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ORIGINAL ARTICLE

Combined analysis of the MF18-02/MF18-03 NEOSENTITURK studies: ypN-positive disease does not necessitate axillary lymph node dissection in patients with breast cancer with a good response to neoadjuvant chemotherapy as long as radiotherapy is provided

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Abstract

Background: The omission of axillary lymph node dissection (ALND) remains controversial for patients with residual axillary disease after neoadjuvant chemotherapy (NAC), regardless of the residual burden. This study evaluated the oncologic safety and factors associated with outcomes in patients with residual axillary

This study was presented in part at the Annual Meeting of the American Society of Breast Surgeons; April 28, 2023; Boston, Massachusetts.

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disease. These patients were treated solely with sentinel lymph node biopsy (SLNB) or targeted axillary dissection (TAD), without ALND, after NAC.

Methods: A joint analysis of two different multicenter cohorts—the retrospective cohort registry MF18-02 and the prospective observational cohort registry MF18-03 (NCT04250129)—was conducted between January 2004 and August 2022. All patients received regional nodal irradiation.

Results: Five hundred and one patients with cT1-4, N1-3M0 disease who achieved a complete clinical response to NAC underwent either SLNB alone (n = 353) or TAD alone (n = 148). At a median follow-up of 42 months, axillary and locoregional recurrence rates were 0.4% (n = 2) and 0.8% (n = 4). No significant difference was found in disease-free survival (DFS) and disease-specific survival (DSS) rates between patients undergoing TAD alone versus SLNB alone, those with breast positive versus negative pathologic complete response, SLN methodology, total metastatic LN of one versus ≥2, or metastasis types as isolated tumor cells with micrometastases versus macrometastases. In the multivariate analysis, patients with nonluminal pathology were more likely to have a worse DFS and DSS, respectively, without an increased axillary recurrence.

Conclusions: The omission of ALND can be safely considered for patients who achieve a complete clinical response after NAC, even if residual disease is detected by pathologic examination. Provided that adjuvant radiotherapy is administered, neither the SLNB method nor the number of excised LNs significantly affects oncologic outcomes.

KEYWORDS
axillary lymph node dissection, breast cancer, neoadjuvant chemotherapy, sentinel lymph node biopsy, targeted axillary dissection

INTRODUCTION

Sentinel lymph node biopsy (SLNB) has become the standard surgical approach for axillary staging in patients with breast cancer without clinical node involvement, which results in fewer arm and shoulder complications than the axillary lymph node dissection (ALND) method.[1–5] In those diagnosed with clinically node-positive breast cancer, neoadjuvant chemotherapy (NAC) has been known to downstage the metastatic nodal disease and boost the pathologic complete response (pCR) rate from 20% up to 61%, which depends on the tumor type.[6–8]

As a result, it has been suggested that post-NAC SLNB could also serve as a more conservative option for clinically node-positive patients, with axillary pCR being seen as an alternative to ALND. Acceptably low (<10%) false-negative rates (FNRs) have been reported in prospective randomized trials such as ACOSOG Z1071 (Alliance),[9] SENTINA,[10] and SN FNAC,[11] particularly when three or more sentinel lymph nodes (SLNs) are removed with dual-mapping techniques. Furthermore, targeted axillary dissection (TAD), which involves the removal of the targeted marked lymph node (LN) in addition to the SLNB procedure, has resulted in continued advancements in axillary surgery, which reduces the FNR to 5.2% or lower in cases of clinically node-positive breast cancer.[12–17]

Ongoing clinical trials, including Alliance A11202 (NCT01901094) and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-51/Radiation Therapy Oncology Group (RTOG) 1304, are evaluating the role of regional nodal irradiation in reducing locoregional recurrences in women with clinically node-positive ypN0 or ypN+ disease after NAC. These trials are anticipated to provide prospective data on oncologic outcomes.[18,19] In the absence of such data, further studies examining the rate of regional recurrences after SLNB without the completion of ALND in patients with ypN0/+ breast cancer are necessary to facilitate informed clinical decision-making. The standard surgical approach has been axillary clearance in patients with residual axillary disease after NAC, except in clinical trials.[20] Recent studies, as well as our previous report about the NEOSENTITURK MF18-02 retrospective registry, have shown that ALND can be spared in carefully selected patients with ypN+ disease who undergo SLNB after NAC. This is possible with low-volume residual nodal disease and favorable pathology, as long as axillary radiotherapy (RT) is provided.[21–23]

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In 2019, we launched a prospective registry study, NEOSENTITURK MF-1803, to assess oncologic safety, quality of life, and lymphedema after SLNB or TAD, with or without ALND.[24] This study's objective was to investigate the survival outcomes, axillary and locoregional recurrence rates, and factors associated with any recurrence in ycN0/ypN+ patients treated with SLNB or TAD alone after NAC. This exploration is based on a combined analysis of the MF18-02 and MF18-03 registries.

MATERIALS AND METHODS

This study is an amalgamation of two distinct multicenter cohorts: the MF18-02 retrospective cohort registry and the MF18-03 prospective observational cohort registry (NCT04250129). The patient pool was sourced from 36 academic, private, and public institutions, 35 of which are located in Turkey and one in Azerbaijan. The study time frame entailed observations made between January 2004 and August 2022, including patients from NEOSENTITURK MF18-02 (n = 176) and MF18-03 (NCT04250129) (n = 325). All ethical approvals were sourced from the ethics committee of the Istanbul Faculty of Medicine, Istanbul University, by the ethical standards of the institutional and national research committees and the Helsinki Declaration of 1964. Informed consent was obtained from all individual participants included in the study.

Patients involved in the study were aged older than 18 years who presented as cT1-4 and cN1-3M0. They all displayed clinical node negativity after NAC and underwent either an SLNB or TAD without ALND. However, those who transitioned from cN1 to ycN0 and were subsequently discovered to be ypN0 after a pathologic examination were removed from the study.

Nodal and regional RT was administered to all patients included in the study. Those who did not receive RT were removed from the pool. Furthermore, individuals with pregnancy-associated or inflammatory breast cancer, systemic metastatic disease, bilateral breast cancer, a secondary malignancy, or who had more than nine LNs removed or undergone ALND were excluded from the analysis.

The direction and guidelines of the study are presented in Figure 1.

Clinical assessment

Clinical evaluation was performed in line with the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Eighth Edition, with physical examinations and imaging.[25] All patients underwent fluorodeoxyglucose positron emission tomography/computed tomography and breast ultrasound. Axillary nodal metastases were identified by axillary ultrasound-guided cytopathology. Axillary LN positivity (cN+) was determined during the initial diagnosis, and subsequently confirmed by cytopathology in all patients. For every patient with TAD (n = 148), the metastatic axillary LN was identified via biopsy and marked with a titanium clip under ultrasound guidance before beginning NAC. After NAC, axillary LNs were assessed by ultrasonography, and the study included patients who had achieved a complete response on radiologic imaging.

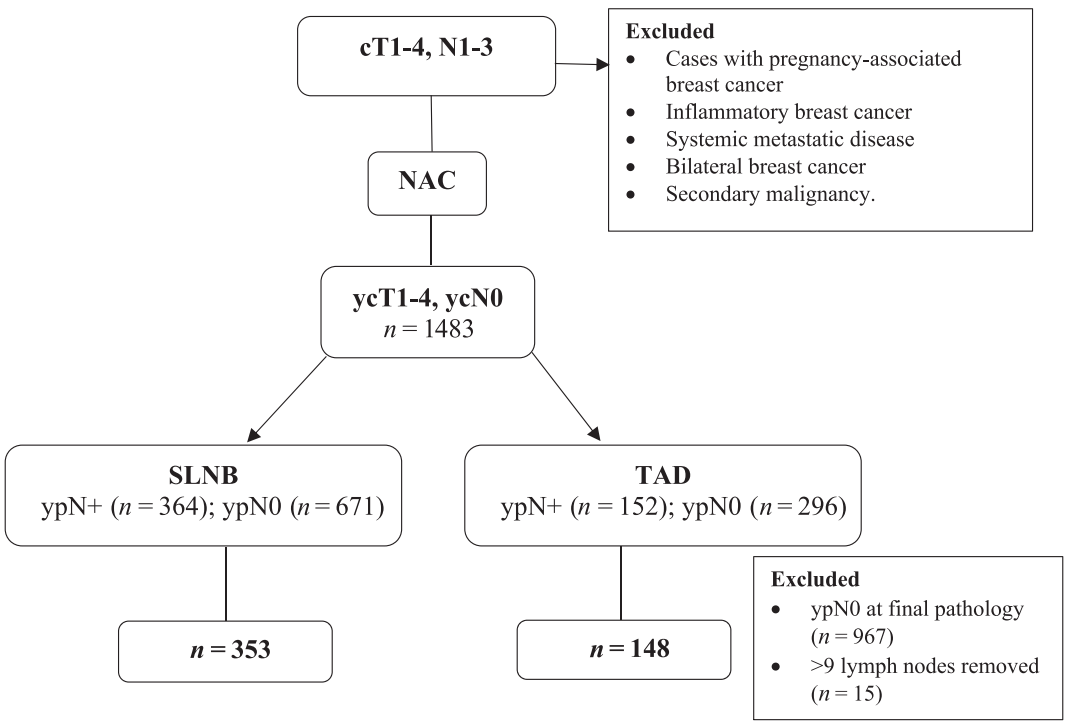


FIGURE 1 Study flowchart. NAC indicates neoadjuvant chemotherapy; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

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Systemic therapy

Of the 501 patients treated with NAC, the majority (n = 314; 62.7%) received four cycles of adriamycin (60 mg/m^2) and cyclophosphamide (500 mg/m^2), followed by 12 weekly cycles of paclitaxel (80 mg/m^2). Another segment of patients (n = 57; 11.4%) received six cycles of adriamycin (60 mg/m^2) and cyclophosphamide (500 mg/m^2), complemented by docetaxel (75 mg/m^2). Of the patients with Her2-neu–positive disease (n = 125; 25%), 90 also received trastuzumab therapy (2 mg/kg) after four cycles of adjuvant chemotherapy (AC); a weekly taxane regimen was adhered to by 74.1% of these patients. An additional 35 patients also received pertuzumab, which was an anti–Her2-neu agent, along with trastuzumab and docetaxel. The remaining 36 patients (7.2%) were treated with AC as part of an anthracycline-inclusive regimen but received no taxanes. In compliance with current guidelines, systemic treatment was administered to triple-negative and Her2-positive patients having residual disease. Patients with hormone receptor positivity received appropriate hormone therapy.

Surgical technique

Patients with a complete clinical response to chemotherapy underwent either SLNB or TAD. The TAD technique requires identifying the SLN and retrieving the clipped node for all patients. The SLNB technique involved the use of either blue dye alone, a ^{99}Tc-labeled colloid injection alone, or a combination of both. Among patients undergoing TAD (n = 148), a variety of techniques were used: wire, ROLL (radio-guided occult lesion localization), carbon tattooing, or ultrasound- or scope-guided targeted lymph node biopsy (TLNB). The ROLL technique involves directly injecting a radiotracer, ^{99}mTc-labeled colloidal albumin, into the targeted LN before surgery. The scope-guided technique was used for a single patient with a portable scope device intraoperatively.

Excision of the clipped node was verified in 26 patients via specimen radiography (n = 21; 14.2%) or single-photon emission computed tomography/computed tomography lymphoscintigraphy (n = 5; 3.4%), as recently reported.[26,27] Palpable suspicious LNs were identified as SLNs, in line with previous reports.[9,28] If necessary, imprint cytology and/or a frozen section were used for the intraoperative assessment of SLNs.[29]

After NAC, LNs containing isolated tumor cells (ITCs), micrometastases, or macrometastases detected by hematoxylin and eosin or cytokeratin immunohistochemistry were classified as positive according to the AJCC Cancer Staging Manual, Eighth Edition. Patients who achieved clinical complete response after NAC but still had residual disease detected by pathologic examination were categorized as having low-volume axillary involvement. pCR in the breast was defined as ypT0 or ypTis.[30] Tumor subtypes were determined according to the 13th St. Gallen International Breast Cancer Conference.[31]

RT

Adjuvant RT was administered at 45–50 Gy in 25 fractions to the entire breast in patients treated with breast-conserving surgery (BCS) or to the chest wall for patients treated with mastectomy, and to axillary (level I–III) areas, which included supraclavicular LN regions, with or without the internal mammary LN region. The decision to include the internal mammary region in the treatment area was made by the radiation oncologist. This decision was based on several factors, including the extent of clinical and residual axillary involvement after NAC, axillary response, T stage, tumor biology, and tumor location. Patients treated with BCS also received boost RT for the tumor bed. The administered boost doses ranged between 10 and 16 Gy in five to eight fractions. RT was delivered via the three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, or volumetric modulated arc therapy treatment techniques.

Statistical analysis

The statistical software program SPSS 26 (Statistical Package for Social Sciences; IBM Corporation, Armonk, New York) was used for statistical analyses. A p value of less than .05 was deemed statistically significant. Categorical variables were evaluated with the Fisher exact test or continuity correction test (Pearson χ^2) in two-tailed univariate analyses. Nonparametric continuous variables' differences were assessed with the Mann–Whitney U test. Locoregional recurrence was defined as recurrence detected in the axillary nodal, infra- or supraclavicular, or internal mammary region. Disease-free survival (DFS) was estimated taking into account local and systemic metastases, and disease-specific survival (DSS) rates were determined on the basis of the mortality related to breast cancer. Survival analyses used the Kaplan–Meier test, and the log-rank test was used to compare different prognostic factors associated with the outcome. Cox regression analysis evaluated the hazard ratio of factors related to the outcome. Survival graphics were produced with the Prism, version 8, software program (GraphPad Software, San Diego, California).

RESULTS

Patient and tumor characteristics

From January 2004 through August 2022, 501 patients with cT1-4, N1-3M0 disease underwent either SLNB only (n = 353) or TAD only (n = 148). The median patient age was 47 years (range, 21–79 years). The SLNB technique involved blue dye alone in 68.7% of cases (n = 344), ^{99}Tc-labeled colloid injection alone in 2.8% of cases (n = 14), and a combination of blue dye and ^{99}Tc-labeled colloid injection in 28.5% of cases (n = 143). The median numbers of SLNs and

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total LNs removed were three[2–5] and four,[3–6] respectively, with a median of one (range, 1–2) total metastatic LNs removed. More than half of the patients presented with macrometastatic nodal involvement (macrometastasis, 51.9%; micrometastasis, 31.5%; ITCs, 16.6%), and only 36.1% of patients were found to have more than one metastatic LN, with merely 18% showing extracapsular extension.

In patients with TAD (n = 148), the following techniques were used: wire (n = 43; 29.1%), ROLL (n = 53; 35.8%), carbon tattooing (n = 5; 3.4%), and ultrasound-guided (n = 20; 13.5%) and scope-guided (n = 1; 0.7%) TLNB.

When comparing patients with SLNB and TAD, it was found that those with TAD were more likely to have cT1-2 disease (72% vs. 91%), undergone BCS (51% vs. 66%), used the combined technique for mapping (20% vs. 49%), have >4 total LNs retrieved (45% vs. 55%), and have a lower LN ratio compared to the SLNB-alone group (median, 33% vs. 27%). No other significant differences were found between the TAD-alone and SLNB-alone groups in terms of other clinicopathologic characteristics. These included age, tumor type (histopathology, breast pCR, estrogen receptor (ER), progesterone receptor (PR), or HER2 positivity, and high Ki-67 score [>20%]), initial clinical nodal presentation, pathologic nodal involvement, ITCs or micrometastasis versus macrometastasis, the number of total metastatic LNs and SLNs, and the presence of extracapsular extension (Table 1).

Compared to those with ITCs and micrometastasis, patients with macrometastases in this cohort were more likely to be aged older than 50 years (35% vs. 44%). They were also more inclined to have luminal pathology or HER2-neu positivity but less likely to achieve breast pCR or have a high (>20%) Ki-67 score. Moreover, patients with macrometastases were more likely (22% vs. 8%) to exhibit metastatic SLNs or total LNs (>2), extracapsular extension, or a high LN ratio (>0.33), as indicated in Table 1. Correspondingly, increased counts of SLNs and total LNs retrieved were observed in patients with TAD compared to the SLNB group (median SLNs, four vs. three; median total LNs, five vs. four). Furthermore, a larger number of metastatic SLNs and total LNs were retrieved from patients with macrometastasis, as opposed to the micrometastasis group (mean SLNs, 1.3 ± 0.7 vs. 1.6 ± 0.9; mean total LNs, 1.4 ± 0.8 vs. 1.8 ± 1.1) (Table 1).

Oncologic outcome

The median follow-up was 42 months (interquartile range, 29–58 months; range, 12–202 months). The rates of ipsilateral axillary and locoregional recurrence were 0.6% (n = 2) for the SLNB group and 1.4% (n = 2) for the TAD group, respectively. Locoregional recurrences occurred in the ipsilateral axilla in two patients and the supraclavicular regions in two other patients. No significant difference was found in the axillary and locoregional recurrence rates between patients treated with SLNB (n = 353) and TAD (n = 148). The respective ipsilateral axillary recurrence rates were 0.3% for SLNB versus 0.7% for TAD (p = .504), and the locoregional recurrence rates were 0.6% for SLNB versus 1.4% for TAD (p = .585). Similarly, there was no significant difference in axillary and locoregional recurrence rates between patients with ITCs/micrometastasis (n = 241) and macrometastasis (n = 260). The ipsilateral axillary recurrence rates were 0.41% for ITCs/micrometastasis versus 0.38% for macrometastasis (p = .999), and the locoregional recurrence rates were 0.4% for ITCs/micrometastasis versus 1.2% for macrometastasis (p = .625). All the recurrences in ipsilateral axillary and locoregional areas occurred concurrently with breast (n = 2) and chest wall recurrences (n = 2). In our relatively large cohort with a short follow-up period (42 months), there were no instances of solitary axillary or supraclavicular metastasis. One patient had simultaneous systemic metastases in lung and bone, and another patient had systemic metastases only in bone (Table 2).

The 5-year DFS and DSS rates in the cohort were 88.5% and 94.7%, respectively. No significant difference was found in DFS or DSS rates between groups, including TAD alone versus SLNB alone (p = .701 and p = .349), cT1-2 versus cT3-4 (p = .243 and .587), breast pCR(+) versus pCR(−) (p = .673 and p = .530), SLN methodology as a dual tracer versus single tracer (p = .148 and p = .474), one to four LNs versus >4 LNs removed (p = .526 and p = .685), total number of metastatic LNs of one versus ≥2 (p = .931 and p = .381), and metastasis type as ITCs with micrometastases versus macrometastases (p = .213 and p = .877) (Table 3). As expected, patients with nonluminal pathology had worse 5-year DFS and DSS rates compared to those with luminal pathology (ER[+] vs. ER[−]: DFS, 90% vs. 80%; DSS, 95% vs. 91%; p = .013 and p = .024; luminal vs. nonluminal: DFS, 89% vs. 81%; DSS, 95% vs. 91%; p = .022 and p = .020) (Table 4). Similarly, a better DFS rate was associated with PR-positive pathology and BCS. Cox regression analysis revealed that the only significant factor associated with DFS or DSS was the presence of nonluminal pathology (DFS: hazard ratio [HR], 2.06; 95% confidence interval [CI], 1.01–4.20; DSS: HR, 2.91; 95% CI, 1.07–7.91; p = .048 and p = .036) (Table 4).

DISCUSSION

Limited axillary surgery has been widely integrated into clinical practice in the treatment of clinically node-negative early breast cancer for many years.[32] With increasingly improved and targeted treatment options, axillary management for primary advanced breast cancer has evolved to become deescalated and individualized. FNRs with SLNB can be as high as 14% in patients who are initially N+.[14] In contrast, TAD is associated with a lower FNR.[16,17] However, the clinical significance of the FNR or limited axillary residual disease resulting from the FNR has not yet been fully established. The concept that the FNR does not affect outcomes is supported by a recent large retrospective single-institution study with a 10-year follow-up of patients who underwent SLNB with three LNs removed with a single tracer, regardless of TAD. This study showed that the FNR after NAC did not lead to impaired clinical outcomes in patients who converted from N1 to ycN0.[33] Our results from a large

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TABLE 1 Clinical and pathologic characteristics of patients who underwent SLNB versus TAD and who had micrometastases or macrometastases.

	Total ($N = 501$)	SLNB ($n = 353$)	TAD ($n = 148$)	p	Micrometastases/ ITCs ($n = 241$)	Macrometastases ($n = 260$)	p
Characteristic							
Age, median (minimum–maximum), years	47 (21–79)	47 (21–79)	49 (27–76)	.351[a]	45 (24–78)	49 (21–79)	.002*[a]
Age, No. (%), years				.399[b]			.032*[b]
≤50	302 (60.3)	217 (61.5)	85 (57.4)		157 (65.1)	145 (55.8)	
>50	199 (39.7)	136 (38.5)	63 (42.6)		84 (34.9)	115 (44.2)	
Clinical T stage, No. (%)				<.001*[b]			.575[b]
cT1/2	390 (77.8)	255 (72.2)	135 (91.2)		185 (76.8)	205 (78.8)	
cT3/4	111 (22.2)	98 (27.8)	13 (8.8)		56 (23.2)	55 (21.2)	
Clinical N stage, No. (%)				.340[b]			.997[b]
cN1	428 (85.4)	305 (86.4)	123 (83.1)		206 (85.5)	222 (85.4)	
cN2/3	73 (14.6)	48 (13.6)	25 (16.9)		35 (14.5)	38 (14.6)	
Type of breast surgery, No. (%)				.002*[a]			.756[b]
BCS	278 (55.5)	180 (51)	98 (66.2)		132 (54.8)	146 (56.2)	
Mastectomy	223 (44.5)	173 (49)	50 (33.8)		109 (45.2)	114 (43.8)	
Histopathology of core biopsy and surgical specimen, No. (%)				.367[b]			.814[b]
Invasive ductal carcinoma	435 (86.8)	305 (86.4)	130 (87.8)		211 (87.6)	224 (86.2)	
Invasive lobular carcinoma	30 (6)	25 (7.1)	5 (3.4)		14 (5.8)	16 (6.2)	
Invasive ductal and lobular carcinoma	22 (4.4)	14 (4)	8 (5.4)		11 (4.6)	11 (4.2)	
Other	14 (2.8)	9 (2.5)	5 (3.4)		5 (2.1)	9 (3.5)	
pCR (breast), No. (%)				.074[b]			.011*[b]
Complete	84 (16.8)	66 (18.7)	18 (12.2)		51 (21.2)	33 (12.7)	
Partial	417 (83.2)	287 (81.3)	130 (87.8)		190 (78.8)	227 (87.3)	
ER, No. (%)				.655[b]			<.001*[b]
Positive	422 (84.2)	299 (84.7)	123 (83.1)		184 (76.3)	238 (91.5)	
Negative	79 (15.8)	54 (15.3)	25 (16.9)		57 (23.7)	22 (8.5)	
PR, No. (%)				.690[b]			.004*[b]
Positive	380 (75.8)	266 (75.4)	114 (77)		169 (70.1)	211 (81.2)	
Negative	121 (24.2)	87 (24.6)	34 (23)		72 (29.9)	49 (18.8)	
HER2-neu, No. (%)				.960[b]			<.001*[b]
Negative	375 (74.9)	264 (74.8)	111 (75)		162 (67.2)	213 (81.9)	
Positive	126 (25.1)	89 (25.2)	37 (25)		79 (32.8)	47 (18.1)	
Ki-67 expression ($n = 484$), No. (%)				.397[b]			.009*[b]
Negative (<%20)	90 (18.6)	66 (19.6)	24 (16.3)		32 (13.8)	58 (23)	
Positive (≥20%)	394 (81.4)	271 (80.4)	123 (83.7)		200 (86.2)	194 (77)	
Tumor subtype (IHC), No. (%)				.981[b]			<.001*[b]
Luminal A	68 (13.6)	50 (14.2)	18 (12.2)		25 (10.4)	43 (16.5)	
Luminal B/HER2(–)	264 (52.7)	184 (52.1)	80 (54.1)		110 (45.6)	154 (59.2)	
Luminal B/HER2(+)	96 (19.2)	68 (19.3)	28 (18.9)		53 (22)	43 (16.5)	

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TABLE 1 (Continued)

	Total (N = 501)	SLNB (n = 353)	TAD (n = 148)	p	Micrometastases/ ITCs (n = 241)	Macrometastases (n = 260)	p
Non–luminal B/HER2(+)	29 (5.8)	20 (5.7)	9 (6.1)		25 (10.4)	4 (1.5)	
Triple-negative	44 (8.8)	31 (8.8)	13 (8.8)		28 (11.6)	16 (6.2)	
SLN methodology, No. (%)				<.001*[b]			.404[b]
Single tracer (blue dye [n = 344]/ radioisotope [n = 14])	358 (71.5)	283 (80.2)	75 (50.7)		168 (69.7)	190 (73.1)	
Combined	143 (28.5)	70 (19.8)	73 (49.3)		73 (30.3)	70 (26.9)	
Blue dye and radioisotope							
Characteristics of metastatic LNs removed, No. (%)				.370[a]			
ITCs	83 (16.6)	61 (17.3)	22 (14.9)		NA	NA	
Micrometastases	158 (31.5)	116 (32.9)	42 (28.4)		NA	NA	
Macrometastases	260 (51.9)	176 (49.9)	84 (56.8)		NA	NA	
Presence of extracapsular extension, No. (%)				.856[b]			<.001*[b]
Yes	89 (17.8)	62 (17.6)	27 (18.2)		20 (8.3)	69 (26.5)	
No	412 (82.2)	291 (82.4)	121 (81.8)		221 (91.7)	191 (73.5)	
LNR, median (IQR), No. (%)	0.33 (0.20–0.50)	0.33 (0.25–0.50)	0.27 (0.20–0.42)	.001*[a]	0.33 (0.20–0.40)	0.33 (0.25–0.50)	.001[a]
SLNs, No. (%)				.037*			.419
Mean (SD)	3.5 (1.7)	3.4 (1.7)	3.8 (1.7)		3.5 (1.8)	3.6 (1.6)	
Median (IQR)	3 (2–5)	3 (2–4)	4 (2–5)		3 (2–5)	3 (2–5)	
Minimum–maximum	1–9	1–9	1–9		1–9	1–9	
Metastatic SLNs, No. (%)				.361			<.001*
Mean (SD)	1.4 (0.8)	1.5 (0.8)	1.4 (0.8)		1.3 (0.7)	1.6 (0.9)	
Median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)		1 (1–1)	1 (1–2)	
Minimum–maximum	1–6	1–6	1–6		1–6	1–6	
Total LNs, No. (%)				.004*			.575
Mean (SD)	4.6 (1.9)	4.4 (1.9)	4.9 (1.8)		4.6 (2.0)	4.5 (1.9)	
Median (IQR)	4 (3–6)	4 (3–6)	5 (4–6)		4 (3–6)	4 (3–6)	
Minimum–maximum	1–9	1–9	1–9		1–9	1–9	
Total metastatic LNs, No. (%)				.702			<.001*
Mean (SD)	1.6 (0.9)	1.6 (1.0)	1.6 (0.9)		1.4 (0.8)	1.8 (1.1)	
Median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)		1 (1–2)	1 (1–2)	
Minimum–maximum	1–6	1–6	1–5		1–6	1–6	

Abbreviations: BCS, breast-conserving surgery; ER, estrogen receptor; IHC, immunohistochemistry; IQR, interquartile range; ITC, isolated tumor cell; LN, lymph node; LNR, lymph node ratio; NA, not available; pCR, pathologic complete response; PR, progesterone receptor; SD, standard deviation; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

[a]Mann–Whitney U test.

[b]Pearson χ^2 test.

*$p < .05$ was considered statistically significant.

prospective cohort, which included patients with limited residual axillary disease who received adjuvant RT, suggest that omitting ALND does not compromise axillary recurrence or survival rates. Our research also revealed that the incidence of axillary recurrence was notably low in cases with low-volume residual axillary disease who underwent SLNB or TAD. This suggests that the FNR does not have

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TABLE 2 Characteristics of patients with locoregional recurrence.

	Age, years	cT	ypSLN	LNR	pCR (breast)	TAD	Subtype	ECI	LVI	Breast surgery	Recurrence time, months	Site of recurrence
Case 1	29	4	Macrometastasis	2/3	No	Yes	Luminal/ Her2(−)	No	Yes	BCS	7	Breast + axilla
Case 4	34	2	ITCs	1/4	Yes	No	Luminal/ Her2(+)	No	NA	BCS	54	Breast + axilla
Case 6	54	2	Macrometastasis	1/5	No	Yes	Luminal/ Her2(−)	Yes	No	Mastectomy	39	Chest wall + supraclavicular region[a]
Case 7	79	3	Macrometastasis	1/5	No	No	Luminal/ Her2(−)	Yes	No	Mastectomy	16	Chest wall + supraclavicular region[b]

Abbreviations: BCS, breast-conserving surgery; ECI, extracapsular invasion; ITC, isolated tumor cell; LN, lymph node; LNR, lymph node ratio; LVI, lymphovascular invasion; pCR, pathologic complete response.

[a]Concomitant bone metastasis.

[b]Concurrent bone and lung metastases.

significant clinical importance. Therefore, the primary issue is to determine the oncologic safety of deescalating ALND on the basis of the results of SLNB and tumor biology.

Currently, there are only a few reports on prognosis in patients with ypN+ disease without ALND.[21–23] Among them, a recent study by van Loevezijn et al. detailed the treatment outcomes of cN+ patients based on a response-tailored treatment plan according to the marking axillary LNs with radioactive iodine seeds (MARI) protocol.[23] Of the ypN+ disease patients treated with axillary RT without ALND (n = 118), an axillary recurrence rate of 3.4% was observed at a median follow-up of 3 years. This was identified in four patients concurrently with regional metastasis or chest wall or distant metastases. Multivariate analysis revealed a significant association between triple-negative breast cancer and remaining tumors in the MARI node with recurrence. The European Institute of Oncology in Milan published a study examining the outcomes of a 10-year follow-up. The study analyzed 688 consecutive cT1-3, cN0/1/2 patients who either remained or became ycN0 after NAC and underwent SLNB with at least one SLN found. ALND was not performed if the SLN was negative, and nodal RT was not mandatory.[33] Axillary failure was reported in 1.8% of the initial cN1/2 patients and 1.5% of the initial cN0 patients. In the multivariate analysis, luminal A pathology, ypN0 disease, and breast pCR were associated with a better systemic outcome in the cohort. These findings are consistent with our previous research and the present report, particularly in patients with cN1-2.[22]

Finally, Almahariq et al.[21] analyzed patients with cT1-3N1M0 from the National Cancer Data Base who also were ypN1 after NAC. They compared the survival rates of patients who received SLNB (n = 304), with fewer than four LNs, to those who underwent ALND (n = 1313). The estimated 5-year overall survival (OS) rate was 71% in the SLNB group, compared to 77% in the ALND group (p = .01). Exploratory subgroup analyses revealed that SLNB was comparable to ALND in patients with either luminal A or B tumors containing a single metastatic LN. Hence, SLNB was recommended for patients with minimal residual disease and favorable tumor biology.

In the combined analysis of the current MF18-02/MF18-03 NEOSENTITURK studies, the axillary and locoregional recurrence rates were found to be 0.4% and 0.7%, respectively. These figures are slightly lower than those reported in prior studies that omitted ALND. All participants in our study had at least one remaining LN after NAC. Despite the high risk for axillary recurrence, the low recurrence rate in this area suggests that the impact of ALND on recurrence rates is not clearcut. Axillary recurrence has been reported as infrequent in patients who are clinically N+ after NAC, provided they underwent RT.[33,34] However, in agreement with past research, our study also found that luminal pathology was one of the most critical factors affecting survival in these patients. The majority of the participants in this study were luminal disease cases with limited LN involvement such as ypN1 (36% with one LN metastasis) and without extracapsular extension. Nevertheless, 14% of our study cohort was nonluminal, and the rate of axillary recurrence was similar to that of the luminal group.

TAD is a procedure that combines targeted axillary biopsy and SLNB, which reduces the rate of false-negative results in axillary sampling after NAC. Recent studies recorded an FNR decrease to 5.2% after TAD.[12–17] In the current study, the majority of patients underwent SLNB with only the blue dye method (69%). Nonetheless, there was no discernable difference in DFS and DSS rates, as well as locoregional and axillary recurrence rates, between patients who underwent SLNB versus TAD or SLNB via a single method, including blue dye or radioactive colloid alone, in comparison to those who underwent the combined technique for patients with limited LN involvement (ypN1). Notably, a larger number of LNs were retrieved in patients who had undergone TAD, compared to the SLNB group.

In a multicenter retrospective cohort study covering 1148 patients, Montagna et al. found no significant difference between TAD and SLNB in patients who transitioned from N+ to ypN0 status. Additionally, they noted a 1% axillary recurrence rate in the same

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TABLE 3 Clinical and pathologic characteristics associated with outcomes in cT1-4, N1-3 patients with ypN+ disease.

	Event, *n* of *N*	5-year DFS, %	*p*	Event, *n* of *N*	5-year DSS, %	*p*
Clinical T stage			.243			.587
cT1/2	30 of 390	89.9		15 of 390	95.3	
cT3/4	12 of 111	83.1		3 of 111	91.9	
Clinical N stage			.354			.111
cN1	38 of 428	88.4		18 of 428	93.8	
cN2/3	4 of 73	89.4		0 of 73	100	
Type of breast surgery			.951			.039*
BCS	24 of 278	89.4		7 of 278	97.6	
Mastectomy	18 of 223	86.9		11 of 223	90.3	
Histopathology of core biopsy and surgical specimen			.234			.853
Invasive ductal carcinoma	39 of 435	88.3		16 of 435	94.9	
Other	3 of 66	89.2		2 of 66	93.5	
pCR (breast)			.673			.530
Complete	8 of 84	84.3		4 of 84	93.5	
Partial	34 of 417	86.1		14 of 417	95	
ER			.013*			.024*
Positive	30 of 422	90.1		11 of 422	95.4	
Negative	12 of 79	80.4		7 of 79	91.3	
PR			.021*			.199
Positive	26 of 380	90.7		11 of 380	94.8	
Negative	16 of 121	82.1		7 of 121	94.4	
HER2-neu			.538			.826
Negative	29 of 375	89.1		13 of 375	95.2	
Positive	13 of 126	86.9		5 of 126	93.7	
Ki-67 expression (n = 484)			.540			.179
Negative (<%20)	6 of 90	87		1 of 90	97.6	
Positive (≥20%)	33 of 394	89.3		15 of 394	94.6	
Tumor subtype (IHC)			.240			.019*
Luminal A	4 of 68	94.2		0 of 68	100	
Luminal B/HER2(−)	19 of 264	91.2		10 of 264	94	
Luminal B/HER2(+)	8 of 96	88.4		1 of 96	96.4	
Non–luminal B/HER2(+)	5 of 29	82.6		4 of 29	84.7	
Triple-negative	6 of 44	79.9		3 of 44	83	
Tumor subtype (IHC)			.022*			.020*
Luminal	31 of 428	89.9		11 of 428	95.4	
Nonluminal	11 of 73	81.1		7 of 73	91	
TAD			.701			.349
Yes	12 of 148	91.2		7 of 148	98.1	
No	30 of 353	87.4		11 of 353	93	

(Continues)

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TABLE 3 (Continued)

	Event, *n* of *N*	5-year DFS, %	*p*	Event, *n* of *N*	5-year DSS, %	*p*
SLN methodology			.158			.474
Blue dye/radioisotope	33 of 358	86		13 of 358	94.2	
Combined (blue dye and radioisotope)	9 of 143	90.4		5 of 143	96	
No. of SLNs			.526			.685
1–4	32 of 367	87.6		14 of 367	95.1	
>4	10 of 134	90.8		4 of 134	93.3	
No. of metastatic SLNs			.931			.381
1	30 of 357	88.8		12 of 357	96.2	
≥2	12 of 144	87.8		6 of 144	90.7	
No. of total LNs			.125			.411
1–4	27 of 262	85.7		12 of 262	93.5	
>4	15 of 239	92.1		6 of 239	95.6	
No. of total metastatic LNs			.969			.566
1	27 of 320	88.5		11 of 320	96.3	
≥2	15 of 181	88.5		7 of 181	91.6	
Characteristics of metastatic LNs removed			.213			.877
ITCs and micrometastases	24 of 241	85.8		9 of 241	94.5	
Macrometastases	18 of 260	91.1		9 of 260	94.7	
Presence of extracapsular extension			.649			.732
Yes	7 of 89	88.6		4 of 89	95.6	
No	35 of 412	88.5		14 of 412	94.5	
LNR group			.194			.212
<0.33	14 of 210	91.5		5 of 210	99	
≥0.33	28 of 291	86.3		13 of 291	91.4	

Abbreviations: BCS, breast-conserving surgery; DFS, disease-free survival; DSS, disease-specific survival; ER, estrogen receptor; IHC, immunohistochemistry; ITC, isolated tumor cell; LN, lymph node; LNR, lymph node ratio; pCR, pathologic complete response; PR, progesterone receptor; SLN, sentinel lymph node; TAD, targeted axillary dissection.

*$p < .05$ was considered statistically significant.

TABLE 4 Cox regression analysis of factors associated with outcome in cT1-4, N1-3 patients with ycN0/ypN+ disease.

	DFS		DSS	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Molecular subtypes (nonluminal vs. luminal[a])	2.06 (1.01–4.20)	.048*	2.91 (1.07–7.91)	.036*
SLN methodology (blue dye/radioisotope vs. combined[a])	1.60 (0.74–3.45)	.236	1.36 (0.45–4.09)	.587
Characteristics of metastatic LNs removed (ITCs and micrometastases vs. macrometastases[a])	0.72 (0.38–1.36)	.317	0.92 (0.36–2.37)	.865
Type of axillary surgery (SLNB vs. TAD)	1.05 (0.52–2.12)	.889	1.89 (0.67–5.36)	.228
LNR (<0.33 vs. ≥0.33[a])	1.60 (0.83–3.08)	.164	2.19 (0.74–6.44)	.155

Abbreviations: CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; ITC, isolated tumor cell; LNR, lymph node ratio; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

[a]Reference value of 1.

*$p < .05$, multivariate Cox regression analysis.

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patient group over a 5-year follow-up.[35] Our analysis, which includes patients with limited axillary residue, reveals a significantly lower axillary recurrence rate. We observed a rate of just 0.4% in the overall cohort, at a median follow-up of 42 months.

Furthermore, the current study found no difference between patients with ITCs/micrometastases or macrometastases. When a ycN0 and ypN0 response in the axilla is attained after NAC, we can conclude it is safe to exclude ALND from axillary surgery. However, various factors could influence whether ALND is preferred in cases of low residual axillary disease. A recent study comparing axillary ITCs or micrometastases (ypNitc/mi) with residual axillary macrometastases (ypN1-3) in a neoadjuvant setting found no significant difference in DFS between ypN0 and ypNitc/mi (71.8% vs. 70.6%; $p = .978$). In contrast, a significant difference in DFS was found between ypN0 and ypN1-3 (71.8% vs. 53.4%; $p = .049$). Additionally, a multivariable Cox regression analysis revealed no significant difference between ypN0 and ypNitc/mi in OS (HR, 0.92; 95% CI, 0.27–2.99; $p = .889$), whereas a significant difference was found between ypN0 and ypN1-3 in OS (HR, 1.70; 95% CI, 1.07–2.71; $p = .026$).[36] These results indicate no significant differences in regional recurrences between patients with ypN0 and ypN+ status. Discrepancies in OS are more linked to tumor biology and the efficacy of systemic therapy rather than additional axillary surgery (ALND).

Adjuvant RT has become a vital component of breast cancer treatment, particularly in preventing local recurrence. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group in 2005 examined the effects of RT on recurrence and survival rates in early breast cancer. The study yielded a significant discovery: the prevention of one local recurrence within 5 years could divert one breast cancer death over 15 years.[37] However, the validity of this evidence within the scope of modern systemic therapy is subject to debate. The AMAROS study suggests that RT is a suitable substitute for ALND in relevant cases.[4] Outcomes from the prospective studies NSABP B-51/RTOG 1304 and Alliance 112022, which demonstrate the impact of nodal RT after NAC on oncologic outcomes, are anticipated.[18,19] In our study, we ensured that all patients received adjuvant RT as a key part of their oncologic treatment on the basis of prior studies and guidelines. Postmastectomy RT can significantly decrease the rate of locoregional recurrence in patients with minimal axillary residual disease after NAC.

The major weaknesses of the study include the relatively short median follow-up period (42 months) and the study design, which is a registry study, not a randomized trial. Some of the data were also collected retrospectively.

To develop a more accurate algorithm for omitting ALND in patients with residual nodal disease after NAC, we need longer follow-up periods and the results from ongoing prospective trials. The omission of ALND will continue to be controversial until the long-term results of the Alliance trial are reported. This trial randomly assigned ypN+ patients to ALND versus axillary RT in a significantly larger cohort. Other prospective studies, including TAXIS, AXSANA, and NEOSENTITURK, which have similar designs, also need to be reported before any conclusive decision can be made.[38,39]

Our analysis suggests that ALND is unnecessary for patients with limited residual nodal burden across all biologic subtypes. There are no differences in axillary recurrence between the luminal and non-luminal groups, including Her2-positive and triple-negative patients. Local treatments such as SLNB or TAD do not affect survival. Variations in survival rates appear to be dependent on tumor biology. In conclusion, similar outcomes are achieved with SLNB/TAD and adjuvant RT as with ALND in patients with residual nodal disease. As a result, consideration of the omission of ALND for patients who have exhibited a complete clinical response to NAC but still present with residual disease by pathology examination might be safe, given that they receive adjuvant RT.

AUTHOR CONTRIBUTIONS

Mahmut Muslumanoglu: Conceptualization, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, writing–review and editing, and writing–original draft. **Neslihan Cabioglu**: Conceptualization, software, investigation, formal analysis, project administration, writing–original draft, writing–review and editing, visualization, supervision, validation, and methodology. **Abdullah Igci**: Conceptualization, formal analysis, investigation, supervision, and visualization. **Hasan Karanlık**: Conceptualization, investigation, formal analysis, supervision, visualization, and writing–review and editing. **Havva Belma Kocer**: Data curation, resources, supervision, writing–review and editing, and writing–original draft. **Kazim Senol**: Data curation, resources, writing–original draft, and writing–review and editing. **Baris Mantoglu**: Data curation, resources, and writing–original draft. **Mustafa Tukenmez**: Formal analysis, investigation, supervision, and visualization. **Guldeniz Karadeniz Çakmak**: Data curation, resources, and supervision. **Enver Ozkurt**: Data curation and resources. **Mehmet Ali Gulcelik**: Supervision, resources, data curation, and writing–review and editing. **Selman Emiroglu**: Formal analysis, investigation, and visualization. **Baran Mollavelioglu**: Formal analysis, investigation, validation, software, visualization, and writing–original draft. **Nilufer Yildirim**: Data curation and resources. **Suleyman Bademler**: Data curation, supervision, and resources. **Baha Zengel**: Data curation, supervision, and resources. **Didem Can Trabulus**: Data curation and resources. **Mustafa Umit Ugurlu**: Data curation, supervision, and resources. **Cihan Uras**: Data curation, supervision, and resources. **Serkan Ilgun**: Data curation, resources, and writing–review and editing. **Gokhan Giray Akgul**: Data curation and resources. **Alper Akcan**: Data curation, supervision, and resources. **Serdar Yormaz**: Data curation, supervision, and resources. **Yeliz Emine Ersoy**: Data curation, supervision, and resources. **Serdar Ozbas**: Data curation, supervision, and resources. **Ece Dilege**: Data curation, supervision, and resources. **Bulent Citgez**: Data curation, supervision, and resources. **Yasemin Bolukbasi**: Data curation, supervision, and resources. **Ayse Altınok**: Data curation and resources. **Ahmet Dag**: Data curation, supervision, and resources. **Gül Basaran**: Data curation, supervision, and resources. **Nihat Zafer Utkan**: Data curation,

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are available from the corresponding author on reasonable request.

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