JAMA Surgery | Original Investigation

Association of Low Nodal Positivity Rate Among Patients With *ERBB2*-Positive or Triple-Negative Breast Cancer and Breast Pathologic Complete Response to Neoadjuvant Chemotherapy

Alison U. Barron, MD; Tanya L. Hoskin, MS; Courtney N. Day, BS; E. Shelley Hwang, MD, MPH; Henry M. Kuerer, MD, PhD; Judy C. Boughey, MD

IMPORTANCE A recent publication reported that of 527 patients with clinically node-negative (cN0) cT1/cT2 triple-negative breast cancer (TNBC) or *ERBB2*-positive disease treated with neoadjuvant chemotherapy (NAC), 100% of those who achieved a breast pathologic complete response (pCR) had pathologic node negativity (pN0). Eliminating axillary surgery in these patients has been suggested as safe based on these results.

OBJECTIVE To evaluate nodal positivity rates in patients with cT1/cT2 N0 *ERBB2*-positive disease and TNBC with a breast pCR after NAC using the National Cancer Database (NCDB), which included academic and community settings.

DESIGN, SETTING, AND PARTICIPANTS This retrospective study reviewed data from the NCDB from January 1, 2010, through December 31, 2015. Participants included patients with cN0/cN1 cT1/cT2 breast cancer who received NAC followed by surgery. Pathologic nodal positivity rates by breast pCR were compared in cN0 and cN1 disease, within each tumor subtype (*ERBB2*-positive, TNBC, and hormone receptor–positive/*ERBB2*-negative). Data were analyzed from September 13, 2017, through January 30, 2018.

EXPOSURES Neoadjuvant chemotherapy followed by surgery.

MAIN OUTCOMES AND MEASURES The pathologic nodal positivity rate after NAC (ypN) specifically in patients with cT1/cT2 cN0 *ERBB2*-positive disease or TNBC who achieve a breast pCR after NAC.

RESULTS A total of 30 821 patients with cT1/cT2 cN0/cN1 breast cancer treated with NAC and surgical resection (99.6% female; mean [SD] age, 52.0 [11.5] years) were identified. Of 6802 patients with cN0 *ERBB2*-positive disease, 3062 (45.0%) achieved breast pCR and of those, 49 (1.6%; 95% CI, 1.2%-2.1%) were ypN positive. In 6222 patients with cN0 TNBC, 2315 (37.2%) achieved breast pCR, and of those, 36 (1.6%; 95% CI, 1.1%-2.1%) were pathologic node positive after NAC. Rates of ypN positivity were higher in patients with cN0 and residual disease in the breast; 632 of 3740 (16.9%) with *ERBB2*-positive disease and 492 of 3907 (12.6%) with TNBC with residual disease in the breast were node positive ($P < .001$). Among 4164 patients with cN1 *ERBB2*-positive disease, 1801 (43.3%) achieved breast pCR, with 223 of those (12.4%) being ypN positive. In 3293 patients with TNBC, 1229 (37.3%) achieved breast pCR, with 173 of these (14.1%) being ypN postive. Breast pCR rates were lower in hormone receptor–positive/*ERBB2*-negative disease (646 of 5069 [12.7%] for cN0; 711 of 5271 [13.5%] for cN1) and ypN positivity rates were 26 of 646 (4.0%) in cN0 vs 217 of 711 (30.5%) in cN1 disease with breast pCR and 1464 of 4423 (33.1%) in cN0 disease vs 3775 of 4560 (82.8%) in cN1 disease with residual disease in the breast.

CONCLUSIONS AND RELEVANCE In this study, the highest rates of breast pCR were seen in *ERBB2*-positive disease and TNBC. In patients with cN0 *ERBB2*-positive disease or TNBC with breast pCR, the nodal positivity rate was less than 2%, which supports consideration of omission of axillary surgery in this subset of patients.

JAMA Surg. 2018;153(12):1120-1126. doi:10.1001/jamasurg.2018.2696
Published online September 5, 2018.

Supplemental content

Author Affiliations: Department of Surgery, Mayo Clinic, Rochester, Minnesota (Barron, Boughey); Division of Health Sciences Research, Mayo Clinic, Rochester, Minnesota (Hoskin, Day); Department of Surgery, Duke University, Durham, North Carolina (Hwang); Division of Surgery, MD Anderson Cancer Center, Houston, Texas (Kuerer).

Corresponding Author: Judy Boughey, MD, Department of Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55902 (boughey.judy@mayo.edu).

With advances and improvements in targeted therapy for breast cancer, response rates to neoadjuvant chemotherapy (NAC) have increased, from pathologic complete response (pCR) rates of 9% to 13% in the era of anthracyclines to 19% to 26% with the addition of taxane chemotherapy and as high as 60% to 70% with the addition of trastuzumab and pertuzumab in *ERBB2* (formerly known as *HER2*; OMIM 164870)-positive disease [1-4] Rates of pCR are higher in patients with *ERBB2*-positive disease and triple-negative breast cancer (TNBC) than in those with hormone receptor (HR)-positive/*ERBB2*-negative disease.[5] Patients who achieve a pCR have significantly higher survival rates compared with those with residual disease. The association of pCR with survival varies by biologic subtype, being the most pronounced in patients with TNBC and *ERBB2*-postive disease.[6]

In the presence of residual disease after NAC, survival is higher with residual disease in the breast only compared with residual disease in the nodes only and lowest with residual disease in both. Patients who achieve an axillary pCR have higher 10-year overall survival and recurrence-free survival (85% and 83%, respectively) compared with those with any residual nodal disease (55% and 58%, respectively).[7]

Knowing that pCR rates are higher in patients with *ERBB2*-positive disease and TNBC compared with patients with HR-positive/ *ERBB2*-negative disease and that a pCR in these patients purports an improved survival, an important emerging question is whether surgery can be avoided in patients who achieve a pCR. Assessing for residual disease in the breast by imaging techniques such as mammography, ultrasonography, or magnetic resonance imaging (MRI) of the breast has been challenging, with accuracy rates ranging from 43% to 84% and the technique with the overall best accuracy being MRI.[8-10] The Translational Breast Cancer Research Consortium trial 017 noted that the sensitivity, negative predictive value, positive predictive value, and accuracy of MRI for estimating pCR differed significantly among biologic subtypes, with the highest negative predictive value in patients with *ERBB2*-positive disease (62%) and TNBC (60%).[10] Although these results are encouraging, these rates do not support the use of MRI alone in detecting a pCR. A recent study[11] evaluated the accuracy rates of vacuum-assisted core biopsies and fine-needle aspiration biopsies of the tumor bed after NAC for *ERBB2*-positive disease and TNBC and correlated with the findings from surgical resection. The investigators[11] reported that combined fine-needle aspiration biopsy and vacuum-assisted core biopsy demonstrated an accuracy of 98%, false-negative rate of 5%, and negative predictive value of 95% in estimating residual breast cancer. Based on these results, a prospective clinical trial has begun omitting breast surgery in patients with a breast pCR determined by results of percutaneous biopsy of the tumor bed. The potential omission of breast surgery in patients with an excellent response to NAC opens the question of whether axillary surgery could also be omitted in these patients. The MD Anderson Cancer Center (MDACC)[12] reviewed their patient data and found that of 290 patients with cT1/cT2 *ERBB2*-positive disease or TNBC with clinical node negative (cN0) findings at presentation, 116 (40.0%) achieved a breast pCR; of those, 100% had pathologic node negative (pN0) disease at surgery. These single-institution data suggest that patients with cN0 *ERBB2*-positive disease or TNBC who achieve a breast pCR can potentially avoid axillary surgery, because the rate of nodal positivity is very low. Although the study results are highly encouraging, the imaging workup at the initial diagnosis of breast cancer at MDACC is very comprehensive, including axillary ultrasonography and ultrasonography of internal mammary, infraclavicular, and supraclavicular lymph nodes.[13] Therefore, the question arises as to how applicable these findings are to practices across the United States. Validation of these findings in a larger sample size that incorporates different practice settings is important. The goal of the present study was to use the National Cancer Database (NCDB) to evaluate rates of nodal positivity in patients with and without a breast pCR after NAC by tumor subtype.

Key Points

Question In patients with cN0 *ERBB2* (formerly known as *HER2*)-positive or triple-negative breast cancer who achieve a breast pathologic complete response after neoadjuvant chemotherapy, what is the rate of node-positive disease at surgery?

Findings This study evaluated a large cancer database including 30 821 patients with cT1/cT2 N0/N1 breast cancer treated with neoadjuvant chemotherapy and surgical resection. Those with cT1/cT2, cN0 *ERBB2*-positive or triple-negative breast cancer who achieved a breast pathologic complete response had less than a 2% rate of axillary nodal positivity.

Meaning Patients with cN0 *ERBB2*-positive or triple-negative breast cancer and who have an excellent response to neoadjuvant chemotherapy have an extremely low rate of nodal positivity at surgery, which supports the consideration of omission of axillary surgery in these patients.

Methods

The data used in this study were derived from a deidentified NCDB Participant User File. The NCDB is a nationwide cancer database sponsored by the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Cases in the NCDB represent approximately 70% of newly diagnosed cancer cases nationwide. The NCDB contains more than 30 million records of individual cancer cases collected by more than 1500 Commission on Cancer–approved facilities across the United States.[14] The institutional review board of the Mayo Clinic deemed analysis of the NCDB Participant User File file to be exempt from review.

We identified all patients with cT1/cT2 cN0/cN1 breast cancer treated with NAC followed by breast and nodal surgery in the NCDB from January 1, 2010, through December 31, 2015. Patients with M1 disease were excluded, as were patients treated with neoadjuvant endocrine therapy or neoadjuvant radiation therapy and those with unknown pathologic breast or node status or unknown biologic subtype. Patients were considered to have received NAC if their chemotherapy was started more than 30 days and less than 1 year before surgery. Estrogen receptor and progesterone receptor status were each classified as positive if at least 1% of cells stained positive. Status was classified as HR positive if the estrogen receptor or progesterone receptor status (or both) was posi-

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Total (N = 30 821)
Age at diagnosis, y, No. (%)	
<50	13 162 (42.7)
50-59	9328 (30.3)
60-69	6263 (20.3)
≥70	2068 (6.7)
Sex, No. (%)	
Male	136 (0.4)
Female	30 685 (99.6)
Race/ethnicity, No. (%)[a]	
White	23 535 (77.0)
Black	5101 (16.7)
Other	1937 (6.3)
Spanish Hispanic origin, No. (%)[b]	
Non-Spanish non-Hispanic origin	27 553 (91.5)
Spanish Hispanic origin	2548 (8.5)
Axillary surgery, No. of nodes, No. (%)[c]	
1-5	16 781 (56.8)
>5	12 748 (43.2)
Clinical T category, No. (%)	
cT1	7214 (23.4)
cT2	23 607 (76.6)
Clinical N category, No. (%)	
cN0	18 093 (58.7)
cN1	12 728 (41.3)
Grade, No. (%)[d]	
Well differentiated	1367 (4.8)
Moderately differentiated	9522 (33.2)
Poorly differentiated/undifferentiated	17 809 (62.1)
Biologic subtype, No. (%)	
HR-positive/*ERBB2*-positive	7233 (23.5)
HR-negative/*ERBB2*-positive	3733 (12.1)
TNBC	9515 (30.9)
HR-positive/*ERBB2*-negative	10 340 (33.5)
Response, No. (%)	
Residual breast disease, No. (%)	21 057 (68.3)
Breast pCR	9764 (31.7)
Pathologic node status after neoadjuvant chemotherapy, No. (%)	
N0	20 933 (67.9)
N1	7405 (24.0)
N2/N3	2483 (8.1)

Abbreviations: HR, hormone receptor; pCR, pathologic complete response; TNBC, triple negative breast cancer.

[a] Data were missing for 248 patients.

[b] Data were missing for 720 patients.

[c] Data were missing for 1292 patients.

[d] Data were missing for 2123 patients.

tive. *ERBB2* status was classified according to the summary results, including immunohistochemistry, fluorescent in situ hybridization, and chromogenic in situ hybridization when performed. We compared rates of pathologic nodal positivity after NAC (ypN positivity) by breast pCR (vs residual breast disease) within each tumor subtype (*ERBB2*-positive, TNBC, and HR-positive/*ERBB2*-negative) in patients with cN0 and cN1 disease at presentation. Breast pCR was defined as no invasive disease (ypT0 or ypTis) on final pathologic results. Micrometastatic or macrometastatic nodal disease was included as ypN positive. Isolated tumor cells were counted as pathologically node negative. Information on race/ethnicity is based on patient self-reporting to the institution and as entered in the NCDB.

Statistical Analysis

Data were analyzed from September 13, 2017, through January 30, 2018. Proportions were compared between groups using χ^2 tests, and 2-sided 95% binomial CIs were calculated for estimated proportions using the Wilson score method.[15] Analysis was performed using SAS software (version 9.4; SAS Institute, Inc). $P < .05$ was considered statistically significant.

Results

We identified a total of 30 821 patients with cT1/cT2 N0/N1 breast cancer treated with NAC and surgical resection. Mean (SD) age at diagnosis was 52.0 (11.5) years. Most patients were female (99.6%). Clinicopathologic features of the cohort are shown in **Table 1**. At presentation, 18 093 patients (58.7%) had cN0 and 12 728 (41.3%) had cN1 disease. Distribution across the approximated biologic subtypes was 23.5% (n = 7233) HR-positive/*ERBB2*-positive, 12.1% (n = 3733) HR-negative/*ERBB2*-positive, 30.9% (n = 9515) triple negative, and 33.5% (n = 10 340) HR-positive/*ERBB2*-negative breast cancer. The overall rate of breast pCR was 31.7%. Higher rates of breast pCR were seen in *ERBB2*-positive disease (4863 of 10 966 [44.3%]) and TNBC (3544 of 9515 [37.2%]) compared with HR-positive/*ERBB2*-negative disease (1357 of 10 340 [13.1%]) (**Table 2**). When we stratified the *ERBB2*-positive group by HR-positive vs HR-negative status, we saw higher rates of breast pCR in the HR-negative/*ERBB2*-positive then the HR-positive/*ERBB2*-positive subgroups (2172 of 3733 [58.2%] vs 2691 of 7233 [37.2%]).

Among patients with cN0 disease at presentation, 3062 of 6802 with *ERBB2*-positive disease (45.0%) had a breast pCR. Of those, only 49 (1.6%; 95% CI, 1.2%-2.1%) were ypN positive. Nodal positivity rates were lower for HR-negative/*ERBB2*-positive disease (13 [1.0%]) than HR-positive/*ERBB2*-positive disease (36 [2.1%]; $P = .01$) (**Table 3**). In 6222 patients with cN0 TNBC, 2315 (37.2%) had breast pCR. Of those, only 36 (1.6%; 95% CI: 1.1%-2.1%) were ypN positive. In those cN0 cases with residual disease in the breast, nodal positivity rates were significantly higher (632 of 3740 [16.9%] in *ERBB2*-positive disease; 492 of 3907 [12.6%] in TNBC; both $P < .001$). The relative risk of positive ypN status for patients with cN0 disease without vs with breast pCR was 10.6 (95% CI, 7.9-14.1) in *ERBB2*-positive disease and 8.1 (95% CI, 5.8-11.3) in TNBC. If patients with residual ypTis were excluded from the breast pCR group, the proportion of positive ypN status among patients with cT1/cT2 N0 disease with ypT0 status at surgery would be 25 of 1327 (1.9%) in HR-positive/*ERBB2*-positive disease, 0.6% (<10 and therefore not reported per the NCDB data use agreement) in HR-negative/*ERBB2*-positive disease, 27 of

2060 (1.3%) in TNBC, and 20 of 544 (3.7%) in HR-positive/*ERBB2*-negative disease.

Among patients with cN1 disease at presentation, the breast pCR rate was 1801 of 4164 (43.3%) in *ERBB2*-positive disease, and of those, the nodal positivity rate was 223 (12.4%). In TNBC, the pCR rate was 1229 of 3293 (37.3%) and of those, 173 (14.1%) had residual positive lymph nodes.

In patients with HR-positive/*ERBB2*-negative disease, breast pCR rates were significantly lower (646 of 5069 [12.7%] for cN0 and 711 of 5271 [13.5%] for cN1) compared with the *ERBB2*-positive disease and TNBC groups ($P < .001$). In patients with cN0 disease, nodal positivity rates were 26 of 646 (4.0%) in those with a breast pCR and 1464 of 4423 (33.1%) in those with residual breast disease. In those with cN1 disease, nodal positivity rates were 217 of 711 (30.5%) with a breast pCR and 3775 of 4560 (82.8%) with residual breast disease. Table 3 shows the rates of nodal disease in the patients with cN0 and cN1 disease by breast pCR stratified by clinical tumor category.

Table 2. Breast pCR by Biologic Cancer Subtype

	No. (%) of Patients	
Biologic Cancer Subtype	Breast pCR	No Breast pCR
HR-positive/*ERBB2*-positive	2691 (37.2)	4542 (62.8)
HR-negative/*ERBB2*-positive	2172 (58.2)	1561 (41.8)
TNBC	3544 (37.2)	5971 (62.8)
HR-positive/*ERBB2*-negative	1357 (13.1)	8983 (86.9)

Abbreviations: HR, hormone receptor; pCR, pathologic complete response; TNBC, triple negative breast cancer.

Table 3. Pathologic Node Status by Response Stratified by Clinical Tumor and Nodal Category

Response					
Breast pCR			Residual Breast Disease		
	Pathologic Node Status, No. (%)[a]			Pathologic Node Status, No. (%)[a]	
Biologic Subtype	ypN0	ypN Positivity	Biologic Subtype	ypN0	ypN Positivity
cN0 Status					
HR-positive/*ERBB2*-positive			HR-positive/*ERBB2*-positive		
cT1 N0	NR (98.3)	NR (1.7)	cT1 N0	689 (85.1)	121 (14.9)
cT2 N0	NR (97.8)	NR (2.2)	cT2 N0	1647 (80.0)	413 (20.0)
cT1/cT2 N0 combined	1696 (97.9)	36 (2.1)	cT1/cT2 N0 combined	2336 (81.4)	534 (18.6)
HR-negative/*ERBB2*-positive			HR-negative/*ERBB2*-positive		
cT1 N0	NR (99.7)	NR (0.3)	cT1N0	197 (88.7)	25 (11.3)
cT2 N0	NR (98.8)	NR (1.2)	cT2 N0	575 (88.7)	73 (11.3)
cT1/cT2 N0 combined	1317 (99.0)	13 (1.0)	cT1/cT2 N0 combined	772 (88.7)	98 (11.3)
TNBC			TNBC		
cT1 N0	581 (98.1)	11 (1.9)	cT1 N0	788 (86.2)	126 (13.8)
cT2 N0	1698 (98.5)	25 (1.4)	cT2 N0	2627 (87.8)	366 (12.2)
cT1/cT2 N0 combined	2279 (98.4)	36 (1.6)	cT1/cT2 N0 combined	3415 (87.4)	492 (12.6)
HR-positive/*ERBB2*-negative			HR-positive/*ERBB2*-negative		
cT1 N0	NR (94.9)	NR (5.1)	cT1 N0	572 (66.5)	288 (33.5)
cT2 N0	NR (96.3)	NR (3.7)	cT2 N0	2387 (67.0)	1176 (33.0)
cT1/cT2 N0 combined	620 (96.0)	26 (4.0)	cT1/cT2 N0 combined	2959 (66.9)	1464 (33.1)
cN1 Status					
HR-positive/*ERBB2*-positive			HR-positive/*ERBB2*-positive		
cT1 N1	209 (84.3)	39 (15.7)	cT1 N1	118 (31.9)	252 (68.1)
cT2 N1	622 (87.5)	89 (12.5)	cT2 N1	463 (35.6)	839 (64.4)
cT1/cT2 N1 combined	831 (86.7)	128 (13.3)	cT1/cT2 N1 combined	581 (34.7)	1091 (65.3)
HR-negative/*ERBB2*-positive			HR-negative/*ERBB2*-positive		
cT1 N1	182 (87.9)	25 (12.1)	cT1 N1	56 (42.1)	77 (57.9)
cT2 N1	565 (89.0)	70 (11.0)	cT2 N1	252 (45.2)	306 (54.8)
cT1/cT2 N1 combined	747 (88.7)	95 (11.3)	cT1/cT2 N1 combined	308 (44.6)	383 (55.4)
TNBC			TNBC		
cT1 N1	264 (81.5)	60 (18.5)	cT1 N1	105 (28.1)	269 (71.9)
cT2 N1	792 (87.5)	113 (12.5)	cT2 N1	632 (37.4)	1058 (62.6)
cT1/cT2 N1 combined	1056 (85.9)	173 (14.1)	cT1/cT2 N1 combined	737 (35.7)	1327 (64.3)
HR-positive/*ERBB2*-negative			HR-positive/*ERBB2*-negative		
cT1 N1	127 (61.4)	80 (38.6)	cT1 N1	132 (14.2)	800 (85.8)
cT2 N1	367 (72.8)	137 (27.2)	cT2 N1	653 (18.0)	2975 (82.0)
cT1/cT2 N1 combined	494 (69.5)	217 (30.5)	cT1/cT2 N1 combined	785 (17.2)	3775 (82.8)

Abbreviations: HR, hormone receptor; NR, numbers not reported; TNBC, triple negative breast cancer.

[a] Cell size of less than 10 was not reported as per National Cancer Database data use agreement.

Table 4. Extent of Nodal Disease at Surgery by Pathologic Nodal Category

Clinical Node Status	No. of Patients	No. (%) of Patients[a]		
		ypN0	ypN1	ypN2/ypN3
Breast pCR				
Biologic subtype of cN0 disease				
HR-positive/*ERBB2*-positive	1732	1696 (97.9)	NR (<3)	NR (<1)
HR-negative/*ERBB2*-positive	1330	1317 (99.0)	13 (1.0)	0
TNBC	2315	2279 (98.4)	NR (<2)	NR (<1)
HR-positive/ *ERBB2*-negative	646	620 (96.0)	26 (4.0)	0
Biologic subtype of cN1 disease				
HR-positive/*ERBB2*-positive	959	831 (86.7)	110 (11.5)	18 (1.9)
HR-negative/*ERBB2*-positive	842	747 (88.7)	NR (<11)	NR (<2)
TNBC	1229	1056 (85.9)	150 (12.2)	23 (1.9)
HR-positive/ *ERBB2*-negative	711	494 (69.5)	187 (26.3)	30 (4.2)
Residual Breast Disease				
Biologic subtype of cN0 disease				
HR-positive/*ERBB2*-positive	2870	2336 (81.4)	475 (16.6)	59 (2.1)
HR-negative/*ERBB2*-positive	870	772 (88.7)	82 (9.4)	16 (1.8)
TNBC	3907	3415 (87.4)	427 (10.9)	65 (1.7)
HR-positive/*ERBB2*-negative	4423	2959 (66.9)	1203 (27.2)	261 (5.9)
Biologic subtype of cN1 disease				
HR-positive/*ERBB2*-positive	1672	581 (34.7)	858 (51.3)	233 (13.9)
HR-negative/*ERBB2*-positive	691	308 (44.6)	299 (43.3)	84 (12.2)
TNBC	2064	737 (35.7)	932 (45.2)	395 (19.1)
HR-positive/*ERBB2*-negative	4560	785 (17.2)	2487 (54.5)	1288 (28.2)

Abbreviations: HR, hormone receptor; pCR, pathologic complete response; TNBC, triple negative breast cancer; NR, not reported; yp, pathologic stage after neoadjuvant chemotherapy; ypN, pathologic nodal stage after neoadjuvant chemotherapy.

[a] Cell size of less than 10 was not reported as per National Cancer Database data use agreement.

Table 4 shows the extent of nodal disease by pathologic nodal category for each group of patients. Further evaluating the group of patients with the lowest likelihood of nodal positivity (ie, the patients with cN0 disease who achieved a breast pCR), the rates of ypN2/ypN3 disease were less than 1% across all the biologic subtypes. For those with cN1 disease and breast pCR, rates of residual nodal disease ranged from 11.3% to 30.5%, and most had ypN1 disease, with 4.2% of cases or fewer having ypN2/ypN3 disease. For patients with breast pCR and pathologic node-positive findings, the rates of ypN2/ypN3 disease did not differ significantly across biologic subtypes for those with cN0 ($P = .42$) or cN1 ($P = .78$) disease.

However, among patients with residual breast disease, those with HR-positive/*ERBB2*-negative disease had higher rates of ypN2/ypN3 disease (261 [5.9%] for cN0 disease and 1288 [28.2%] for cN1 disease) compared with *ERBB2*-positive disease (75 [2.0%] for cN0 [$P < .001$] and 317 [13.4%] for cN1 [$P < .001$]) and TNBC (65 [1.7%] for cN0 disease [$P < .001$] and 395 [19.1%] for cN1 disease [$P < .001$]). Patients with TNBC also had significantly higher nodal disease burden (395 [19.1%] with ypN2/ypN3 disease) than patients with *ERBB2*-positive disease among the subset with cN1 and residual breast and nodal disease ($P < .001$) (Table 4).

Data by age and race/ethnicity are shown in eTables 1 and 2 in the Supplement. The scope of axillary surgery was defined in the NCDB from 2012 onward and is shown in eTable 3 in the Supplement. Limited to 2012 onwards, of 14 468 patients with cN0 disease, 9970 (68.9%) had sentinel lymph node surgery, 2586 (17.9%) had sentinel lymph node surgery and axillary lymph node dissection, and 1912 (13.2%) had axillary lymph node dissection only. Of 9448 patients presenting with cN1 disease, 2174 (23.0%) had sentinel lymph node surgery, 2146 (22.7%) had sentinel lymph node surgery and axillary lymph node dissection, and 5128 (54.3%) had axillary lymph node dissection only.

Discussion

This study demonstrates an extremely low rate of nodal disease in patients who present with clinically node-negative breast cancer, are treated with NAC, and achieve a breast pCR. In particular, in 5377 patients with cT1/cT2 cN0 *ERBB2*-positive disease and TNBC with breast pCR, rates of nodal positivity were less than 2% (1.6% in *ERBB2*-positive disease and 1.6% in TNBC). These findings are in keeping with the single-institution report from MDACC,[12] which found that of 116 patients with *ERBB2*-positive disease or TNBC and cN0 status on physical examination and ultrasonographic findings at presentation and who achieved a pCR in the breast, 100% had negative lymph nodes.

Patients with *ERBB2*-positive disease or TNBC treated with NAC have higher rates of overall pCR compared with patients with HR-positive/*ERBB2*-negative disease, and studies have shown that pCR in patients with *ERBB2*-positive disease and TNBC yields better overall and recurrence-free survival compared with patients with residual disease.[6] Consistent with previous studies, the rates of breast pCR in the NCDB cohort were significantly higher in *ERBB2*-positive disease (44.3%) and TNBC (37.2%) than in HR-positive/*ERBB2*-negative disease (13.1%). To potentially identify subgroups of patients in whom axillary surgery may be avoided, the high rate of breast pCR and the low rate of nodal positivity in the *ERBB2*-positive and TNBC groups makes this a reasonable group to consider. In addition, among the fewer than 2% of patients with cT1/cT2 cN0 *ERBB2*-positive disease and TNBC,

with a breast pCR, and who had residual nodal disease, the nodal disease burden was low, with disease predominantly limited to 1 to 3 positive lymph nodes (ie, ypN1 disease). This finding further supports the potential to omit axillary surgery. We acknowledge that 1.6% of patients with cN0 TNBC and breast pCR could have ypN-positive disease, and if axillary surgery is omitted, these patients will miss an opportunity for additional therapy that may improve survival, such as capecitabine. However, this percentage of patients is extremely low, and most patients with cN0 TNBC and breast pCR could avoid axillary surgery safely.

In the MDACC series, all patients underwent axillary ultrasonography at presentation to rule out occult nodal disease, whereas in the NCDB the use of axillary ultrasonography is unknown and was likely not uniform across all sites. Therefore, patients with low-volume occult nodal disease may be staged as clinically N0 in the absence of axillary ultrasonography. This possibility may account for the lower nodal positivity rates seen in the MDACC cohort than that of the NCDB.

The rate of positive ypN status was also low in the patients with cN0 HR-positive/*ERBB2*-negative disease with a breast pCR (4.0%); however, the overall rate of breast pCR in this group was much lower, limiting the applicability in this patient group. In addition, NAC is less commonly used in cT1/cT2 cN0 HR-positive/*ERBB2*-negative disease.

Patients with residual disease in the breast are known to have a poorer survival than those with breast pCR, and this study further demonstrates that in those patients with residual breast disease, nodal positivity is significantly more likely across all tumor subtypes. In our study, the nodal positivity rate in patients with *ERBB2*-positive disease or TNBC who had residual disease in the breast was 1124 of 7647 (14.7%) in cN0 with residual breast disease, which is higher than the 10 of 174 (5.7%) rate seen in the MDACC study.

In patients with cN1 disease at presentation, nodal positivity rates after NAC were much higher across all tumor subtypes, indicating the importance of axillary staging in these patients. However, again within the cN1 subgroup, the likelihood of nodal positivity was much higher in those cases with residual disease in the breast and lower in cases with a breast pCR. This finding supports evaluation of the clinical and radiologic response in the breast and axilla as a useful guide to decision making regarding sentinel lymph node surgery vs routine axillary dissection to stage residual axillary disease after NAC for cN1 disease.[16-19]

The extent of residual nodal disease burden after NAC has been shown to vary by tumor subtype. In the American College of Surgeons Z1071 trial of patients with cN1 disease treated with NAC, among patients with residual nodal disease at surgery, the mean number of positive nodes was higher in patients with HR-positive/*ERBB2*-negative disease (5.0 nodes) than in those with TNBC and *ERBB2*-positive disease (3.5 nodes and 3.3 nodes, respectively).[20] Our analysis of the NCDB data also showed higher rates of ypN2/ypN3 disease in patients with HR-positive/*ERBB2*-negative disease than in those with *ERBB2*-positive disease or TNBC among the group without breast pCR. This was seen in the cN0 and cN1 subsets. With high rates of pCR in patients with *ERBB2*-positive disease and with TNBC, consideration of omission of breast surgery has become an important question. In the past, this omission has not been pursued because no reliable way to detect breast pCR with imaging alone existed. A recent single-institution clinical feasibility trial to compare image-guided large core biopsies with surgical excision[11] found image-guided biopsy to be a reliable method to detect pCR in the breast, thereby supporting the idea that breast surgery may be omitted in this specific subset of patients. In addition, a larger multicenter phase 2 trial (NRG-BR005) is currently accruing patients to assess the accuracy of tumor bed biopsies in estimating pathologic response.[21] Avoiding breast surgery at this time is not a standard of care; however, these trial results, once available, may support elimination of breast surgery in patients with complete response to NAC. In turn, our results on nodal positivity can then be used to promote omission of axillary surgery in this particular subset of patients (cN0 *ERBB2*-positive disease or TNBC with pCR in the breast).

A recently presented study of 298 patients with cN0 disease[22] showed low rates of nodal positivity after NAC in TNBC (1.5%) and HR-negative/*ERBB2*-positive disease (0%); the investigators proposed omission of axillary surgery in all such cases regardless of breast response and omission of axillary surgery in cases of HR-positive disease with a breast pCR. Our study has a larger cohort and demonstrates higher rates of nodal positivity for cN0 *ERBB2*-positive disease and TNBC with residual disease in the breast (11.3% for HR-negative/*ERBB2*-positive, 18.6% for HR-positive/*ERBB2*-positive, and 12.6% for TNBC).

At present, a prospective clinical trial has commenced in which breast surgery is omitted in patients with *ERBB2*-positive disease and TNBC with an excellent response to NAC who achieve a breast pCR by image-guided biopsy of the tumor bed. If residual disease is present, the patient undergoes standard surgery with radiotherapy. If no residual disease is present on percutaneous biopsy, the patient forgoes breast surgery and is treated with whole-breast radiotherapy alone. The primary end point is local regional recurrence. In regard to the axillary management of patients with no residual breast disease by percutaneous biopsy, those who had cN0 disease at presentation undergo no axillary surgery, and those with cN1 disease at presentation undergo sentinel lymph node surgery with resection of the clipped node proceeding to axillary lymph node dissection if any lymph node is positive. The findings from this study further support this algorithm of axillary management for this trial.

Limitations

Limitations of the present study include the use of a large national database with the inherent issues of missing and inconsistent data without the ability to resolve such issues. Imaging studies used in patient workup and staging and pathologic evaluation to determine clinical and pathologic staging likely varied across practices. However, these limitations are countered by the strength of a large sample size, and thus the ability to provide precise estimates of the pathologic node positive rate in pertinent subgroups. Also, a huge strength of this data is the wide variety of settings, including community and academic practices, which reflect that the findings are robust in general clinical practice and validate the previously published findings from a single-institution academic national comprehensive cancer center.[12]

Conclusions

The findings from this study of the NCDB data evaluating a large group of patients with breast cancer treated across the United States in community and academic practices supports possible omission of axillary surgery in patients with cN0 *ERBB2*-positive disease or TNBC who achieve a breast pCR, because nodal positivity rates are extremely low in this setting. Patients with *ERBB2*-positive disease or TNBC treated with NAC have higher rates of pCR when compared with patients with HR-positive/*ERBB2*-negative disease. In patients with cT1/cT2 cN0 *ERBB2*-positive disease or TNBC who achieve a breast pCR, nodal positivity rates are low (<2%), and omission of axillary surgery can be considered.

ARTICLE INFORMATION

Accepted for Publication: May 17, 2018.

Published Online: September 5, 2018. doi:10.1001/jamasurg.2018.2696

Author Contributions: Dr Boughey had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Barron, Hwang, Kuerer, Boughey.
Acquisition, analysis, or interpretation of data: Barron, Hoskin, Day, Kuerer.
Drafting of the manuscript: Barron, Hoskin, Day, Kuerer, Boughey.
Critical revision of the manuscript for important intellectual content: Barron, Hwang, Kuerer, Boughey.
Statistical analysis: Hoskin, Day.
Supervision: Kuerer, Boughey.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by the Mayo Clinic Kerns Center for the Science of Health Care Delivery (Mss Hoskin and Day).

Role of the Funder/Sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB and the participating hospitals are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

REFERENCES

1. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol*. 1997;15(7):2483-2493. doi:10.1200/JCO.1997.15.7.2483

2. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2006;24(13):2019-2027. doi:10.1200/JCO.2005.04.1665

3. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*. 2008;26(5):778-785. doi:10.1200/JCO.2007.15.0235

4. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with *HER2*-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278-2284. doi:10.1093/annonc/mdt182

5. Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. *Eur J Cancer*. 2012;48(18):3342-3354. doi:10.1016/j.ejca.2012.05.023

6. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796-1804. doi:10.1200/JCO.2011.38.8595

7. Mougalian SS, Hernandez M, Lei X, et al. Ten-year outcomes of patients with breast cancer with cytologically confirmed axillary lymph node metastases and pathologic complete response after primary systemic chemotherapy. *JAMA Oncol*. 2016;2(4):508-516. doi:10.1001/jamaoncol.2015.4935

8. Croshaw R, Shapiro-Wright H, Svensson E, Erb K, Julian T. Accuracy of clinical examination, digital mammogram, ultrasound, and MRI in determining postneoadjuvant pathologic tumor response in operable breast cancer patients. *Ann Surg Oncol*. 2011;18(11):3160-3163. doi:10.1245/s10434-011-1919-5

9. Shin HJ, Kim HH, Ahn JH, et al. Comparison of mammography, sonography, MRI and clinical examination in patients with locally advanced or inflammatory breast cancer who underwent neoadjuvant chemotherapy. *Br J Radiol*. 2011;84(1003):612-620. doi:10.1259/bjr/74430952

10. De Los Santos JF, Cantor A, Amos KD, et al. Magnetic resonance imaging as a predictor of pathologic response in patients treated with neoadjuvant systemic treatment for operable breast cancer: Translational Breast Cancer Research Consortium trial 017. *Cancer*. 2013;119(10):1776-1783. doi:10.1002/cncr.27995

11. Kuerer HM, Rauch GM, Krishnamurthy S, et al. A clinical feasibility trial for identification of exceptional responders in whom breast cancer surgery can be eliminated following neoadjuvant systemic therapy. *Ann Surg*. 2018;267(5):946-951. doi:10.1097/SLA.0000000000002313

12. Tadros AB, Yang WT, Krishnamurthy S, et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. *JAMA Surg*. 2017;152(7):665-670. doi:10.1001/jamasurg.2017.0562

13. Fornage BD. Local and regional staging of invasive breast cancer with sonography: 25 years of practice at MD Anderson Cancer Center. *Oncologist*. 2014;19(1):5-15. doi:10.1634/theoncologist.2013-0323

14. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15(3):683-690. doi:10.1245/s10434-007-9747-3

15. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med*. 1998;17(8):857-872. doi:10.1002/(SICI)1097-0258(19980430)17:8<857::AID-SIM777>3.0.CO;2-E

16. Boughey JC, Suman VJ, Mittendorf EA, et al; Alliance for Clinical Trials in Oncology. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(14):1455-1461. doi:10.1001/jama.2013.278932

17. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol*. 2013;14(7):609-618. doi:10.1016/S1470-2045(13)70166-9

18. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol*. 2015;33(3):258-264. doi:10.1200/JCO.2014.55.7827

19. Lyman GH. Appropriate role for sentinel node biopsy after neoadjuvant chemotherapy in patients with early-stage breast cancer. *J Clin Oncol*. 2015;33(3):232-234. doi:10.1200/JCO.2014.58.9838

20. Boughey JC, McCall LM, Ballman KV, et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. *Ann Surg*. 2014;260(4):608-614. doi:10.1097/SLA.0000000000000924

21. ClinicalTrials.gov. Assessing the Accuracy of Tumor Biopsies After Chemotherapy to Determine if Patients Can Avoid Breast Surgery. NCT03188393. https://clinicaltrials.gov/ct2/show/NCT03188393. Accessed on July 5, 2018.

22. van der Noordaa. Omitting sentinel lymph node biopsy after neoadjuvant systemic therapy in selected breast cancer patients with clinical node-negative disease. Presented at the 11th European Breast Cancer Conference; March 21-23, 2018; Barcelona, Spain. Abstract 20. https://www.ecco-org.eu/Events/EBCC11/Searchable-Programme#anchorScpr. Accessed July 9, 2018.