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

Anita Mamtani, MD¹, Andrea V. Barrio, MD¹, Tari A. King, MD², Kimberly J. Van Zee, MD¹, George Plitas, MD¹, Melissa Pilewskie, MD¹, Mahmoud El-Tamer, MD¹, Mary L. Gemignani, MD¹, Alexandra S. Heerdt, MD¹, Lisa M. Sclafani, MD¹, Virgilio Sacchini, MD¹, Hiram S. Cody III, MD¹, Sujata Patil, PhD³, and Monica Morrow, MD¹

¹Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

²Department of Breast Surgery, Dana Farber/Brigham and Women's Cancer Center, Boston, MA

³Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Background—In breast cancer patients with nodal metastases at presentation, false-negative rates <10% have been demonstrated for sentinel node biopsy (SLNB) after neoadjuvant chemotherapy (NAC) when ≥3 negative sentinel nodes (SLNs) are retrieved, but the frequency with which axillary dissection (ALND) can be avoided is uncertain.

Methods—Among 534 prospectively identified consecutive patients with clinical stage II–III cancer receiving NAC from 11/2013–11/2015, all biopsy-proven node-positive (N+) cases were identified. Patients who were clinically node-negative post-NAC were SLNB-eligible. ALND was indicated for failed mapping, <3 SLNs retrieved, or positive SLNs.

Results—Of 288 N+ patients, 195 completed surgery. 132/195 (68%) were SLNB-eligible. Of these, median age was 50yrs, 73(55%) were ER+, 21(16%) ER–/HER2+, 38(29%) triple negative. SLNB was deferred intraoperatively in 4 cases. Among 128 SLNB attempts, ≥3 SLNs were retrieved in 110 (86%), 1–2 SLNs in 15(12%), 3 (2%) failed mapping. ALND was indicated in 66 cases: 54(82%) for positive SLNs, 9(14%) for <3 negative SLNs, 3(4%) for failed mapping. 17% with <3 negative SLNs retrieved had persistent disease. 62/128 (48%) had SLNB alone with ≥3 SLNs retrieved. Among 195 N+ patients completing surgery, nodal pathologic complete response (pCR) was achieved in 49%, ranging from 21% in ER+/HER2– to 97% in ER–/HER2+ cases, and was significantly more common than breast pCR in ER+/HER2– and triple-negative cases.

Corresponding author: Monica Morrow, MD, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, (T) 646-888-5350, (F) 646-888-5365, morrowm@mskcc.org.

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

Keywords

nodal metastases; neoadjuvant chemotherapy; axillary lymph node dissection; sentinel lymph node biopsy

INTRODUCTION

Neoadjuvant chemotherapy (NAC) has become a valuable tool for downstaging of breast cancer tumor size without increasing the risk of locoregional recurrence (LRR), thus enabling breast-conserving surgery (BCS) in many patients who would have previously required mastectomy.¹ NAC can also eliminate axillary nodal metastases. While sentinel lymph node biopsy (SLNB) is widely accepted post-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 in patients presenting with nodal metastases (N+), both in a clinically node-positive population⁴ and in a population with histologically confirmed metastases.^{5,6} These studies demonstrated false-negative rates of < 10% provided that 3 negative sentinel lymph nodes (SLNs) were retrieved.^{4,6} However, the feasibility of identifying an adequate number of SLNs has been questioned since in prospective studies of upfront surgery, the median number of SLNs identified was 2,^{7–12} with 3 SLNs identified in a minority of patients.^{7,9–11} These findings suggest that a significant number of patients will not have 3 identifiable sentinel nodes after NAC. Thus, the technical feasibility of NAC as a strategy to avoid axillary lymph node dissection (ALND) in 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 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.^{1,13–16} We 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 in patients presenting with axillary nodal metastases who received NAC, had no palpable nodes at the conclusion of NAC, and were found to have 3 or more sentinel nodes which 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 were also 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. ALND was also

indicated for failed SLN mapping or retrieval of fewer than 3 SLNs, even if the identified SLNs did not contain metastases (Fig. 1). Patients with clinical stage II–III breast cancer receiving NAC at Memorial Sloan Kettering Cancer Center (MSKCC) were entered into a prospective, 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 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 response to NAC. Of the remainder, those who became node negative by physical examination after NAC were eligible for SLNB, while those who remained node positive by examination required ALND. Axillary ultrasound was not routinely obtained post NAC. Patients who were candidates for breast-conserving surgery had post-NAC magnetic resonance imaging and a mammogram. Clinical data, including the surgeon's pre-NAC 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 of < 0.05 was considered statistically significant.

RESULTS

From November 2013 to November 2015, 534 patients with clinical stage II–III breast cancer initiated NAC at MSKCC. Two hundred and eighty-eight (54%) patients had biopsy-proven N+. Of these, 195 completed surgery by November 2015 and constitute our study population.

Median age was 50 years (range 27–85), median tumor size was 4.0 cm (occult–14.0), 110 (56%) were ER positive, 30 (15%) were ER negative/HER2 positive, and 55 (28%) were TN. The majority (95%) of cancers were ductal, and 80 (41%) had lymphovascular invasion. Forty (21%) patients presented with features that rendered them ineligible for SLNB, regardless of response to NAC (Fig. 1). Table 1 compares the clinical characteristics of patients ineligible for SLNB and those with the potential for downstaging and avoidance of ALND ($n = 155$). Ineligible patients were older (median age 54 vs. 50 years, $p = 0.03$), and had larger tumors (median size 5.0 vs. 4.0 cm, $p = 0.01$), consistent with their more advanced disease stage, but receptor status did not differ between groups.

The overall rate of nodal pCR was 49% (96 of 195). Of the 155 patients potentially eligible for avoidance of ALND at presentation, post-NAC, 23 (15%) remained clinically node positive by examination and underwent ALND, while SLNB was planned in the remaining 132 (85%) (Fig. 1). An intraoperative clinical decision was made to proceed directly to ALND in 4 patients. SLNs were successfully identified in 125 of 128 (98%) cases in which SLNB was attempted, with a median of 4 (1–14) SLNs identified. Three patients (2%) failed to map despite the use of dual tracer technique, 1 or 2 SLNs were identified in 15 cases (12%), and 3 SLNs were retrieved in 110 (86%). Among 15 patients with < 3 SLNs retrieved, 6 had positive frozen sections and underwent ALND. Of the remaining 9 cases with 1 or 2 negative SLNs retrieved, 1 patient refused ALND, 2 patients did not have ALND

per the surgeon's clinical judgment, and 6 patients underwent ALND: 1 of 6 (17%) had persistent nodal metastases, with 2 positive nodes. All patients with 3 pathologically negative SLNs (n = 62) had SLNB alone, and were spared ALND. Thus, of 155 patients potentially eligible at presentation for avoidance of ALND by downstaging with NAC, ALND was avoided in 62 (40%), comprising 48% of 128 attempted SLNBs. Fig. 2 summarizes pathologic outcomes among the 132 patients who became clinically node negative and therefore SLNB-eligible.

All 63 SLNB-ineligible patients, encompassing those who were ineligible for SLNB at presentation (n = 40) and those who remained clinically node positive by examination post-NAC (n = 23), underwent ALND with a median of 19 (1–38) nodes removed. 23 patients were node negative (36.5%). Five of the node-negative patients were in the group of 23 patients felt to be clinically node positive post NAC and represent a false-positive physical exam finding. A median of 5 positive nodes (range 1–30) were identified in the 40 patients with positive nodes.

The overall rate of pCR in the nodes was 49% and did not differ significantly between patients with pre-NAC contraindications to SLNB and those with the potential for downstaging to avoid ALND (45% vs 50%, respectively; $p = 0.5$). Nodal pCR did vary based on hormone receptor and HER2 status, with rates ranging from 21% in ER positive/HER2 negative patients to 97% in ER negative/HER2 positive 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 in ER positive/HER2 negative patients (4%), with the highest rates seen in ER negative/HER2 positive 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 patients had a breast pCR compared to nodal pCR in 49% ($p < 0.0001$). When pCR in the breast was considered to be the absence of invasive cancer, a definition we feel is more appropriate for this comparison since intraductal cancer is not present in lymph nodes, rates of pCR in the breast increased to 37% compared to 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 positive/HER2 negative 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, as many patients are already candidates for BCS at presentation, or desire mastectomy. Golshan et al, in an evaluation of surgical treatment in 2 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.¹⁷

The demonstration in patients presenting with node-positive breast cancer that the retrieval of ≥ 3 negative sentinel nodes after NAC reliably stages the axilla as node negative provides another potential rationale for NAC.^{4,6} Our prospective study demonstrates that ALND can be avoided in 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 one which is amenable to improvement with further advances in targeted therapy, so the proportion of women able to avoid ALND with this approach is likely to increase in the future. It is important to recognize that achieving nodal pCR is only one element of avoiding ALND after NAC. The ACOSOG Z1071 and SENTINA trials demonstrated false-negative rates of $< 10\%$ only when ≥ 3 sentinel nodes were retrieved.^{4,6} In our study, only 18 patients (14%) had < 3 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 with NAC (arm C) in the SENTINA trial, only 34% had ≥ 3 SLNs removed, with an overall median of 2 nodes removed.⁴ Similarly, of the 651 biopsy-proven cN1 patients who converted to clinically node negative after NAC in the Z1071 trial, 57% had ≥ 3 SLNs removed.⁶ However, in our study, a median of 4 SLNs per patient were identified and ≥ 3 SLNs were removed in 86% of 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 dual tracer technique, 2% of patients failed mapping, identical to reported failed mapping rates 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 in patients with nodal metastases at presentation.^{22,23} We did not employ 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 al²³ only 56% of patients had dual tracer mapping, and many did not have 3 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 3 negative SLNs were retrieved, a standard supported by the results of 2 prospective randomized trials.^{4,6} Identification of treatment effect in the sentinel nodes is another method of ensuring that nodes which were 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

The overall rate of nodal pCR among all 195 N+ patients in our study was 49%, and did not differ significantly based upon eligibility for SLNB at presentation. As anticipated, rates of nodal pCR varied based on ER and HER2 status. In the era of dual HER2 blockade with trastuzumab and pertuzumab, rates of nodal pCR in ER negative/HER2 positive patients and ER positive/HER2 positive patients were 97% and 70%, respectively, attesting to the benefit of the neoadjuvant approach in HER2 overexpressing patients. Reported rates of nodal pCR

observed in patients with HER2 overexpressing cancers treated with trastuzumab have ranged from 19% to 74%,^{15,25} with rates of above 60% seen in the era of dual HER2 blockade.²⁶ The lowest rate of nodal pCR, 21%, was seen in the ER positive/HER2 negative patients. Although lower than in other subsets, this still represents a substantial proportion of patients and was somewhat surprising in view of the historically low rates of overall pCR after NAC seen in ER positive patients, reported as < 12% in large pooled studies.^{27,28} However, in a recent follow-up study of the original Z1071 cohort, the nodal pCR rate among ER positive/HER2 negative patients was also 21%.²⁶ We examined 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 and 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 increased to 10% in the breast, 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 in 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, $p < 0.0001$). pCR in the breast was also 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 patients who were eligible for, and had SLNB attempted post-NAC ($n = 128$) achieved a nodal pCR with retrieval of 3 sentinel nodes at SLNB, thereby avoiding ALND. An additional 5 patients who had 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, there are no large trials reporting long-term outcomes in such N+ patients who are able to downstage with NAC and are managed with SLNB alone. A small single-institution experience of 79 stage II–III patients with cN0-2 disease who received NAC and SLNB with subsequent ALND in all cases prior to 2003 and ALND only for positive SLNs after 2003 reported no axillary recurrences in either group at a median follow-up 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 felt that eliminating axillary dissection in patients found to be node negative after NAC was safe based upon observations that rates of local recurrence after BCS in patients who require NAC to avoid mastectomy are not elevated.^{29,30} Follow-up of our study cohort will determine rates of regional failure and determine 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 cases, making a strong argument for the use of NAC in N+ patients to downstage the axilla, particularly in the HER2+ and TN tumor subtypes. In ER positive/HER2 negative

patients, a differential rate of pCR was observed, higher in the axilla than in the breast, with over 20% of this group achieving nodal pCR. This study provides support for the feasibility of SLNB after NAC in patients presenting with nodal metastases, with a median of 4 SLNs retrieved, and 3 SLNs retrieved in 86% of cases. Longer follow-up is needed to determine rates of regional failure in this cohort.

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Synopsis

In this prospective study of 195 biopsy-proven node-positive patients, 48% of SLNB-eligible patients had ≥ 3 negative sentinel nodes after neoadjuvant chemotherapy and were spared ALND. 17% of cases with <3 negative sentinel nodes retrieved had persistent nodal disease, warranting ALND.

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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

*2 patients randomized to radiation therapy in the Alliance A011202 trial

^aALND deferred in 3 patients with < 3 negative SLNs: 2 by clinical judgment, 1 by patient preference

Fig. 2. Outcomes in 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

*2 patients randomized to radiation therapy in the Alliance A011202 trial

**Intraoperative decision (n = 3), patient preference (n = 1)

‡2 by clinical judgment, 1 by patient preference

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
Age, years, median (range)	54 (35–85)	50 (27–82)	0.03
Tumor size, cm, median (range)	5.0 (occult–14.0)	4.0 (occult–12.0)	0.01 *
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%)	**
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	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; pCR, pathologic complete response

* n = 2 with occult breast primary, excluded from analysis

** No p-value calculated because stage is one criterion used to ascertain potential for downstaging to avoid ALND

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)*			Breast pCR (ypT0/is)*		
	N	%	N	%	N	%	p**	N	%	p**
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

* n = 2 with occult breast primary, excluded from analysis

** p-value calculations performed versus nodal pCR