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How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study

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ABSTRACT

Background. In breast cancer patients with nodal metastases at presentation, false-negative rates lower than 10 % have been demonstrated for sentinel node biopsy (SLNB) after neoadjuvant chemotherapy (NAC) when three or more negative sentinel nodes (SLNs) are retrieved. However, the frequency with which axillary dissection (ALND) can be avoided is uncertain.

Methods. Among 534 prospectively identified consecutive patients with clinical stages 2 and 3 cancer receiving NAC from November 2013 to November 2015, all biopsy-proven node-positive (N+) cases were identified. Patients clinically node-negative after NAC were eligible for SLNB. The indications for ALND were failed mapping, fewer than three SLNs retrieved, and positive SLNs.

Results. Of 288 N+ patients, 195 completed surgery, with 132 (68 %) of these patients eligible for SLNB. The median age was 50 years. Of these patients, 73 (55 %) were estrogen receptor-positive (ER+), 21 (16 %) were ER− and human epidermal growth factor receptor-2-positive (HER2+), and 38 (29 %) were triple-negative. In four cases, SLNB was deferred intraoperatively. Among 128 SLNB attempts, three or more SLNs were retrieved in 110 cases (86 %), one or two SLNs were retrieved in 15 cases (12 %), and failed mapping occurred in three cases (2 %). In 66 cases, ALND was indicated: 54 (82 %) for positive SLNs, 9 (14 %) for fewer than three negative SLNs, and 3 (4 %) for failed mapping. Persistent disease was found in 17 % of the patients with fewer than three negative SLNs retrieved. Of the 128 SLNB cases, 62 (48 %) had SLNB alone with three or more SLNs retrieved. Among 195 N+ patients who completed surgery, nodal pathologic complete response (pCR) was achieved for 49 %, with rates ranging from 21 % for ER+/HER2− to 97 % for ER−/HER2+ cases, and was significantly more common than breast pCR in ER+/HER2− and triple-negative cases.

Conclusions. Nearly 70 % of the N+ patients were eligible for SLNB after NAC. For 48 %, ALND was avoided, supporting the role of NAC in reducing the need for ALND among patients presenting with nodal metastases.

Neoadjuvant chemotherapy (NAC) has become a valuable tool for downstaging breast cancer tumor size without increasing the risk of locoregional recurrence (LRR), thus enabling breast-conserving surgery (BCS) to be performed for many patients who previously would have required mastectomy.[1] In addition, NAC can eliminate axillary nodal metastases. Although sentinel lymph node biopsy (SLNB) is widely accepted after NAC for patients who are clinically node-negative at presentation,[2,3] the management of the axilla in patients who present with nodal metastases and appear to downstage with NAC remains controversial.

Prospective studies have evaluated the accuracy of post-NAC SLNB for patients presenting with nodal metastases

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(N+), both in a clinically node-positive population[4] and in a population with histologically confirmed metastases.[5,6] These studies have demonstrated false-negative rates lower than 10 % provided that three or more negative sentinel lymph nodes (SLNs) were retrieved.[4,6] However, the feasibility of identifying an adequate number of SLNs has been questioned because in prospective studies of upfront surgery, the median number of SLNs identified was two,[7–12] with three or more SLNs identified in a minority of patients.[7,9–11]

These findings suggest that a significant number of patients will not have three identifiable sentinel nodes after NAC. Thus, the technical feasibility of NAC as a strategy to avoid axillary lymph node dissection (ALND) for patients presenting with axillary nodal metastases is uncertain. Additionally, the rate of pathologic complete response (pCR) is well documented to vary with hormone receptor and human epidermal growth factor receptor-2 (HER2) expression, being higher in HER2-overexpressing (HER2+) and triple-negative (TN) breast cancers and less frequent in the more common hormone receptor-positive cancers.[13–16] This study sought to determine the frequency with which ALND is avoided after NAC in a cohort of biopsy-proven N+ patients and to identify patient populations likely to benefit from this approach.

METHODS

Beginning in 2013, we instituted a policy of omitting ALND for patients presenting with axillary nodal metastases who received NAC, had no palpable nodes at the conclusion of NAC, and were found to have three or more sentinel nodes that did not contain tumor. Clips were not placed in nodes at the time of histologic confirmation of metastases. The method of SLNB was standardized, and all patients undergoing SLNB had dual-tracer lymphatic mapping using technetium-99m sulfur colloid and isosulfan blue dye. Palpably abnormal nodes identified intraoperatively also were considered sentinel nodes. Patients found to have any tumor in the SLNs, including micrometastases and isolated tumor cells (ITCs), underwent ALND. Immunohistochemistry was not routinely performed. In addition, ALND was indicated for failed SLN mapping or retrieval of fewer than three SLNs, even if the identified SLNs did not contain metastases (Fig. 1).

Patients with clinical stages 2 and 3 breast cancer receiving NAC at Memorial Sloan Kettering Cancer Center (MSKCC) were entered into a prospective Health Insurance Portability and Accountability Act (HIPAA)-compliant database to allow evaluation of surgical outcomes. After institutional review board approval, consecutive patients with biopsy-proven axillary metastases at presentation, seen between November 2013 and November 2015, were identified.

Dose-dense doxorubicin, cyclophosphamide, and a taxane were given to 97 % of the patients, and 9 % also received carboplatin. All HER2-overexpressing patients received trastuzumab and pertuzumab. Those who presented with cT4 or cN2/N3 disease were considered ineligible for SLNB regardless of their response to NAC. Of the remainder, those who became node-negative after NAC, as shown by physical examination, were eligible for SLNB, whereas those who remained node-positive, as shown by examination, required ALND. Axillary ultrasound was not routinely obtained after NAC. Patients who were candidates for BCS had post-NAC magnetic resonance imaging and a mammogram. Clinical data, including the surgeon's pre- and post-NAC clinical assessment of the axilla, were entered into the database at the time of each office visit. Statistical comparisons were made using Chi square and Fisher's exact tests, and a p value lower than 0.05 was considered statistically significant.

RESULTS

From November 2013 to November 2015, 534 patients with clinical stage 2 or 3 breast cancer initiated NAC at MSKCC, and 288 (54 %) patients had biopsy-proven N+. Of these patients, 195 completed surgery by November 2015 and constituted the study population.

The median age of the patients was 50 years (range, 27–85 years). The median tumor size was 4 cm (occult, 14 cm). Of the 195 tumors, 110 (56 %) were estrogen receptor-positive (ER+), 30 (15 %) were ER−/HER2+, and 55 (28 %) were TN. The majority of the cancers (95 %) were ductal, and 80 (41 %) had lymphovascular invasion. A total of 40 patients (21 %) presented with features that rendered them ineligible for SLNB regardless of their response to NAC (Fig. 1).

Table 1 compares the clinical characteristics of the patients ineligible for SLNB and those with the potential for downstaging and avoidance of ALND ($n = 155$). The ineligible patients were older (median age, 54 vs 50 years; $p = 0.03$) and had larger tumors (median size, 5 vs 4 cm; $p = 0.01$), consistent with their more advanced disease stage, but receptor status did not differ between the groups.

The overall rate of nodal pCR was 49 % (96 of 195). Of the 155 patients potentially eligible for avoidance of ALND at presentation, 23 (15 %) remained clinically node-positive after NAC, as shown by examination, and underwent ALND, whereas SLNB was planned for the remaining 132 patients (85 %) (Fig. 1). An intraoperative clinical decision was made to proceed directly to ALND for four patients.

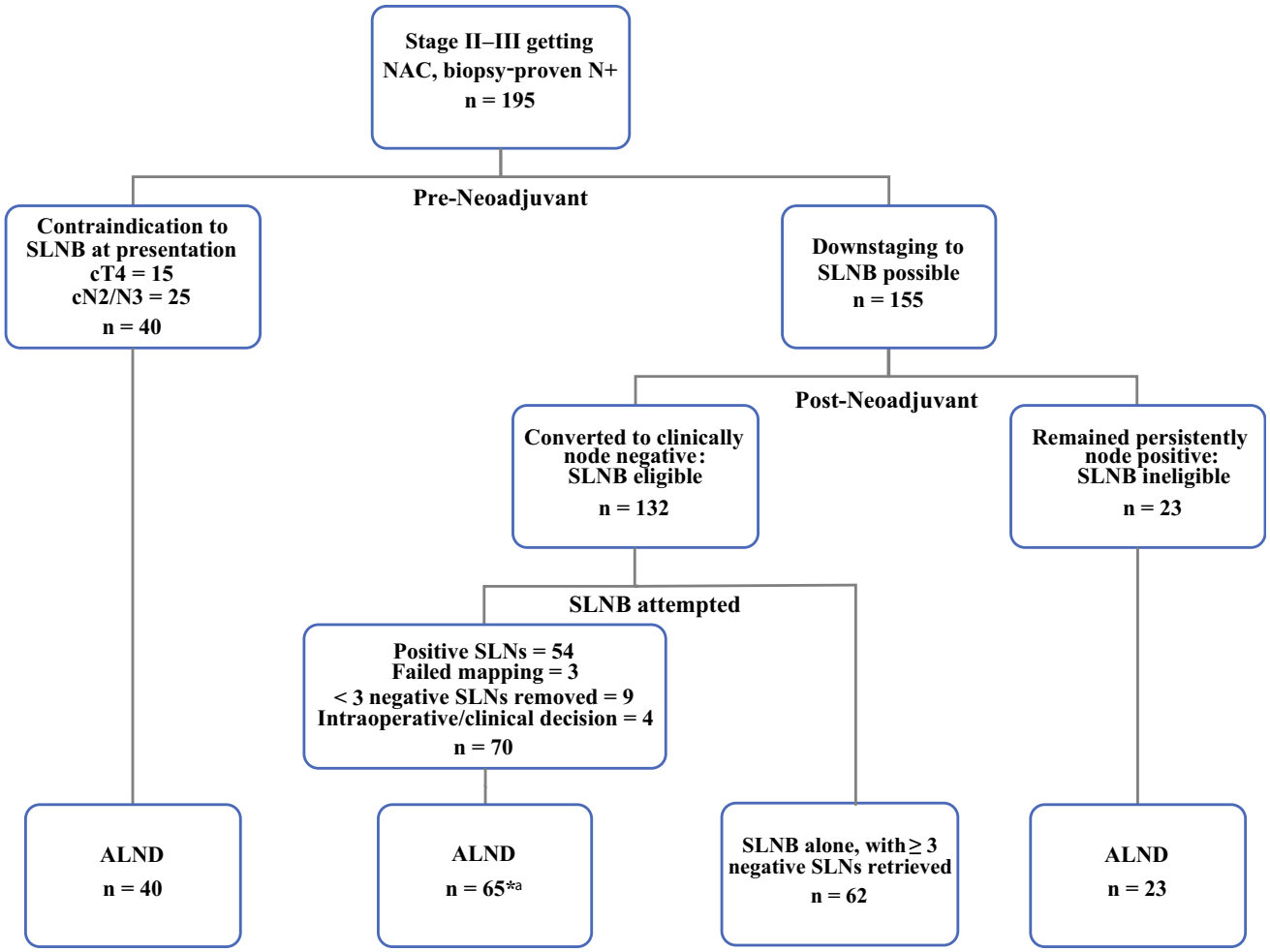

FIG. 1 Flow diagram. *NAC* neoadjuvant chemotherapy, *N+* confirmed nodal metastases at presentation, *SLNB* sentinel lymph node biopsy, *SLNs* sentinel lymph nodes, *ALND* axillary lymph node dissection. *Two patients were randomized to radiation therapy in the Alliance A011202 trial. [a]ALND was deferred for three patients with fewer than three negative SLNs, two by clinical judgment and one by patient preference

For 125 (98 %) of 128 cases in which SLNB was attempted, SLNs were successfully identified, with a median of four SLNs (range, 1–14 SLNs) identified. Three patients (2 %) failed to map despite the use of a dual-tracer technique. One or two SLNs were identified in 15 cases (12 %), and three or more SLNs were retrieved in 110 cases (86 %). Among 15 patients with fewer than three SLNs retrieved, 6 had positive frozen sections and underwent ALND. Of the remaining nine patients with one or two negative SLNs retrieved, one refused ALND, two did not have ALND per the surgeon's clinical judgment, and six underwent ALND. One of these six (17 %) patients had persistent nodal metastases, with two positive nodes. All the patients with three or more pathologically negative SLNs ($n = 62$) had SLNB alone and were spared ALND. Thus, for 62 (40 %) of 155 patients potentially eligible at presentation for avoidance of ALND by downstaging with NAC, ALND was avoided, comprising 48 % of 128 attempted SLNBs. Figure 2 summarizes the pathologic outcomes for the 132 patients who became clinically node-negative and therefore SLNB-eligible. All 63 SLNB-ineligible patients, including those ineligible for SLNB at presentation ($n = 40$) and those who remained clinically node-positive by examination after NAC ($n = 23$), underwent ALND, with a median of 19 nodes (range, 1–38 nodes) removed. A total of 23 patients were node-negative (36.5 %). Five of these node-negative patients were in the group of 23 patients thought to be clinically node-positive after NAC and represent a false-positive physical exam finding. A median of five (range, 1–30) positive nodes were identified in the 40 patients with positive nodes.

The overall rate of pCR in the nodes was 49 %. The rate did not differ significantly between the patients with pre-NAC contraindications to SLNB (45 %) and those with the potential for downstaging to avoid ALND (50 %) ($p = 0.5$). Nodal pCR did vary based on hormone receptor

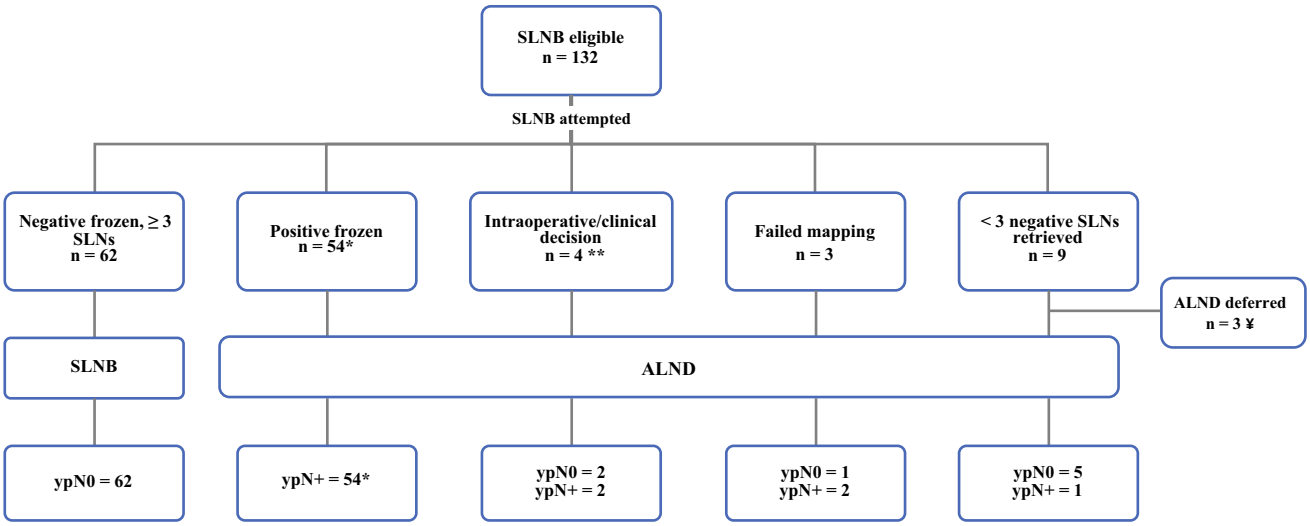

FIG. 2 Outcomes for SLNB eligible patients ($n = 132$). *SLNB* sentinel lymph node biopsy, *SLNs* sentinel lymph nodes, *ALND* axillary lymph node dissection; *ypN0* pathologically node-negative, *ypN+* pathologically node-positive. *Two patients were randomized to radiation therapy in the Alliance A011202 trial. **Intraoperative decision ($n = 3$), patient preference ($n = 1$). ¥Two by clinical judgment and one by patient preference

and HER2 status, with rates ranging from 21 % for ER+/HER2− patients to 97 % for ER−/HER2+ patients (Table 2).

Pathologic complete response, defined as the absence of invasive or intraductal carcinoma in both the breast and axillary lymph nodes, was observed in 24 % of the 195 patients in this study. As anticipated, the lowest rates of pCR were seen for ER+/HER2− patients (4 %), with the highest rates seen for ER−/HER2+ patients (57 %; $p < 0.0001$). A differential effect of NAC on pCR in the breast and nodes was observed. When the definition of pCR in the breast included the absence of intraductal carcinoma, 28 % of the patients had a breast pCR, compared with nodal pCR in 49 % ($p < 0.0001$). When pCR in the breast was considered to be the absence of invasive cancer, a definition we believe is more appropriate for this comparison because intraductal cancer is not present in lymph nodes, the rates of pCR in the breast increased to 37 %, compared with the 49 % nodal rate ($p < 0.0001$). As illustrated in Table 2, this differential effect in the breast and the nodes was observed in ER+/HER2− cancers and in TN cancers but not in cancers overexpressing HER2, regardless of ER status.

DISCUSSION

The implementation of NAC to downstage operable breast cancer has changed the landscape of surgical decision making, particularly with the availability of newer targeted therapeutic agents that have increased rates of complete response. However, the rationale for NAC in patients with operable cancer not participating in a clinical trial is sometimes unclear because many patients are already candidates for BCS at presentation or desire mastectomy. Golshan et al.,[17] evaluating surgical treatment in two Cancer and Leukemia Group B (CALGB) NAC trials involving 696 women with TN or HER2-overexpressing breast cancers, showed that although 49 % were eligible for breast conservation at presentation, only 42.5 % ultimately had the procedure.

The demonstration that retrieval of three or more negative sentinel nodes after NAC from patients presenting with node-positive breast cancer reliably stages the axilla as node-negative provides another potential rationale for NAC.[4,6]

Our prospective study demonstrated that ALND can be avoided for 40 % of patients with nodal metastases and no standard contraindications to sentinel node biopsy at presentation. The most common reason for ALND, persistent positive nodes, is amenable to improvement with further advances in targeted therapy, so the proportion of women who can avoid ALND with this approach is likely to increase in the future. It is important to recognize that achievement of nodal pCR is only one element in avoiding ALND after NAC. The American College of Surgeons Oncology Group (ACOSOG) Z1071 and Sentinel Neoadjuvant (SENTINA) trials demonstrated false-negative rates lower than 10 % only when three or more sentinel nodes were retrieved.[4,6]

In our study, only 18 patients (14 %) had fewer than three identifiable sentinel nodes, a substantially lower proportion than reported in ACOSOG Z1071 or SENTINA. Of the 592 clinically N1 patients who converted to clinically negative status with NAC (arm C) in the SENTINA

TABLE 1 Clinicopathologic characteristics of N+ patients by pre-NAC eligibility for potential post-NAC use of SLNB and avoidance of ALND

Characteristic	Pre-NAC contraindication to SLNB ($n = 40$)	Pre-NAC potential for downstaging to avoid ALND ($n = 155$)	P value
Median age: years (range)	54 (35–85)	50 (27–82)	0.03
Median tumor size: cm (range)	5.0 (occult–14.0)	4.0 (occult–12.0)	0.01[a]
Palpable nodes at presentation: *n* (%)	38 (95.0)	134 (86.5)	0.17
Receptor status: *n* (%)			
ER+ HER2−	18 (45.0)	55 (35.5)	0.4
ER+ HER2+	6 (15.0)	31 (20.0)	
ER− HER2+	8 (20.0)	22 (14.2)	
ER− HER2−	8 (20.0)	47 (30.3)	
Histology: *n* (%)			
Ductal	36 (90.0)	150 (96.8)	0.1
Lobular or mixed	4 (10.0)	4 (2.6)	
Neuroendocrine	0 (0.0)	1 (0.6)	
Lymphovascular invasion: *n* (%)	18 (45.0)	62 (40.0)	0.6
Clinical stage: *n* (%)			
2a	0 (0.0)	20 (12.9)	[b]
2b	0 (0.0)	82 (52.9)	
3a	13 (32.5)	42 (27.1)	
3b	14 (35.0)	11 (7.1)	
3c	13 (32.5)	0 (0.0)	
Nodal pCR: *n* (%)	18 (45.0)	78 (50.3)	0.5

N+ confirmed nodal metastases at presentation, *NAC* neoadjuvant chemotherapy, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *ER* estrogen receptor, *PR* progesterone receptor, *HER* human epidermal growth factor receptor, *pCR* pathologic complete response

[a] Two patients with occult breast primary, excluded from analysis

[b] No p value calculated because stage is one criterion used to ascertain potential for downstaging to avoid ALND

trial, only 34 % had three or more SLNs removed, with an overall median of two nodes removed.[4] Similarly, of the 651 biopsy-proven cN1 patients who converted to clinically node-negative status after NAC in the ACOSOG Z1071 trial, 57 % had three or more SLNs removed.[6] However, in our study, a median of four SLNs per patient were identified, and three or more SLNs were removed in 86 % of the patients. This may be attributable to the standardized use of dual-tracer mapping, surgeon experience, and our practice of defining palpably abnormal nodes as sentinel nodes. Successful mapping is known to be affected by both technique and structural composition of tracers,[18–20] and surgeon experience and comfort with the procedure has been proposed as a significant factor in the identification of sentinel nodes.[21] Despite use of the dual-tracer technique, 2 % of the patients failed mapping, identical to the failed mapping rates reported in studies of upfront surgery.[8–12]

Others have described marking cancerous nodes with a clip at the time of biopsy and removing the clipped node as a method of decreasing the false-negative rate of SLN biopsy after NAC for patients with nodal metastases at presentation.[22,23] We did not use this technique, and it is unclear from the published literature how much clipping decreases the false-negative rate when the sentinel node biopsy technique is optimized. In the study of Caudle et al.,[23] only 55 % of the patients had dual-tracer mapping, and many did not have three SLNs identified. Clips may become dislodged from nodes during the response to NAC, particularly if they are not placed in the cortex and require some form of localization to ensure their removal at surgery. Given the increased complexity of clipping nodes and the uncertainty of benefit, we chose to perform ALND if fewer than three negative SLNs were retrieved, a standard supported by the results of two prospective randomized trials.[4,6]

Identification of treatment effect in the sentinel nodes is another method of ensuring that nodes determined to be initially positive have been sampled. Treatment effect was noted in 88 % of sentinel nodes and 97 % of axillary dissection specimens in a study of 204 patients with biopsy-proven nodal metastases who had a pCR to NAC.[24]

TABLE 2 Rates of pathologic complete response in entire cohort ($n = 195$) stratified by receptor status

Receptor status	Overall pCR (ypT0 N0)		Nodal pCR (ypN0)		Breast pCR (ypT0)[a]			Breast pCR (ypT0/is)[a]		
	n	%	*n*	%	*n*	%	*p* value[b]	*n*	%	*p* value[b]
Any	47/195	24	96/195	49	53/193	28	<0.0001	71/193	37	<0.0001
ER+ HER2−	3/73	4	15/73	21	4/73	5	0.03	7/73	10	0.003
ER+ HER2+	13/37	35	26/37	70	17/37	46	0.5	22/37	59	0.3
ER− HER2+	17/30	57	29/30	97	17/30	57	0.4	21/30	70	0.3
ER− HER2−	14/55	25	26/55	47	15/53	28	0.0005	21/53	40	<0.0001

pCR pathologic complete response, *ER* estrogen receptor, *PR* progesterone receptor

[a] Two patients with occult breast primary, excluded from analysis

[b] *p* value calculations performed vs nodal pCR

The overall rate of nodal pCR among all 195 N+ patients in our study was 49 % and did not differ significantly based on eligibility for SLNB at presentation. As anticipated, the rates of nodal pCR varied based on ER and HER2 status. In the era of dual HER2 blockade with trastuzumab and pertuzumab, the rates of nodal pCR in ER−/HER2+ patients and ER+/HER2+ patients were 97 and 70 %, respectively, attesting to the benefit of the neoadjuvant approach for HER2-overexpressing patients. The reported rates of nodal pCR observed for patients with HER2-overexpressing cancers treated with trastuzumab have ranged from 19 to 74 %,[15,25] with rates above 60 % seen in the era of dual HER2 blockade.[26] The lowest rate of nodal pCR (21 %) was seen in the ER+/HER2− patients. Although lower than in other subsets, this rate still represents a substantial proportion of patients and was somewhat surprising in view of the historically low rates for overall pCR after NAC seen in ER+ patients, reported to be lower than 12 % in large pooled studies.[27,28] However, in a recent follow-up study of the original Z1071 cohort, the nodal pCR rate among the ER+/HER2− patients also was 21 %.[26] We examined the rates of breast pCR in this subset and found that the overall rate of pCR, defined as no invasive or intraductal cancer in the breast or the nodes, was only 4 %, suggesting a differential effect of NAC on disease in the nodes and the breast. When we considered pCR to be only the eradication of invasive disease in the breast, the rate of pCR in the breast increased to 10 %, still significantly lower than the 21 % rate observed in the nodes ($p = 0.003$). If confirmed in other studies, this provides a compelling rationale for the use of NAC to treat a group traditionally considered to be relatively chemotherapy resistant. A similar statistically significant differential response was noted in patients with TN cancer (47 % in nodes, 40 % in breast; $p < 0.0001$). Pathologic complete response in the breast was also found to be lower than nodal pCR noted among patients with HER2-overexpressing cancers, but this difference was not statistically significant.

In our study, 48 % of the patients eligible for SLNB who had it attempted after NAC ($n = 128$) achieved a nodal pCR with retrieval of three or more sentinel nodes at SLNB, thereby avoiding ALND. An additional five patients who underwent ALND due to persistent palpable nodes after NAC were found to be pathologically node-negative and could have undergone SLNB, emphasizing the importance of biopsy confirmation of residual tumor in patients with borderline physical findings. To our knowledge, no large trials have reported on long-term outcomes for such N+ patients, who are able to downstage with NAC and receive treatment with SLNB alone.

A small single-institution experience of 79 stages 2 and 3 patients with cN0-2 disease who received NAC and SLNB with subsequent ALND in all cases before 2003, and ALND only for positive SLNs after 2003, reported no axillary recurrences in either group during a median follow-up period of 62 months.[21] Important information regarding rates of nodal recurrence after downstaging will come from the ongoing NRG 9353 trial in which patients with biopsy-proven nodal disease who are found to be node-negative by sentinel node biopsy or axillary dissection after NAC will be randomized to receive nodal irradiation or no nodal irradiation. In the absence of information from this study, we thought that eliminating axillary dissection in patients found to be node-negative after NAC was safe based on observations that rates of local recurrence after BCS for patients who require NAC to avoid mastectomy are not elevated.[29,30] Follow-up evaluation of our study cohort will determine rates of regional failure and the safety of SLNB alone among women presenting with N+ disease who achieve nodal pCR after NAC.

CONCLUSIONS

In this prospective study, 85 % of 155 biopsy-proven N+ patients with potential for downstaging became eligible for SLNB after NAC. The morbidity of ALND was

avoided in 48 % of the cases, making a strong argument for the use of NAC with N+ patients to downstage the axilla, particularly in the HER2+ and TN tumor subtypes. For ER+/HER2− patients, a differential rate of pCR was observed, higher in the axilla than in the breast, with more than 20 % of this group achieving nodal pCR. This study provides support for the feasibility of SLNB after NAC for patients presenting with nodal metastases, with a median of four SLNs retrieved and three or more SLNs retrieved in 86 % of cases. A longer follow-up period is needed to determine the rates of regional failure in this cohort.

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