JAMA Surgery | Original Investigation

De-Escalation of Nodal Surgery in Clinically Node-Positive Breast Cancer

Neslihan Cabıoğlu, MD, PhD; Havva Belma Koçer, MD; Hasan Karanlık, MD; Mehmet Ali Gülçelik, MD; Abdullah Iğci, MD; Mahmut Müslümanoğlu, MD; Cihan Uras, MD; Barış Mantoğlu, MD; Didem Can Trabulus, MD; Giray Akgül, MD; Mustafa Tükenmez, MD; Kazım Şenol, MD; Enver Özkurt, MD; Ebru Şen, MD; Güldeniz Karadeniz Çakmak, MD; Süleyman Bademler, MD; Selman Emiroğlu, MD; Nilüfer Yıldırım, MD; Halil Kara, MD; Ahmet Dağ, MD; Ece Dilege, MD; Ayşe Altınok, MD; Gül Başaran, MD; Ecenur Varol, MD; Ümit Uğurlu, MD; Yasemin Bölükbaşı, MD; Yeliz Emine Ersoy, MD; Baha Zengel, MD; Niyazi Karaman, MD; Serdar Özbaş, MD; Leyla Zer, MD; Halime Gül Kılıç, MD; Orhan Ağcaoğlu, MD; Gürhan Sakman, MD; Zafer Utkan, MD; Aykut Soyder, MD; Alper Akcan, MD; Sefa Ergün, MD; Ravza Yılmaz, MD; Adnan Aydıner, MD; Atilla Soran, MD; Kamuran Ibiş, MD; Vahit Özmen, MD

IMPORTANCE Increasing evidence supports the oncologic safety of de-escalating axillary surgery for patients with breast cancer after neoadjuvant chemotherapy (NAC).

OBJECTIVE To evaluate the oncologic outcomes of de-escalating axillary surgery among patients with clinically node (cN)–positive breast cancer and patients whose disease became cN negative after NAC (ycN negative).

DESIGN, SETTING, AND PARTICIPANTS In the NEOSENTITURK MF-1803 prospective cohort registry trial, patients from 37 centers with cT1-4N1-3M0 disease treated with sentinel lymph node biopsy (SLNB) or targeted axillary dissection (TAD) alone or with ypN-negative or ypN-positive disease after NAC were recruited between February 15, 2019, and January 1, 2023, and evaluated.

EXPOSURE Treatment with SLNB or TAD after NAC.

MAIN OUTCOMES AND MEASURES The primary aim of the study was axillary, locoregional, or distant recurrence rates; disease-free survival; and disease-specific survival. Number of axillary lymph nodes removed was also evaluated.

RESULTS A total of 976 patients (median age, 46 years [range, 21-80 years]) with cT1-4N1-3M0 disease underwent SLNB (n = 620) or TAD alone (n = 356). Most of the cohort had a mapping procedure with blue dye alone (645 [66.1%]) with (n = 177) or without (n = 468) TAD. Overall, no difference was found between patients treated with TAD and patients treated with SLNB in the median number of total lymph nodes removed (TAD, 4 [3-6] vs SLNB, 4 [3-6]; $P = .09$). Among patients with ypN-positive disease, those who underwent TAD were more likely to have a lower median lymph node ratio (TAD, 0.28 [IQR, 0.20-0.40] vs SLNB, 0.33 [IQR, 0.20-0.50]; $P = .03$). At a median follow-up of 39 months (IQR, 29-48 months), no significant difference was found in the rates of ipsilateral axillary recurrence (0.3% [1 of 356] vs 0.3% [2 of 620]; $P \geq .99$) or locoregional recurrence (0.6% [2 of 356] vs 1.1% [7 of 620]; $P = .50$) between the TAD and SLNB groups, with an overall locoregional recurrence rate of 0.9% (9 of 976). The initial clinical tumor stage, pathologic complete response, and use of blue dye alone as a mapping procedure were not associated with the outcome. Even though patients with TAD demonstrated an increased disease-free survival rate compared with the SLNB group, this difference did not reach statistical significance (94.9% vs 92.6%; $P = .07$). Factors associated with decreased 5-year disease-specific survival were cN2-3 axillary stage (cN1, 98.7% vs cN2-3, 96.8%; $P = .03$) and nonluminal type tumor pathologic characteristics (luminal, 98.9% vs nonluminal, 96.9%; $P = .007$).

CONCLUSIONS AND RELEVANCE The short-term results suggest very low rates of axillary and locoregional recurrence in a select group of patients with cN-negative disease after NAC treated with TAD alone or SLNB alone followed by regional nodal irradiation regardless of the SLNB technique or nodal pathology. Whether TAD might provide a clear survival advantage compared with SLNB remains to be proven in studies with longer follow-up.

JAMA Surg. 2025;160(3):257-266. doi:10.1001/jamasurg.2024.5913
Published online January 2, 2025.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Neslihan Cabıoğlu, MD, PhD, Breast Unit, Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Çapa, Şehremini, Turgut Özal Millet Cd, 34093 Fatih/İstanbul, Türkiye (neslicab@yahoo.com).

Long-term results of prospective studies have demonstrated comparable outcomes regarding locoregional recurrence rates for patients with clinically node (cN)-negative breast cancer with limited nodal involvement undergoing sentinel lymph node biopsy (SLNB) with or without axillary lymph node dissection (ALND), followed by adjuvant systemic therapy and radiotherapy.[1-6] Decreasing the extent of axillary surgery to limit morbidity in these studies has led to evaluations of SLNB among women who had metastasis to regional lymph nodes (LNs) and responded favorably to neoadjuvant chemotherapy (NAC). However, the use of SLNB alone remains controversial because of the false-negative rate, which could lead to inaccurate staging and misinterpretations guiding further treatment decisions. The false-negative rate decreases to less than 10% when applying modalities such as the identification of 3 or more sentinel LNs (SLNs) with or without dual-mapping techniques and the removal of the marked LN.[7-16]

Among women with cN-positive breast cancer, treatment with more conservative approaches after NAC, including SLNB alone, targeted LN (TLN) biopsy, or a combined procedure of SLNB with TLN biopsy, are being researched in clinical practice. Targeted LN biopsy involves the removal of a marked LN, whereas the combination of SLNB and TLN biopsy involves targeted axillary dissection (TAD). Increasing evidence supports the oncologic safety of de-escalating axillary surgery for selected patients with good response to NAC.[17-24]

However, there are limited data comparing the advantages and oncologic safety associated with TAD vs SLNB.[25] The NEOSENTITURK MF18-03 study was launched as a prospective multicenter study by the Turkish Breast Diseases Federation and supported by the Breast Health Working Group International.[26] The objective of the present study was to compare the advantages and oncologic safety associated with TAD vs SLNB among patients with cN-positive disease in a subgroup analysis of the ongoing NEOSENTITURK MF-1803 study, whose cancer became cN negative after NAC.

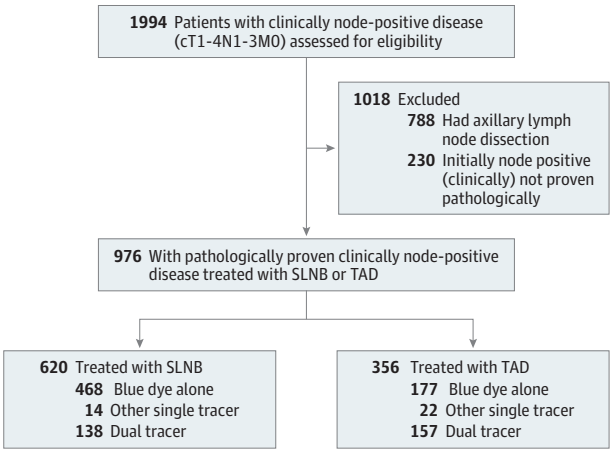
Key Points

Question Is omission of axillary dissection oncologically safe among patients with initially clinically node-positive breast cancer after neoadjuvant chemotherapy?

Findings This multicenter cohort study included 976 patients with cT1-4N1-3M0 disease treated with sentinel lymph node biopsy (SLNB; n = 620) or targeted axillary dissection (TAD; n = 356). At a median follow-up of 39 months, pathologic complete response, use of blue dye alone for mapping, or TAD was not associated with the outcome, with an overall locoregional recurrence rate of 0.9%.

Meaning This study suggests low rates of locoregional recurrence in a select group of patients with clinically node-positive disease who became clinically node negative after neoadjuvant chemotherapy treated with TAD or SLNB alone followed by nodal radiation regardless of the SLNB technique or nodal pathology.

Figure. Study Cohort



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

Methods

Patients with cN-positive disease who were treated with either SLNB alone or TAD alone without ALND after NAC were included in the present subgroup analysis from the prospective, nonrandomized, multicenter NEOSENTITURK MF-1803 cohort registry study (NCT04250129). Patients were recruited from 37 centers (36 in Turkey and 1 in Azerbaijan) between February 15, 2019, and January 1, 2023. Most centers were academic (n = 29), 5 were public, and 3 were private. Ethical approval was obtained from the Istanbul University, Istanbul Faculty of Medicine, and written informed consent was obtained from all patients. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Population

Patients included in the study presented with cT1-4N1-3M0 disease that became cN negative after NAC and underwent SLNB or TAD without ALND. Patients were excluded from the NEOSENTITURK MF-1803 study if they had pregnancy-associated breast cancer, inflammatory breast cancer, distant metastasis, secondary breast cancer, or other malignant neoplasms; no successful SLNB mapping; and no irradiation. Patients were also excluded from the analysis if they underwent axillary dissection, removal of more than 9 LNs, or had no biopsy-proven axillary LN metastases (**Figure**). All patients treated with TAD (n = 356) underwent titanium clip placement in the most suspicious index biopsy–verified metastatic LN under axillary ultrasonography before starting NAC.

Treatment

Patients were treated with NAC according to institutional guidelines. Most patients in the cohort had a taxane-containing chemotherapy regimen with or without anthracyclines. Some patients (40 [4.1%]) also received carboplatin in addition to taxanes. Patients with *ERBB2* (formerly *HER2* or *HER2/neu*)-

positive disease received anti-*ERBB2*-directed therapies, including trastuzumab either alone or in combination with pertuzumab, in addition to the taxane-containing regimen. Some patients (21 [2.2%]) received anthracycline-containing regimens. As adjuvant treatment after surgery, patients with estrogen receptor and/or progesterone receptor positivity were treated with hormone therapy according to international guidelines. Furthermore, patients with *ERBB2* positivity had trastuzumab therapy for up to 1 year, whereas patients with residual disease received trastuzumab emtansine. Similarly, patients with residual triple-negative breast cancer were treated with capecitabine as an adjuvant.

The clinical response to NAC was evaluated using both physical examination and imaging. Axillary LNs were routinely assessed by ultrasonographic examination, in addition to magnetic resonance imaging, in some cases after NAC. All patients with a complete clinical axillary response to chemotherapy underwent SLNB with a single tracer (681 of 976 [69.8%]; blue dye: 645 of 681 [94.7%]; or radioisotope: 36 of 681 [5.3%]) or dual tracer as a combined procedure with blue dye and radioisotope injection (295 of 976 [30.2%]). Using a dual tracer and removing at least 3 LNs were suggested in the protocol, even though the removal of fewer than 3 LNs was not an exclusion criterion. Because some centers do not have nuclear scintigraphy facilities to perform lymphoscintigraphy or due to some restrictions at the nuclear scintigraphy centers to perform lymphoscintigraphy on the day of surgery, most patients had LNs that were mapped with a single tracer as blue dye.

Patients treated with TAD underwent SLNB along with the removal of the marked TLN. The TLN was removed as the SLN in 54 patients without the need for imaging guidance, as detected in the specimen graph (38 of 356 [10.7%]) or preoperative single-photon emission computed tomography-computed tomography lymphoscintigraphy (16 of 356 [4.5%]).[27,28] Of the remaining patients, the following techniques were used to remove the marked LN: wire (68 of 356 [19.1%]), radio-guided occult lesion localization (143 of 356 [40.2%]), carbon tattooing (32 of 356 [9.0%]), and intraoperative imaging-guided surgery (59 of 356 [16.6%]) using ultrasonography (27 of 356 [7.6%]) or a scope (32 of 356 [9.0%]). The choice of the SLNB mapping technique and whether to proceed with TAD was at the discretion of the surgeon or based on the institutional facilities.

The ypN positivity was defined by the presence of isolated tumor cells, micrometastases, or macrometastases detected by hematoxylin-eosin staining or cytokeratin immunohistochemistry. Pathologic complete response (pCR) was defined as the absence of invasive cancer in the breast and axillary LNs, whereas the presence of ductal carcinoma in situ was also considered a pCR.[29]

All patients underwent regional nodal irradiation. Adjuvant radiotherapy was delivered at 45 to 50 Gy in 25 fractions to the whole breast for patients treated with breast-conserving surgery or to the chest wall for patients with mastectomy and axillary levels I to III, including the supraclavicular LN regions with or without the internal mammary LN region. Boost radiotherapy for the tumor bed was delivered at 10 to 16 Gy in 5 to 8 fractions to patients with breast-conserving surgery.

Study End Points

The primary aim of the study was to evaluate axillary, locoregional, or distant recurrence rates; disease-free survival (DFS); and disease-specific survival (DSS) among patients treated with TAD vs SLNB. The secondary aim was to evaluate the outcome in other subgroups according to the mapping techniques and ypN status. The numbers of SLNs and total LNs, including non-SLNs, were also evaluated, and the lymph node ratio (LNR) was determined by dividing the number of pathologically positive LNs by the total number of LNs removed.

Statistical Analysis

Statistical analyses were performed using the software SPSS, version 26 (IBM Corp). GraphPad Prism, version 8 (GraphPad Software) was used to generate the survival curves. Categorical variables were assessed using the Fisher exact test or the continuity correction test or the Pearson χ^2 test in 2-tailed univariate analyses to test the differences between the SLNB and TAD groups. The differences between nonparametric continuous variables were assessed using the Mann-Whitney test. Axillary and regional recurrences were considered as recurrences in the ipsilateral axilla and regional LNs (contralateral axilla and infraclavicular, supraclavicular, or internal mammary region), including the axilla. Locoregional recurrence was defined as recurrence detected in the axillary nodal, infraclavicular, supraclavicular, or internal mammary region, in addition to breast or chest wall recurrences after breast-conserving surgery or mastectomy.

Disease-free survival was calculated for local and distant metastases, whereas DSS was estimated for breast cancer-related mortality. Survival analyses were performed using Kaplan-Meier tests. Factors associated with outcomes were determined using the log-rank test. All statistical tests were 2-sided, with statistical significance set at $P \leq .05$.

Results

Between February 2019 and January 2023, 976 patients (median age, 46 years [range, 21-80 years]) with cT1-4N1-3M0 disease from 37 centers underwent SLNB alone (n = 620) or TAD alone (n = 356). Demographic and clinicopathologic features of the patients are presented in **Table 1**. Patients who underwent TAD (median age, 46 years; range, 24-76 years) and patients who underwent SLNB (median age, 46 years; range, 21-80 years) had similar age distributions. Patients who underwent TAD were more likely than patients who underwent SLNB to have cT1-2 disease (91.9% [327 of 356] vs 78.7% [488 of 620]; $P < .001$), cN1 disease (85.7% [305 of 356] vs 78.5% [487 of 620]; $P = .02$), histologic grade I or II (63.2% [146 of 231] vs 54.4% [147 of 270]; $P = .047$), and breast-conserving surgery (66.0% [235 of 356] vs 51.3% [318 of 620]; $P < .001$). Most patients in both the TAD and SLNB groups had fewer than 3 metastatic suspicious axillary LNs (TAD, 64.6% [203 of 314] vs SLNB, 62.0% [362 of 584]; $P = .47$) at the initial clinical presentation

Table 1. Clinical and Pathologic Characteristics of Patients Treated With TAD or SLNB

Characteristic	Patients, No. (%)			*P* value
	Overall (N = 976)	TAD (n = 356)	SLNB (n = 620)	
Median follow-up for patients (IQR), mo	39 (29-48)	39 (28-47)	39 (30-48)	NA
Mean follow-up for patients (SD), mo	38.9 (11.9)	38.3 (11.5)	39.3 (12.1)	NA
Median age (range), y	46 (21-80)	46 (24-76)	46 (21-80)	.84[a]
Clinical T stage				
cT1	134 (13.7)	58 (16.3)	76 (12.3)	<.001[b]
cT2	681 (69.8)	269 (75.6)	412 (66.5)	
cT3	105 (10.8)	22 (6.2)	83 (13.4)	
cT4	56 (5.7)	7 (2.0)	49 (7.8)	
Clinical N stage				
cN1	792 (81.1)	305 (85.7)	487 (78.5)	.02[b]
cN2	153 (15.7)	42 (11.8)	111 (17.9)	
cN3	31 (3.2)	9 (2.5)	22 (3.5)	
No. of metastatic or suspicious axillary lymph nodes in imaging (n = 898)[c]				
<3	565 (62.9)	203 (64.6)	362 (62.0)	.47
≥3	333 (37.1)	111 (35.4)	222 (38.0)	
Type of breast surgery				
Breast-conserving therapy	553 (56.7)	235 (66.0)	318 (51.3)	<.001[b]
Mastectomy	423 (43.3)	121 (34.0)	302 (48.7)	
Sentinel lymph node methodology				
Blue dye (n = 645) or radioisotope (n = 36)	681 (69.8)	199 (55.9)	482 (77.7)	<.001[b]
Combined (blue dye and radioisotope)	295 (30.2)	157 (44.1)	138 (22.3)	
Histopathologic findings				
Invasive ductal	881 (90.3)	319 (89.6)	562 (90.6)	.19[b]
Invasive lobular	29 (3.0)	7 (2.0)	22 (3.5)	
Mixed invasive ductal and lobular	30 (3.1)	15 (4.2)	15 (2.4)	
Other	36 (3.7)	15 (4.2)	21 (3.4)	
Grade (n = 501)[d]				
I or II	293 (58.5)	146 (63.2)	147 (54.4)	.047[b]
III	208 (41.5)	85 (36.8)	123 (45.6)	
Presence of LVI (n = 513)[e]				
Yes	179 (34.9)	57 (30.2)	122 (37.7)	.09[b]
No	334 (65.1)	132 (69.8)	202 (62.3)	
Tumor subtype (IHC)				
Luminal *ERBB2* negative	430 (44.1)	165 (46.3)	265 (42.7)	.42[b]
Luminal *ERBB2* positive	244 (25.0)	84 (23.6)	160 (25.8)	
Nonluminal *ERBB2* positive	153 (15.7)	49 (13.8)	104 (16.8)	
Triple negative	149 (15.3)	58 (16.3)	91 (14.7)	
Tumor subtype (IHC)				
Luminal	674 (69.1)	249 (69.9)	425 (68.5)	.65[b]
Nonluminal	302 (30.9)	107 (30.1)	195 (31.5)	
Ki-67 expression (n = 965)[f]				
Negative (<20%)	150 (15.5)	62 (17.5)	88 (14.4)	.20[b]
Positive (≥20%)	815 (84.5)	292 (82.5)	523 (85.6)	
pCR (breast and axilla)				
Yes	391 (40.1)	151 (42.4)	240 (38.7)	.26[b]
No	585 (59.9)	205 (57.6)	380 (61.3)	
Type of metastasis (n = 341)[g]				
Macrometastasis	178 (52.2)	59 (53.2)	119 (51.7)	.96[b]
Micrometastasis	105 (30.8)	34 (30.6)	71 (30.9)	
Isolated tumor cell	58 (17.0)	18 (16.2)	40 (17.4)	
Presence of extracapsular invasion				
Yes	52 (15.2)	16 (14.4)	36 (15.7)	.77[b]
No	289 (84.8)	95 (85.6)	194 (84.3)	

Abbreviations: *EBBR2*, formerly *HER2* or *HER2/neu*; IHC, immunohistochemistry; LVI, lymphovascular invasion; NA, not applicable; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

[a] Mann-Whitney test.

[b] χ^2 Test (Pearson or Fisher exact test).

[c] Evaluation by imaging included evaluation by ultrasonography, magnetic resonance imaging, or positron emission tomography–computed tomography for 898 patients overall (314 patients with TAD and 584 patients with SLNB).

[d] Data for histologic grade were available for 501 patients treated with TAD (n = 231) or SLNB alone (n = 270 [missing data were excluded]).

[e] Data for LVI were available for 513 patients treated with TAD (n = 189) or SLNB alone (n = 324 [missing data were excluded]).

[f] Data for Ki-67 expression were available for 965 patients treated with TAD (n = 354) or SLNB alone (n = 611 [missing data were excluded]).

[g] Data were available for patients with ypN-positive disease treated with TAD (n = 111) or SLNB alone (n = 230 [patients with ypN-negative disease were excluded]).

Table 2. Locoregional and Systemic Recurrences in Patients With cT1-4N1-3MO Disease Treated With TAD or SLNB

Recurrence type[a]	Recurrence rate, % (No.)				Recurrence rate, % (No.)		
	Overall (N = 976)	TAD (n = 356)	SLNB (n = 620)	*P* value	ypN-negative disease (n = 635)	ypN-positive disease (n = 341)	*P* value
Locoregional recurrence	0.9 (9)	0.6 (2)	1.1 (7)	.50[b]	0.8 (5)	1.2 (4)	.73[b]
Regional recurrence	0.5 (5)	0.3 (1)	0.6 (4)	.66[b]	0.5 (3)	0.6 (2)	≥.99[b]
Ipsilateral axillary recurrence	0.3 (3)	0.3 (1)	0.3 (2)	≥.99[b]	0.3 (2)	0.3 (1)	≥.99[b]
Systemic recurrence	4.9 (48)	3.4 (12)	5.8 (36)	.09[c]	4.4 (28)	5.9 (20)	.32[c]
Mortality	1.2 (12)	0.6 (2)	1.6 (10)	.23[b]	1.3 (8)	1.2 (4)	≥.99[b]

Abbreviations: SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

[a] Regional: ipsilateral and contralateral axillary, infraclavicular and supraclavicular, and mammaria interna. Locoregional: local (breast or chest wall) with regional recurrences.

[b] Fisher exact test.

[c] Pearson χ^2 test.

for those with a preoperative imaging indicating the suspicious LN numbers (n = 898). No significant differences were found in pathologic characteristics, including tumor type, pCR, nonluminal disease characteristics such as *ERBB2* positivity or triple-negative disease, Ki-67 scores, lymphovascular invasion, type of axillary metastasis (macrometastasis vs micrometastasis vs isolated tumor cell), or presence of extracapsular extension. The tumor subtype according to the immunohistochemistry was well balanced between the 2 groups. Therefore, the chemotherapy regimens were similar in the 2 groups.

Most of the cohort had a single-agent SLNB technique, including blue dye alone for 645 patients (66.1%) or radioisotopes for 36 patients (3.7%). Patients who underwent TAD were more likely than patients who underwent SLNB to have a combined mapping technique (44.1% [157 of 356] vs 22.3% [138 of 620]; *P* < .001).

Overall, the median number of SLNs removed was 3 (IQR, 2-4), and the median number of total LNs removed was 4 (IQR, 3-6) nodes. No difference was found between patients treated with TAD and patients treated with SLNB in the median number of total LNs removed (TAD, 4 [3-6] vs SLNB, 4 [3-6]; *P* = .09). In subgroup analysis, however, among those with ypN-negative disease, patients who underwent TAD were found to have more LNs removed than those who underwent SLNB (TAD: median, 4 [IQR, 3-5] vs SLNB: median, 4 [IQR, 2-5]; *P* = .03; eTable in Supplement 1). Of those with ypN-positive disease, patients who underwent TAD were more likely to have SLNs than those who underwent SLNB (TAD: median, 4 [IQR, 3-5] vs SLNB: median, 3 [IQR, 2-5]; *P* = .06), which may have resulted in a decreased median LNR compared with those who underwent SLNB (TAD, 0.28 [IQR, 0.20-0.40] vs 0.33 [IQR, 0.20-0.50]; *P* = .03). Use of a dual tracer for patients who underwent TAD (n = 334) was associated with a significant increase in the number of total LNs retrieved compared with those who underwent a mapping technique using blue dye alone (blue dye [n = 177]: median, 4 [IQR, 3-5] vs dual tracer [n = 157]: median, 5 [IQR, 3-6]; *P* < .001). Among patients with ypN-positive disease, patients who underwent TAD were more likely than those who underwent SLNB to have a lower median lymph node ratio (TAD, 0.28 [IQR, 0.20-0.40] vs SLNB, 0.33 [IQR, 0.20-0.50]; *P* = .03).

The mean (SD) follow-up time was 38.9 (11.9) months. At a median follow-up of 39 months (IQR, 29-48 months), the ipsilateral axillary recurrence rate was 0.3% (3 of 976), the regional recurrence rate was 0.5% (5 of 976), the locoregional recurrence rate was 0.9% (9 of 976), and the systemic recurrence rate was 4.9% (48 of 976) (**Table 2**). No significant difference was found in the rates of ipsilateral axillary recurrence (0.3% [1 of 356] vs 0.3% [2 of 620]; *P* ≥ .99) or locoregional recurrence (0.6% [2 of 356] vs 1.1% [7 of 620]; *P* = .50) between the TAD and SLNB groups. Similarly, no significant difference was detected in the rates of ipsilateral axillary recurrence (0.3% [2 of 635] vs 0.3% [1 of 341]; *P* ≥ .99) or locoregional recurrence (0.8% [5 of 635] vs 1.2% [4 of 341]; *P* = .73) between the ypN-negative and ypN-positive groups (Table 2). No significant difference was found in ipsilateral axillary, regional, locoregional, and systemic recurrence rates between cohorts treated with TAD alone vs SLNB alone or between patients with ypN-negative disease and patients with ypN-positive disease. Of patients treated with SLNB alone (n=620), no significant difference could be found in the ipsilateral axillary recurrence rate (blue dye, 0.4% [2 of 468] vs dual tracer, 0% [0 of 138]; *P* = .44) and the locoregional recurrence rate (blue dye, 1.3% [6 of 468] vs dual tracer, 0.7% [1 of 138]; *P* = .19) between patients with a mapping procedure with blue dye alone and patients with a mapping procedure with a dual tracer. All locoregional recurrences (n = 9) were detected in the first 3 years after surgery; most (77.8% [7 of 9]) had nonluminal aggressive tumor biology, and 44.4% of the patients (4 of 9) had synchronous systemic metastases.

The 5-year DFS rate was 93.5%, and the 5-year DSS rate was 98.3%. Patients treated with TAD had a lower systemic recurrence rate (3.4% vs 5.8%; *P* = .09) and had a higher 5-year DFS rate than patients treated with SLNB (94.9% vs 92.6%; *P* = .07), but these differences did not reach statistical significance (Table 2 and **Table 3**; eFigure in Supplement 1). Patients treated with SLNB alone had an increased hazard ratio (HR) compared with those treated with TAD in terms of DFS (HR, 1.76; 95% CI, 0.94-3.29) and DSS (HR, 1.76; 95% CI, 0.94-3.29). No significant difference was detected in the 5-year DFS and DSS rates with respect to the initial clinical T stage (cT1-2 vs cT3-4), SLNB identification method (blue dye alone vs dual tracer), axillary pathologic findings (ypN negative vs ypN positive), LNR

Table 3. Outcome in Patients With cT1-4N1-3M0 Disease Treated With TAD or SLNB After Neoadjuvant Chemotherapy

Outcome	No.	5-y DFS, %	*P* value	5-y DSS, %	*P* value
Overall	NA	93.5	NA	98.3	NA
Clinical T stage					
cT1-2	815	93.7	.23	98.2	.99
cT3-4	161	91.9		98.7	
Clinical N stage					
cN1	792	94.4	.11	98.7	.03
cN2-3	184	88.3		96.8	
Axillary surgery					
TAD	356	94.9	.07	99.3	.16
SLNB	620	92.6		97.8	
ypN-negative disease					
TAD	245	94.1	.28	99.0	.44
SLNB	390	93.8		98.2	
ypN-positive disease					
TAD	111	96.1	.15	100	.16
SLNB	230	90.6		97.1	
LNR, %					
<0.33	150	93.4	.76	98.6	.79
≥0.33	191	91.7		97.8	
LNR, <0.33%					
TAD	57	94.6	.76	100	.27
SLNB	93	92.8		97.8	
LNR, ≥0.33%					
TAD	54	97.9	.10	100	.36
SLNB	137	89.3		96.9	
SLNB method (overall)					
Blue dye alone	645	93.2	.87[a]	98.5	.46
Dual tracer	295	94.1		98.2	
Radioisotope alone	36	97.1		96.9	
SLNB method (overall)					
Single tracer	681	93.4	.89	98.4	.72
Dual tracer	295	94.1		98.2	
SLNB method: single tracer (overall)	681				
SLNB	482	92.3	.03	97.9	.29
TAD	199	95.7		99.5	
SLNB method: dual tracer (overall)	295				
SLNB	138	93.6	.86	97.4	.28
TAD	157	94.5		98.0	
SLNB group (overall)	620				
Blue dye alone	468	92.2	.62[a]	97.9	.75
Dual tracer	138	93.6		97.4	
Radioisotope alone	14	100		100	
TAD group (overall)	356				
Blue dye alone	177	96.0	.12[a]	100	.23
Dual tracer	157	94.5		98.9	
Radioisotope alone	22	95.5		95.0	
Axillary pathologic finding					
ypN-negative disease	635	94.1	.32	98.5	.86
ypN-positive disease	341	92.4		98.1	
pCR (breast and axilla)					
Yes	391	95.0	.24	98.1	.45
No	585	92.5		98.5	
Tumor subtype					
Luminal	674	94.3	.27	98.9	.007
Nonluminal	302	91.3		96.9	

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; LNR, lymph node ratio; NA, not available; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

[a] Significance among patients with a mapping technique using blue dye alone vs dual tracer in the SLNB group.

(<0.33 vs ≥0.33), and breast pCR (Table 3; eFigure in Supplement 1). Significant factors associated with decreased 5-year DSS were cN2-3 axillary stage (cN1, 98.7% vs cN2-3, 96.8%; $P = .03$) and nonluminal type tumor pathologic characteristics (luminal, 98.9% vs nonluminal, 96.9%; $P = .007$; eFigure in Supplement 1).

Discussion

In recent years, there has been debate about whether there is any benefit associated with clipping the most suspicious metastatic index LN before NAC to perform TAD with image-guided axillary surgery in comparison with a standard SLNB procedure.[30,31] Despite reports demonstrating low false-negative rates with TAD, none of the clinical studies have confirmed the clinical significance of a lower false-negative rate, which could potentially decrease the locoregional recurrence rates, as long as axillary radiotherapy is provided.[19,23,25]

We have shown here that there are acceptable outcomes in both cohorts of patients treated with SLNB or TAD whose disease became cN negative after NAC (ycN negative), with a median follow-up greater than 3 years. Our findings from the short-term follow-up suggest axillary and locoregional recurrences at very low rates in a selected group of patients with ycN-negative disease with SLNB or TAD without ALND, regardless of the SLN pathologic findings, including both ypN-negative and ypN-positive cohorts. Consistent with these results, previous studies have demonstrated very low axillary and locoregional recurrence rates in patients with cN-positive and ypN-negative disease.[18,19] The previous MF-18-02 study was a retrospective multicenter registry study that included 303 patients (including patients with ypN-negative and ypN-positive disease) treated with SLNB alone without any axillary recurrence.[18] In that study, the 5-year DSS rate at the median follow-up of 3 years was 95.3%, and the 5-year DFS rate was 86.7%. In concordance with the previous study, we have shown here that factors, including an advanced clinical axillary stage of cN2-3 and nonluminal tumor pathologic findings, were significantly associated with decreased DSS. However, no difference was found between the patients with ypN-negative disease and those with ypN-positive disease, which might have been due to selection bias. The Alliance (11202) trial examined patients with ypN-positive disease who were randomized after NAC to receive ALND or axillary radiotherapy in a much larger cohort of patients.[32] However, the Alliance (11202) trial recruited only patients with cT3N1 disease, which distinguished it from the present cohort with cT4N1-3 disease. The results from the Alliance (11202) trial are expected to be released in 2029.

In the present study, similar to the previous MF18-02 study,[18] most of the cohort (645 [66.1%]) had a mapping procedure with blue dye alone, and a median number of 3 SLNs were retrieved. In the subgroup analysis of patients treated with SLNB alone, we could not find any difference in outcome regarding recurrence rates and survival between patients whose SLNB technique used blue dye alone and those whose SLNB technique used a dual tracer. To our knowledge, this is the first and largest study that compared the outcomes of patients with a mapping procedure of blue dye and dual tracer. Of those treated with SLNB alone, we could not find any difference in the SLN and total LN numbers removed and in outcome regarding recurrence rates and survival between patients with a SLNB technique that used blue dye alone and patients with a SLNB technique that used a dual tracer. Cavalcante et al[33] recently reported the use of blue dye alone for SLNB in 100 patients with initially cN-positive breast cancer whose disease became cN negative after NAC. The identification rate was 96%, and the detection rate of 3 or more SLNs was 78%, with a median of 3.1 LNs (range, 1-6). In a median of 3 years of follow-up, 5-year DFS was 85.9% and overall survival was 96.3%, with no axillary recurrence.

The OPBC-04/EUBREAST-06/OMA study that has been recently published has a similar design to the present trial.[25] Both studies were multicenter and included academic, public, and private hospitals. However, the OPBC-04/EUBREAST-06/OMA study was retrospective and intercontinental and included patients with ypN-negative disease, whereas the present study was nonrandomized, prospective, mostly national, and included patients with ypN-negative disease and patients with ypN-positive disease. Sentinel lymph node biopsy was performed with dual-tracer mapping in the cohort with SLNB in the OPBC-04/EUBREAST-06/OMA trial, whereas dual-tracer mapping was not mandatory for patients in the TAD group. However, SLNB was performed mostly with blue dye without any compromise in outcome in the present study (SLNB group, 77.7%; TAD group, 55.9%), whereas patients with TAD were more likely to undergo SLNB with a dual tracer. The median numbers of SLNs and total LNs were 3 and 4 nodes in both studies, respectively. Finally, the OPBC-04/EUBREAST-06/OMA study included patients without regional nodal irradiation (19%), whereas all patients in the NEOSENTITURK MF18-03 study received regional nodal irradiation. Very low 3-year axillary and locoregional recurrences with similar outcomes were detected in the TAD and SLNB groups in both studies.

Limitations

This study has some limitations. The major limitation is its prospective nonrandomized nature and relatively short median follow-up of 39 months. Furthermore, patients in the SLNB group were more likely to have cT3-4 and cN2-3 disease presenting with more advanced stages than those in the TAD group. However, no difference could be found in the number of suspicious axillary LNs (<3) in imaging between these 2 groups at initial diagnosis. Furthermore, the LNR was notably decreased in patients with ypN-positive disease with TAD compared with the LNR in the SLNB group. Increased DFS and decreased locoregional recurrence rates were observed in the TAD group, which might have been due to these factors; however, these differences did not reach statistical significance because there were very few locoregional recurrences in both groups. Because these are initial early findings, more convincing data could be generated with increasing patient accrual and follow-up time in the future.

Conclusions

Our initial findings from a cohort in the short-term follow-up of the NEOSENTITURK MF18-03 study suggest that axillary and locoregional recurrences were observed at very low rates in patients with initially node-positive disease whose cancer was downstaged to cN-negative disease and who were treated either with SLNB or TAD alone without ALND. This occurred regardless of the mapping procedure using blue dye alone or the presence of residual disease in the axilla after NAC. The present cohort had a median retrieval of 3 or more SLNs, and all patients underwent regional nodal irradiation. Targeted axillary dissection may lead to unnecessary LN removal in patients who are more likely to achieve an axillary pCR due to triple-negative or *ERBB2*-positive breast cancer or breast clinical complete response, which may be significant in arm and shoulder dysfunction. However, TAD might be more advantageous in patients with axillary residual disease, resulting in a decreased LNR. The long-term results of the Alliance (11202) trial, the present study, and other prospective trials, including the NSABP B-51/RTOG 1304 and AXSANA trials, could lead to a more international consensus regarding the de-escalation of axillary surgery or radiotherapy after NAC.[34-36]

ARTICLE INFORMATION

Accepted for Publication: October 17, 2024.

Published Online: January 2, 2025. doi:10.1001/jamasurg.2024.5913

Author Affiliations: Breast Unit, Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye (Cabıoğlu, Iğci, Müslümanoğlu, Tükenmez, Emiroğlu, Gül Kılıç, Özmen); Department of General Surgery, Sakarya University Faculty of Medicine, Sakarya, Türkiye (Koçer, Mantoğlu); Division of Surgical Oncology, Institute of Oncology, Istanbul University, Istanbul, Türkiye (Karanlık, Bademler); Division of Surgical Oncology, Health Sciences University Gulhane Faculty of Medicine, Ankara, Türkiye (Gülçelik, Akgül); Department of General Surgery, American Hospital, Istanbul, Türkiye (Iğci, Yıldırım); Department of General Surgery, School of Medicine, Acıbadem Mehmet Ali Aydınlar University, Istanbul, Türkiye (Uras, Kara); Department of General Surgery, Health Sciences University, Istanbul Samatya Training and Research Hospital, Istanbul, Türkiye (Trabulus); Now with Department of General Surgery, Istanbul Bahcesehir University, Istanbul, Türkiye (Trabulus); Department of General Surgery, Uludag University Faculty of Medicine, Bursa, Türkiye (Şenol); Department of General Surgery, Faculty of Medicine, Istanbul Demiroğlu Bilim University, Istanbul, Türkiye (Özkurt); Department of General Surgery, University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye (Şen); Department of General Surgery, School of Medicine, Zonguldak Bulent Ecevit University, Zonguldak, Türkiye (Karadeniz Çakmak); Department of General Surgery, Faculty of Medicine, Mersin University, Mersin, Türkiye (Dağ); Department of General Surgery, Koç University School of Medicine, Istanbul, Türkiye (Dilege, Ağcaoğlu); Department of Radiation Oncology, Altınbas University, Bahçelievler Medical Park Hospital, Istanbul, Türkiye (Altınok); Department of Medical Oncology, School of Medicine, Acıbadem Mehmet Ali Aydınlar University, Altunizade Acıbadem Hospital, Istanbul, Türkiye (Başaran); Department of General Surgery, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye (Varol, Utkan); Department of General Surgery, Marmara University School of Medicine, Istanbul, Türkiye (Uğurlu); Department of Radiation Oncology, School of Medicine, Koç University, Istanbul, Türkiye (Bölükbaşı); Department of General Surgery, Bezmialem Vakif University Faculty of Medicine, Istanbul, Türkiye (Ersoy); Department of General Surgery, Izmir Bozyaka Training and Research Hospital, Izmir, Türkiye (Zengel); Now with Department of General Surgery, School of Medicine, Izmir University of Economics, Medical Point Hospital, Istanbul, Türkiye (Zengel); Department of Surgical Oncology, University of Health Sciences, Ankara Oncology Training and Research Hospital, Ankara, Türkiye (Karaman); Breast and Endocrine Surgeon, Private Practice, Ankara, Türkiye (Özbaş); Department of Surgery, Ataşehir Florence Nightingale Hospital, Istanbul, Türkiye (Zer); Department of General Surgery, School of Medicine, Çukurova University, Adana, Türkiye (Sakman); Department of General Surgery, School of Medicine, Acıbadem Mehmet Ali Aydınlar University, Altunizade Acıbadem Hospital, Istanbul, Türkiye (Soyder); Department of General Surgery, Erciyes University School of Medicine, Kayseri, Türkiye (Akcan); Department of General Surgery, Cerrahpaşa Faculty of Medicine, Istanbul University–Cerrahpaşa, Istanbul, Türkiye (Ergün); Department of Radiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye (Yılmaz); Department of Medical Oncology, Institute of Oncology, Istanbul University, Istanbul, Türkiye (Aydıner); Department of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Soran); Department of Radiation Oncology, Institute of Oncology, Istanbul University, Istanbul, Türkiye (Ibiş); Breast Center, Istanbul Florence Nightingale Hospital, Istanbul, Türkiye (Özmen).

Author Contributions: Dr Cabıoğlu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Cabıoğlu, Karanlık, Gülçelik, Igci, Akgül, Tükenmez, Özkurt, Şen, Karadeniz Çakmak, Bademler, Emiroğlu, Dilege, Varol, Uğurlu, Bölükbaşı, Ersoy, Zer, Sakman, Utkan, Soyder, Akcan, Yılmaz, Aydıner, İbiş, Özmen.
Acquisition, analysis, or interpretation of data: Cabıoğlu, Koçer, Müslümanoğlu, Uras, Mantoğlu, Trabulus, Şenol, Özkurt, Karadeniz Çakmak, Bademler, Emiroğlu, Yıldırım, Kara, Dağ, Dilege, Altınok, Başaran, Varol, Zengel, Karaman, Özbaş, Zer, Gül Kılıç, Ağcaoğlu, Sakman, Soyder, Akcan, Ergün, Yılmaz, Soran.
Drafting of the manuscript: Cabıoğlu, Koçer, Trabulus, Akgül, Şenol, Özkurt, Karadeniz Çakmak, Bademler, Emiroğlu, Yıldırım, Dilege, Altınok, Varol, Uğurlu, Ersoy, Zengel, Karaman, Özbaş, Gül Kılıç, Ağcaoğlu, Sakman, Soyder, Akcan, Ergün, Yılmaz, Soran.
Critical review of the manuscript for important intellectual content: Cabıoğlu, Karanlık, Gülçelik, Igci, Müslümanoğlu, Uras, Mantoğlu, Tükenmez, Özkurt, Şen, Karadeniz Çakmak, Bademler, Emiroğlu, Kara, Dağ, Başaran, Varol, Bölükbaşı, Zer, Utkan, Soyder, Akcan, Aydıner, Soran, İbiş, Özmen.
Statistical analysis: Cabıoğlu, Özkurt, Emiroğlu, Varol, Soyder, Akcan.
Obtained funding: Emiroğlu, Varol, Gül Kılıç, Soyder, Akcan.
Administrative, technical, or material support: Cabıoğlu, Koçer, Karanlık, Gülçelik, Trabulus, Akgül, Tükenmez, Şenol, Şen, Karadeniz Çakmak, Bademler, Emiroğlu, Dağ, Dilege, Altınok, Başaran, Varol, Ersoy, Zengel, Karaman, Özbaş, Zer, Gül Kılıç, Ağcaoğlu, Sakman, Soyder, Akcan, Ergün, Yılmaz, İbiş.
Supervision: Cabıoğlu, Karanlık, Müslümanoğlu, Mantoğlu, Özkurt, Karadeniz Çakmak, Bademler, Emiroğlu, Dilege, Varol, Bölükbaşı, Gül Kılıç, Sakman, Utkan, Akcan, Soran, Özmen.

Conflict of Interest Disclosures: None reported.

Meeting Presentation: This study was presented at the 46th Annual Breast Cancer Symposium; December 5, 2023; San Antonio, Texas.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We would like to thank A. Bozdoğan, MSc (Istanbul Breast Society) for statistical analyses; B. Çitgez, MD (Department of General Surgery, Seyrantepe Hamidiye Etfal Hospital, Health Sciences University, Istanbul, Türkiye), B. Yiğit, MD (Department of General Surgery, Seyrantepe Hamidiye Etfal Hospital, Health Sciences University, Istanbul, Türkiye), E. Baran, MD (Department of General Surgery, Seyrantepe Hamidiye Etfal Hospital, Health Sciences University, Istanbul, Türkiye), I. Al Jorani, MD (Department of General Surgery, Uludağ University Faculty of Medicine, Bursa, Türkiye), S. Ilgün, MD (Breast Center, Istanbul Florence Nightingale Hospital, Istanbul, Türkiye), B. Ozçınar, MD, PhD (Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye), A. Çelik, MD (Department of General Surgery, Bağcılar Training and Research Hospital, Health Sciences University, Istanbul, Türkiye), G. Ercan, MD (Department of General Surgery, Bağcılar Training and Research Hospital, Health Sciences University, Istanbul, Türkiye), F. Çalıkoğlu, MD (Department of General Surgery, Bağcılar Training and Research Hospital, Health Sciences University, Istanbul, Türkiye), B. Celik, MD (Koç University School of Medicine, Department of General Surgery, Istanbul, Türkiye), M. Velidedeoğlu, MD (Department of General Surgery, Cerrahpaşa Faculty of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Türkiye), L. Yeniay, MD (Department of General Surgery, School of Medicine, Ege University, Izmir, Türkiye),

B. Göktepe, MD (Department of General Surgery, School of Medicine, Ege University, Izmir, Türkiye), L. Dogan, MD (Department of Surgical Oncology, Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey), M. Dogan, MD (Department of Medical Oncology, Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey), F. Erozgen, MD (Department of General Surgery, Haseki Training and Research Hospital, Health Sciences University, Istanbul, Türkiye), M. Akıncı, MD (Department of General Surgery, Haseki Training and Research Hospital, Health Sciences University, Istanbul, Türkiye), T. Kıvılcım, MD (Department of General Surgery, School of Medicine, Okan University, Istanbul, Türkiye), A. Kebudi, MD (Department of General Surgery, School of Medicine, Okan University, Istanbul, Türkiye), S. Yormaz, MD (Department of General Surgery, School of Medicine, Selçuk University, Konya, Türkiye), I. A. Ozemir, MD (Department of General Surgery, Göztepe Training and Research Hospital, School of Medicine, Istanbul Medeniyet University, Istanbul, Türkiye), A. Sevinç, MD (Department of General Surgery, School of Medicine, Dokuz Eylül University, Izmir, Türkiye), K. Atahan, MD (Department of General Surgery, School of Medicine, Izmir Katip Çelebi University, Izmir, Türkiye), V. Valiyeva, MD (Department of Breast Surgery, Oncology Clinic, Azerbaijan Medical University, Baku, Azerbaijan), P. Alekberova, MD (Department of Breast Surgery, Oncology Clinic, Azerbaijan Medical University, Baku, Azerbaijan), B. Mollavelioglu, MD (Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye), B. Kılıç, MD (Division of Surgical Oncology, Institute of Oncology, Istanbul University, Istanbul, Türkiye), F. L. Balci, MD (Breast and Endocrine Surgeon, Private Practice, Istanbul, Türkiye), B. M. Gulluoglu, MD (Department of General Surgery, School of Medicine, Marmara University, Istanbul, Türkiye), and A. Kamali Polat, MD (Ondokuz Mayıs University, School of Medicine, Department of General Surgery, Samsun, Türkiye), for patient recruitment and collaboration; and B. R. Oner, F. Sezer, E. O. Güneş, E. Esen, and H. Ustubec for secretarial assistance. A. Bozdoğan, B. R. Oner, F. Sezer, E. O. Güneş, E. Esen, and H. Ustubec were compensated for their contributions.

REFERENCES

1. Giuliano AE, Ballman K, McCall L, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. *Ann Surg*. 2016;264(3):413-420. doi:10.1097/SLA.0000000000001863

2. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*. 2017;318(10):918-926. doi:10.1001/jama.2017.11470

3. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(12):1303-1310. doi:10.1016/S1470-2045(14)70460-7

4. Bartels SAL, Donker M, Poncet C, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS trial. *J Clin Oncol*. 2023;41(12):2159-2165. doi:10.1200/JCO.22.01565

5. Galimberti V, Cole BF, Zurrida S, et al; International Breast Cancer Study Group Trial 23-01 Investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013;14(4):297-305. doi:10.1016/S1470-2045(13)70035-4

6. Galimberti V, Cole BF, Viale G, et al; International Breast Cancer Study Group Trial 23-01. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19(10):1385-1393. doi:10.1016/S1470-2045(18)30380-2

7. Boughey JC, Suman VJ, Mittendorf EA, et al; Alliance for Clinical Trials in Oncology. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(14):1455-1461. doi:10.1001/jama.2013.278932

8. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol*. 2013;14(7):609-618. doi:10.1016/S1470-2045(13)70166-9

9. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol*. 2015;33(3):258-264. doi:10.1200/JCO.2014.55.7827

10. Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J Clin Oncol*. 2016;34(10):1072-1078. doi:10.1200/JCO.2015.64.0094

11. Tee SR, Devane LA, Evoy D, et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br J Surg*. 2018;105(12):1541-1552. doi:10.1002/bjs.10986

12. Simons JM, van Nijnatten TJA, van der Pol CC, Luiten EJT, Koppert LB, Smidt ML. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy for node-positive breast cancer: a systematic review and meta-analysis. *Ann Surg*. 2019;269(3):432-442. doi:10.1097/SLA.0000000000003075

13. Cabıoğlu N, Karanlık H, Kangal D, et al. Improved false negative rates with intraoperative identification of clipped nodes in patients undergoing sentinel lymph node biopsy after neoadjuvant chemotherapy. *Ann Surg Oncol*. 2018;25(10):3030-3036. doi:10.1245/s10434-018-6575-6

14. Simons JM, van Pelt MLMA, Marinelli AWKS, et al. Excision of both pretreatment marked positive nodes and sentinel nodes improves axillary staging after neoadjuvant systemic therapy in breast cancer. *Br J Surg*. 2019;106(12):1632-1639. doi:10.1002/bjs.11320

15. Kuemmel S, Heil J, Rueland A, et al. A prospective, multicenter registry study to evaluate the clinical feasibility of targeted axillary dissection (TAD) in node-positive breast cancer patients. *Ann Surg*. 2022;276(5):e553-e562. doi:10.1097/SLA.0000000000004572

16. Swarnkar PK, Tayeh S, Michell MJ, Mokbel K. The evolving role of marked lymph node biopsy (MLNB) and targeted axillary dissection (TAD) after neoadjuvant chemotherapy (NACT) for node-positive breast cancer: systematic review and pooled analysis. *Cancers (Basel)*. 2021;13(7):1539. doi:10.3390/cancers13071539

17. Almahariq MF, Levitin R, Quinn TJ, et al. Omission of axillary lymph node dissection is associated with inferior survival in breast cancer patients with residual N1 nodal disease following neoadjuvant chemotherapy. *Ann Surg Oncol*. 2021;28(2):930-940. doi:10.1245/s10434-020-08928-2

18. Cabıoğlu N, Karanlık H, Yıldırım N, et al. Favorable outcome with sentinel lymph node biopsy alone after neoadjuvant chemotherapy in clinically node positive breast cancer at diagnosis: Turkish Multicentric NEOSENTI-TURK MF-18-02-Study. *Eur J Surg Oncol*. 2021;47(10):2506-2514. doi:10.1016/j.ejso.2021.06.024

19. Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, et al. Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up. *Eur J Surg Oncol*. 2021;47(4):804-812. doi:10.1016/j.ejso.2020.10.014

20. Classe JM, Loaec C, Gimbergues P, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 Study. *Breast Cancer Res Treat*. 2019;173(2):343-352. doi:10.1007/s10549-018-5004-7

21. Cocco D, Shah C, Wei W, Wilkerson A, Grobmyer SR, Al-Hilli Z. Axillary lymph node dissection can be omitted in patients with limited clinically node-positive breast cancer: a National Cancer Database analysis. *Br J Surg*. 2022;109(12):1293-1299. doi:10.1093/bjs/znac305

22. van Loevezijn AA, van der Noordaa MEM, Stokkel MPM, et al. Three-year follow-up of de-escalated axillary treatment after neoadjuvant systemic therapy in clinically node-positive breast cancer: the MARI-protocol. *Breast Cancer Res Treat*. 2022;193(1):37-48. doi:10.1007/s10549-022-06545-z

23. Barrio AV, Montagna G, Mamtani A, et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy—a rare event. *JAMA Oncol*. 2021;7(12):1851-1855. doi:10.1001/jamaoncol.2021.4394

24. Kuemmel S, Heil J, Bruzas S, et al. Safety of targeted axillary dissection after neoadjuvant therapy in patients with node-positive breast cancer. *JAMA Surg*. 2023;158(8):807-815. doi:10.1001/jamasurg.2023.1772

25. Montagna G, Mrdutt MM, Sun SX, et al. Omission of axillary dissection following nodal downstaging with neoadjuvant chemotherapy. *JAMA Oncol*. 2024;10(6):793-798. doi:10.1001/jamaoncol.2024.0578

26. Cabıoğlu N, Karanlık H, Iğci A, et al. Is sentinel lymph node biopsy with radiotherapy alone without axillary lymph node dissection safe following neoadjuvant chemotherapy in initially clinically axilla positive patients: Neosentiturk-Trial/MF-18-03. Poster presented at: American Society of Breast Surgeons 23rd Annual Meeting; April 6-10, 2022; Las Vegas, Nevada. Accessed February 26, 2020. http://clinicaltrials.gov/ct2/show/NCT04250129

27. Şimsek DH, Emiroğlu S, Yılmaz R, et al. SPECT/CT lymphoscintigraphy guidance simplifies and improves targeted axillary dissection of the clipped nodes after neoadjuvant chemotherapy in initially node-positive breast cancer. *Clin Nucl Med*. 2022;47(11):e682-e688. doi:10.1097/RLU.0000000000004340

28. Dilege E, Celik B, Falay O, et al. SPECT/CT lymphoscintigraphy accurately localizes clipped and sentinel nodes after neoadjuvant chemotherapy in node-positive breast cancer. *Clin Nucl Med*. 2023;48(7):594-599. doi:10.1097/RLU.0000000000004669

29. Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. *J Clin Oncol*. 2007;25(19):2650-2655. doi:10.1200/JCO.2006.08.2271

30. Montagna G, Lee MK, Sevilimedu V, Barrio AV, Morrow M. Is nodal clipping beneficial for node-positive breast cancer patients receiving neoadjuvant chemotherapy? *Ann Surg Oncol*. 2022;29(10):6133-6139. doi:10.1245/s10434-022-12240-6

31. Weiss A, King C, Grossmith S, et al. How often does retrieval of a clipped lymph node change adjuvant therapy recommendations? a prospective, consecutive, patient cohort study. *Ann Surg Oncol*. 2022;29(6):3764-3771. doi:10.1245/s10434-022-11324-7

32. Alliance A11202 trial. Comparison of axillary lymph node dissection with axillary radiation for patients with node-positive breast cancer treated with chemotherapy. ClinicalTrials.gov identifier: NCT01901094. Accessed February 11, 2024. https://clinicaltrials.gov/study/NCT01901094

33. Cavalcante FP, Zerwes FP, Souza ABA, et al. The use of blue dye alone for sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initially node-positive breast cancer. *Eur J Surg Oncol*. 2024;50(3):107967. doi:10.1016/j.ejso.2024.107967

34. Mamounas E, Bandos H, White JR, et al. Loco-regional irradiation in patients with biopsy-proven axillary node involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: primary outcomes of NRG Oncology/NSABP B-51/RTOG 1304. Presented at: San Antonio Breast Cancer Symposium 2023; December 5-9, 2023; San Antonio, Texas.

35. Henke G, Knauer M, Ribi K, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. *Trials*. 2018;19(1):667. doi:10.1186/s13063-018-3021-9

36. Banys-Paluchowski M, Gasparri ML, de Boniface J, et al; Axsana Study Group. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: current status, knowledge gaps, and rationale for the EUBREAST-03 AXSANA study. *Cancers (Basel)*. 2021;13(7):1565. doi:10.3390/cancers13071565