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Identification of Patients With Documented Pathologic Complete Response in the Breast After Neoadjuvant Chemotherapy for Omission of Axillary Surgery

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IMPORTANCE A pathologic complete response (pCR; no invasive or in situ cancer) occurs in 40% to 50% of patients with *HER2*-positive (*HER2*+) and triple-negative (TN) breast cancer. The need for surgery if percutaneous biopsy of the breast after neoadjuvant chemotherapy (NCT) indicates pCR in the breast (hereinafter referred to as breast pCR) has been questioned, and appropriate management of the axilla in such patients is unknown.

OBJECTIVE To identify patients among exceptional responders to NCT with a low risk for axillary metastases when breast pCR is documented who may be eligible for an omission of surgery clinical trial design.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study at a single-institution academic national comprehensive cancer center included 527 consecutive patients with *HER2*+/TN (T1/T2 and N0/N1) cancer treated with NCT followed by standard breast and nodal surgery from January 1, 2010, through December 31, 2014.

MAIN OUTCOMES AND MEASURES Patients who achieved a breast pCR were compared with patients who did not based on subtype, initial ultrasonographic findings, and documented pathologic nodal status. Incidence of positive findings for nodal disease on final pathologic review was calculated for patients with and without pCR and compared using relative risk ratios with 95% CIs.

RESULTS The analysis included 527 patients (median age, 51 [range, 23-84] years). Among 290 patients with initial nodal ultrasonography showing N0 disease, 116 (40.4%) had a breast pCR and 100% had no evidence of axillary lymph node metastases after NCT. Among 237 patients with initial biopsy-proved N1 disease, 69 of 77 (89.6%) with and 68 of 160 (42.5%) without a breast pCR had no evidence of residual nodal disease ($P < .01$). Patients without a breast pCR had a relative risk for positive nodal metastases of 7.4 (95% CI, 3.7-14.8; $P < .001$) compared with those with a breast pCR.

CONCLUSIONS AND RELEVANCE Breast pCR is highly correlated with nodal status after NCT, and the risk for missing nodal metastases without axillary surgery in this cohort is extremely low. These data provide the fundamental basis and rationale for management of the axilla in clinical trials of omission of cancer surgery when image-guided biopsy indicates a breast pCR.

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The dramatic therapeutic effects of neoadjuvant chemotherapy (NCT) in the breast and documented nodal metastases has been demonstrated for several decades.[1-3] During this time, our understanding of the biology of breast cancer, response to NCT, and integration of these findings into clinical practice has changed the surgical management of breast cancer. A pathologic complete response (pCR) in the breast (hereinafter referred to as breast pCR) to NCT, defined as no residual invasive or in situ disease, is known to confer disease-free and overall survival benefits.[1,4,5] The variability of breast pCR rates among different subtypes of breast cancer has been extensively studied. Patients with *HER2* (now *ERBB2*)-positive (*HER2*+)/triple-negative (TN) subtypes have a higher incidence of breast pCR than patients with luminal type A or B.[6,7] Tumor size is also an independent predictor of pCR, with T1 and T2 tumors having higher rates of pCR than T3 or T4 tumors. The implementation of dual systemic agent therapy for breast cancer targeting human epidermal growth factor receptor 2 is now routinely incorporated for patients with *HER2*+ tumors.[8] This process has led to increased rates of breast pCR among patients with the *HER2*+ subtype.[9]

The indications for NCT from initial use only in locally advanced breast cancer to earlier-stage disease have been increasing during the past decade. Neoadjuvant chemotherapy allows for the opportunity to evaluate the in vivo efficacy of chemotherapy on the primary breast tumor. For this reason, NCT is now increasingly used in smaller tumors (T1/T2) and *HER2*+/TN tumors, which are associated with a higher pCR.[1] Likewise, axillary pCR alone confers a disease-free and overall survival advantage.[10,11] An initial early study[2] reported that patients who achieve an axillary pCR after receiving standard NCT are more likely to have smaller tumors that are negative for the estrogen receptor, and patients with an axillary pCR are more likely to have a primary tumor pCR. Since the development of systemic agents targeting *HER2*, the axillary pCR rate among patients with *HER2*+ tumors has ranged from 40% to 74%.[9,12,13]

Overall pCR rates as high as 50% in the breast and axilla among these subtypes have questioned the necessity of surgery in such patients.[14] Initial attempts at elimination of surgery among patients with a complete clinical response were unsuccessful, because imaging of the breast and lymph nodes had a poor negative predictive value for a pCR and therefore was associated with unacceptable local regional recurrence rates after radiotherapy alone.[14] However, use of improved imaging techniques with extensive vacuum-assisted core biopsy and fine-needle aspiration (FNA) biopsy of the known tumor bed (with removal of the initially placed clip) has recently been shown to accurately identify patients with a pCR and in whom significant residual disease in the breast is unlikely.[15] In the initial results of the MD Anderson feasibility clinical trial with 34 patients,[15] the use of image-guided biopsy was associated with 100% accuracy and no false-negative findings for the determination of residual disease in the breast after NCT. Similar prospective, multicenter, cooperative group studies are planned or have been commenced by the NRG Oncology Group (formerly the National Surgical Adjuvant Breast and Bowel Project [NSABP], Radiation Therapy Oncology Group [RTOG], and Gynecologic Oncology Group [GOG]), the German Breast Group, and other national and international single centers.[16,17]

Key Points

Question What is the risk for axillary metastases in patients who have a pathologic complete response in the breast after neoadjuvant chemotherapy?

Finding In this cohort study of 527 consecutive patients with *HER2*+/triple negative (T1/T2 and N0/N1) cancer who achieved a pathologic complete response in the breast after neoadjuvant chemotherapy, 185 of 193 (95.9%) achieved an axillary pathologic complete response.

Meaning The risk for axillary metastases in patients who have a pathologic complete response in the breast after neoadjuvant chemotherapy is extremely low and provides the rationale for management of the axilla in clinical trials of omission of cancer surgery.

The present study of 527 patients with TN and *HER2*+ breast cancer who were receiving NCT was undertaken to determine the best way to manage the axilla in a clinical trial in which no breast surgery will be performed based on the pathologic response in the breast. The results of the present study examining the rationale for management of the axilla when no breast surgery will be performed, together with results of the MD Anderson feasibility clinical trial, were used to develop the MD Anderson Eliminating Breast Cancer Surgery in Exceptional Responders with Neoadjuvant Systemic Therapy prospective trial, which has just opened at our institution.[18]

Methods

From January 1, 2010, through December 31, 2014, 527 consecutive patients with initial clinical T1/T2, N0/N1 (documented by FNA or core biopsy results), and TN and *HER2*+ subtypes were identified from the prospectively managed Breast Cancer Management System Database. Participants were treated at University of Texas MD Anderson Cancer Center, Houston, with NCT followed by standard breast and nodal surgery. This study was reviewed and approved by the University of Texas MD Anderson Cancer Center institutional review board, which waived the need for informed consent.

Clinical and pathologic data for each patient were reviewed. Before the initiation of NCT, patients underwent evaluation by a multidisciplinary team. During this evaluation, patients underwent clinical disease staging with a clinical examination and mammography and ultrasonography of the breast and axilla. Standard ultrasonographic features consistent with normal lymph nodes included a cortex of less than 2 mm, uniform cortical thickening, oval shape, and normal plump echogenic hilum. All suspicious-appearing lymph nodes were evaluated, and specimens were obtained using FNA or core needle biopsy before the initiation of treatment. Patients received anthracycline- and/or taxane-based NCT. Patients with *HER2*+ cancer (amplified by fluorescence in situ hybridization and/or positive immunohistochemistry findings) also received trastuzumab with or without pertuzumab (217 [82.5%]

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	Study Group[a]		
	HER2+ (n = 263)	TN (n = 264)	All (N = 527)
Age, median (range), y	52 (25-84)	50 (23-77)	51 (23-84)
Race/ethnicity			
Asian/Pacific Islander	27 (10.3)	13 (4.9)	40 (7.6)
Black	31 (11.8)	53 (20.1)	84 (15.9)
Hispanic	47 (17.9)	43 (16.3)	90 (17.1)
White	156 (59.3)	150 (56.8)	306 (58.1)
Native American	1 (0.4)	2 (0.8)	3 (0.6)
Other	1 (0.4)	3 (1.1)	4 (0.8)
Menopausal status			
Premenopausal	101 (38.4)	113 (42.8)	214 (40.6)
Postmenopausal	158 (60.1)	140 (53.0)	298 (56.5)
Perimenopausal	4 (1.5)	9 (3.4)	13 (2.5)
Unknown	0	2 (0.8)	2 (0.4)
Clinical stage			
T1N0	14 (5.3)	19 (7.2)	33 (6.3)
T1N1	27 (10.3)	15 (5.7)	42 (8.0)
T2N0	118 (44.9)	139 (52.7)	257 (48.8)
T2N1	104 (39.5)	91 (34.5)	195 (37.0)
Initial T size, median (range), cm	2.8 (0.6-5)	3 (0.7-5)	2.9 (0.6-5)
Histologic finding			
Invasive ductal	259 (98.5)	259 (98)	518 (98.3)
Other	4 (1.5)	5 (1.9)	9 (1.7)
Grade			
I	NA	NA	4 (0.8)
II	NA	NA	90 (18.0)
III	NA	NA	407 (81.2)

Abbreviations: NA, not applicable; TN, triple-negative; +, positive.

[a] Data are presented as number (percentage) of patients unless otherwise indicated. Percentages have been rounded and may not total 100.

single and 46 [17.5%] dual *HER2*-targeted therapy). After completion of NCT, all patients underwent standard breast and nodal surgery. The final surgery performed was left to the discretion of the surgeon and patient preference.

A breast pCR was defined as no evidence of residual invasive or in situ carcinoma. A pCR of the axilla was defined as no evidence of metastatic carcinoma. Standard hematoxylin-eosin staining was performed to assess each axillary node for evidence of carcinoma. If suspicious cells were identified, immunohistochemistry for cytokeratin was then performed. Associations between breast and nodal pCR were compared between groups.

For statistical analysis, patients achieving a breast pCR were compared with patients who did not achieve a breast pCR. All statistical analyses were performed using SPSS statistical software (version 22; SPSS Inc). A 2-sided $P < .05$ was considered to be statistically significant. Categorical variables were compared using a 2-sided χ^2 test. Continuous variables were compared using the independent-sample *t* test. Incidence of positive nodal disease on final pathologic review was calculated for patients with and without pCR and compared using relative risk ratios with 95% CIs.

Results

Table 1 summarizes the patient, tumor, and treatment characteristics of the study population. Of the 527 patients included in the study (median age, 51 years [range, 23-84 years]), 263 had *HER2*+ and 264 had TN disease. A total of 237 patients had documented biopsy-proved clinical N1 disease at initial presentation, including 131 patients in the *HER2*+ group and 106 patients in the TN group. The remaining 290 patients had clinical N0 disease at presentation: 132 in the *HER2*+ group and 158 in the TN group. The patients had no significant difference in menopausal status, initial T size, or histologic findings based on subtype. Most of the tumors were grade III. In this cohort, 251 patients underwent segmental mastectomy and 276 underwent mastectomy. Women with *HER2*+ breast cancer were more likely to undergo mastectomy (149 of 263 [56.7%]) than were women with TN breast cancer (127 of 264 [48.1%]). Final nodal surgery consisted of sentinel node biopsy in 302 patients and axillary lymph node dissection in 225.

Breast pCR and Correlation With Pathologic Axillary Nodal Status

Overall, 193 of 527 patients (36.6%) achieved a breast pCR. The rate of breast pCR was slightly higher in the TN group (99 of 264 [37.5%]) compared with the *HER2*+ group (94 of 263 [35.7%]; $P = .94$). Patients presenting with clinical N1 disease were less likely to have a breast pCR (77 of 237 [32.5%]) compared with patients presenting with clinical N0 disease (116 of 290 [40.0%]; $P = .08$).

All 116 patients with a breast pCR who presented with initial clinical N0 disease (100%) were found to have no

Table 2. Pathologic Axillary Status in 527 Patients With and Without a Breast pCR After NCT

Breast Cancer Subtype	No. of Nodes With Positive Histologic Finding, No. (%) of Patients				
	0	1	2	≥3	All
Breast pCR					
HER2+					
T1N0	6 (100)	0	0	0	6 (100)
T2N0	46 (100)	0	0	0	46 (100)
T1N1	10 (76.9)	2 (15.4)	1 (7.7)	0	13 (100)
T2N1	27 (93.1)	1 (3.4)	0	1 (3.4)	29 (100)
TN					
T1N0	12 (100)	0	0	0	12 (100)
T2N0	52 (100)	0	0	0	52 (100)
T1N1	6 (100)	0	0	0	6 (100)
T2N1	26 (89.7)	2 (6.9)	0	1 (3.4)	29 (100)
HER2+ and TN					
T1N0	18 (100)	0	0	0	18 (100)
T2N0	98 (100)	0	0	0	98 (100)
T1N1	16 (84.2)	2 (10.5)	1 (5.3)	0	19 (100)
T2N1	53 (91.4)	3 (5.2)	0	2 (3.4)	58 (100)
No Breast pCR					
HER2+					
T1N0	8 (100)	0	0	0	8 (100)
T2N0	71 (98.6)	1 (1.4)	0	0	72 (100)
T1N1	10 (71.4)	1 (7.1)	1 (7.1)	2 (14.3)	14 (100)
T2N1	36 (48.0)	7 (9.3)	16 (21.3)	16 (21.3)	75 (100)
TN					
T1N0	6 (85.7)	1 (14.3)	0	0	7 (100)
T2N0	79 (90.8)	8 (9.2)	0	0	87 (100)
T1N1	3 (33.3)	0	3 (33.3)	3 (33.3)	9 (100)
T2N1	19 (30.6)	4 (6.5)	16 (25.8)	23 (37.1)	62 (100)
HER2+ and TN					
T1N0	14 (93.3)	1 (6.7)	0	0	15 (100)
T2N0	150 (94.3)	9 (5.7)	0	0	159 (100)
T1N1	13 (56.5)	1 (4.3)	4 (17.4)	5 (21.7)	23 (100)
T2N1	55 (40.1)	11 (8.0)	32 (23.4)	39 (28.5)	137 (100)

Abbreviations: NCT, neoadjuvant chemotherapy; pCR, pathologic complete response; TN, triple-negative; +, positive.

evidence of metastatic nodal disease at the time of surgery (**Table 2**). Seventy-seven patients with clinical N1 disease were found to have a breast pCR. Of these patients, only 8 did not have an axillary pCR (8 of 77 [10.4%]). Among these 8 patients, 5 had 1 positive lymph node on the final pathologic review, 1 had 2 positive lymph nodes, and 2 had more than 3 positive lymph nodes. Overall, we found no significant difference in axillary pCR rates between the *HER2*+ (89 of 94 [94.7%]) and TN (96 of 99 [97.0%]) groups who also achieved a breast pCR ($P = .43$).

Patients who presented with initial clinical N0 disease but did not achieve a breast pCR had a 5.7% chance of having positive nodal disease at final pathologic review. Patients who presented with initial clinical N1 disease but did not achieve a breast pCR had a 57.5% chance of having positive nodal disease at final pathologic review ($P < .01$). Of these 102 patients who did not achieve a pCR and who had remaining positive disease on final pathologic findings, 44 (43.1%) had more than 3 positive nodes. With use of relative risk ratios to compare patients with and without pCR, patients without a pCR had a relative risk for positive final nodal pathologic findings of 7.4 (95% CI, 3.7-14.8; $P < .001$) compared with patients with a pCR (**Table 3**). Subgroup relative risk analysis of patients with *HER2*+/TN and N1 disease also demonstrated a significant increase in the relative risk for positive final nodal pathologic findings for patients without a pCR (relative risk, 5.3; 95% CI, 2.7-10.3; $P < .001$). The greatest increase in relative risk was seen in patients who presented with N0 disease and who did not have a breast pCR (14.0; 95% CI, 0.8-237.0), although this difference did not reach statistical significance ($P = .07$).

Discussion

The primary findings of this study set the stage to select patients for clinical trials in which no breast and axillary surgery might be safe given that patients will continue with whole-breast radiotherapy after proving no residual invasive or in situ cancer in the breast. No patients were found to have axillary metastases in this study of 116 patients with initial negative clinical and axillary ultrasonographic findings and a breast pCR

after NCT. Thus, among patients in the upcoming clinical trial for eliminating surgery after NCT and documentation with image-guided extensive vacuum-assisted core biopsy, missing residual disease without surgery in the axilla will be very unlikely.[18]

In the present study, we identified patients with the highest likelihood of achieving a pCR after NCT. This subset of patients included those with *HER2*+ and TN disease with small tumors that had a low clinical nodal disease burden.[6,7] The use of NCT has the well-known capability of eradicating nodal metastases.[2,4,9] The clinical nodal status in our population was determined by clinical examination findings and axillary ultrasonography with FNA or core biopsy of any suspicious nodes. The addition of ultrasonography to the physical examination allows for a more reliable and sensitive way to preoperatively determine lymph node status, because some lymph nodes may not be palpable but are clearly positive at ultrasonography. Image-guided FNA or core biopsy was performed on all suspicious lymph nodes in this study as standard institutional practice. At our institution, a previous investigation[19] reported that the sensitivity of ultrasonography-guided FNA is 86.4% and specificity is 100%, with a false-negative rate of 11.6%. In the present study, among *HER2*+/TN T1/T2 cancers with a documented breast pCR and initial N1 disease at presentation (n = 77), 69 (89.6%) were found to have a pCR in the axilla as well. Conversely and of importance, patients with initial N1 disease and residual cancer documented in the breast are at a significantly higher risk for residual nodal disease (57.5%), and thus these patients would not be appropriate candidates for clinical trials of omission of surgery.

Because nearly 90% of patients in our study who had documented nodal metastases before beginning NCT were not found to harbor any residual axillary metastases when a breast pCR was demonstrated, the clinical trial multidisciplinary design team also chose to include such patients for eligibility in the elimination of surgery trial if targeted axillary dissection demonstrated no nodal disease.[18] This decision was made because in approximately 90% of these cases, breast surgery can still be eliminated and a small incision can be made in the axillary region to ensure that the prior lymph node with cancer documented with the clip and any other sentinel lymph nodes are removed.[3] Using this technique, the MD Anderson group[18] demonstrated a very acceptable false-negative rate for missing nodal metastases of approximately 2% among patients with initial documented nodal metastases. Patients found to have metastases in these lymph nodes will undergo standard axillary dissection and can proceed with whole-breast and regional nodal irradiation but avoid breast surgery.

Many examples exist in which medical therapy has replaced the need for surgery, including infections, peptic ulcer disease, and other solid organ malignant neoplasms, when new drugs and improved radiotherapy techniques have been identified and developed to treat or prevent complications of disease. For breast cancer, pCR rates in the primary tumor have been increasing among patients with *HER2*+/TN disease undergoing NCT, reflecting a greater understanding of response to therapy based on subtypes and new targeted agents. The challenge that follows is the preoperative identification of patients who have achieved breast pCR to determine whether breast surgery can be omitted in these patients, who will be treated with radiotherapy alone.[20] Prior clinical studies that aimed to eliminate surgery in exceptional responders[21] did not meet the threshold of success for the routine omission of surgery among these patients owing to the inability to reliably identify patients with a breast pCR. Outstanding initial results from the MD Anderson feasibility trial[15] using extensive image-guided sampling of the tumor bed after NCT have provided an opportunity to test the hypothesis that surgery may be eliminated in many patients with a documented breast pCR.

Table 3. Relative Risk for Residual Axillary Nodal Metastases After NCT in Patients Without vs With Breast pCR

Subgroup	RR (95% CI)	*P* Value
N0	14.0 (0.8-237.0)	.07
N1	5.3 (2.7-10.3)	<.001
HER2+	4.9 (2.0-11.9)	<.001
TN	11.6 (3.7-36.0)	<.001
All	7.4 (3.7-14.8)	<.001

Abbreviations: NCT, neoadjuvant chemotherapy; pCR, pathologic complete response; RR, relative risk; TN, triple-negative; +, positive.

Limitations

Although this study was well performed and represents a novel level of inquiry in designing trials for the potential safety of eliminating axillary surgery in breast cancer for exceptional responders undergoing NCT, potential limitations also need mention. Nodal ultrasonography to determine the need for biopsy of suspicious nodes for metastases is not routinely performed in all centers treating breast cancer; the procedure is user dependent and requires a highly technical experience level. Toward this end, applicability of this procedure and findings from this retrospective database analysis from one of the largest academic comprehensive national comprehensive cancer centers will depend on further studies to replicate these findings among similar patients treated with NCT.

Conclusions

The results of our study demonstrate the ability to reliably estimate the patients with early-stage *HER2*+/TN cancers and a breast pCR who are highly unlikely to have residual axillary nodal metastasis if presenting with initial clinical stage T1N0M0 or T2N0M0 disease. The risk for missing nodal metastases in these patients without axillary surgery is extremely low. Findings from this study and the new elimination of breast surgery protocol will need to be replicated by other groups before broad implementation of similar clinical trials at the single and multicenter level and are anticipated shortly. Together these data provide a strong rationale for these highly selective patients to proceed with clinical trials designed to test the safety of omission of surgery followed by standard whole-breast radiotherapy after large-bore image-guided vacuum-assisted core biopsy indicates a breast pCR.[18]

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Study concept and design: Tadros, Smith, Valero, DeSnyder, Hunt, Kuerer.
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