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GEORGE N. PETERS AWARD AND SCIENTIFIC IMPACT AWARD

Patient Selection for Clinical Trials Eliminating Surgery for HER2-Positive Breast Cancer Treated with Neoadjuvant Systemic Therapy

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ABSTRACT

Background. Patients with epidermal growth factor receptor 2-positive (HER2+) breast cancer and pathologic complete response (pCR) after neoadjuvant systemic therapy (NST) may be candidates for nonoperative clinical trials if residual invasive and in situ disease are eradicated.

Methods. This study analyzed 280 patients with clinical T1-2N0-1 HER2+ breast cancer who underwent NST followed by surgical resection to determine key characteristics of patients with pCR in the breast and lymph nodes compared with those with residual disease.

Results. Of the 280 patients, 102 (36.4%) had pCR in the breast and lymph nodes after NST, and 50 patients (17.9%) had residual ductal carcinoma in situ (DCIS) in the breast only. For 129 patients (46.1%), DCIS was present on the pretreatment biopsy, and NST failed to eradicate the DCIS component in 64.3%. Patients with residual disease were more likely to have hormone receptor-positive (HR+) tumors than those with negative tumors (73.4% vs. 50.8%; $p < 0.0001$). Radiologic response (odds ratio [OR], 5.62; $p = 0.002$) and HR+ status (OR, 2.56; $p < 0.0001$) were predictive of residual disease. Combined imaging methods after NST had a sensitivity of 97.1% and a negative predictive value of 70.6% for detection of residual disease. Patients with invasive disease and DCIS shown on the pretreatment core biopsy were less likely than those without DCIS to achieve pCR in the breast (31% vs. 43%; $p = 0.038$).

Conclusion. The study results delineate and identify unique characteristics associated with HER2+ breast cancers that are important in selecting patients for inclusion in clinical trials assessing nonoperative management after NST, and the low negative predictive value of imaging mandates image-guided biopsy for selection.

The use of neoadjuvant systemic therapy (NST) in epidermal growth factor receptor 2-positive (HER2+) breast cancer has been extensively studied, and findings have shown HER2+ tumors to be highly chemo-sensitive, especially with the addition of humanized anti-HER2 monoclonal antibody therapies.[1–5] Pathologic complete response (pCR) rates are reported to be as high as 60%.[5–9]

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Patients with HER2+ or triple-negative tumors who have a pCR after NST experience better overall survival and lower rates of recurrence than patients who do not have a pCR, similar to patients with low-proliferating luminal A tumors.[10]

The high rates of pCR for HER2+ breast cancer patients highlight the potential for nonoperative management after NST, which is the ultimate breast-conserving strategy. However, it is imperative to accurately identify patients who achieve pCR before enrolling them in clinical trials assessing the safety of omitting breast surgery for exceptional responders.

Although findings have shown multiple different imaging methods to be insensitive in identifying patients with pCR due to low predictive values, we have previously determined that patients with clinically significant residual disease can be accurately identified using a combination of multimodality imaging and extensive image-guided vacuum-assisted core biopsy of the tumor bed.[11]

Furthermore, for a patient to be considered eligible for clinical trials evaluating nonoperative management of breast cancer after NST, both the invasive and in situ components need to be eradicated. We have previously shown that in approximately 45% of cases, NST can specifically eradicate the ductal carcinoma in situ (DCIS) component in triple-negative invasive breast cancers receiving NST.[12] Furthermore, patients with residual triple-negative disease are more likely to present with malignant-appearing microcalcifications and DCIS identified on the initial core biopsy than patients without residual disease (pCR, 27% vs. 40%; odds ratio [OR], 2.5; $p < 0.02$).[12]

To our knowledge, similar types of analyses have not been performed to date regarding HER2+ invasive breast cancer after NST and are the subject of the current analysis. The optimal patient for inclusion in eliminating surgery trials is a patient with no residual invasive carcinoma in the breast or lymph nodes and no residual in situ disease in the breast that could become a nidus for recurrence in the future. This study aimed to identify unique clinicopathologic characteristics associated with finding residual disease in HER2+ breast cancer after NST. A secondary aim was to assess the effect of NST on the invasive and DCIS components of HER2+ breast cancer.

METHODS

Data and Patient Selection

The prospectively managed Breast Cancer Management System Database at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) was queried for patients with HER2+ clinical T1-2 N0-1 disease treated with neoadjuvant chemotherapy-based, HER2-targeted regimens followed by surgical resection (breast-conserving surgery or mastectomy) with sentinel lymph node biopsy or axillary lymph node dissection.

Patients treated between January 2010 and December 2015 were included in the analysis. At the time of diagnosis, all the patients underwent a diagnostic mammogram as well as a breast and axillary ultrasound per institutional protocol. Those with abnormalities found via axillary lymph node ultrasound underwent a percutaneous biopsy to assess for metastatic disease. Breast magnetic resonance imaging (MRI) was used at the discretion of the treating practitioner with guidance from a radiologist. Approval was obtained from the University of Texas MD Anderson Cancer Center Intuitional Review Board before initiation of this study.

Outcome

The primary study aim was to identify baseline clinicopathologic characteristics associated with residual disease in the breast, lymph nodes, or both after completion of NST. A secondary aim was to assess the effectiveness of NST in eliminating the invasive and DCIS components of patients with HER2+ breast cancer.

Covariates

Baseline demographics and clinicopathologic characteristics were evaluated, and tumor volumes before and after NST were measured by each imaging method. Classification of complete radiologic response required complete resolution of the tumor on all subsequent imaging across all methods. Complete resolution of the mass via ultrasound with residual calcification seen on mammogram was classified as partial response. For the patients with biopsy-proven axillary nodal disease, response was grouped as no response, decrease in size or number of metastatic nodes, and complete radiologic response.

Statistical Analysis

The statistical analysis was designed to assess for variables associated with the presence of residual disease after neoadjuvant chemotherapy. Baseline clinicopathologic characteristics were compared between patients with residual disease in the breast, lymph nodes, or both and those who achieved pCR using Student's t tests for continuous variables and Chi square tests for binary and categorical variables. Logistic regression was used to model residual disease as a function of other covariates. All variables with a p value lower than 0.1 in the univariate analysis were included in the regression model for the

TABLE 1 Baseline characteristics, imaging response, and pathologic outcome after neoadjuvant chemotherapy for 280 patients with human HER2+ breast cancer

Variables	HER2+ (n = 280)	%
Age (years)		
≤ 40	42	15.0
> 40	238	85.0
Ethnicity		
Black	33	11.8
White	170	60.7
Hispanic	48	17.1
Other	29	10.4
Imaging by mammography and ultrasonography		
Mass lesion/architectural distorsion only	111	39.9
Malignant microcalcifications ± mass	167	60.1
Tumour histology		
Invasive ductal	272	97.1
Other	8	2.9
Nuclear grade		
1	3	1.1
2	68	24.3
3	209	74.6
DCIS (with invasive disease) identified on initial diagnostic core biopsy		
Absent	151	53.9
Present	129	46.1
Clinical tumor size		
T1	46	16.4
T2	234	83.6
Clinical/initial nodal status (cytology/histology)		
N0	149	53.2
N1 (percutaneous biopsy proven)	131	46.8
Hormone receptor status		
Negative (ER- and PR-negative)	122	43.6
Positive (ER- and/or PR-positive)	158	56.4
Ki-67 (%)[a]		
≤ 35	66	38.8
> 35	104	61.2
Necrosis		
Absent	184	65.7
Present	96	34.3
Lymphovascular invasion		
Absent	264	94.3
Present	16	5.7
Radiographic response in the breast after NST[b]		
Complete response	19	7.0
Partial response	234	87.0
Stable disease/progressive disease	16	6.0
Radiologic nodal response among patients with initial N1, biopsy-proven disease after NST		
No response	6	4.8
Decrease in size and/or number	73	58.9
Documented complete resolution	45	36.3
Radiographic breast and nodal response status combined		
Complete response	17	6.3
No complete response	252	93.7
Pathologic response in the breast after NST		
Residual invasive and DCIS	90	32.1
Residual invasive only	35	12.5
Residual DCIS only (ypTis)	50	17.9
No residual invasive or DCIS (ypT0)	105	37.5
Pathologic nodal status after NST		
Residual nodal disease	49	17.5
No residual nodal disease (ypN0)	231	82.5
Pathologic status in the breast and nodes after NST		
Residual disease present	178	63.6
No residual disease (ypT0ypN0)	102	36.4

HER2+ epidermal growth factor receptor-positive, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor, *PR* progesterone receptor, *NST* neoadjuvant systemic treatment

[a]Ki-67 was not performed for 110 patients (39.3%)

[b]Radiologic breast response was not evaluated for 11 patients (3.9%)

multivariate analysis. Statistical analysis was performed using SPSS software version 24.0 (IBM, Armonk, New York, NY, USA). Statistical significance was defined by a p value lower than 0.05.

RESULTS

Demographics and Baseline Tumor Characteristics

The baseline characteristics of the 280 patients included in the study are presented in Table 1. The mean patient age was 53 years (median, 52 years). The predominant tumor type was invasive ductal carcinoma (97.1%), and the majority of the patients (83.6%) had clinical T2 disease. In this study, NST consisted of taxane-based chemotherapy plus trastuzumab for 255 patients (91.1%) and taxane-based chemotherapy plus trastuzumab and pertuzumab for 25 patients (8.9%). Of the 280 patients, 105 (37.5%) achieved breast pCR (no residual invasive or in situ disease [ypT0]), 50 (17.9%) achieved breast pCR with residual DCIS only (ypT*is*), and 102 (36.4%) had pCR in the breast and lymph nodes (ypT0ypN0).

TABLE 2 Univariate analysis of clinicopathologic baseline variables associated with finding residual disease in the breast and nodes as well as within the breast and nodes after NST for 280 patients with T1/T2 HER2+ breast cancer

Variables	No residual breast invasive or in situ disease (ypT0) (n = 105, %) n (%)	Residual breast disease (n = 175, %) n (%)	p Value (X^2)	No residual nodal disease (ypN0) (n = 231, %) n (%)	Residual nodal disease (n = 49, %) n (%)	p Value (X^2)	No residual breast and/or nodal disease (ypT0ypN0) (n = 102, %) n (%)	Residual breast and/or nodal disease (n = 178, %) n (%)	p Value (X^2)
Mean age (years)	54 ± 10.6	52 ± 11.3	0.037	53 ± 11.3	51 ± 10.4	0.245	54 ± 10.6	52 ± 11.3	0.056
≤ 40	10 (23.8)	32 (76.2)	0.057	33 (78.6)	9 (21.4)	0.509	10 (23.8)	32 (76.2)	0.082
> 40	95 (39.9)	143 (60.1)		198 (83.2)	40 (16.8)		92 (38.7)	146 (61.3)	
Ethnicity									
Black	10 (30.3)	23 (69.7)	0.602	28 (84.8)	5 (15.2)	0.405	9 (27.3)	24 (72.7)	0.504
White	66 (38.8)	104 (61.2)		135 (79.4)	35 (20.6)		64 (37.6)	106 (62.4)	
Hispanic	16 (33.3)	32 (66.7)		43 (89.6)	5 (10.4)		16 (33.3)	32 (66.7)	
Other	13 (44.8)	16 (55.2)		25 (86.2)	4 (13.8)		13 (44.8)	16 (55.2)	
Imaging by mammography and ultrasonography									
Mass lesion/architectural distorsion only	47 (42.3)	64 (57.7)	0.209	95 (85.6)	16 (14.4)	0.335	46 (41.4)	65 (58.6)	0.204
Malignant microcalcifcations ± mass	58 (34.7)	109 (65.3)		135 (80.8)	32 (19.2)		56 (33.5)	111 (66.5)	
Tumour histology									
Invasive ductal	102 (37.5)	170 (62.5)	1.000	223 (82.0)	49 (18.0)	0.358	99 (36.4)	173 (63.6)	1.000
Other	3 (37.5)	5 (62.5)		8 (100)	-		3 (37.5)	5 (62.5)	
Nuclear grade									
1–2	25 (35.2)	46 (64.8)	0.673	57 (80.3)	14 (19.7)	0.590	25 (35.2)	46 (64.8)	0.887
3	80 (38.3)	129 (61.7)		174 (83.3)	35 (16.7)		77 (36.8)	132 (63.2)	
DCIS (with invasive disease) identified on initial diagnostic core biopsy									
No	65 (43.0)	86 (57.0)	0.047	129 (85.4)	22 (14.6)	0.207	62 (41.1)	89 (58.9)	0.105
Yes	40 (31.0)	89 (69.0)		102 (79.1)	27 (20.9)		40 (31.0)	89 (69.0)	
Clinical tumor size									
T1	18 (39.1)	28 (60.9)	0.868	39 (84.8)	7 (15.2)	0.683	17 (37.0)	29 (63.0)	1.000
T2	87 (37.2)	147 (62.8)		192 (82.1)	42 (17.9)		85 (36.3)	149 (63.7)	
Clinical nodal status									
N0	56 (37.6)	93 (62.4)	1.000	142 (95.3)	7 (4.7)	< 0.0001	56 (37.6)	93 (62.4)	0.710
N1, biopsy proven	49 (37.4)	82 (62.6)		89 (67.9)	42 (32.1)		46 (35.1)	85 (64.9)	
Hormone receptor status									
Negative (ER- and PR-negative)	61 (50.0)	61 (50.0)	< 0.0001	107 (87.7)	15 (12.3)	0.056	60 (49.2)	62 (50.8)	< 0.0001
Positive (ER- and/or PR-positive)	44 (27.8)	114 (72.2)		124 (78.5)	34 (21.5)		42 (26.6)	116 (73.4)	
Ki-67 (%)[a]									
≤ 35	21 (31.8)	45 (68.2)	0.256	59 (89.4)	7 (10.6)	0.369	21 (31.8)	45 (68.2)	0.332

TABLE 2 continued

Variables	No residual breast invasive or in situ disease (ypT0) (n = 105, %) n (%)	Residual breast disease (n = 175, %) n (%)	p Value (X^2)	No residual nodal disease (ypN0) (n = 231, %) n (%)	Residual nodal disease (n = 49, %) n (%)	p Value (X^2)	No residual breast and/or nodal disease (ypT0ypN0) (n = 102, %) n (%)	Residual breast and/or nodal disease (n = 178, %) n (%)	p Value (X^2)
> 35	43 (41.3)	61 (58.7)		87 (83.7)	17 (16.3)		41 (39.4)	63 (60.6)	
Necrosis									
No	75 (40.8)	109 (59.2)	0.152	154 (83.7)	30 (16.3)	0.509	72 (39.1)	112 (60.9)	0.239
Yes	30 (31.3)	66 (68.8)		77 (80.2)	19 (19.8)		30 (31.3)	66 (68.7)	
LVI									
No	102 (38.6)	162 (61.4)	0.182	219 (83.0)	45 (17.0)	0.494	99 (37.5)	165 (62.5)	0.182
Yes	3 (18.8)	13 (81.2)		12 (75.0)	4 (25.0)		3 (18.8)	13 (81.2)	

NST neoadjuvant systemic treatment, *HER2+* human epidermal growth factor receptor-positive, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor, *PR* progesterone receptor, *LVI* lymphovascular invasion

[a]Ki-67 was not performed for 110 patients (39.3%)

Residual Disease in the Breast After NST

The patients with residual disease in the breast after NST were more likely to be younger (52 vs. 54 years; p = 0.037), to present with associated DCIS in addition to invasive disease on pretreatment core biopsy (69% vs. 57%; p = 0.047), and to have HR+ tumors (72.2% vs. 50%; $p < 0.0001$; Table 2). In the multivariate analysis, HR+ status was associated with increased odds for residual disease (odds ratio [OR], 2.55; $p < 0.0001$; Table 3).

Residual Disease in the Lymph Nodes After NST

The presence of clinical node involvement was associated with residual nodal disease after NST compared with the presence of no clinical nodal disease (32.1% vs. 4.7%, respectively; $p < 0.0001$). The patients with HR+ tumors had residual nodal disease more often than those with HR– tumors (21.5% vs. 12.3%; p = 0.056; Table 2). In the multivariate analysis, clinical nodal involvement (OR, 10.2; $p < 0.0001$) and HR+ status (OR, 2.29; p = 0.021) were independently predictive of residual disease in the lymph nodes after NST (Table 3).

Combined Residual Disease in the Breast and/or Lymph Nodes After NST

In the univariate analysis, the patients with HR+ tumors were more likely to have residual disease than those with HR– tumors (73.4% vs. 50.8%; $p < 0.0001$). In the univariate analysis, younger patients (52 vs. 54 years) showed a trend toward being more likely to have residual breast and/or nodal disease (p = 0.056; Table 3). After controlling for potential confounders, we found that only HR+ status was independently predictive of residual disease in the breast, lymph nodes, or both (OR, 2.67; $p < 0.0001$; Table 3).

Multimodality Imaging Response and pCR After NST

Combined imaging methods (mammogram, ultrasound, MRI) to assess for response after NST had a sensitivity of 97.1% (95% confidence interval [CI], 95.1–99.1%), a specificity of 12.2% (95% CI, 8.33–1.62%), a negative predictive value of 65.9% (95% CI, 60.2–71.5%), and a positive predictive value of 70.6% (95% CI, 65.1–76.0%) for predicting residual disease in the breast and lymph nodes (Table 4).

In the univariate analysis, more patients showing a partial response or stable disease on combined imaging were found to have residual disease in the breast and lymph nodes than those showing complete response on imaging (65.9% vs. 29.4%; p = 0.004). However, when only lymph

TABLE 3 Multivariate analysis of baseline initial clinicopathologic variables associated with prediction for finding residual disease after NST for HER2+ breast cancer

Variables	OR	95% CI	*p* value
Residual carcinoma in the breast (No ypT0)			
Hormone receptor status			
Negative (ER- and PR-negative)	Ref		
Positive (ER- and/or PR-positive)	2.547	1.545–4.201	< 0.0001
DCIS identified on initial core biopsy			
No	Ref		
Yes	1.628	0.982–2.699	0.059
Residual carcinoma in the nodes (No ypN0)			
Clinical/initial nodal status			
N0	Ref		
N1 (percutaneous biopsy proven)	10.200	4.351–23.910	< 0.0001
Hormone receptor status			
Negative (ER- and PR-negative)	Ref		
Positive (ER- and/or PR-positive)	2.292	1.131–4.644	0.021
Residual carcinoma in breast and nodes (No ypT0N0)			
Hormone receptor status			
Negative (ER- and PR-negative)	Ref		
Positive (ER- and/or PR-positive)	2.673	1.620–4.409	< 0.0001

NST neoadjuvant systemic treatment, *HER2+* human epidermal growth factor receptor-positive, *OR* odds ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor, *Ref* reference group, *DCIS* ductal carcinoma in situ

TABLE 4 Breast and nodal combined imaging performance in predicting residual disease after NST for HER2+ breast cancer

Measure	Breast % (CI)	Lymph nodes % (CI)	Breast and lymph nodes % (CI)
Sensitivity	96.5 (94.3–98.7)	66.3 (57.9–74.6)	97.1 (95.1–99.1)
Specificity	13.3 (9.2–17.3)	40.9 (32.3–49.6)	12.2 (8.33–16.2)
Positive–predictive value	66 (60.3–71.7)	67.1 (58.8–75.4)	65.9 (60.2–71.5)
Negative predictive value	68.4 (62.9–74.0)	40.0 (31.4–48.6)	70.6 (65.1–76.0)

Values in parentheses are 95% CIs

Combined imaging (MMG, US, MRI) for 209 (74.6%) of 280 patients defined as complete radiologic response versus no complete radiologic response. Only 13 patients (4.6%) had a response evaluation performed by MRI

NST neoadjuvant systemic treatment, *HER2+* human epidermal growth factor receptor-positive, *CI* confidence interval, *MMG* mammogram, *US* ultrasound, *MRI* magnetic resonance imaging

node response was assessed, the percentage of patients with residual disease and pCR did not differ significantly based on response observed on imaging (67.1% vs. 60.0%; $p = 0.442$). After controlling for potential confounders in the multivariate analysis, we found that HR+ tumors (OR, 2.56; $p < 0.0001$) and incomplete response observed on imaging (OR, 5.62; $p = 0.002$) were predictive of residual breast and lymph node disease at the time of surgery.

Effect of NST on the DCIS Component

A secondary goal of this study was to assess the response of the DCIS component of HER2+ invasive breast cancers to NST because it is important to eradicate both the invasive and in situ disease in patients who are omitting breast surgery. The pretreatment core biopsy showed DCIS in 129 patients (46.1%). Of these 129 patients, 51 (39.5%) had residual invasive disease and DCIS after NST, 6 (4.7%) had residual invasive disease only, and 32 (24.8%) had DCIS only. In the DCIS cohort, pCR (no residual invasive or in situ disease) was achieved for 40 patients (31%). For 46 patients (35.7%), DCIS was successfully eradicated. In the evaluation of final surgical pathology between patients with invasive only disease and those with invasive cancer and DCIS shown on the pre-treatment core biopsy, the patients with invasive cancer and DCIS were more likely to have residual disease in the breast after NST than those with only invasive disease (43% vs. 31%; $p = 0.038$).

Effect of Dual- Versus Single-Agent HER2-Targeted Therapy

In our study, NST consisted of taxane-based chemotherapy plus trastuzumab for 255 patients (91.1%) and taxane-based chemotherapy plus trastuzumab and pertuzumab for 25 patients (8.9%). The ability to compare the response rates between those who received dual and those who had single HER2-targeted therapy was limited by the small number of patients who had received dual therapy. However when subanalysis was performed, more patients who had undergone dual therapy achieved pCR in the breast and lymph nodes than those who had received Herceptin only (53.3% vs. 34.4%; $p = 0.042$). In the multivariate analysis, dual HER2-targeted therapy was not predictive of pCR.

DISCUSSION

This study found that HR+ tumors and DCIS in addition to invasive cancer observed on the pretreatment core biopsy were associated with residual disease after completion of NST for HER2+ breast cancer. With currently accruing trials evaluating the safety of omitting surgery for patients with HER2+ breast cancer and the exceptional response to NST, it is important to identify clinicopathologic predictors of residual disease for accurate selection of patients to include in these studies.

Many trials have evaluated pCR in HER2+ breast cancer after NST. However, the definition of pCR varies. Whereas some studies define pCR as no residual invasive cancer in the breast only, others define pCR as the eradication of both invasive and in situ disease, and some include nodal response.[1,3,7,8,10,13,14] However, residual lymph node disease or the role of in situ disease most often has not been specifically evaluated. Untch et al.[1] found that HR– status was the only independent predictor of pCR in their multivariate analysis. Hamy-Petit et al.[13] found that 47.7% of their 199-patient cohort had no residual invasive cancer in the breast or lymph nodes after receiving neoadjuvant chemotherapy and trastuzumab, with HR– status and older age being predictive of pCR.

The current study found that DCIS shown on the pretreatment core biopsy is a novel feature associated with residual disease, both invasive and DCIS, in final surgical specimen analyses after NST. Because in situ disease may serve as a nidus for future recurrence, it is important that pCR be defined as absence of residual in situ or invasive disease, especially in patients selected to participate in nonoperative trials for HER2+ breast cancer. van la Parra et al.[12] found that patients with residual disease after NST for triple-negative breast cancer more likely had presented with DCIS on the initial core biopsy (76% vs. 24%; $p = 0.03$) and malignant microcalcifications on imaging (76% vs. 24%; $p = 0.02$). In their triple-negative cohort, DCIS was found only in 24% and calcifications in 25% of the patients. This is in contrast to the current HER2+ cohort, in which 60% had calcifications, and 46% were found to have DCIS. Although the percentages of patients with calcifications and DCIS were higher in the HER2 population than in the triple-negative cohort, they were not associated with residual disease after NST.

This study found HR+ status to be another variable associated with residual disease after NST. Although 37.5% of the overall HER2+ patient cohort had pCR, defined as ypT0ypN0, 49.2% of the patients with HER2+/HR– tumors achieved pCR compared with 26.6% of the patients with HR+ tumors. The high pCR rate of HR–/HER2+ tumors is similar to that for triple-negative breast cancers, thus increasing their potential for inclusion in omission-of-surgery trials.[15–17]

In a study by van la Parra et al.[12] that evaluated the baseline factors predicting response to NST in triple-negative breast cancer (TNBC), the rate of pCR (ypT0N0) was 34.7%. These authors also identified DCIS on the initial core biopsy as a unique feature associated with residual DCIS (irrespective of the invasive component) on the final surgical pathology.

In the current patient cohort, multimodality imaging was used to evaluate radiologic response after NST, and nodal status on the final pathology did not differ significantly based on radiographic nodal response. The pathologic status of the axilla has been shown to correlate with response in the breast after NST.[18] In a study performed at MD Anderson, pCR in the breast correlated with nodal pCR in patients with TNBC/HER2+ breast cancer after NST. Of the 116 patients with cN0 disease who achieved pCR in the breast, 0% had evidence of nodal involvement on the final surgical pathology. Among the 237 patients with biopsy-proven cN1 disease, 89.6% with breast pCR had no evidence of lymph node metastasis after NST, and 57.5% of the patients with residual disease in the breast had residual metastatic disease in the axillary lymph nodes.[18]

Another study by Kuerer et al.[11] showed that for 98% of the patients, pCR in the breast correlated with pCR in the axilla. In the current patient cohort, nodal status on the final pathology did not differ significantly based on radiographic nodal response. Therefore, multimodality nodal imaging cannot be used for reliable prediction of pathologic nodal response, especially for patients with residual disease in the breast. However, based on previously published studies, the risk of missing nodal metastasis without axillary surgery is extremely low for patients with initial cN0 disease and with HER2+ disease documented by ultrasound who have a breast pCR.[18] On the other hand, approximately 10% of cases with initial node-positive disease and a breast

pCR will still have residual axillary nodal metastases.[18] This suggests that in trials assessing the safety of nonoperative management for exceptional responders with HER2+ breast cancer after NST, surgical evaluation for nodal involvement still is necessary to assess reliably for nodal involvement in patients with a high risk for residual lymph node disease who present with initial biopsy-proven lymph node metastasis.

We have recently shown that a percutaneous biopsy of initial biopsy-proven nodal metastases delineated with a clip after NST to assess response and need for additional therapy is inaccurate, with a false-negative rate of 53%.[19] Therefore, in our currently accruing multicenter trial for eliminating surgery after NST, a surgical-targeted axillary lymph node dissection is indicated if the patient presents with initial documented nodal metastases.[20] This study also showed that multimodality imaging is clinically ineffective in accurately detecting residual disease and confirms the need for image-guided biopsy to assess for pathologic response.

CONCLUSION

With the increasing rate of pCR among patients with HER2+ cancer, the current challenge is the ability to identify patients correctly who achieve pCR and to determine whether breast surgery can be safely omitted in clinical trials with this patient cohort. The novel features identified in this study will aid in meaningful patient discussions and selection for current ongoing trials evaluating the safety of nonoperative management followed by radiotherapy.

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REFERENCES

1. Untch M, Rezai M, Loibl S, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol.* 2010;28:2024–31.
2. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet.* 2010;375:377–84.
3. Untch M, Fasching PA, Konecny GE, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol.* 2011;29:3351–7.
4. Mariani G, Fasolo A, De Benedictis E, Gianni L. Trastuzumab as adjuvant systemic therapy for HER2-positive breast cancer. *Nat Clin Pract Oncol.* 2009;6:93–104.
5. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res.* 2007;13:228–33.
6. Tanioka M, Sasaki M, Shimomura A, et al. Pathologic complete response after neoadjuvant chemotherapy in HER2-overexpressing breast cancer according to hormonal receptor status. *Breast.* 2014;23:466–72.
7. Kim MM, Allen P, Gonzalez-Angulo AM, et al. Pathologic complete response to neoadjuvant chemotherapy with trastuzumab predicts for improved survival in women with HER2-overexpressing breast cancer. *Ann Oncol.* 2013;24:1999–2004.
8. Sanchez-Munoz A, Navarro-Perez V, Plata-Fernandez Y, et al. Proliferation determined by Ki-67 defines different pathologic response to neoadjuvant trastuzumab-based chemotherapy in HER2-positive breast cancer. *Clin Breast Cancer.* 2015;15:343–7.
9. Hamy AS, Pierga JY, Sabaila A, et al. Stromal lymphocyte infiltration after neoadjuvant chemotherapy is associated with aggressive residual disease and lower disease-free survival in HER2-positive breast cancer. *Ann Oncol.* 2017;28:2233–40.
10. 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;30:1796–804.
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;267:946–51.
12. van la Parra RFD, Tadros AB, Checka CM, et al. Baseline factors predicting a response to neoadjuvant chemotherapy with implications for non-surgical management of triple-negative breast cancer. *Br J Surg.* 2018;105:535–43.
13. Hamy-Petit AS, Belin L, Bonsang-Kitzis H, et al. Pathological complete response and prognosis after neoadjuvant chemotherapy for HER2-positive breast cancers before and after trastuzumab era: results from a real-life cohort. *Br J Cancer.* 2016;114:44–52.
14. Natoli C, Vici P, Sperduti I, et al. Effectiveness of neoadjuvant trastuzumab and chemotherapy in HER2-overexpressing breast cancer. *J Cancer Res Clin Oncol.* 2013;139:1229–40.
15. Jung YY, Hyun CL, Jin MS, et al. Histomorphological factors predicting the response to neoadjuvant chemotherapy in triple-negative breast cancer. *J Breast Cancer.* 2016;19:261–7.
16. Kraus JA, Beriwal S, Dabbs DJ, et al. Predictors of pathologic complete response after standard neoadjuvant chemotherapy in triple-negative breast carcinoma. *Appl Immunohistochem Mol Morphol.* 2012;20:334–9.
17. Masuda H, Masuda N, Kodama Y, et al. Predictive factors for the effectiveness of neoadjuvant chemotherapy and prognosis in triple-negative breast cancer patients. *Cancer Chemother Pharmacol.* 2011;67:911–7.
18. 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;152:665–70.

19. Caudle AS, Kuerer HM, Krishnamurthy S, et al. Feasibility of fine-needle aspiration for assessing responses to chemotherapy in metastatic nodes marked with clips in breast cancer: a prospective registry study. *Cancer*. 2019;125(3):365–73.
20. Kuerer HM. Eliminating breast cancer surgery in exceptional responders with neoadjuvant systemic therapy 2018. Retrieved May 6, 2019 from https://clinicaltrials.gov/ct2/show/NCT02945579.