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ORIGINAL REPORT

High Risk of Recurrence for Patients With Breast Cancer Who Have Human Epidermal Growth Factor Receptor 2–Positive, Node-Negative Tumors 1 cm or Smaller

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See accompanying editorial on page 5671 and articles on pages 5685, 5693, and 5838

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ABSTRACT

Purpose
To evaluate the risk of recurrence in women diagnosed with T1a and T1b, node-negative, human epidermal growth factor receptor 2 (HER2) –positive breast cancer.

Methods
We reviewed 965 T1a,bN0M0 breast cancers diagnosed at our institution between 1990 and 2002. Dedicated breast pathologists confirmed HER2 positivity if 3+ by immunohistochemistry or if it had a ratio of 2.0 or greater by fluorescence in situ hybridization (FISH). Patients who received adjuvant chemotherapy or trastuzumab were excluded. Kaplan-Meier product was used to calculate recurrence-free survival (RFS) and distant recurrence–free survival (DRFS). Cox proportional hazard models were fit to determine associations between HER2 status and survival after adjustment for patient and disease characteristics. Additionally, 350 breast cancers from two other institutions were used for validation.

Results
Ten percent of patients had HER2-positive tumors. At a median follow-up of 74 months, there were 72 recurrences. The 5-year RFS rates were 77.1% and 93.7% in patients with HER2-positive and HER2-negative tumors, respectively ($P < .001$). The 5-year DRFS rates were 86.4% and 97.2% in patients with HER2-positive and HER2-negative tumors, respectively ($P < .001$). In multivariate analysis, patients with HER2-positive tumors had higher risks of recurrence (hazard ratio [HR], 2.68; 95% CI, 1.44 to 5.0; $P = .002$) and distant recurrence (HR, 5.3; 95% CI, 2.23 to 12.62; $P < .001$) than those with HER2-negative tumors. Patients with HER2-positive tumors had 5.09 times (95% CI, 2.56 to 10.14; $P < .0001$) the rate of recurrences and 7.81 times (95% CI, 3.17 to 19.22; $P < .0001$) the rate of distant recurrences at 5 years compared with patients who had hormone receptor–positive tumors.

Conclusion
Patients with HER2-positive T1abN0M0 tumors have a significant risk of relapse and should be considered for systemic, anti-HER2, adjuvant therapy.

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INTRODUCTION

Approximately 25% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2), and overexpression has been associated with worse disease-free and overall survivals.[1-4] The HER2-positive phenotype correlates with poorly differentiated tumors, markers of high proliferative rate, and lack of expression of estrogen and progesterone receptors. In addition, many studies suggest that HER2 positivity is an independent predictor of disease recurrence and breast cancer–related mortality.[1-3]

Five randomized, phase III, clinical trials reported significant improvement in disease-free and overall survivals with trastuzumab administered in conjunction with adjuvant chemotherapy for early-stage, HER2-positive breast cancer.[5-8] However, these studies included principally node-positive occurrences and, with the exception of BCIRG-006, excluded patients with tumors 1 cm or smaller that were node negative.[5-8]

In the setting of node-negative small tumors (ie, 1 cm or less), available data regarding HER2-positive disease recurrence at 5 and 10 years is limited.[9] Consensus guidelines, such as those of the National Comprehensive Cancer Network, do not recommend systemic anti-HER2 therapy for tumors less than 1 cm because of the lack of supportive information.[10] Mammography has facilitated the detection of smaller tumors; therefore, our experience in managing such tumors is limited.[11,12] The purpose of this study was to evaluate the risk of recurrence in women diagnosed with T1a and T1b, node-negative, HER2-positive breast cancer.

METHODS

The Breast Cancer Management System database of The University of Texas M. D. Anderson Cancer Center (MDACC) identified women who were diagnosed before May 2002 with newly diagnosed, node-negative, invasive breast cancers that were 1 cm or smaller. Patients with ductal carcinoma in situ and microinvasion, and patients with recurrent breast cancer at presentation, were excluded. Of the 1,390 patients identified, 425 were excluded from the analysis because of male sex (n = 1), lack of receptor information (n = 237), treatment with adjuvant chemotherapy (n = 138), non–T1ab stage (n = 2), or diagnosis before 1990 (n = 47). A total of 965 patients were eligible: 77% had hormone receptor (HR) –positive tumors, 13% had triple-receptor–negative tumors (TNs), and 10% had HER2-positive tumors. Five hundred twenty-six patients (55%) received adjuvant hormonal therapy. None received adjuvant trastuzumab therapy.

A second set of patients with the same inclusion criteria and similar follow-up time was obtained from collaborators at the General Hospital Leoben, Austria, and at the Institute Jules Bordet, Brussels, Belgium. These 350 tumors were used to validate the findings of the MDACC population. The institutional review boards at the three different institutions reviewed and approved this research.

Pathology Methods

Dedicated breast pathologists at the three institutions reviewed all pathologic specimens. Immunohistochemical (IHC) analysis to determine HR status was performed by using standard procedures on 4-μm sections of paraffin-embedded tissues stained with monoclonal antibodies for estrogen and progesterone receptors. Nuclear staining $\geq$ 10% of either estrogen receptor or progesterone receptor was considered a positive result. HER2 status was evaluated by IHC or by fluorescence in situ hybridization (FISH). HER2 positivity was defined as 3+ receptor overexpression on IHC staining (ie, strong membranous staining in at least 10% of cells) and/or as gene amplification found on FISH. A gene copy-to–CEP-17 ratio greater than 2.0 was considered amplified.

Statistical Methods

Patients were categorized according to the HER2 status. Patient characteristics were tabulated by median and range and were compared between groups with the χ^2 test or Wilcoxon rank sum test, as appropriate. Time to recurrence was measured from the date of diagnosis to the date of first local or distant disease recurrence or to last follow-up. Patients who died before experiencing a disease recurrence were considered censored at their dates of death. Time to distant recurrence was measured from the date of diagnosis to the date of first distant recurrence or to last follow-up. Patients who died before experiencing a distant recurrence were considered censored at their dates of death, and patients who experienced local recurrence as the first recurrence were considered censored at their dates of local recurrence. Because the at-risk proportion of patients became too small at 5 years, and because most of the recurrences occurred by then, follow-up time was truncated at 5 years. Time to recurrence and time to distant recurrence were estimated according to the

Table 1. MDACC Patient Demographic and Clinical Characteristics by HER2 Status

Characteristic	HER2 Negative (n = 867)		HER2 Positive (n = 98)		
	No.	%	No.	%	*P*
Age, years					
Minimal	26		28		
Median	57		51.5		
Maximal	87		78		< .0001
Ethnicity					
Black	61	7.0	9	9.2	
Hispanic	78	9.0	10	10.2	
Other	35	4.0	4	4.1	
White	693	79.9	75	76.5	.843
Menopausal status					
Premenopausal	201	23.2	43	43.9	
Postmenopausal	665	76.8	55	56.1	< .0001
Histology					
Other	206	23.8	8	8.2	
Ductal	661	76.2	90	91.8	.0004
T stage					
Ia	280	32.3	43	43.9	
Ib	587	67.7	55	56.1	.021
Hormone receptor status					
Negative	125	14.4	38	38.8	
Positive	742	85.6	60	61.2	< .0001
Nuclear grade					
1	116	17.3	1	1.5	
2	386	57.6	17	25.4	
3	168	25.1	49	73.1	< .0001

Abbreviations: MDACC, M. D. Anderson Cancer Center; HER2, human epidermal growth factor receptor 2.

Kaplan-Meier method and were compared between groups with the log-rank statistic. Cox proportional hazards models were fit to determine the association of HER2 status with the risk of recurrence after adjustment for other patient and disease characteristics. Each model contained terms for HER2 status, HR status, age at diagnosis, nuclear grade, and T stage. Analyses were also performed that considered HR and HER2 status combined into one of three groups: HER2-positive status (regardless of HR status), HR-positive status (and HER2-negative status), and TN (ie, HR- and HER2-negative status). *P* values less than .05 were considered statistically significant. SAS 9.1 (SAS Institute, Cary, NC) was used.

The primary analyses considered patients diagnosed and treated at MDACC. Patients diagnosed and treated at other institutions were used to confirm the MDACC results. Because there were few recurrence events in the confirmatory cohort, multivariate models were not fit.

We also considered the cumulative incidence of any recurrence given death as a competing risk, we considered the cumulative incidence of distant recurrence given both death and local recurrence as competing risks. However, both the estimates and the inference tended to be similar to those obtained by the Kaplan-Meier method; therefore, only the survival analyses are presented.[13,14]

RESULTS

MDACC

Patient characteristics are listed in Table 1. Median age was 57 years (range, 26 to 87 years). Ten percent of patients had HER2-positive tumors, 68% had HR-positive disease, and 23% had TN breast cancer. Compared with patients who had HER2-negative tumors, those who had HER2-positive tumors were younger ($P = .001$), presented more frequently with T1a tumors ($P = .001$), had HR-positive disease less frequently ($P < .001$), and had tumors with higher nuclear grade ($P < .001$). Sixty patients were both HER2 positive and HR positive, and 31 patients received either adjuvant tamoxifen or an aromatase inhibitor.

Within maximum follow-up time of 5 years, there were 72 recurrences, including 34 distant recurrences. The 5-year recurrence-free survival (RFS) estimates are listed in Table 2. Among all patients, 5-year RFS was 92.0% (95% CI, 90.1%, 93.6%). Patients who had HER2-positive breast cancer had worse RFS than patients who had HER2-negative breast cancer (77.1% *v* 93.7% at 5 years; $P < .0001$; Fig 1A). HR status, age, menopausal status, and nuclear grade also were significantly associated with RFS among these patients (Table 2). When patients were considered in groups according to HER2 and HR status, patients who had HER2-positive breast cancer had worse RFS than patients who had either HR-positive breast cancer or TN breast cancer ($P < .0001$; Fig 1B). There were no differences in RFS estimates in patients who had HER2-positive and HR-negative tumors compared with patients who had HER2-positive and HR-positive tumors. There were 21 recurrences in the patients who had HER2-positive disease; 13 (21%) of 60 patients who had HER2-positive and HR-positive tumors experienced recurrences; and eight (21%) of 38 patients who had HER2-positive and HR-negative tumors experienced recurrences. In addition, in the group of 60 patients who had both HER2- and HR-positive tumors, there were 13 recurrences; seven of the recurrences were in the no–hormonal therapy group, and six were in the tamoxifen or aromatase inhibitor group.

Distant recurrence–free survival (DRFS) estimates are listed in Table 2. Among all patients, DRFS at 5 years was 96.2% (95% CI, 94.7% to 97.2%). Patients who had HER2-positive breast cancer had worse DRFS than patients who had HER2-negative breast cancer (86.4% *v* 97.2% at 5 years; $P < .0001$; Fig 2A). In addition to HER2, only age was significantly associated with DRFS ($P = .001$). There were trends towards a significant association with HR, grade, and menopausal status. When patients were considered in groups according to both HER2 and HR status, patients who had HER2-positive breast cancer had worse DRFS than patients who had either HR-positive disease or TN disease ($P < .0001$; Fig 2B).

Table 3 lists the results of the multivariable models for RFS and DRFS. After adjustment for HR status, age at diagnosis, T stage, and nuclear grade, patients who had HER2-positive breast cancer had a significantly increased risk of both recurrence (hazard ratio [HR], 2.68; 95% CI, 1.44 to 5; $P = .002$) and distant recurrence (HR, 5.3; 95% CI, 2.23 to 12.62; $P = .0002$) compared with patients who had HER2-negative breast cancer. Similarly, when patients were grouped according to both HER2 and HR status, patients with HER2-positive breast cancer had 5.09 times (95% CI, 2.56 to 10.14; $P < .0001$) the risk of disease recurrence and 7.81 times (95% CI, 3.17 to 19.22; $P < .0001$) the risk of distant recurrence compared with patients who had HR-positive disease. Patients who had TN breast cancer had 3.89 times (95% CI, 2.56 to 10.14; $P < .0001$) the risk of recurrence and 2.84 times (95% CI, 0.99 to 8.14; $P = .053$) the risk of distant recurrence compared with patients who had HR-positive breast cancer.

Other Institutions

Data on 350 additional patients treated at two other institutions were obtained and used to show reproducibility. In this cohort of patients, 21 (6%) were HER2 positive. The median age was 60 years (range, 29 to 88 years); 79% were postmenopausal; 86% had T1b primaries; 48% had HR-positive tumors; and 86% had nuclear grade 1 or 2 disease. At 5 years, only 10 patients had experienced a recurrence, and RFS was 96.4% (95% CI, 93.4% to 98.1%). The 5-year RFS rates were 87.4% (95% CI, 57.7% to 96.8%) and 97.0% (95% CI, 93.9% to 98.5%) for patients who had HER2-positive and HER2-negative tumors, respectively ($P = .043$). In addition, 5-year RFS were 99.3% (95% CI, 95.1% to 99.9%) and 94.7% (95% CI, 88.8% to 97.5%) for patients who had HR-positive and TN breast cancer, respectively. Patients who had HER2-positive disease had significantly worse RFS than patients with HR-positive or TN disease ($P = .002$). Nine of the 10 recurrence events in this group of patients were distant recurrences. Although the trend of the results remained consistent with the MDACC analyses, statistical significance was not attained. The 5-year DRFS rates were 92.3% (95% CI, 56.6% to 98.9%) and 97.0% (95% CI, 93.9% to 98.5%) for patients who had HER2-positive and HER2-negative tumors, respectively ($P = .449$). Among patients who had HR-positive breast cancer, the 5-year DRFS rate was 99.3% (95% CI, 95.1% to 99.9%), and the 5-year DRFS rate among patients who had TN tumors was 94.7% (95% CI, 89.0% to 97.5%).

DISCUSSION

Increased expression of HER2 or amplification of the *HER2/neu* gene has been associated with a more aggressive phenotype of early-stage breast cancer.[11] Several large trials that incorporated the humanized monoclonal antibody against HER2, trastuzumab, into adjuvant chemotherapy regimens have demonstrated marked improvements in both disease-free survival and overall survival in patients who had HER2-positive disease. However, most of these trials consistently excluded patients with node-negative tumors that were 1 cm or

Table 2. MDACC Survival Estimates

Variable by Type of Survival	Survival Estimates and Analyses				
	No. at Risk	No. of Events	5-Year Estimate (%)	95% CI (%)	*P*
Recurrence-free survival					
All patients	965	72	92.0	90.1 to 93.6	
HER2 status					
Negative	867	51	93.7	91.8 to 95.2	
Positive	98	21	77.1	67 to 84.5	< .0001
HR status					
Negative	163	26	83.3	76.3 to 88.3	
Positive	802	46	93.9	91.9 to 95.4	< .0001
Breast cancer subgroup					
HER2 positive	98	21	77.1	67 to 84.5	
HR positive	742	33	95.2	93.3 to 96.6	
Triple-receptor negative	125	18	85.2	77.6 to 90.4	< .0001
Age, years					
≤ 50	437	42	85.0	80.3 to 88.7	
> 50	528	30	95.2	93.2 to 96.6	< .0001
Menopausal status					
Premenopausal	244	33	85.8	80.6 to 89.7	
Postmenopausal	720	39	94.2	92.1 to 95.7	< .0001
Histology					
Other	214	14	93.0	88.4 to 95.8	
Ductal	751	58	91.8	89.5 to 93.6	.547
T stage					
Ia	323	23	92.5	88.9 to 94.9	
Ib	642	49	91.8	89.3 to 93.8	.723
Grade					
1-2	520	29	93.8	91.1 to 95.6	
3	217	30	85.4	79.8 to 89.6	< .0001
Distant recurrence–free survival					
All patients	965	34	96.2	94.7 to 97.2	
HER2 status					
Negative	867	22	97.2	95.8 to 98.2	
Positive	98	12	86.4	77.3 to 92.1	< .0001
HR status					
Negative	163	9	93.9	88.5 to 96.8	
Positive	802	25	96.6	95 to 97.7	.111
Breast cancer subgroup					
HER2 positive	98	12	86.4	77.3 to 92.1	
HR positive	742	17	97.5	96 to 98.4	
Triple-receptor negative	125	5	95.6	89.8 to 98.2	< .0001
Age, years					
≤ 50	437	19	92.9	89.1 to 95.4	
> 50	528	15	97.6	96 to 98.5	.001
Menopausal status					
Premenopausal	244	13	94.2	90.2 to 96.6	
Postmenopausal	720	21	96.8	95.1 to 97.9	.069
Histology					
Other	214	8	95.9	92 to 97.9	
Ductal	751	26	96.2	94.5 to 97.4	.882
T stage					
Ia	323	10	96.6	93.8 to 98.2	
Ib	642	24	95.9	94 to 97.3	.576
Grade				94.7 to 97.2	
1-2	520	19	96.0	93.7 to 97.4	
3	217	12	94.0	89.6 to 96.5	.188

Abbreviations: MDACC, M. D. Anderson Cancer Center; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

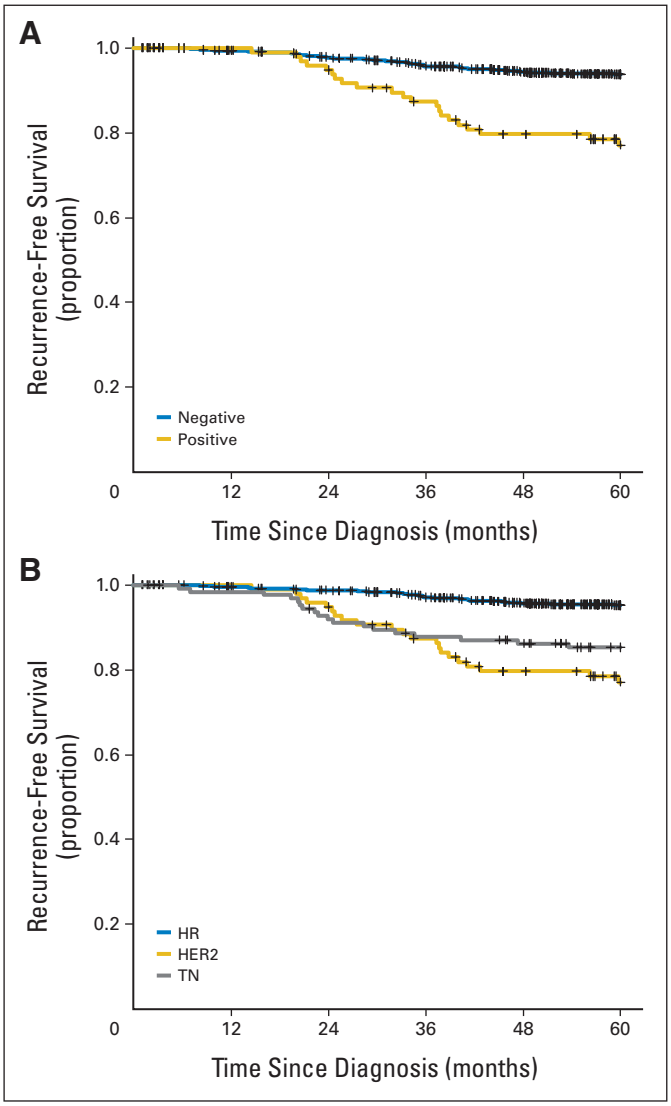

Fig 1. Recurrence-free survival by (A) human epidermal growth factor receptor 2 status and (B) breast cancer subtype.

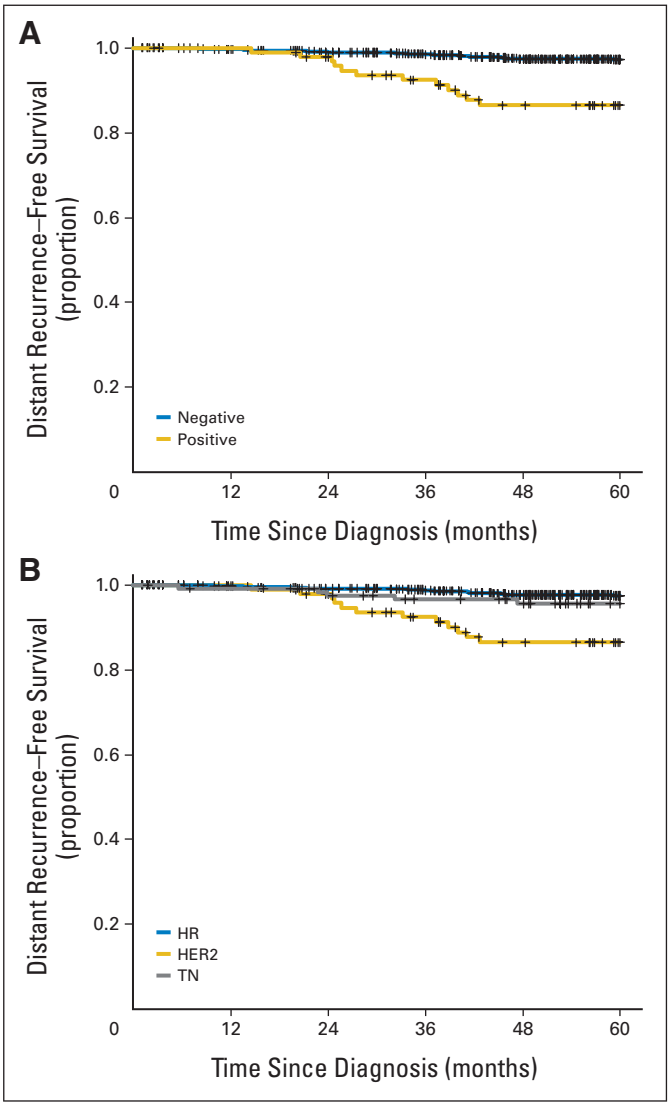

Fig 2. Distant recurrence–free survival by (A) human epidermal growth factor receptor 2 (HER2) status and (B) breast cancer subtype. HR, hormone receptor–positive status; HER2, HER2-positive status; TN, triple-receptor–negative status.

smaller.[5-8] Data from these studies were summarized in a meta-analysis, which demonstrated that patients who had HER2-positive breast cancer had approximately a 50% reduction in the risk of early recurrence and mortality, irrespective of nodal status. Therefore, it is likely that patients who have T1a,bN0 tumors would benefit similarly from treatment with trastuzumab.[9] Guidelines generally have not recommended treatment of such patients, in part because unselected patients with T1a,bN0 tumors have an excellent prognosis and because the uncertainty if HER2 is a powerful independent unfavorable prognostic factor for patients with these otherwise low-risk cancers.[10] Our analysis suggests that HER2 is a powerful negative prognostic factor for patients with T1a,bN0 tumors. These results are consistent with evolving literature that addresses this question. Joensuu et al[11] described a large cohort of 852 unilateral pathologic T1N0 tumors, 313 of which were 1 cm or smaller. The rate of HER2 amplification or overexpression was 12%, similar to the 10% that we report. When this group evaluated the effect of HER2 positivity on the entire 852 patients, there was an increased risk of recurrence (HR, 2.56; 95% CI, 1.05 to 6.23; $P = .04$). Interestingly, in these and other small-tumor cohorts, HER2 positivity appears to be less frequent than in cohorts of larger, node-positive tumors.[11,12]

We have collaborated with two additional institutions to additionally examine the generalizability of these observations. Although the CIs for RFS in the confirmatory cohort are wider than the MDACC group—because there are both fewer patients and fewer recurrence events—the results of the analysis of this additional cohort appear consistent with our primary results.

Our findings show that patients who have HER2-positive tumors 1 cm or smaller have a high risk of relapse and likely should be considered for future clinical trials that include adjuvant anti-HER2 therapy, given that it will be difficult to do a clinical trial exclusively including these patients. Two trastuzumab-based adjuvant trials already have shown significant improvement in DFS when compared with chemotherapy alone in stages I to II, node-negative, HER2-positive breast cancer.[6,8] In the absence of direct evidence to support

Table 3. MDACC Multivariable Models

	Multivariable Analyses by Survival Status					
	Recurrence Free			Distant Recurrence–Free		
Comparative Variable	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
HER2 status						
Positive *v* negative	2.68	1.44 to 5	.002	5.30	2.23 to 12.62	.0002
Hormone receptor status						
Positive *v* negative	0.41	0.23 to 0.72	.002	0.59	0.25 to 1.37	.219
Age at diagnosis, years*	0.96	0.94 to 0.98	.001	0.73	0.32 to 1.7	.467
Tumor grade						
3 *v* 1-2	1.34	0.75 to 2.41	.320	0.97	0.94 to 1	.080
Stage						
Ib *v* Ia	1.59	0.91 to 2.78	.103	1.47	0.68 to 3.18	.329

Abbreviations: MDACC, M. D. Anderson Cancer Center; HER2, human epidermal growth factor receptor 2.
*Continuous variable.

such intervention, and in the absence of randomized, clinical trials to test the hypothesis, patients who have HER2-positive, T1a,bN0 tumors should be informed about the risk of recurrence and the availability of HER2-directed therapy, and there should be a clear discussion of potential risks, adverse effects, and benefits.[15]

Limitations of this study include its retrospective nature. However, HER2 status, in many cases, was not known and was tested only later, after the cohort was identified. For patients whose HER2 status was known, those given systemic chemotherapy or anti-HER2 therapy were excluded. Another important bias is that patients may have presented to our center with recurrence as their initial presentation, thereby artificially raising the recurrence rate. We accounted for this bias by excluding patients that initially presented to our institution with recurrent disease. It is also important to comment on the issue that patients with HER2-positive disease were more likely to have smaller tumors (ie, T1aN0); this may be explain by the selection bias, in which patients with T1b disease were treated with adjuvant chemotherapy and were excluded from the analysis.

Given the known, aggressive nature of HER2-positive tumors, clinicians struggle with therapeutic decisions because of a scarcity of clinical data in patients with tumors 1 cm or smaller. This large analysis was conducted in an effort to address such uncertainty in this population of patients with breast cancer. With the advent of digital mammography and MRI as screening modalities for breast cancer, the T1ab population could additionally increase, which would make this data even more powerful in the future as early detection improves.[16] With the incidence of T1ab tumors increasing, our results strongly suggest that a large number of women may benefit from adjuvant anti-HER2 therapy. This ultimately may translate into more cures of breast cancer, if the curative efficacy of adjuvant trastuzumab therapy in this setting truly is validated.

In summary, we report that HER2 is a powerful independent prognostic factor in T1a,bN0 breast cancer. These findings, together with the evolving literature, suggest that a change in current guidelines would be appropriate and that systemic treatment with anti-HER2 therapies are worthy of consideration in the T1a,bN0 population. In addition, clinical trials to determine the benefit-to-risk ratio of adjuvant anti-HER2 therapy in this group of patients are needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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