Factors Associated with Nodal Pathologic Complete Response Among Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: Results of CALGB 40601 (HER2+) and 40603 (Triple-Negative) (Alliance)

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ABSTRACT

Background. De-escalation of axillary surgery after neoadjuvant chemotherapy (NAC) requires careful patient selection. We seek to determine predictors of nodal pathologic complete response (ypN0) among patients treated on CALGB 40601 or 40603, which tested NAC regimens in HER2+ and triple-negative breast cancer (TNBC), respectively.

Patients and Methods. A total of 760 patients with stage II–III HER2+ or TNBC were analyzed. Those who had axillary surgery before NAC ($N = 122$), or who had missing pretreatment clinical nodal status (cN) ($N = 58$) or ypN status ($N = 41$) were excluded. The proportion of patients with ypN0 disease was estimated for those with and without breast pathologic complete response (pCR) according to pretreatment nodal status.

Results. In 539 patients, the overall ypN0 rate was 76.3% (411/539) to 93.2% (245/263) in patients with breast pCR and 60.1% (166/276) with residual breast disease (RD) ($P < 0.0001$). For patients who were cN0 pretreatment, the ypN0 rate was 88.8% (214/241), 96.3% (104/108) with breast pCR, and 82.7% (110/133) with RD. For patients who were cN1, 66.2% (157/237) converted to ypN0, 91.7% (111/121) with breast pCR and 39.7% (46/116) with RD. For patients who were cN2/3, 65.6% (40/61) converted to ypN0, 88.2% (30/34) with breast pCR and 37.0% (10/27) with RD. On multivariable analysis, only pretreatment clinical nodal status and breast pCR/RD were associated with ypN0 status (both $P < 0.0001$).

Conclusions. Breast pCR and pretreatment nodal status are predictive of ypN0 axillary nodal involvement, with < 5% residual nodal disease among cN0 patients who experience breast pCR. These findings support the incorporation of axillary surgery de-escalation strategies into NAC trials.

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TABLE 1 Patient characteristics

(Row percentages)	ypN0 N = 411 (76.3%)	ypN+ N = 128 (23.7%)	Total N = 539	P value
Trial				0.26[a]
CALGB 40601	163 (73.8%)	58 (26.2%)	221	
CALGB 40603	248 (78.0%)	70 (22.0%)	318	
Treatment arm				0.013[a]
Paclitaxel	65 (83.3%)	13 (16.7%)	78	
Paclitaxel and bevacizumab	52 (66.7%)	26 (33.3%)	78	
Paclitaxel and carboplatin	65 (79.3%)	17 (20.7%)	82	
Paclitaxel, carboplatin, and bevacizumab	66 (82.5%)	14 (17.5%)	80	
Paclitaxel and trastuzumab	66 (74.2%)	23 (25.8%)	89	
Paclitaxel, trastuzumab, and lapatinib	68 (81.0%)	16 (19.0%)	84	
Paclitaxel and lapatinib	29 (60.4%)	19 (39.6%)	48	
Age at registration (years)				0.18[b]
Mean (SD)	48.8 (10.3)	50.5 (10.7)	49.2 (10.4)	
Median	49.0	49.0	49.0	
Range	(24.0–79.0)	(26.0–75.0)	(24.0–79.0)	
Racial group				0.93[a]
Missing	15	7	22	
Asian	15 (71.4%)	6 (28.6%)	21	
Black	67 (77.0%)	20 (23.0%)	87	
Other	5 (71.4%)	2 (28.6%)	7	
White	309 (76.9%)	93 (23.1%)	402	
Ethnicity				0.49[a]
Missing	34	20	54	
Hispanic/Latino	36 (81.8%)	8 (18.2%)	44	
Non-Hispanic	341 (77.3%)	100 (22.7%)	441	
Tumor subtype				
HER2+	163 (73.8%)	58 (26.2%)	221	0.26[a]
TNBC	248 (78.0%)	70 (22.0%)	318	
Clinical stage				< 0.0001[a]
2	291 (82.0%)	64 (18.0%)	355	
3	120 (65.2%)	64 (34.8%)	184	
Clinical tumor size (cm)				0.0019[b]
N	404	123	527	
Mean (SD)	4.5 (2.5)	5.5 (3.1)	4.8 (2.7)	
Median	4.0	5.0	4.0	
Range	(0.0–22.0)	(0.0–16.0)	(0.0–22.0)	
Clinical T category				0.0016[a]
Missing	9	5	14	
1	20 (69.0%)	9 (31.0%)	29	
2	265 (82.3%)	57 (17.7%)	322	
3	105 (67.3%)	51 (32.7%)	156	
4	12 (66.7%)	6 (33.3%)	18	
Clinical N category				< 0.0001[a]
0	214 (88.8%)	27 (11.2%)	241	
1	157 (66.2%)	80 (33.8%)	237	
2	33 (67.3%)	16 (32.7%)	49	
3	7 (58.3%)	5 (41.7%)	12	

TABLE 1 continued

(Row percentages)	ypN0 N = 411 (76.3%)	ypN+ N = 128 (23.7%)	Total N = 539	P value
Tumor grade				0.40[a]
Missing	21	12	33	
High	309 (78.4%)	85 (21.6%)	394	
Intermediate	73 (72.3%)	28 (27.7%)	101	
Low	8 (72.7%)	3 (27.3%)	11	
Breast surgery				0.048[a]
Missing	0	1	1	
Lumpectomy	203 (80.2%)	50 (19.8%)	253	
Mastectomy	208 (73.0%)	77 (27.0%)	285	
Axillary surgery				< 0.0001[a]
Missing	70	7	77	
SLNB	124 (91.9%)	11 (8.1%)	135	
ALND	217 (66.4%)	110 (33.6%)	327	
Breast outcome				< 0.0001[a]
Breast RD	166 (60.1%)	110 (39.9%)	276	
Breast pCR	245 (93.2%)	18 (6.8%)	263	

[a]Chi squared

[b]Kruskal–Wallis

In the treatment of breast cancer patients, there has been a significant increase in the use of neoadjuvant chemotherapy (NAC) and a corresponding decrease in upfront surgery.[1–3] Patients treated with NAC experience overall survival and local–regional recurrence rates equivalent to those treated with adjuvant chemotherapy,[4] but NAC has become standard for most cases of stage II–III human epidermal growth factor receptor 2 (HER2)-positive (+) and triple-negative breast cancer (TNBC)[5,6] for two reasons. First, NAC allows for an in vivo assessment of response to prognosticate and identify patients with residual disease as candidates for additional systemic therapy.[7,8] Second, NAC can optimize local–regional outcomes by converting patients with inoperable breast tumors to operable, or by transforming those deemed candidates for mastectomy-only into candidates for breast conservation.[9] Moreover, NAC often downstages axillary disease, potentially allowing some patients to have less invasive nodal surgery.[10,11]

Downstaging axillary disease with NAC provides an opportunity to de-escalate axillary surgery and reduce the morbidity of treatment. However, this requires accurate prediction of axillary response to NAC. Several large clinical trials tested the feasibility of performing sentinel lymph node biopsy (SLNB) to surgically stage the axilla for cN1 patients who converted to cN0 after NAC.[11–15] Rates of SLN identification ranged from 80.1% to 92.9%, and SLNB false-negative rates ranged from 9.6% to 15%, which largely exceeded the trials' prespecified acceptable failure rates. Similarly, axillary imaging has failed to reliably predict the ypN status of the axilla after NAC, with sensitivity rates reported between 48.5% and 69.8% for ultrasound,[16–18] 38% and 61% for MRI,[18,19] and 63.2% for PET-CT.[18] Thus, current surgical techniques and imaging modalities lack the sensitivity to accurately predict the ypN0 axilla.

Accurate preoperative identification of the ypN0 axilla after NAC could potentially avoid unnecessary axillary surgery. Two neoadjuvant trials, Cancer and Leukemia Group B (CALGB) 40601 (HER2+)[20] and 40603 (TNBC),[21] tested NAC regimens with a primary endpoint of pCR in the breast. In this current study, we seek to determine rates of nodal pCR (ypN0), as well as factors associated with ypN0 among patients treated on the trials. We hypothesize that there will be very low rates of residual disease (RD) in the lymph nodes (ypN+) among patients who had breast pCR, including both clinically node negative and node positive at presentation. The goal of this

TABLE 2 ypN0 and ypN+ rates among patients who experienced breast pCR or had residual disease (RD), by clinical nodal status, N = 539

| N (%)	ypN0	ypN+	Total	P value
Breast pCR (N = 263)				
cN0, 108 (41.1%)	104 (96.3%)	4 (3.7%)	108	1[a]
HER2+	35 (97.2%)	1 (2.8%)	36	
TNBC	69 (95.8%)	3 (4.2%)	72	
cN1, 121 (46.0%)	111 (91.7%)	10 (8.3%)	121	1[a]
HER2+	50 (90.9%)	5 (9.1%)	55	
TNBC	61 (92.4%)	5 (7.6%)	66	
cN2/cN3, 34 (12.9%)	30 (88.2%)	4 (11.8%)	34	1[a]
HER2+	11 (91.7%)	1 (8.3%)	12	
TNBC	19 (86.4%)	3 (13.6%)	22	
Breast RD (N = 276)				
cN0, 133 (48.2%)	110 (82.7%)	23 (17.3%)	133	0.24[a]
HER2+	38 (77.6%)	11 (22.4%)	49	
TNBC	72 (85.7%)	12 (14.3%)	84	
cN1, 116 (42.0%)	46 (39.7%)	70 (60.3%)	116	0.34[a]
HER2+	25 (44.6%)	31 (55.4%)	56	
TNBC	21 (35.0%)	39 (65.0%)	60	
cN2/cN3, 27 (9.8%)	10 (37.0%)	17 (63.0%)	27	0.69[a]
HER2+	4 (30.8%)	9 (69.2%)	13	
TNBC	6 (42.9%)	8 (57.1%)	14	

[a]Fisher exact P value

study is to identify factors that would have the potential to further refine patient selection for axillary surgery de-escalation strategies.

PATIENTS AND METHODS

Data Source

A total of 759 patients were enrolled on the CALGB 40601/40603 trials. CALGB is now part of the Alliance for Clinical Trials in Oncology. CALGB 40601 tested lapatinib, trastuzumab, or both in addition to paclitaxel.[20] Inclusion criteria for CALGB 40601 were patients over 18 years with stage II–III HER2-postive breast cancer, with tumors at least 1 cm in size. Multicentric and bilateral disease were allowed if at least one of the tumors met inclusion criteria. CALGB 40603 tested the addition of carboplatin and/or bevacizumab to paclitaxel, followed by dose dense doxorubicin and cyclophosphamide with or without bevacizumab.[21] Inclusion criteria for CALGB 40603 were patients with stage II–III operable, noninflammatory TNBC who were otherwise well. In both trials, estrogen and progesterone receptor expression < 10% was considered negative, and HER2 was considered negative if
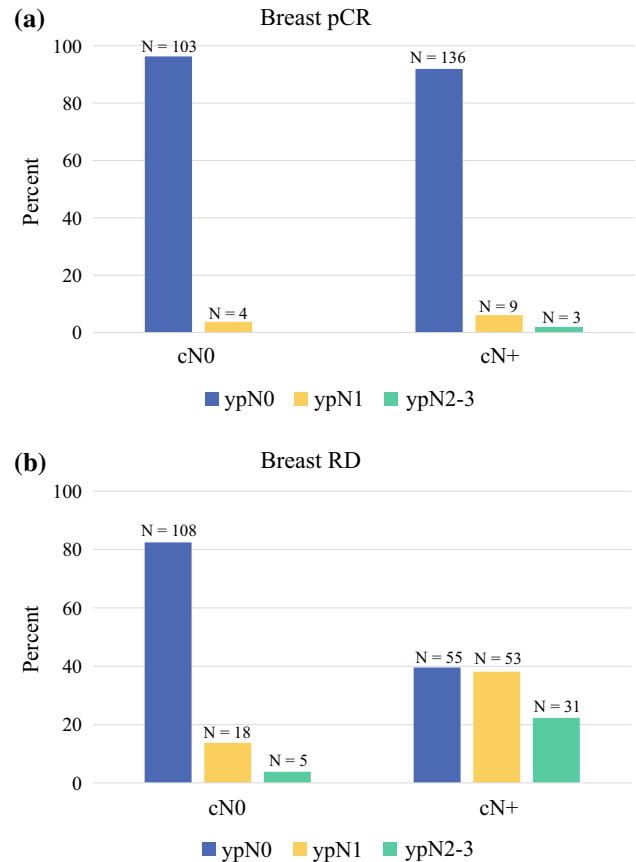
FIG. 1 a, b ypN0, ypN1, and ypN2-3 disease rates for patients with cN0 and cN+ disease and experienced **a** breast pCR (N = 255) or **b** breast RD (N = 270). Patients with missing clinic T category were excluded

the immunohistochemical (IHC) staining was 0–1 + , or 2 + with a fluorescence in situ hybridization HER2/CEP17 ratio of < 2.0. For the current analysis, patients who underwent axillary surgery prior to NAC (n = 122), or those with missing cN status (n = 58) or missing ypN status (n = 41) were excluded.

Definition of Variables

The rates of breast pCR,[20,21] eligibility, and rates of breast conservation,[9] and axillary management[22] from the CALGB 40601/40603 trials have been reported previously. Per-protocol imaging assessments and surgical assessments were consistent for both trials. Receptor statuses including HER2 were determined locally. Clinical nodal (cN) status was determined by physical examination; axillary imaging at presentation was strongly encouraged but not required. For patients with clinically palpable lymph nodes, percutaneous sampling was strongly encouraged but not required. The performance of SLNB or ALND before NAC was allowed. Following NAC, ALND was recommended

TABLE 3 Multivariable analysis to determine factors associated with nodal pCR (ypN0 disease) among patients in trials 40601/40603 (N = 493, patients with missing grade[N = 32], missing T category [N = 13], or missing both grade/T category [N = 1] were excluded from the total study population [N = 539] for this analysis)

	Events/total	Odds ratio (95% CI)	P value
Treatment arm			0.26[b]
Paclitaxel	62/74	Reference	
Paclitaxel and bevacizumab	48/65	0.38 (0.14, 0.99)	0.049[a]
Paclitaxel and carboplatin	55/70	0.54 (0.20, 1.45)	0.22[a]
Paclitaxel, carboplatin, and bevacizumab	57/68	0.59 (0.20, 1.70)	0.33[a]
Paclitaxel and trastuzumab	63/87	0.60 (0.24, 1.50)	0.27[a]
Paclitaxel, trastuzumab, and lapatinib	66/83	0.74 (0.28, 1.94)	0.54[a]
Paclitaxel and lapatinib	29/46	0.30 (0.11, 0.82)	0.018[a]
Clinical T category			0.11[b]
1	18/26	Reference	
2	251/306	2.42 (0.81, 7.23)	0.12[a]
3	101/146	1.33 (0.44, 4.09)	0.61[a]
4	10/15	1.14 (0.21, 6.37)	0.88[a]
Clinical N category			< 0.0001[b]
0	198/223	Reference	
1	146/217	0.16 (0.09, 0.30)	< 0.0001[a]
2	30/44	0.18 (0.07, 0.47)	0.0004[a]
3	6/9	0.17 (0.03, 1.02)	0.053[a]
Tumor subtype			1[b]
HER2+	158/216	Reference	
TNBC	222/277	1.00 (1.00, 1.00)	1[a]
Tumor grade			0.15[b]
High	304/385	1.18 (0.24, 5.78)	0.84[a]
Intermediate	68/97	0.62 (0.12, 3.25)	0.57[a]
Low	8/11	Reference	
In-breast response			< 0.0001[b]
RD	155/252	Reference	< 0.0001[a]
pCR	225/241	12.55 (6.73, 23.42)	

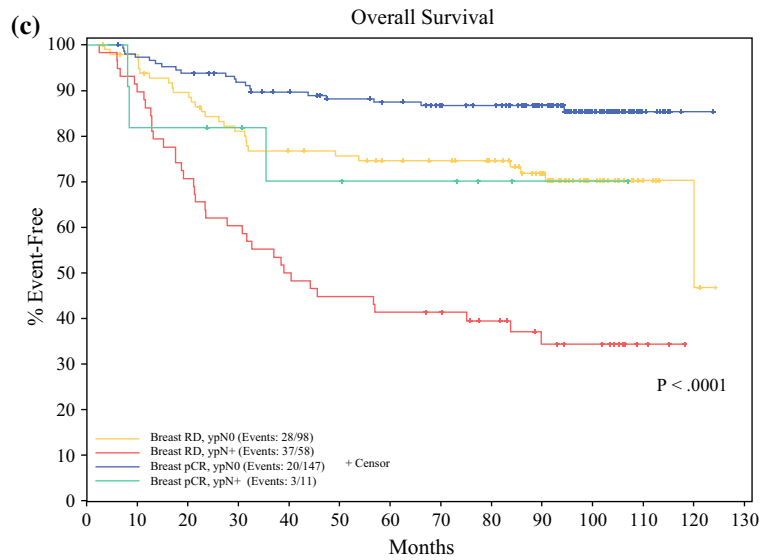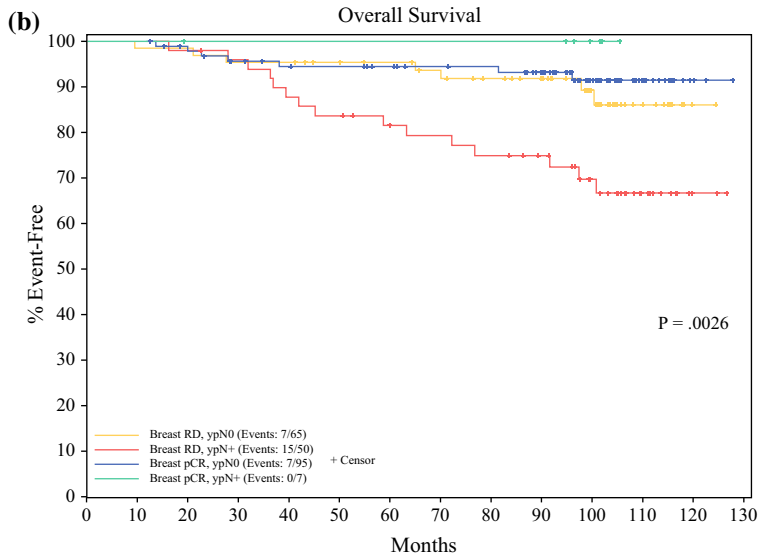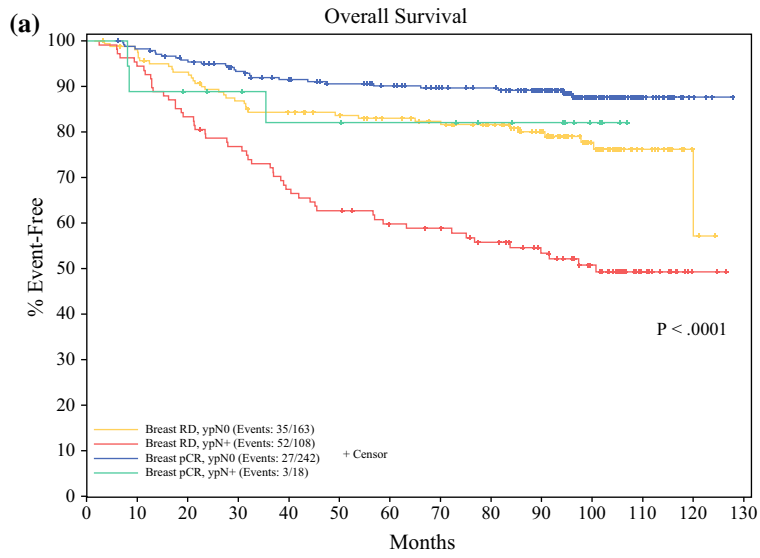[a]Covariate Wald *P* value

[b]Type 3 Wald *P* value

for patients with pretreatment cN+ disease, regardless of clinical nodal response, but definitive axillary surgery was left to the discretion of the treating surgeon.[22] Breast pCR was defined as no residual invasive disease (ypT0/ypTis). Nodal RD (ypN+) disease was considered ≥ 0.2 mm of disease determined by hematoxylin and eosin staining. Immunohistochemical staining for nodal assessment was used per institutional standards and ypN0 (i +) was considered ypN0 disease.

Statistical Analysis

The primary endpoint was the nodal status after NAC (ypN0 vs. ypN+) for patients treated on CALGB 40601 or CALGB 40603. Baseline patient and disease characteristics were compared between patients with ypN0 disease and those with ypN+ disease. Chi square tests (or Fisher's exact test, when required) were used for categorical variables, and the Wilcoxon rank-sum test was used for continuous variables. The proportion of patients who had ypN0 disease was estimated with a binomial point estimate and corresponding 95% confidence interval overall, and for subgroups defined by baseline cN status, baseline cT category, and post-NAC breast disease status (pCR vs. RD). These rates were also determined within each pre-NAC cN cohort (cN0, cN1, cN2-3) by constructed tumor subtype (HER2+/HR + , HER2+/HR − , TNBC). To determine patient selection criteria for consideration of axillary surgery de-escalation, analyses determined the rate of ypN0 disease among patients who had breast pCR, within pre-NAC cN0 and cN+ cohorts by tumor subtype and pre-NAC clinical T category; these analyses were repeated for patients who had breast RD. Multivariable logistic models were used to determine factors associated with ypN0 status in the presence of others. The models included treatment arm as an adjusting variable and included cT, cN, tumor

(a)

Overall Survival

% Event-Free

Breast RD, ypN0 (Events: 35/163)
Breast RD, ypN+ (Events: 52/108)
Breast pCR, ypN0 (Events: 27/242)
Breast pCR, ypN+ (Events: 3/18)

+ Censor

P < .0001

Months

(b)

Overall Survival

% Event-Free

Breast RD, ypN0 (Events: 7/65)
Breast RD, ypN+ (Events: 15/50)
Breast pCR, ypN0 (Events: 7/95)
Breast pCR, ypN+ (Events: 0/7)

+ Censor

P = .0026

Months

(c)

Overall Survival

% Event-Free

Breast RD, ypN0 (Events: 28/98)
Breast RD, ypN+ (Events: 37/58)
Breast pCR, ypN0 (Events: 20/147)
Breast pCR, ypN+ (Events: 3/11)

+ Censor

P < .0001

Months

subtype, tumor grade, and in-breast response as variables. Long-term outcomes [overall survival (OS) and local–regional recurrence-free survival (LRRFS)] were compared among the patient groups defined by ypN status and breast disease status using Cox proportional hazard models. Time variables for these long-term outcomes were calculated by the time from randomization on their original studies. Statistical significance was determined at a 0.05 two-sided alpha level. Analyses were performed in SAS (3.8). National Cancer Institute Central Institutional Review Board (IRB) approval was obtained for the CALGB 40601 and CALGB 40603 trials [ClinicalTrials.gov identifiers are NCT00770809 (CALGB 40601) and NCT00861705 (CALGB 40603)]. Each participant signed an IRB-approved, protocol-specific informed consent document in accordance with federal and institutional guidelines. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. All analyses were based on the study database frozen on 15 July 2020.

RESULTS

A total of 539 patients were included in the analysis, 41.0% (221) from CALGB 40601 and 59.0% (318) from CALGB 40603. Patients were evenly allocated to treatment regimens as they were randomly assigned, except to the paclitaxel plus lapatinib arm of CALGB 40601, which closed early[20] and thus comprises only 21.7% of patients from that study [8.9% (48/539) of total patients in this study].

Of the 539 patients, 44.7% (241) presented with cN0 disease, 44.0% (237) with cN1, and 11.3% (61) with cN2–3. Overall, 48.8% (263/539) of patients experienced breast pCR. Of patients, 76.3% (411/539) were determined to have ypN0 disease. ypN0 rates varied by treatment regimen (Table 1, $P = 0.013$), which is consistent with parent trials.[20,21] Compared with patients with residual nodal disease, ypN0 patients had smaller tumors (mean size of 4.5 vs. 5.5 cm, $P = 0.0019$), had lower clinical T stage ($P = 0.0016$), were more likely to have been cN0 at baseline ($P < 0.0001$), were more likely to have been treated with SLNB as definitive axillary surgery ($P < 0.0001$), and were more likely to have experienced breast pCR ($P < 0.0001$). Patient age, race, ethnicity, menopausal status, tumor subtype, and tumor grade did not significantly differ between ypN0 and ypN+ patients (Table 1).

Among cN0 patients at presentation, 88.7% (214/241) were ypN0: the ypN0 rate was 96.3% (104/108) for patients with a breast pCR, and 82.7% (110/133) for patients with breast RD. Among cN1 patients at presentation, 66.2% (157/237) were ypN0: the ypN0 rate was 91.7% (111/121) for patients with breast pCR and 39.7% (46/116) for patients with breast RD. Among cN2/3 patients at presentation, 65.6% (40/61) were ypN0; the ypN0 rate was 88.2% (30/34) among those with breast pCR, and 37.0% (10/27) among those with breast RD. There were no significant differences in ypN disease rates by tumor subtype, for patients with breast pCR or breast RD (Table 2).

After excluding patients with missing cT category, estimated ypN disease rates (ypN0, ypN1, or ypN2–3) for patients with breast pCR or breast RD are shown in Fig. 1. There were no differences in ypN disease rates by cT category in any tumor subtype (Supplementary Tables 1, 2). However, among these patients with known cT category and a breast pCR, there was an increasing volume of residual nodal disease based on cN status. The four patients who were cN0, experienced breast pCR, but had residual nodal disease each had only one positive lymph node. Of the nine patients who were cN1, experienced a breast pCR, but had residual nodal disease, six patients had one positive node, two had two positive nodes, and one had three positive nodes. Lastly, the three patients who were cN2/3 experienced a breast pCR, but had residual nodal disease had 5, 14, and 15 positive nodes.

On multivariable analysis, presenting clinical nodal status and breast pathologic response were significantly associated with ypN0 disease (Table 3). Compared with cN0 patients, patients with cN+ disease at presentation are over 80% less likely to have ypN0 disease, with odds ratios (OR) ranging from 0.16 to 0.18 ($P < 0.0001$). Compared with patients with breast RD, patients with breast pCR were 12 times more likely to have ypN0 disease (OR 12.55, CI 6.73–23.42, $P < 0.0001$). Treatment arm was not significantly associated with nodal pCR on multivariable analysis ($P = 0.25$).

Median follow-up for the combined cohort was 103.0 months. Overall survival was significantly worse among patients with breast RD and ypN+ disease than those with either breast or nodal pCR, and best among patients with both breast pCR/ypN0 disease among all patients ($P < 0.0001$), and among both CALGB 40601 ($P = 0.0026$) and CALGB 40603 patient cohorts ($P < 0.0001$) (Fig. 2). Median overall survival at 5 years was 59.9% (95% CI 51.3–69.9%) for all patients with breast RD and ypN+ disease, 83.0% (77.4–89.1%) for all patients with breast RD and ypN0 disease, 82.1% (65.4–100%) for all patients with breast pCR and ypN+ disease, and 90.2% (86.4–94.1%) for all patients

FIG. 3 a–c Local–regional recurrence-free survival for patients based on breast RD/breast pCR and nodal RD (ypN+)/nodal pCR (ypN0) for **a** all patients included in analysis **b** 40601 patient cohort, and **c** 40603 patient cohort
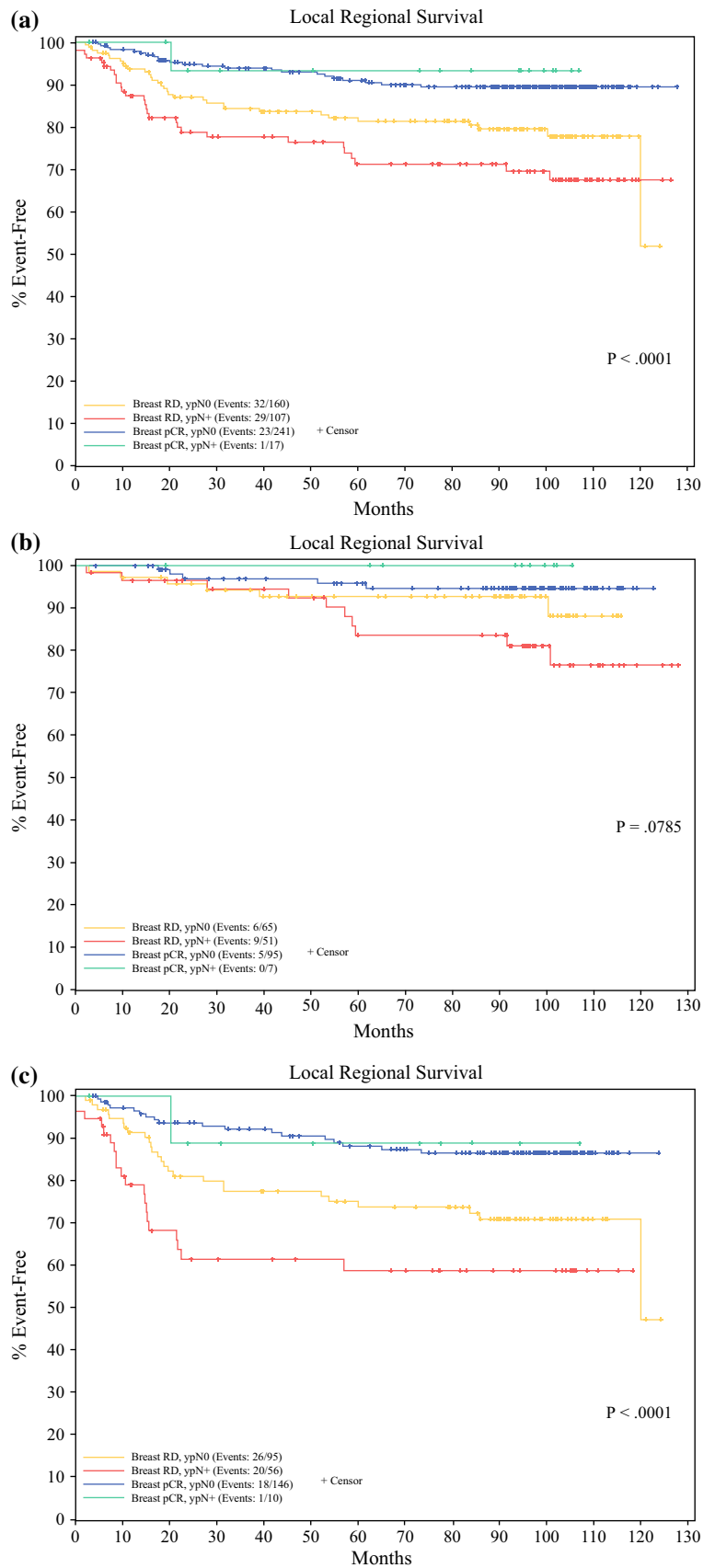
with breast pCR and ypN0 disease. This was also true of LRRFS among all patients ($P < 0.0001$) and the CALGB 40603 patient cohort ($P < 0.0001$), but not the CALGB 40601 patient cohort ($P = 0.0785$) (Fig. 3). LRRFS at 5 years was 71.2% (62.5–81.2%) for all patients with breast RD and ypN+ disease, 81.4 (75.3–87.9%) for all patients with breast RD and ypN0 disease, 93.3% (81.5–100%) for all patients with breast pCR and ypN+ disease, and 91.0% (87.3–94.9%) for all patients with breast pCR and ypN0 disease. For all patient cohorts defined by breast pathologic response and nodal status, LRRFS and OS were superior for HER2+ patients treated on CALGB 40601 compared with TNBC patients treated on CALGB 40603.

DISCUSSION

Over the last three decades, one of the major goals of breast cancer surgery research has been to determine which breast cancer patients can safely forgo ALND and avoid the associated surgical morbidity and potential for lymphedema. As a result, far fewer ALNDs are being performed in both the upfront surgery[23,24] and NAC populations.[25,26] This reduction has been more pronounced in patients choosing upfront surgery, in whom the safe omission of ALND is based on large randomized clinical trial data and predicated on proper patient selection, including negative clinical nodal status (cN0)[23] and negative axillary imaging.[27] In the NAC setting, de-escalation of axillary surgery demands careful patient selection to ensure that this will not compromise long-term oncologic outcomes. Among patients treated with NAC, those with chemotherapy-responsive disease, low to moderate axillary burden, and high likelihood of pCR are reasonable candidates to consider for future axillary surgery de-escalation trials.[28–30] The current study examines two large NAC trials, CALGB 40601 and 40603, to determine rates and variables associated with pathologic nodal disease after NAC among HER2+ and TNBC, two subtypes now conventionally treated with neoadjuvant timing of systemic therapy.

Overall, this study revealed high rates of nodal clearance among patients with HER2+ and TNBC who received NAC, consistent with prior reports.[31,32] We demonstrate that 76% of all stage II–III HER2+ and TNBC patients treated with NAC will have ypN0 disease. Among clinically node-negative patients, nearly 90% of patients have ypN0 disease. Among patients with involved axillary nodes up front, two-thirds of cN1–3 patients will have their nodal metastases eradicated after NAC. While these results might suggest that pretreatment clinical nodal status (cN0) might be sufficient to support omission of axillary surgery in

these tumor subtypes, the presence of residual nodal disease in about 10% of such patients raises concerns about such an approach.

In this analysis, we found that clinical nodal status and breast response were associated with nodal pCR, independent of phenotype, clinical tumor size, and treatment regimen on multivariable analysis. For example, of cN0 patients who experience breast pCR, only 3.7% have ypN+ disease. These findings are consistent with several prior retrospective analyses demonstrating that breast pCR is highly associated with ypN0 disease (range 97.7–100%).[33–38] Thus, if we knew there was a breast pCR, we could start to consider the omission of axillary staging, which supports efforts to noninvasively or less invasively identify breast pCR. Several prospective multicenter studies have tested the feasibility of using post-NAC percutaneous tumor biopsy to try to accurately identify patients who experienced a breast pCR. However, these trials have fallen short thus far, reporting false-negative rates between 18% and 50%.[39–42] Despite these disappointing early results, investigators have persisted in trying to improve the prediction of breast pCR and identify patients less likely to have residual nodal disease after NAC. In a study out of the Netherlands, 303 cT1–3 N0 patients underwent NAC, MRI, and axillary surgical staging. Overall, 95.5% of patients with a radiologic complete response by MRI experienced a nodal pCR, including 100% of HER2+ and 98% of TNBC patients.[43] Whether this is sufficient to justify omission of pathologic examination of the axillary nodes has not been evaluated prospectively. To this end, the Netherlands Cancer Institute is designing a trial called "Avoiding Sentinel Lymph Node Biopsy in Breast Cancer Patients After Neoadjuvant Chemotherapy (ASICS),"[44] which plans to enroll 340 patients in a prospective noninferiority single-arm registration trial to examine the use of imaging response to select patients for omission of axillary surgery. An alternative trial design is being undertaken in the European Breast Cancer Research Association of Surgical Trialists (EUBREAST)-01 clinical trial.[45] Investigators plan to enroll 267 patients with cT1–3 N0 HER2+ or TNBC to a single-arm prospective registration trial to examine the use of breast response as determined by lumpectomy after NAC to select patients for omission of axillary surgery. These are the type of forward-thinking clinical trials that could support de-escalation of axillary surgery in NAC patients.

However, in the quest for axillary surgery de-escalation, it is important to exhibit caution for some patient subgroups. Specifically, in the current study, cN2/3 patients had higher rates of ypN+ disease even among patients who experienced a breast pCR (12%). Patients with cN2 disease have been understudied thus far. The prior trials of SLNB after NAC included cN2 patients but represented very

small samples sizes—only 38 patients in ACOSOG Z1071[13] and 10 patients in SN FNAC.[15] A single-institution study of 602 cN+ patients treated with NAC and axillary surgery revealed low regional recurrence rates after SLNB alone for patients who had ypN0 disease at median follow up of 34 months, but this study only included 19 cN2 and 42 cN3 patients, 6 and 13 of whom, respectively, underwent SLNB.[46] In a retrospective study of 221 cN2 patients treated with NAC, 40.3% had ypN0 disease and 59.7% had ypN+ disease. Clinical and radiologic response, and HER2+ and TNBC constructed subtypes were associated with ypN0 disease.[47] The current standard of care is for all cN2/3 patients to undergo ALND independent of their response to NAC. Clearly, more research is needed to identify patients with advanced nodal disease who can be considered for axillary de-escalation strategies after NAC.

The current study does have some limitations. First, axillary imaging and biopsy of abnormal nodes were strongly recommended but not required; documentation of axillary imaging was variable. Thus, clinical nodal status may be inaccurate; for example, some patients who were deemed cN0 by physical examination only may have been classified as cN1 by ultrasound/percutaneous nodal sampling pre-NAC. Furthermore, we cannot compare patients who had physical examination-detected cN1 disease versus those who had imaging-detected cN1 disease, which is a current topic of debate. Another limitation is that clinical nodal status was only recorded at baseline; we do not know what the ypN0 rates might have been in cN+ patients who became ycN0, by physical examination or imaging studies, after NAC. The standard of care for management of the axilla in patients receiving NAC has changed substantially since these studies were designed. Overall, 122 (presumably cN0 by physical examination) were excluded from this analysis because they underwent SLNB or ALND before NAC, approaches which have largely been replaced by nodal sampling after NAC since the status of the nodes after NAC is felt to have greater prognostic value, especially for determining which patients should receive more intensive postoperative systemic therapy. Interestingly, the HER2+ patients in CALGB 40601 received only taxol and anti-HER2 directed therapy. Conventional therapy at the time would have been polychemotherapy, so nodal conversion may be even higher than we report. Overall though, the incidence of ypN+ disease was low, so it is difficult to draw firm conclusions from this relatively small sample size, specifically regarding further refinement of patient selection by cT category. Lastly, we only examined HER2+ and TNBC subtypes, so these findings cannot be applied to all breast cancer patients, such as those with hormone receptor-positive disease. Despite these limitations, this study reports low rates of pathologic nodal disease among HER2+ and TNBC patients who were treated with NAC, especially among patients who achieved breast pCR, in the context of two multicenter prospective randomized clinical trials.

CONCLUSIONS

Patients with chemotherapy-sensitive disease who experience breast pCR may be candidates for axillary surgery de-escalation. Overall, 89% of cN0 patients were indeed ypN0 and 66% of cN1 and cN2/3 patients had eradication of disease in the axilla. Among patients with breast pCR, only 4% of cN0 patients and 8% of cN1 patients had ypN+ disease. However, further studies are needed, including well-designed clinical trials and long-term oncologic outcomes data, before we may be able to recommend omission of axillary staging in select patients receiving NAC. Should such trials be pursued, clinical nodal status and breast pathologic complete response should be considered as selection criteria.

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