

# Omission of Axillary Dissection Following Nodal Downstaging With Neoadjuvant Chemotherapy

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## + Supplemental content

**IMPORTANCE** Data on oncological outcomes after omission of axillary lymph node dissection (ALND) in patients with breast cancer that downstages from node positive to negative with neoadjuvant chemotherapy are sparse. Additionally, the best axillary surgical staging technique in this scenario is unknown.

**OBJECTIVE** To investigate oncological outcomes after sentinel lymph node biopsy (SLNB) with dual-tracer mapping or targeted axillary dissection (TAD), which combines SLNB with localization and retrieval of the clipped lymph node.

**DESIGN, SETTING, AND PARTICIPANTS** In this multicenter retrospective cohort study that was conducted at 25 centers in 11 countries, 1144 patients with consecutive stage II to III biopsy-proven node-positive breast cancer were included between April 2013 and December 2020. The cumulative incidence rates of axillary, locoregional, and any invasive (locoregional or distant) recurrence were determined by competing risk analysis.

**EXPOSURE** Omission of ALND after SLNB or TAD.

**MAIN OUTCOMES AND MEASURES** The primary end points were the 3-year and 5-year rates of any axillary recurrence. Secondary end points included locoregional recurrence, any invasive (locoregional and distant) recurrence, and the number of lymph nodes removed.

**RESULTS** A total of 1144 patients (median [IQR] age, 50 [41-59] years; 78 [6.8%] Asian, 105 [9.2%] Black, 102 [8.9%] Hispanic, and 816 [71.0%] White individuals; 666 SLNB [58.2%] and 478 TAD [41.8%]) were included. A total of 1060 patients (93%) had N1 disease, 619 (54%) had *ERBB2* (formerly *HER2*)-positive illness, and 758 (66%) had a breast pathologic complete response. TAD patients were more likely to receive nodal radiation therapy (85% vs 78%;  $P = .01$ ). The clipped node was successfully retrieved in 97% of TAD cases and 86% of SLNB cases (without localization). The mean (SD) number of sentinel lymph nodes retrieved was 3 (2) vs 4 (2) ( $P < .001$ ), and the mean (SD) number of total lymph nodes removed was 3.95 (1.97) vs 4.44 (2.04) ( $P < .001$ ) in the TAD and SLNB groups, respectively. The 5-year rates of any axillary, locoregional, and any invasive recurrence in the entire cohort were 1.0% (95% CI, 0.49%-2.0%), 2.7% (95% CI, 1.6%-4.1%), and 10% (95% CI, 8.3%-13%), respectively. The 3-year cumulative incidence of axillary recurrence did not differ between TAD and SLNB (0.5% vs 0.8%;  $P = .55$ ).

**CONCLUSIONS AND RELEVANCE** The results of this cohort study showed that axillary recurrence was rare in this setting and was not significantly lower after TAD vs SLNB. These results support omission of ALND in this population.

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Neoadjuvant chemotherapy (NAC) allows for de-escalation of axillary surgery by eradicating nodal disease in more than 40% of patients with node-positive breast cancer (BC).<sup>1</sup> The false-negative rate (FNR) of sentinel lymph node biopsy (SLNB) in this setting exceeds 10%, but optimization with dual-tracer mapping and removal of 3 or more sentinel lymph nodes lowers the FNR to less than 10%.<sup>2</sup> Single-center studies have demonstrated low rates of axillary recurrence (AR) after SLNB alone,<sup>3,4</sup> but there is concern about generalizability.

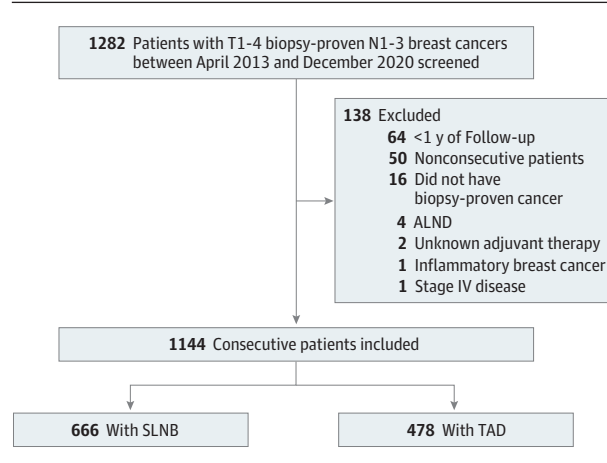
The combination of SLNB with imaging-guided localization and selective retrieval of the sampled clipped lymph node, termed *targeted axillary dissection* (TAD), is associated with a further reduced FNR,<sup>5,6</sup> but whether this reduction decreases the rate of AR is unknown. In this article, we evaluate oncologic outcomes after omission of ALND in a large clinical cohort of patients with node-positive BC whose cancer converted to ypNO with treatment with NAC and compare outcomes after SLNB with dual-tracer mapping vs TAD.

## Methods

### Study Population

This cohort study was a retrospective analysis of prospectively maintained databases from 25 cancer centers in 11 countries (eMethods 1 in Supplement 1). Institutional review board approval was obtained at each US site, Enhancing the Quality and Transparency Of Health Research (EQUATOR) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed, and informed consent was waived because deidentified data were used. At non-US sites, informed consent was obtained according to ethical approval that was either study specific or based on general consent, according to site-specific and country-specific standards. A data use agreement was executed between Memorial Sloan Kettering Cancer Center and the other North American institutions and between Memorial Sloan Kettering

Figure. Flow Diagram



ALND indicates axillary lymph node dissection; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

## Key Points

**Question** What is the rate of axillary recurrence after omission of axillary lymph node dissection (ALND) in patients with node-positive breast cancer that downstages to ypNO with neoadjuvant chemotherapy, and does this rate differ based on surgical technique?

**Findings** This multicenter retrospective cohort study of 1144 patients with node-positive breast cancer found that axillary recurrence after omission of ALND was rare (1.0% [95% CI, 0.49%-2.0%] at 5 years) with no difference by type of surgery (sentinel lymph node biopsy with dual-tracer mapping vs targeted axillary dissection).

**Meaning** The findings of this study support omission of ALND in patients with ypNO after axillary staging with sentinel lymph node biopsy or targeted axillary dissection.

Cancer Center and the University Hospital of Basel, Switzerland, where data from all non-US sites were collected.

Patients with clinical T1 to 4 biopsy-proven N1 to 3 BC treated with NAC between April 2013 and December 2020 who achieved nodal pathological complete response (pCR) as determined by SLNB or TAD only were selected. Nonconsecutive patients, those with T4d or stage IV disease and with follow-up of less than 1 year (to allow for complete collection of adjuvant therapy data) were excluded.

### Surgical Technique

SLNB was performed with dual-tracer mapping (isosulfan or methylene blue and technetium-99m). TAD consisted of SLNB with single or dual mapping together with imaging-guided localization of the biopsy-proven positive clipped lymph node. For patients undergoing SLNB alone, removal of 3 sentinel lymph nodes or more was recommended. Surgery/RT details specific to each center are provided in eMethods 2 in Supplement 1.

### End Points and Statistical Analysis

The primary end points were the 3-year and 5-year rates of any AR, defined as either isolated AR or AR combined with in-breast or distant recurrence. Secondary end points included locoregional recurrence (LRR), any invasive recurrence (locoregional or distant), and the number of lymph nodes removed. Cumulative incidence was assessed using a competing risk analysis (eMethods 3 in Supplement 1). Three-year cumulative incidence rates were compared between TAD and SLNB using the Gray test.  $P < .05$  was considered statistically significant. Statistical analysis was performed using R, version 4.2 (R Core Development Team).

## Results

### Patient and Treatment Characteristics

We collected data from 1282 patients, 1144 of whom met inclusion criteria (Figure). A total of 666 (58.2%) underwent SLNB, and 478 (41.8%) underwent TAD. The Table lists clinicopathological characteristics as stratified by surgical group.

Table. Clinicopathological Features of the Study Cohort as Stratified by Surgical Group

Characteristic	No. (%)			P value <sup>a</sup>
	Overall (N = 1144)	SLNB (n = 666)	TAD (n = 478)	
Age, median (IQR), y	50 (41-59)	49 (40-59)	50 (42-60)	.34
Race and ethnicity <sup>b</sup>				
Asian	78 (6.8)	63 (9.5)	15 (3.1)	<.001
Black	105 (9.2)	67 (10)	38 (7.9)	
Hispanic	102 (8.9)	74 (11)	28 (5.9)	
White	816 (71.0)	432 (65)	384 (80)	
Other/unknown	43 (3.8)	30 (4.5)	13 (2.7)	
Clinical T stage at presentation				
1	229 (20)	123 (18)	106 (22)	.14
2	655 (57)	379 (57)	276 (58)	
3	218 (19)	135 (20)	83 (17)	
4	33 (2.9)	21 (3.2)	12 (2.5)	
X	9 (0.8)	8 (1.2)	1 (0.2)	
Clinical N stage at presentation				
1	1060 (93)	624 (94)	436 (91)	.20
2	52 (4.5)	27 (4.1)	25 (5.2)	
3	32 (2.8)	15 (2.3)	17 (3.6)	
Tumor subtype				
HR <sup>+</sup> /ERBB2 <sup>-</sup>	263 (23)	163 (24)	100 (21)	.11
ERBB2 <sup>+</sup>	619 (54)	364 (55)	255 (53)	
HR <sup>-</sup> /ERBB2 <sup>-</sup>	262 (23)	139 (21)	123 (26)	
Histology				
Ductal	1067 (94)	625 (95)	442 (93)	.16
Lobular or mixed	45 (4.0)	23 (3.5)	22 (4.6)	
Other	20 (1.8)	8 (1.2)	12 (2.5)	
Unknown	12	10	2	
Tumor differentiation				
Well	16 (1.5)	5 (0.8)	11 (2.4)	<.001
Moderately	295 (27)	143 (23)	152 (33)	
Poorly	777 (71)	480 (76)	297 (65)	
Unknown	56	38	18	
LVI				
Present	145 (14)	94 (15)	51 (12)	.10
Unknown	88	47	41	
Type of breast surgery				
BCS	615 (54)	352 (53)	263 (55)	.33
Mastectomy	522 (46)	308 (46)	214 (45)	
No breast surgery <sup>c</sup>	7 (0.6)	6 (0.9)	1 (0.2)	
Breast pCR (ypT0/is)				
Yes	758 (66)	434 (65)	324 (68)	.14
No	377 (33)	224 (34)	153 (32)	
Occult primary tumor	9 (0.8)	8 (1.2)	1 (0.2)	
NAC regimen ERBB2 <sup>-</sup> (n = 525)				
AC-T	376 (72)	239 (79)	137 (61)	<.001
AC-T + carbo	102 (19)	50 (17)	52 (23)	
Anthracycline-free regimen <sup>d</sup>	7 (1.3)	5 (1.7)	2 (0.9)	
Other <sup>e</sup>	40 (7.6)	8 (2.6)	32 (14)	
NAC regimen ERBB2 <sup>+</sup> (n = 619)				

(continued)

Table. Clinicopathological Features of the Study Cohort as Stratified by Surgical Group (continued)

Characteristic	No. (%)			P value <sup>a</sup>
	Overall (N = 1144)	SLNB (n = 666)	TAD (n = 478)	
AC-TTr	97 (16)	63 (17)	34 (13)	<.001
AC-THP	291 (47)	235 (65)	56 (22)	
TCTrP	170 (27)	36 (10)	134 (53)	
Other	61 (9.9)	30 (8.0)	31 (12.2)	
No. of sentinel lymph nodes removed, mean (SD)	4 (2)	4 (2)	3 (2)	<.001
Total No. of lymph nodes removed, mean (SD)	4.2 (2.03)	4.4 (2.04)	3.9 (1.97)	<.001
Breast RT (n = 622)	608 (98)	349 (98)	259 (98)	.95
Chest wall RT (n = 522)	416 (80)	244 (79)	172 (80)	.80
Nodal RT	928 (81)	522 (78)	406 (85)	.01
Adjuvant chemotherapy <sup>f</sup>	71 (6.2)	30 (4.5)	41 (8.6)	.01
Adjuvant endocrine therapy (n = 645)	584 (91)	336 (90)	248 (92)	.63
Adjuvant anti- <i>ERBB2</i> therapy (n = 619)	601 (97)	350 (96)	251 (98)	.99

Abbreviations: AC-T, doxorubicin hydrochloride and cyclophosphamide, followed by paclitaxel; BCS, breast-conserving surgery; carbo, carboplatin; HR, hormone receptor; LVI, lymphovascular invasion; NAC, neoadjuvant chemotherapy; P, pertuzumab; pCR, pathologic complete response; RT, radiotherapy; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; TC, docetaxel and carboplatin; Tr, trastuzumab.

<sup>a</sup> Results are from the Wilcoxon rank-sum test for continuous variables and Fisher exact test or the  $\chi^2$  test of independence for categorical variables.

<sup>b</sup> Race and ethnicity was self-reported.

<sup>c</sup> Occult carcinomas.

<sup>d</sup> Includes cyclophosphamide, methotrexate, and fluorouracil and taxotere and cyclophosphamide.

<sup>e</sup> Includes any immunotherapy-based regimens and any experimental regimen.

<sup>f</sup> Capecitabine was the most common type of adjuvant chemotherapy (72%).

### Surgical Procedure

SLNB was performed with dual-tracer mapping (isosulfan or methylene blue and technetium-99m). In 150 of 666 (23%) of these cases, the biopsied node was clipped at diagnosis, and in 129 of 150 patients (86%), the clip was removed with the SLNB without localization. In the TAD group, dual-tracer mapping was used for 378 of 478 patients (79%), and the clipped node was retrieved for 466 of 478 (97%). Localization was performed with radioactive seed (343 of 478 [71.8%]) or wire (115 of 478 [24%]) for most patients. The mean (SD) number of sentinel lymph nodes and total lymph nodes removed was lower with TAD vs SLNB (3.00 [2.00] vs 4.00 [2.00];  $P < .001$ ; and 3.95 [1.97] vs 4.44 [2.04];  $P < .001$ , respectively).

### Oncological Outcomes After Omission of Axillary Dissection

Median (IQR) follow-up of the entire cohort was 3.5 years (2.1-5.2) and was longer in the SLNB group (4.2 years [IQR, 2.5-5.7]) compared with the TAD cohort (2.7 years [IQR, 1.6-4.3];  $P < .001$ ). The 3-year and 5-year rates of any AR in the entire cohort were 0.65% (95% CI, 0.29%-1.30%) and 1.0% (95% CI, 0.49%-2.00%), respectively (eFigure in Supplement 1). At 3 years, there was no significant difference in the rate of AR between TAD and SLNB (0.5% vs 0.8%;  $P = .55$ ) (eFigure in Supplement 1). Four isolated ARs occurred during the study period, 2 in each group (eTable in Supplement 1). The 3-year and 5-year rates of LRR and any invasive recurrence in the entire cohort were 1.5% (95% CI, 0.83%-2.40%) and 2.7% (95% CI, 1.6%-4.1%) and 7.5% (95% CI, 5.9%-9.3%) and 10% (95% CI,

8.3%-13.0%), respectively (eFigure in Supplement 1). At 3 years, LRR or invasive recurrence rates did not differ between TAD and SLNB (0.8% vs 1.9%;  $P = .19$ ; and 7.3% vs 7.8%;  $P = .60$ , respectively) (eFigure in Supplement 1).

### Discussion

In this cohort study of 1144 patients with node-positive BC who achieved nodal pCR with NAC as determined by SLNB or TAD, the AR rate was very low (0.65% and 1% at 3 and 5 years, respectively). These results support prior single-center observations of low AR rates in this population.<sup>3,4,7,8</sup>

All patients in the SLNB group had an optimized procedure with dual-tracer mapping and a mean of 4 sentinel lymph nodes removed. At 3.5 years of median follow-up, the AR rate was not significantly different between TAD and SLNB (0.5% vs 0.8%;  $P = .55$ ). This is not unexpected, as both procedures have a low FNR (4% [0%-9%] with removal of  $\geq 3$  sentinel lymph nodes; 2%-4.1% with TAD).<sup>5,6,9</sup>

Forty-seven of 666 patients (7%) in the SLNB group had fewer than 3 sentinel lymph nodes removed, and only 1 of them experienced an AR, suggesting that, as in the upfront surgery setting, FNR does not translate to AR in most cases. However, given that residual disease affects adjuvant therapy, efforts should be made to decrease the FNR.

Compared with SLNB, TAD allowed for removal of 1 fewer lymph node. Ongoing prospective studies will provide in-

sight into whether this difference is associated with lymphedema rates and arm function.<sup>10-12</sup> Meanwhile, surgeons should be reassured that SLNB with dual-tracer mapping and TAD have similar outcomes.

While the study data support ALND omission in ypNO patients, our findings are inapplicable to patients with residual nodal disease, for whom the likelihood of additional non-sentinel node disease exceeds 60%.<sup>13</sup> Two randomized trials (ALLIANCE A011202 and OPBC-03/TAXIS) are evaluating whether axillary RT is noninferior to ALND in this population.<sup>14,15</sup> Until results become available, ALND should remain standard of care in patients with residual nodal disease.

### Strengths and Limitations

To our knowledge, this was the first study to compare oncological outcomes after SLNB and TAD. Other strengths included its multicenter, international design and inclusion of patients who were treated in large academic institutions as well

as small breast units. This study had several limitations; these included the retrospective design and differences in median follow-up, which limited the comparison to 3 years. However, AR is an early event, and we expect these results to be confirmed with longer follow-up. Because of the low number of ARs, we were unable to adjust for baseline and treatment differences between groups and the random effect caused by the treatment site. Also, due to the low number of ARs, the study may have been underpowered to detect small outcome differences between groups.

### Conclusions

The results of this cohort study suggest that early AR after omission of ALND in patients whose cancer converts to ypNO is a very rare event and was not significantly lower after TAD vs SLNB. Although longer follow-up is needed, these results support omission of ALND in patients with nodal pCR after NAC.

#### ARTICLE INFORMATION

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