vs 68% and 68.8% for the private and government insured, respectively; $p < 0.001$). Stage concordance was also lower for ER-negative (vs ER-positive), PR-negative (vs PR-positive), grade 3 (vs grade 1 or 2), and invasive lobular carcinomas (vs other invasive carcinomas; all $p < 0.001$).

In the adjusted analysis (Table 3), factors associated with downstaging (vs concordance) included non-Hispanic black race (OR 1.24, vs non-Hispanic white), uninsured (OR 1.36, vs private insurance), grade 3 (OR 10.56, vs grade 1), HER2-negative (OR 3.79, vs HER2-positive), and lobular histology (OR 1.51, vs ductal). These same factors were also associated with upstaging (vs concordance): non-Hispanic black race (OR 1.24, vs non-Hispanic white), uninsured (OR 1.25, vs private insurance), grade 3 (OR 10.56, vs grade 1), HER2-negative (OR 1.25, vs HER2-positive), and lobular histology (OR 2.47, vs ductal). Lumpectomy receipt (vs mastectomy) was associated with stage concordance (vs downstaged OR 0.51; vs upstaged OR 0.38). While ER-negative status (vs ER-positive) was associated with stage concordance (vs downstaged OR 0.52; vs

Table 1
Select patient, tumor, and treatment factors by stage concordance and discordance (downstaged or upstaged) based on breast cancer data from the National Cancer Database from 2004 to 2014; N = 433,514. Data presented as N (%) unless otherwise specified. Percentages represent column proportions for 'All Patients', and row proportions for subgroups, and may not add up to 100 due to rounding or missing values. IQR: interquartile range. ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2. RT: radiation therapy.

	All Patients (N = 433,514)	Clinical and Pathological Stage			P-value
		Downstaged (N = 100,167)	Concordant (N = 295,639)	Upstaged (N = 37,708)	
Age (years)					<0.001
≤50	88553 (20.4%)	24866 (28.1%)	54289 (61.3%)	9398 (10.6%)	
>50	344961 (79.6%)	75301 (21.8%)	241350 (70%)	28310 (8.2%)	
Median (IQR)	62 (53–71)	61 (51–70)	63 (53–71)	60 (51–70)	
Gender					<0.001
Female	429292 (99%)	98667 (23%)	293349 (68.3%)	37276 (8.7%)	
Male	4222 (1%)	1500 (35.5%)	2290 (54.2%)	432 (10.2%)	
Race/Ethnicity					<0.001
Non-Hispanic white	336293 (77.6%)	73527 (21.9%)	235186 (69.9%)	27580 (8.2%)	
Non-Hispanic black	42041 (9.7%)	12140 (28.9%)	24613 (58.5%)	5288 (12.6%)	
Hispanic	20367 (4.7%)	5626 (27.6%)	12629 (62%)	2112 (10.4%)	
Other	17320 (4%)	4501 (26%)	11327 (65.4%)	1492 (8.6%)	
ER Status					<0.001
ER-positive	365071 (84.2%)	81492 (22.3%)	259907 (71.2%)	23672 (6.5%)	
ER-negative	68409 (15.8%)	18675 (27.3%)	35698 (52.2%)	14036 (20.5%)	
PR Status					<0.001
PR-positive	322704 (74.4%)	72021 (22.3%)	235140 (72.9%)	15543 (4.8%)	
PR-negative	110491 (25.5%)	28146 (25.5%)	60180 (54.5%)	22165 (20.1%)	
HER2 Status					<0.001
HER2-positive	54573 (12.6%)	8463 (15.5%)	37371 (68.5%)	8739 (16%)	
HER2-negative	378941 (87.4%)	91704 (24.2%)	258268 (68.2%)	28969 (7.6%)	
Triple Negative Disease	49835 (11.5%)	15719 (31.5%)	24450 (49.1%)	9666 (19.4%)	<0.001
Histology					<0.001
Invasive ductal	383375 (88.4%)	86640 (22.6%)	264895 (69.1%)	31840 (8.3%)	
Invasive lobular	46422 (10.7%)	11736 (25.3%)	29396 (63.3%)	5290 (11.4%)	
Other invasive	3717 (0.9%)	1791 (48.2%)	1348 (36.3%)	578 (15.6%)	
Grade					<0.001
1	116152 (26.8%)	16491 (14.2%)	97133 (83.6%)	2528 (2.2%)	
2	207891 (48%)	40049 (19.3%)	152731 (73.5%)	15111 (7.3%)	
3	109471 (25.3%)	43627 (39.9%)	45775 (41.8%)	20069 (18.3%)	
Oncotype DX					<0.001
0-10	22388 (5.2%)	4366 (19.5%)	17658 (78.9%)	364 (1.6%)	
11-100	71660 (16.5%)	17340 (24.2%)	51845 (72.3%)	2475 (3.5%)	
Measured, value unknown	17450 (4%)	4085 (23.4%)	12802 (73.4%)	563 (3.2%)	
Unknown	322016 (74.3%)	74376 (23.1%)	213334 (66.2%)	34306 (10.7%)	
Tumor Size (cm) – Median (IQR)	1.5 (1–2.4)	2.4 (1.8–3.1)	1.2 (0.8–1.7)	2.5 (2.1–3.6)	<0.001
Clinical T Stage					<0.001
T0	151 (0%)	72 (47.7%)	41 (27.2%)	38 (25.2%)	
T1	308888 (71.3%)	18123 (5.9%)	266862 (86.4%)	23903 (7.7%)	
T1IS	<10 (<0.1%)	<10 (<0.1%)	<10 (<0.1%)	0	
T2	111059 (25.6%)	73770 (66.4%)	25203 (22.7%)	12086 (10.9%)	
T3	10541 (2.4%)	6892 (65.4%)	2025 (19.2%)	1624 (15.4%)	
T4	2826 (0.7%)	1293 (45.8%)	1477 (52.3%)	56 (2%)	
Clinical N Stage					<0.001
N0	386893 (89.2%)	71227 (18.4%)	285274 (73.7%)	30392 (7.9%)	
N1	38404 (8.9%)	24356 (63.4%)	7333 (19.1%)	6715 (17.5%)	
N2	5861 (1.4%)	3695 (63%)	1594 (27.2%)	572 (9.8%)	
N3	2356 (0.5%)	889 (37.7%)	1438 (61%)	29 (1.2%)	
Pathological T Stage					<0.001
T0	105 (0%)	48 (45.7%)	34 (32.4%)	23 (21.9%)	
T1	294750 (68%)	33549 (11.4%)	253010 (85.8%)	8191 (2.8%)	
T1IS	477 (0.1%)	472 (99%)	3 (0.6%)	2 (0.4%)	
T2	120790 (27.9%)	60149 (49.8%)	37110 (30.7%)	23531 (19.5%)	
T3	14076 (3.2%)	5275 (37.5%)	4038 (28.7%)	4763 (33.8%)	
T4	3279 (0.8%)	666 (20.3%)	1434 (43.7%)	1179 (36%)	
Pathological N Stage					<0.001
N0	320096 (73.8%)	67161 (21%)	245858 (76.8%)	7077 (2.2%)	
N1	68581 (15.8%)	23401 (34.1%)	31435 (45.8%)	13745 (20%)	
N1MI	15992 (3.7%)	3368 (21.1%)	10660 (66.7%)	1964 (12.3%)	
N2	19592 (4.5%)	5498 (28.1%)	5937 (30.3%)	8157 (41.6%)	
N3	9229 (2.1%)	739 (8%)	1749 (19%)	6741 (73%)	
Surgery Type					<0.001
Lumpectomy	260291 (60%)	47861 (18.4%)	197666 (75.9%)	14764 (5.7%)	
Mastectomy	173223 (40%)	52306 (30.2%)	97973 (56.6%)	22944 (13.2%)	
Days from Diagnosis to Surgery – Median (IQR)	32 (21–47)	32 (21–48)	31 (21–47)	33 (21–49)	<0.001
Surgery and Radiation					<0.001
Lumpectomy + No RT	36281 (8.4%)	6655 (18.3%)	27504 (75.8%)	2122 (5.8%)	
Lumpectomy + RT	222620 (51.4%)	40913 (18.4%)	169162 (76%)	12545 (5.6%)	
Mastectomy + No RT	131874 (30.4%)	38619 (29.3%)	82597 (62.6%)	10658 (8.1%)	

(*continued on next page*)

Table 1 (*continued*)

	All Patients (N = 433,514)	Clinical and Pathological Stage			P-value
		Downstaged (N = 100,167)	Concordant (N = 295,639)	Upstaged (N = 37,708)	
Mastectomy + RT	39486 (9.1%)	13089 (33.1%)	14316 (36.3%)	12081 (30.6%)	
Chemotherapy Receipt	161577 (37.3%)	52335 (32.4%)	80630 (49.9%)	28612 (17.7%)	<0.001
Endocrine Therapy Receipt					
All patients[a]	302265 (69.7%)	68889 (22.8%)	212800 (70.4%)	20576 (6.8%)	<0.001
ER-positive or PR-positive[b]	300218 (81.3%)	68366 (22.8%)	211670 (70.5%)	20182 (6.7%)	<0.001

[a] Out of all patients.
[b] Out of 369,074 ER-positive or PR-positive patients.

Table 2
Change from clinical to pathological stage (N = 433,514) for patients with breast cancer in the National Cancer Database from 2004 to 2014. Values represent frequency and row percentage. Counts of concordance between clinical and pathological stage are highlighted in gray, downstaged counts are highlighted in blue, and upstaged counts are highlighted in yellow.

		Pathological Stage											
		0	IA	IB	IIA	IIB	IIIA	IIIB	IIIC	IV	Total Downstaged	Total Upstaged	Total
Clinical Stage	IA	388	241323	7937	3408	902	1242	286	0	218	388	13993	255704
		0.15%	94.38%	3.10%	1.33%	0.35%	0.49%	0.11%	0.00%	0.09%	0.15%	5.47%	100%
	IB	64	47307	35756	6200	419	1991	373	451	210	47371	9644	92771
		0.07%	50.99%	38.54%	6.68%	0.45%	2.15%	0.40%	0.49%	0.23%	51.06%	10.40%	100%
	IIA	9	6045	19047	9577	3531	2272	932	0	202	25101	6937	41615
		0.02%	14.53%	45.77%	23.01%	8.48%	5.46%	2.24%	0.00%	0.49%	60.32%	16.67%	100%
	IIB	9	708	2015	16700	3910	3044	1122	1070	126	19432	5362	28704
		0.03%	2.47%	7.02%	58.18%	13.62%	10.60%	3.91%	3.73%	0.44%	67.70%	18.68%	100%
	IIIA	2	61	79	253	2066	1357	421	133	46	2461	600	4418
		0.05%	1.38%	1.79%	5.73%	46.76%	30.72%	9.53%	3.01%	1.04%	55.70%	13.58%	100%
	IIIB	0	195	273	586	338	3681	1869	1044	91	5073	1135	8077
		0.00%	2.41%	3.38%	7.26%	4.18%	45.57%	23.14%	12.93%	1.13%	62.81%	14.05%	100%
	IIIC	0	4	30	101	24	168	14	1847	37	341	37	2225
		0.00%	0.18%	1.35%	4.54%	1.08%	7.55%	0.63%	83.01%	1.66%	15.33%	1.66%	100%
	Total	472	295643	65137	36825	11190	13755	5017	4545	930	100167	37708	433514
		0.11%	68.20%	15.03%	8.49%	2.58%	3.17%	1.16%	1.05%	0.21%	23.11%	8.70%	100%

upstaged OR 0.87), PR-negative status (vs PR-positive) was associated with concordance when compared to downstaged (OR 0.83) and was associated with upstaging when compared to concordance (OR 3.41). Furthermore, triple negative status (vs not triple negative) was not associated with stage concordance when compared to downstaging (OR 0.99), implying similar odds of downstaging vs concordance regardless of triple negative status, while it was associated with stage concordance when compared to upstaging (OR 0.77). (Fig. 1).

Overall, rates of stage concordance improved over time (61% in 2004 > 70.4% in 2014) with decreasing rates of upstaging (16.6% in 2004 > 8.4% in 2014) and generally stable rates of downstaging (22.5% in 2004 > 21.2% in 2014) (Fig. 2). Facility type and volume were not independently associated with discordance between clinical and pathologic staging.

Associations between stage concordance/discordance and overall survival

Unadjusted OS rates were similar for patients with clinical stages I and II disease, regardless of concordance between clinical and pathologic stage. However, those with clinical stage III disease had an improved OS if they were downstaged compared to concordant (Supplemental Fig. 2). Given patients with the same final pathological stage, the unadjusted 5-year survival rate varied based on the initial clinical stage (Supplemental Table 1), likely reflecting additional insight into the extent of disease. However, unadjusted 5- and 10-year OS rates were similar for all equivalent clinical and pathological stages (i.e. overlapping 95% CI when clinical stage = pathological stage), except stage IIA, which had a slightly higher 5-year survival rate for clinical stage IIA than pathological stage IIA (0.835 vs 0.817, respectively) (Supplemental Table 2).

Discussion

Breast cancer staging was initially developed to communicate efficiently among clinicians and to provide prognostic estimates for patients. Given the treatment and prognostic implications associated with each stage, we sought to evaluate the agreement between preoperative clinical staging and final pathological staging. In our study, we found a clinical to pathological stage discordance rate of 31.8% (23.1% downstaged, 8.7% upstaged) for patients with stages I-III invasive breast cancer who underwent surgery prior to

Table 3
Factors associated with clinical to pathological upstaging and downstaging versus stage concordance (N = 397,979*) using breast cancer data from the National Cancer Database from 2004 to 2014. Odds ratio >1 indicates association with downstaging or upstaging compared to stage concordance, and odds ratios <1 indicates association with concordance. OR: odds ratio; CI: confidence interval; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

	Downstaged vs. Concordant		Upstaged vs. Concordant		Overall P-Value
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	
Age (Years)	0.994 (0.993–0.995)	<0.001	0.99 (0.989–0.992)	<0.001	<0.001
Race/Ethnicity					<0.001
Non-Hispanic white	REF		REF		
Non-Hispanic black	1.237 (1.204–1.271)	<0.001	1.24 (1.195–1.287)	<0.001	
Hispanic	1.193 (1.149–1.238)	<0.001	1.153 (1.093–1.217)	<0.001	
Other	1.131 (1.087–1.177)	<0.001	0.961 (0.903–1.021)	0.20	
Insurance Status					<0.001
Private	REF		REF		
Government	1.089 (1.068–1.112)	<0.001	1.118 (1.086–1.152)	<0.001	
Not Insured	1.362 (1.282–1.446)	<0.001	1.247 (1.144–1.36)	<0.001	
Facility Type					0.05
Academic	REF		REF		
Integrated network	0.996 (0.966–1.026)	0.77	1.047 (1.003–1.094)	0.04	
Comprehensive	1.021 (0.999–1.043)	0.06	1.023 (0.991–1.055)	0.16	
Community	1.036 (1–1.073)	0.05	0.996 (0.946–1.05)	0.89	
Facility Location					<0.001
South	REF		REF		
Midwest	0.974 (0.953–0.995)	0.02	1.139 (1.104–1.176)	<0.001	
Northeast	0.914 (0.892–0.936)	<0.001	0.92 (0.888–0.953)	<0.001	
West	1.065 (1.04–1.091)	<0.001	1.142 (1.102–1.184)	<0.001	
Hospital Volume (annual)					<0.001
High	REF		REF		
Moderate	1.017 (0.995–1.038)	0.13	0.976 (0.946–1.007)	0.13	
Low	1.108 (1.08–1.136)	<0.001	1.066 (1.026–1.107)	<0.001	
Grade					<0.001
1	REF		REF		
2	1.581 (1.548–1.615)	<0.001	3.285 (3.139–3.438)	<0.001	
3	10.557 (10.262–10.86)	<0.001	10.561 (10.035–11.115)	<0.001	
ER Status					<0.001
ER-positive	REF		REF		
ER-negative	0.523 (0.497–0.551)	<0.001	0.867 (0.823–0.913)	<0.001	
PR Status					<0.001
PR-positive	REF		REF		
PR-negative	0.827 (0.805–0.85)	<0.001	3.411 (3.302–3.523)	<0.001	
HER2 Status					<0.001
HER2-positive	REF		REF		
HER2-negative	3.79 (3.669–3.915)	<0.001	1.245 (1.196–1.295)	<0.001	
Triple Negative					
No					
Yes	0.992 (0.937–1.049)	0.77	0.769 (0.725–0.817)	<0.001	<0.001
Histology					<0.001
Invasive ductal	REF		REF		
Invasive lobular	1.509 (1.471–1.548)	<0.001	2.472 (2.383–2.564)	<0.001	
Other invasive	2.515 (2.315–2.733)	<0.001	1.366 (1.225–1.523)	<0.001	
Surgery					<0.001
Mastectomy	REF		REF		
Lumpectomy	0.508 (0.5–0.517)	<0.001	0.383 (0.373–0.392)	<0.001	

*35,535 (8.2%) of patients were excluded from this model due to missingness of one or more covariate.

systemic therapy. After adjustment, stage concordance was associated with ER-negative status, clinical stage N3 disease, and lumpectomy receipt, while discordance was associated with ethnicity/race, higher tumor grade, PR-negative status, HER2-negative status, tumor histology, clinical T stage, and clinical stage N1/2 disease. Stage discordance was associated with differences in survival (better for downstaging and worse for upstaging), even after adjusting for select patient, facility, tumor, and treatment variables.

Taken together, our findings will aid clinicians in their initial discussions with patients on the likelihood that management recommendations may change after surgery. For example, the National Comprehensive Cancer Network (NCCN) guidelines for treating breast cancer[13] strongly recommend consideration of regional nodal irradiation if a patient has positive lymph nodes. In our study, 17.9% of clinically node-negative patients were found to have positive nodes, thus potentially changing management recommendations for nearly 70,000 patients. Furthermore, the recommendation for anti-HER2 therapy, such as trastuzumab, is dependent on both tumor size and nodal status. The observed high rates of stage discordance in our study highlight the importance of accurate staging, as it may significantly alter treatment recommendations.

Regardless of the staging tools employed, under-and over-estimation are common (noted in nearly one third of our study population). Our study is one of the first to demonstrate that tumor biology may be associated with stage discordance in invasive breast cancer. Mustafa et al. demonstrated that patients with ER-positive/PR-positive/HER2-negative disease were 50% less likely to be upstaged.[14] These results are similar to those observed in our study, where stage concordance and discordance were associated with receptor status. Regarding HER2 specifically, HER2-negative status was associated with stage discordance after multivariate analysis.[14,15] In the current era of endocrine therapy and targeted anti-

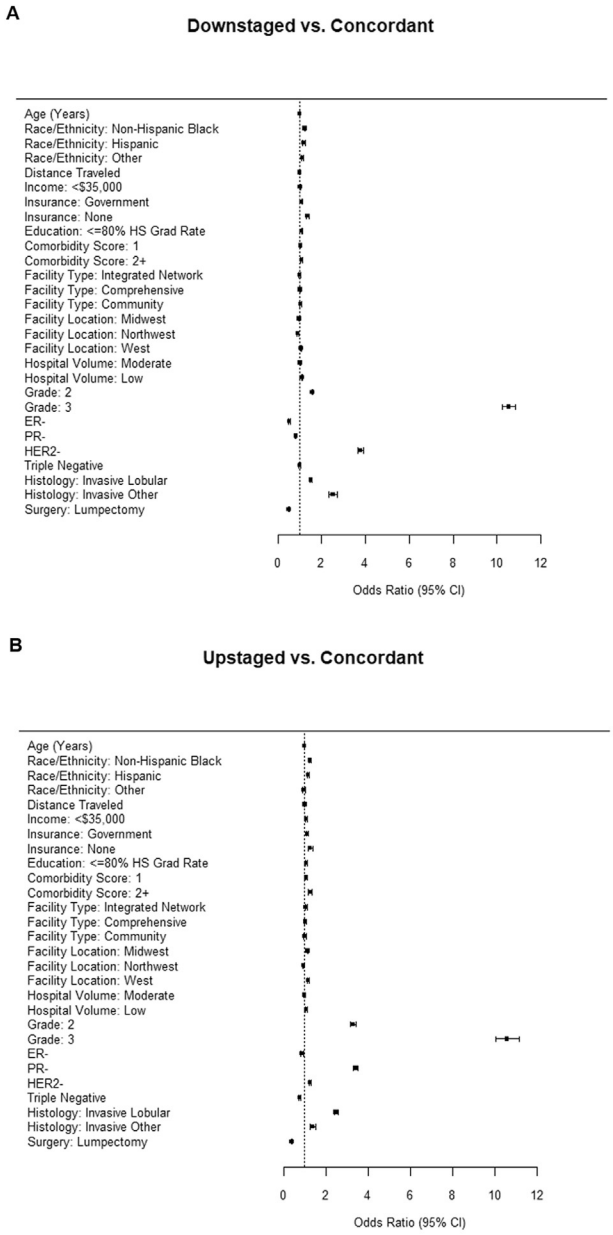

Fig. 1. Forest plot of generalized logistic regression results (N = 397,979) based on data from patients with breast cancer in the National Cancer Database from 2004 to 2014; (A) downstaged vs concordant; (B) upstaged vs concordant. Odds ratio (OR) > 1 indicates association with stage discordance (downstaged or upstaged) and OR <1 indicates association with stage concordance.

HER2 therapy, the prognostic implications of ER, PR, and HER2 status are now reflected in the staging guidelines.[1] However, particularly for HER2-negative patients, the association between tumor biomarkers and stage concordance/discordance may require additional consideration.

In addition to tumor biology, patient race/ethnicity was associated with stage discordance in our study. However, this too may be partially explained by racial variation in breast cancer tumor biology, as black patients experience a higher incidence of triple negative and biologically aggressive tumors.[16] Iqbal et al. reviewed 373,563 women diagnosed with invasive breast cancer from 2004 to 2011 in the Surveillance, Epidemiology, and End Results (SEER) 18 registries database.[17] In this study, black women were less likely to be diagnosed with stage I breast cancer (OR 0.65, $p < 0.001$), and were more likely to die of breast cancer with small tumors, even after adjusting for income and ER status (HR 1.96, $p < 0.001$).[17] Similarly, we also found that race/ethnicity were associated with stage discordance (58.5% stage concordance for non-Hispanic black patients, 62% for Hispanic patients, vs 69.9% for non-Hispanic white patients). Some of these differences in race/ethnicity may also be attributed to variables not captured in our data set, such as types and frequency of pre-operative imaging, physical exam reliability, and access to care.

Currently, clinical staging is based primarily on physical examination, imaging, and biopsies of affected sites. Physical exam remains an essential preoperative component of the evaluation of tumor size (T) and nodal involvement (N). In a retrospective review of 320 patients with palpable breast masses, Wai et al. reported that physical exam demonstrated a 92% accuracy in predicting malignancy.[18] Though specific, the sensitivity of the physical exam in determining T and N stage is low.[19] Therefore, diagnostic mammograms and breast ultrasound are conventionally used to supplement physical exam findings and to clinically stage new breast cancer patients.[20,21] However, variation in staging protocols (by provider, institution, and insurance coverage) and imperfect staging tools will inevitably result in some degree of stage discordance among providers and practice settings.

Some have advocated breast MRI and/or axillary ultrasound as superior tools for clinical staging. Some surgeons routinely order preoperative breast MRIs, due to its high negative predictive value and improved sensitivity in dense breast tissue.[21–23] However, the benefits of routine preoperative MRIs remain uncertain due to high false positive rates, negligible added sensitivity to conventional imaging, and high associated costs.[24–27] Breast MRIs have been shown to increase mastectomy rates, but have not been shown to decrease the rates of positive margins, re-excision, or recurrence.[28–30]

In addition, the best tool for assessing nodal status remains controversial. Clinical staging of the axilla via physical exam alone has been shown to have >99% specificity, but <3% sensitivity.[19] While clinical exam remains the initial assessment tool for most patients, some have proposed routine use of axillary ultrasound to improve accuracy, as it may result in fewer two-stage axillary surgeries.[31] Studies are currently underway to evaluate the possibility of replacing sentinel node biopsies in clinically node negative patients with axillary ultrasound, and if negative, omitting surgical axillary nodal evaluation completely.[32,33] Presently, however, the AJCC breast cancer staging guidelines maintain that routine imaging is not necessary to determine clinical nodal status,[1] and several meta-analyses have reported that preoperative axillary ultrasound detects only half of clinically occult nodal metastases.[34,35]

Our study limitations include those associated with retrospective studies based on large national databases and data collection/entry. In addition, nearly 800,000 patients with missing clinical or pathological staging information were excluded from our analysis, which could have implications for our study's conclusions. This included 641,321 patients with missing HER2 status, and the remainder were missing cT and/or cN stage. In addition, it is important to recognize that although the anatomic staging variables (T/N) are typically entered at both diagnosis (clinical stage) and after surgery (pathological stage), other variables such as receptor status and tumor grade are only entered at one time point. While tumor grade is most likely taken from the final pathology report, the receptors are often determined based on the needle biopsy specimen and are rarely repeated after surgery. However, tumor grade and receptor status are often consistent between the biopsy and surgical specimens. Lastly, institutional variation in clinical staging and data interpretation may have also affected the reported staging, and thus stage concordance.

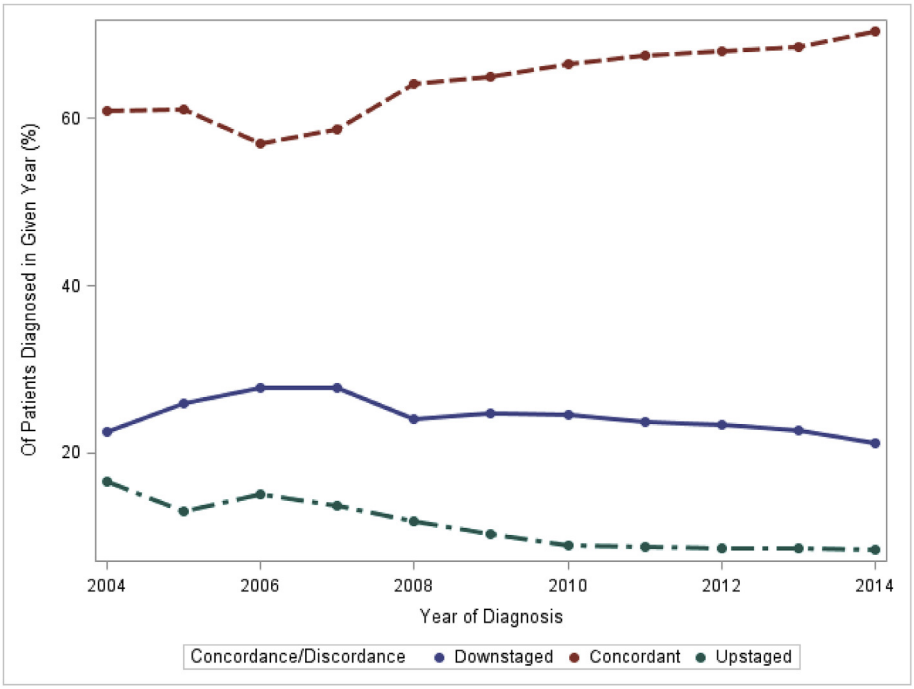

Fig. 2. Clinical-pathological stage concordance and discordance rates over time based on data from patients with breast cancer in the National Cancer Database from 2004 to 2014. The red dashed line represents concordant cases, the blue solid line represents downstaged cases, and the green dash-dot-dash line represents upstaged cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In conclusion, patients with stages I-III invasive breast cancer who underwent surgery prior to any systemic therapy were found to have a 23.1% downstaging rate and 8.7% upstaging rate. Numerous factors were noted to be associated with stage concordance or discordance, including patient race/ethnicity, tumor grade, ER status, PR status, HER2 status, tumor histology, and clinical T/N stage. Specifically, grade 3 tumors appeared to have a strong association with stage discordance, and this characteristic in particular may alert clinicians to discuss staging with caution. Discordance itself was not a negative prognostic indicator. Not surprisingly, patients who were ultimately upstaged with surgery were found to have a worse survival than those with the same clinical stage who were not upstaged. Conversely, patients that were downstaged often had a better survival than those with the same clinical stage who were not downstaged. Our findings highlight the vital importance of accurate staging, achieved through surgery, as this information is often used to relay prognostic information to patients and providers, and it may also influence subsequent treatment recommendations. In today's era of personalized medicine, patients are eager to discuss their specific case and prognosis. However, as clinicians, it is our responsibility to temper the preoperative discussion and consider deferring in depth discussions regarding outcomes and prognosis until more information is obtained after surgery.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.07.016.

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