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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast Cancer Recurrence in Initially Clinically Node-Positive Patients Undergoing Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in the NEOSENTITURK-Trials MF18-02/18-03

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ABSTRACT

Background. This study aims to identify factors predicting recurrence and unfavorable prognosis in cN+ patients who have undergone sentinel lymph node biopsy (SLNB) following neoadjuvant chemotherapy (NAC).

Methods. The retrospective multi-centre "MF18-02" and the prospective multi-centre cohort registry trial "MF18-03" (NCT04250129) included patients with cT1-4N1-3M0 with SLNB+/− axillary lymph node dissection (ALND) post-NAC.

Results. A total of 2407 cN+ patients, who later achieved cN0 status after NAC and subsequently underwent SLNB, were studied. The majority had cT1-2 (79.1%) and N1 (80.7%). After a median follow-up time of 41 months, the rates of locoregional recurrence and axillary recurrence (AR) were 1.83% and 0.37%, respectively. No significant difference in locoregional recurrence or AR rates was observed between the SLNB/targeted axillary dissection-only (n = 1470) and ALND (n = 937) groups. Factors significantly linked with AR included age younger than 45 years, non-pathological complete response (non-pCR) in the breast, and nonluminal pathology. Locoregional recurrences were associated with nonluminal or HER2(+) pathology, non-pCR in the breast, and ALND. Poor prognostic factors for disease-free survival (DFS) included having cT3-T4, no breast pCR (non-pCR), ypN(+), and nonluminal pathology. No significant difference was found in DFS or disease-specific survival (DSS) rates among ypN0, ypN-isolated tumour cells, ypN-mic, and ypN1. However, significant decreases in DFS and DSS rates were observed when comparing ypN2 or ypN3 disease with ypN0.

Conclusions. The present large registry data indicate that younger patients (<45), those with nonluminal pathology, and those who only partially respond in the breast are more susceptible to axillary and locoregional recurrences.

Keywords Sentinel lymph node biopsy · Axillary dissection · Neoadjuvant chemotherapy · Axillary recurrence · Locoregional recurrence · Regional nodal irradiation · Breast cancer recurrence · Survival · Young age · Non-luminal pathology

The implementation of sentinel lymph node biopsy (SLNB), which replaces axillary lymph node dissection (ALND), has become standard in clinically node-negative breast cancer, comprising both pathologically node-negative and node-positive disease with limited nodal involvement.[1–4] This scaled-down axillary surgery improves arm morbidity and quality of life.[3–5] However, the debate continues about whether patients with initially clinically positive axilla can avoid ALND following SLNB after neoadjuvant chemotherapy (NAC) owing to a high false-positive rate (FNR).[6,7] As shown in the ACOSOG Z1071 (Alliance) and SENTINA prospective trials, the FNR can be reduced to under 10% when three or more sentinel lymph nodes (SLN) are removed, with or without dual tracer or via the removal of the marked lymph node (MLN) in a procedure known as targeted axillary dissection (TAD).[6–12] Recent studies suggest that axillary recurrence (AR) is rare in patients who demonstrate a good response to NAC and ypN0 disease.[13] Retrospective studies further highlight the oncological safety of deescalating axillary surgery in selected patients who respond well to NAC; this is based on relatively shorter follow-up periods compared with early breast cancer trials.[13–24] Outcomes from prospective studies, including NSABP-B51/RTOG, A011202, TAXIS, and AXSANA, are still pending publication.[25–28]

In our previous NEOSENTITURK MF-18-02 study—a retrospective multicentre registry study that included cN+ patients with ypN0 and ypN+ disease who were treated with SLNB-alone after NAC—we observed favourable oncological outcomes with no AR at a median follow-up of 3 years.[18] In 2019, we initiated the NEOSENTITURK MF18-03 study, a prospective multicentre study supported by the Turkish Breast Diseases Federation and the Breast Health Working Group International.[29] Given the limited data currently available, we investigated the factors associated with recurrence and poor prognosis through a combined analysis of the updated retrospective MF18-02 and the ongoing prospective MF18-03 studies. This research includes cN+ patients who became clinically node-negative following NAC and underwent SLNB with/without ALND.

MATERIALS AND METHODS

This study examines two diverse multicentre cohorts: the retrospective MF1802 registry from 14 Turkish centres ($N = 700$) and the MF1803 prospective observational registry (NCT04250129) from 45 Turkish centres and one Azerbaijani centre ($N = 1707$). Ethical approval was obtained from the Istanbul University's Faculty of Medicine, and participants of the prospective cohort offered informed consent. The prospective protocol additionally included patient-reported outcome, including quality of life, and assessment of lymphedema, which will be published later.

The study included participants older than 18 years with cT1-4, cN1-3M0 breast cancer, who were clinically node-negative after NAC and who underwent a sentinel lymph node biopsy (SLNB) or TAD with/without ALND and regional nodal radiation therapy (RNI). Exclusion criteria included cases of pregnancy-associated breast cancer, inflammatory breast cancer, systemic metastatic disease, bilateral breast cancer, secondary malignancy, those who did not have an SLNB, or those with unsuccessful lymphatic mapping (Fig. 1). Additionally, patients who did not receive an SLNB or radiation therapy also were excluded from the analysis. Axillary nodal metastases were identified by using one or more of the following modalitites, including axillary ultrasonography (US), fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), breast magnetic resonance imaging (MRI) in addition to physical exam. Moreover, clinically, nodal positivity

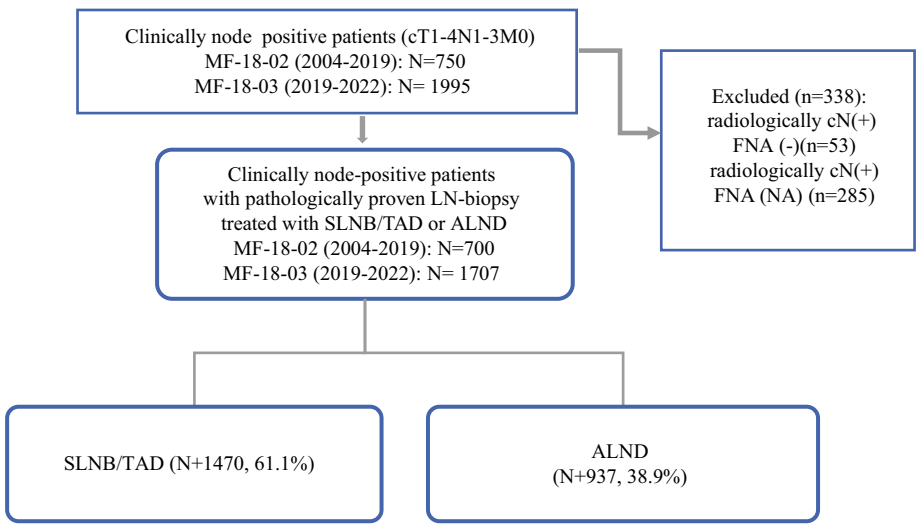


FIG. 1 Study flow; NA= not available

(cN+) was affirmed through fine-needle aspiration (FNA) or a core biopsy from the most suspicious metastatic lymph node. Patients without cytopathology-proven nodal positivity were excluded from the study (Fig. 1). According to the preference of certain surgeons, 697 (29%) patients had an ultrasound-guided marking procedure with a titanium clip and carbon dye injected into the most suspicious index biopsy-verified metastatic lymph node under axillary ultrasound before NAC.

SYSTEMIC THERAPY

The vast majority of the patients (n = 2357, 97.93%) received neoadjuvant systemic therapy between 2014 and 2022 consistent with the international guidelines. Of 2407 patients, the majority (n = 2204, 91.6%) were treated with a regimen containing antracycline and taxane. A subset of patients, 138 (5.7%), received a regimen containing antracycline without taxanes, whereas 60 patients (2.5%) had a regimen with taxanes but no antracycline. Only five patients (0.2%) were given other, different chemotherapy regimens. For patients with HER2-neu-positive disease, trastuzumab therapy (2 mg/kg) was added to their taxane regimen. Additionally, 200 of these patients (8.3%) received pertuzumab as an extra anti-HER2-neu targeted therapy along with trastuzumab. For cases of triple-negative breast cancer, carboplatin was administered to 67 patients (2.8%) and pembrolizumab to 2 more, in addition to NAC.

ADJUVANT MANAGEMENT

Patients underwent SLNB using either blue dye alone, the 99Tc-labeled colloid injection technique alone, or a combination of both at the discretion of the surgeon at different study centers following NAC. Lymph nodes deemed suspicious through intraoperative palpation were also classified as SLNs.[6] During axillary surgery, the MLN and SLNs were removed by TAD. The retrieved LNs underwent intraoperative pathological evaluation via imprint cytology and/or a frozen section.[30] The AJCC 8th edition's definition of nodal metastases was used, which included isolated tumour cells (ITCs), micrometastases, and macrometastases detected by hematoxylin and eosin (H&E) or cytokeratin immunochemistry (IHC) staining.[31] A pathologic complete response (pCR) was defined as the vanishing of invasive cancer in the breast and axillary nodes, with the presence of ductal carcinoma in situ also categorized as pCR.[32] The tumor subtypes according to the IHC staining of core biopsies before NAC were defined as reported previously, considering a Ki67 ≥20% as high cutoff value.[33]

Adjuvant radiotherapy (RT) of 45–50 Gray in 25 fractions was administered to the entire breast in patients who underwent breast-conserving surgery (BCS), or to the chest wall after mastectomy, and to axillary (level I–II–III) and supraclavicular lymph node regions in all patients with ypN0 and ypN+ disease. The radiation oncologist decided on the irradiation of the internal mammary lymph nodes based on factors, such as tumour location, clinical stage, and tumour characteristics. A boost RT of 10–16 Gy in 5–8 fractions was applied following BCS.

Patients' follow-up protocol included 6-month ultrasound of the breast and axilla and yearly mammogram of the breast after surgery followed by radiotherapy. Breast MRI or PET-CT after surgery were ordered based on the patients complaints or suspicious physical exam findings.

STATISTICAL ANALYSIS

The statistical analyses were conducted by using the SPSS 25 software program (Statistical Package for Social Sciences; SPSS, IBM Corp., Armonk, NY). The Mann-Whitney U test or Student t-test was used to estimate the differences between continuous variables, while Pearson's chi-square and Fisher's exact tests assessed categorical variables. The mean or median values of the continuous variables were determined either with standard deviation or interquartile range (IQR), respectively. Locoregional recurrences encompassed ipsilateral and contralateral ARs, infra- and supraclavicular recurrences, and recurrences in the mammaria interna region, as well as breast and chest wall recurrences. Regional recurrences included ipsilateral and contralateral ARs, infra- and supraclavicular recurrences, and recurrences in the mammaria interna region, whereas ARs were defined as ipsilateral axillary recurrences. Disease-free survival (DFS) considered locoregional and systemic metastases, whereas disease-specific survival (DSS) rate took into account breast cancer-related mortality. Prognostic factors that influenced survival were evaluated with Kaplan–Meier analyses and the log-rank test. The multivariate Cox regression model calculated the hazard ratios associated with the outcome. Statistical significance was set at p-value <0.05. The study's primary endpoints were the rates of axillary nodal recurrence and locoregional recurrence (LRR) at a minimum of 3 years median follow-up and the identification of factors related to AR and LRR. The secondary endpoints included DFS and DSS.

RESULTS

This combined analysis examined 2407 patients with cytopathology-proven cT1-4/cN1-3 disease who became cN0 (ycN0) after NAC and underwent SLNB with/without ALND between January 2004 and January 2022 as shown in the study flow (Fig. 1). Patient demographics and clinical features can be found in Table 1. Patients' median age was 47 (range 21–86) years. The majority had

TABLE 1 Factors associated with a decision for axillary lymph node dissection (ALND) following sentinel lymph node (SLN) biopsy (SLNB) or targeted axillary dissection (TAD)

Characteristics	Overall (n = 2407) n (%)	SLNB/TAD-alone (n = 1470) n (%)	ALND (n = 937) n (%)	p
Median follow-up, IQR	41 (30–53)	41 (30–54)	41 (30–52)	
Median age (min–max)	47 (21–86)	47 (21–80)	48 (21–86)	
Clinical T stage				0.022
cT1	288 (12)	189 (12.9)	99 (10.6)	
cT2	1615 (67.1)	1001 (68.1)	614 (65.5)	
cT3	325 (13.5)	179 (12.2)	146 (15.6)	
cT4	179 (7.4)	101 (6.9)	78 (8.3)	
Clinical N stage				<0.001
cN1	1943 (80.7)	1247 (84.8)	696 (74.3)	
cN2	377 (15.7)	183 (12.4)	194 (20.7)	
cN3	87 (3.6)	40 (2.7)	47 (5)	
Type of breast surgery				<0.001
BCT	1252 (52)	863 (58.7)	389 (41.5)	
Mastectomy	1155 (48)	607 (41.3)	548 (58.5)	
TAD				0.296
Yes	697 (29)	437 (29.7)	260 (27.7)	
No	1710 (71)	1033 (70.3)	677 (72.3)	
Histopathology of core biopsy and surgical specimen				0.115
Invasive ductal carcinoma	2090 (86.8)	1285 (87.4)	805 (85.9)	
Invasive lobular carcinoma	105 (4.4)	53 (3.6)	52 (5.5)	
Invasive ductal & lobular carcinoma	85 (3.5)	50 (3.4)	35 (3.7)	
Other	127 (5.3)	82 (5.6)	45 (4.8)	
pCR (breast)				<0.001
Yes	814 (33.8)	646 (43.9)	168 (17.9)	
No	1593 (66.2)	824 (56.1)	769 (82.1)	
pCR (axilla)				<0.001
Yes	1089 (45.2)	955 (65)	134 (14.3)	
No	1318 (54.8)	515 (35)	803 (85.7)	
pCR (breast and axilla)				<0.001
Yes	636 (26.4)	564(38.4)	72 (7.7)	
No	1771 (73.6)	906(61.6)	865 (92.3)	
ER				<0.001
Yes	1688 (70.1)	968 (65.9)	720 (76.8)	
No	719 (29.9)	502 (34.1)	217 (23.2)	
PR				<0.001
Yes	1458 (60.6)	835 (56.8)	623 (66.5)	
No	949 (39.4)	635 (43.2)	314 (33.5)	
HER2-neu				<0.001
Positive	835 (34.7)	578 (39.3)	257 (27.4)	
Negative	1572 (65.3)	892 (60.7)	680 (72.6)	
Ki-67 expression (n = 2239)				<0.001
Negative (<20%)	452 (20.2)	236(17.5)	216 (24.2)	
Positive (≥20%)	1787 (79.8)	1112(82.5)	675 (75.8)	
Tumor subtypes (IHC)				<0.001
Luminal HER2(−)	1212 (50.4)	655 (44.6)	557 (59.4)	
Luminal HER2(+)	526 (21.9)	355 (24.1)	171 (18.2)	
Non-luminal HER2(+)	309 (12.8)	223 (15.2)	86 (9.2)	

Table 1 (continued)

Characteristics	Overall (n = 2407) n (%)	SLNB/TAD-alone (n = 1470) n (%)	ALND (n = 937) n (%)	p
Triple-negative	360 (15)	237 (16.1)	123 (13.1)	
Mapping technique				
Blue-dye alone				
Dual tracer				
Other				
Characteristics of metastatic lymph nodes (LNs) removed (n = 1318)				<0.001
Isolated tumor cells	130 (9.9)	88 (17.1)	42 (5.2)	
Micrometastasis	254 (19.3)	158 (30.7)	96 (12)	
Macrometastasis	934 (70.9)	269 (52.2)	665 (82.8)	
Presence of extracapsular extension (n = 1318)				<0.001
Yes	363 (27.5)	78 (15.1)	285 (35.5)	
No	955 (72.5)	437 (84.9)	518 (64.5)	
Number of total metastatic LN (SLN+non-SLN) (n = 1318)				<0.001
1	537 (40.7)	328 (63.7)	209 (26)	
2	279 (21.2)	122 (23.7)	157 (19.6)	
≥3	502 (38.1)	65 (12.6)	437 (54.4)	

BCT breast conserving therapy; *PCR* pathologic complete response; *ER* estrogen receptor; *PR* progesteronereceptor; *IHC* immunohistochemistry

cT1-2 (79.1%) and N1 (80.7%) disease. Post-NAC, 52% of these patients received BCS, whereas 48% required a mastectomy. The most frequently found pathology was invasive ductal carcinoma at 86.7%. Tumour subtypes were divided according to immunohistochemical staining into luminal-HER2(−) at 50.4% (n = 1,212), luminal or nonluminal HER(+) at 34.7% (n = 835), and triple-negative at 15% (n = 360). The pCR rates were as follows: 45.2% for the axilla, 33.8% for the breast, and 26.4% for both axilla and breast.

Post-NAC, patients underwent SLNB using either blue dye alone (N = 1628, 67.6%), the 99Tc-labeled colloid injection technique alone (n = 99, 4.1%), or a combination of both (n = 680, 28.3%). Overall, 937 (37.9%) had ALND following SLN (ypN+, 85.7%) and 1470 (62.1%) underwent SLNB- or TAD-alone (ypN0, 65%). Of those treated with SLNB/TAD alone, 68.10% (n = 1001) underwent SLNB with blue dye alone. The median number of lymph nodes removed was 4 (IQR, 3–5) in the SLNB/TAD-group, whereas the median number retrieved was 14 (IQR, 11–18) in the ALND-group.

The factors influencing the decision to complete ALND following SLNB or TAD are detailed in Table 1. These included clinical tumour stage 3–4 (cT3–4), clinical node stage 2–3 (cN2–3), mastectomy, luminal tumour pathology, partial pathological response (non-pCR) to NAC, axillary nodal macrometastasis, extracapsular extension, and the presence of more than two metastases.

OUTCOME

As expected, patients in the retrospective cohort who were operated before 2019 February had longer follow-up compared with those in the prospective cohort (month, 48.90 ± 22.95 vs. 30.07 ± 12.74). After a median follow-up period of 41 months (IQR, 30–53), the systemic recurrence, LRR, regional recurrence, and AR rates were 7.23% (n = 174), 1.83% (n = 44), 0.79% (n = 19), and 0.37% (n = 9), respectively (Table 2). No significant difference was found in LRR and AR rates between the SLNB-alone and ALND groups in both the ypN0 and ypN+ subgroups. Axillary recurrences were observed typically at a median of 12 (range, 7–54) months postsurgery, and all cases contained residual invasive cancer in the breast surgical specimen. Only three of the nine ARs were isolated, whereas the remaining six were concurrent with ipsilateral breast cancer recurrence. Three of these also presented systemic metastases in the lung, liver, and bone. Interestingly, 67% (n = 6) of these had HER2(+) or triple-negative breast cancer (TNBC) at initial diagnosis. The other three cases had luminal B breast tumours. Factors associated with AR included age younger than 45, invasive cancer in the breast, and nonluminal pathology (Table 2).

TABLE 2 Clinicopathological factors associated with axillary and locoregional recurrences at a median follow-up of 41 months (IQR, 30–53)

Variables ($N = 2407$)	AR	OR (95% CI)	*p*	L-RR	OR(95% CI)	*p*	*SR*	OR (95% CI)	*p*
Age group (years)			0.004[a]			0.322[b]			0.224[b]
<45 ($n = 974$) (ref)	8 (0.8%)	11.86 (1.48–94.97)		21 (2.2%)	1.35 (0.74–2.46)		78 (8%)	1.21 (0.89–1.65)	
≥45 ($n = 1433$)	1 (0.1%)			23 (1.6%)			96 (6.7%)		
Molecular subtype			0.127[a]			0.008[b]			0.002[b]
Nonluminal (ref) ($n = 669$)	5 (0.7%)	3.23 (0.88–12.50)		20 (3.0%)	2.22 (1.21–4)		66 (9.9%)		
Luminal ($n = 1738$)	4 (0.2%)			24 (1.4%)			108 (6.2%)	0.61 (0.44–0.83)	
HER2 status			0.508[a]			0.067[b]			0.471[b]
HER2(+) ($n = 835$) (ref)	4 (0.5%)	1.51 (0.40–5.63)		21 (2.5%)	1.74 (0.96–3.16)		56 (6.7%)	0.89 (0.64–1.23)	
HER2(−) ($n = 1572$)	5 (0.3%)			23 (1.5%)			118 (7.5%)		
TNBC			0.631[a]			0.858[b]			0.001[b]
Triple neg ($n = 360$) (ref)	2 (0.6%)	1.63 (0.34–7.87)		7 (1.9%)	1.08 (0.48–2.44)		41 (11.4%)	1.85 (1.28–2.68)	
Nontriple ($n = 2047$)	7 (0.3%)			37 (1.8%)			133(6.5%)		
pCR (axilla)			0.999[a]			0.560[b]			0.008[b]
ypN(+) ($n = 1318$) (ref)	5 (0.4%)	1.03 (2.78–3,85)		26 (2.0%)	1.19 (0.65–2.17)		112 (8.5%)	1.54 (1.12–2.13)	
ypN0 ($n = 1089$)	4 (0.4%)			18 (1.7%)			62 (5.7%)		
cT stage			0.999[a]			0.936[b]			<0.001[b]
T3-4 ($n = 504$) (ref)	2 (0.4%)	1.11 (0.22–5.26)		9 (1.8%)	0.97 (0.46–2.04)		63 (12.5%)	2.33 (1.67–3.23)	
T1-2 ($n = 1903$)	7 (0.4%)			35 (1.8%)			111 (5.8%)		
cN stage			0.388[a]			0.568[b]			0.059[b]
cN2-3 ($n = 464$) (ref)	3 (0.6%)	2.1 (0.52–8.33)		7 (1.5%)	0.79 (0.35–1.79)		43 (9.3%)	1.41(0.98–2.04)	
cN1 ($n = 1943$)	6 (0.3%)	0.48 (0.12–1.91)		37 (1.9%)			131 (6.7%)		
pCR (breast)			0.033[a]			0.117[b]			0.001[b]
Non-pCR ($n = 1593$) (ref)	9 (0.6%)	na		34 (2.1%)	1.75 (0.86–3.57)		136 (8.5%)	1.89 (1.32–2.78)	
pCR ($n = 814$)	0 (0%)			10 (1.2%)			38 (4.7%)		
Presence of extracapsular extension (n = 1318)			0.620[a]			0.664[a]			0.043[b]
Yes ($n = 363$)	2 (0.6%)	1.76 (0.29–10.57)		8 (2.2%)	1.17 (0.51–2.72)		40 (11%)	1.52 (1.01–2.28)	
No ($n = 955$)	3 (0.3%)			18 (1.9%)			72 (7.5%)		
Axillary surgery			0.742[a]			0.128[b]			<0.001[b]
ALND ($n = 937$) (ref)	4 (0.4%)	1.27 (0.34–4.76)		22 (2.3%)	1.59 (0.87–2.86)		90 (9.6%)	1.75 (1.28–2.38)	
SLNB/TAD ($n = 1470$)	5 (0.3%)			22 (1.5%)			84 (5.7%)		

na not available; *ref* reference; *TNBC* triple negative breast cancer; *pCR* pathologic complete response; *ALND* axillary lymph node dissection; *SLNB* sentinel lymph node biopsy; *TAD* targeted axillary dissection

[a]Fisher's exact test

[b]Pearson chi-square test

Nonluminal or HER2(+) pathology, non-pCR in the breast, and having ALND were associated with locoregional recurrences. Patients with systemic metastases likely had cT3-4 or cN2-3 disease, nonluminal or TNBC, a non-pCR in the breast or axilla, and nodal extracapsular extension (ECE). Of note, because of the limited cases of AR and LRR, no multivariate logistic regression analysis was conducted.

The 5-year DFS rate was 86.9%, and the 5-year DSS rate was 96.5%. Reduced DFS was associated with factors, such as cT3-4, nonpathological complete response (pCR) in the breast or axilla or both, nonluminal pathology, and completion ALND. Similarly, cT3-4 of cN2-3, non-pCR in the breast or both, nonluminal pathology, and completion of ALND contributed to lowered DSS (Table 3; Fig. 2). When analyzing subgroups for posttreatment pathological nodal

TABLE 3 Factors associated with disease-free survival (DFS) and disease-specific survival (DSS) in patients with cT1-4N1-3 disease who became ycN0 after neoadjuvant chemotherapy and underwent a SLNB or TAD with/without ALND ($N = 2407$) at a median follow-up of 41 months (IQR, 30–53)

Factors	5-year DFS (%)	*p*	5-year DSS (%)	*p*
All	89.6		96.5	
Axillary surgery type		<0.001*		0.009*
SLNB	91.4		97.4	
SLNB and ALND	86.7		94.9	
Age group (years)		0.084		0.912
<45	88		95.7	
≥45	90.6		96.5	
Clinical T stage		<0.001*		<0.001*
cT1/2	90.6		97.5	
cT3/4	85.5		91.2	
Clinical N stage group		0.322		0.022*
cN1	89.9		96.8	
cN2/3	88.1		95.1	
Molecular subtypes		<0.001*		<0.001*
Luminal group	91.1		97.7	
Non-numinal group	85.6		93.4	
Pathologic complete response (breast)		<0.001*		0.049*
Yes	92.7		97.1	
No	88		95.7	
Lymph node status		0.005*		0.073
ypN-negative (=axillary pCR yes)	91.7		97.4	
ypN-positive (=axillary pCR no)	87.8		95.8	
pCR (breast and axilla)		<0.001*		0.010*
Yes	94		97.8	
No	88		95.6	
Ki-67 expression (n = 2239)		0.085		0.104
Negative (<20%)	91.7		97.7	
Positive (≥20%)	89.1		95.7	
Molecular subtype		0.001*		<0.001*
Luminal A/B/HER2(−)	91		97.7	
Luminal B/HER2(+)	91.4		96	
Non luminal B/HER2(+)	87		95	
Triple negative	84.4		92.1	
Pathological axillary stage		<0.001*		0.003*
ypN0	91.7		97.4	
ypN-ITC	90.5		94.5	
ypN-mic	90.6		97.5	
ypN1 (1–3)	90.8		96.6	
ypN2 (4–9)	80.8		95.5	
ypN3 (≥9)	80.6		89.1	
Presence of extracapsular extension (n = 1318)		0.111		0.989
Yes	84.5		95.6	
No	89.1		95.9	

SLNB sentinel lymph node biopsy; *TAD* targeted axillary dissection; *ALND* axillary lymph node dissection; *pCR* pathologic complete response; *ITC* isolated tumor cell; *mic* micrometastasis

*$p < 0.05$, Kaplan-Meier analysis (log-rank test)

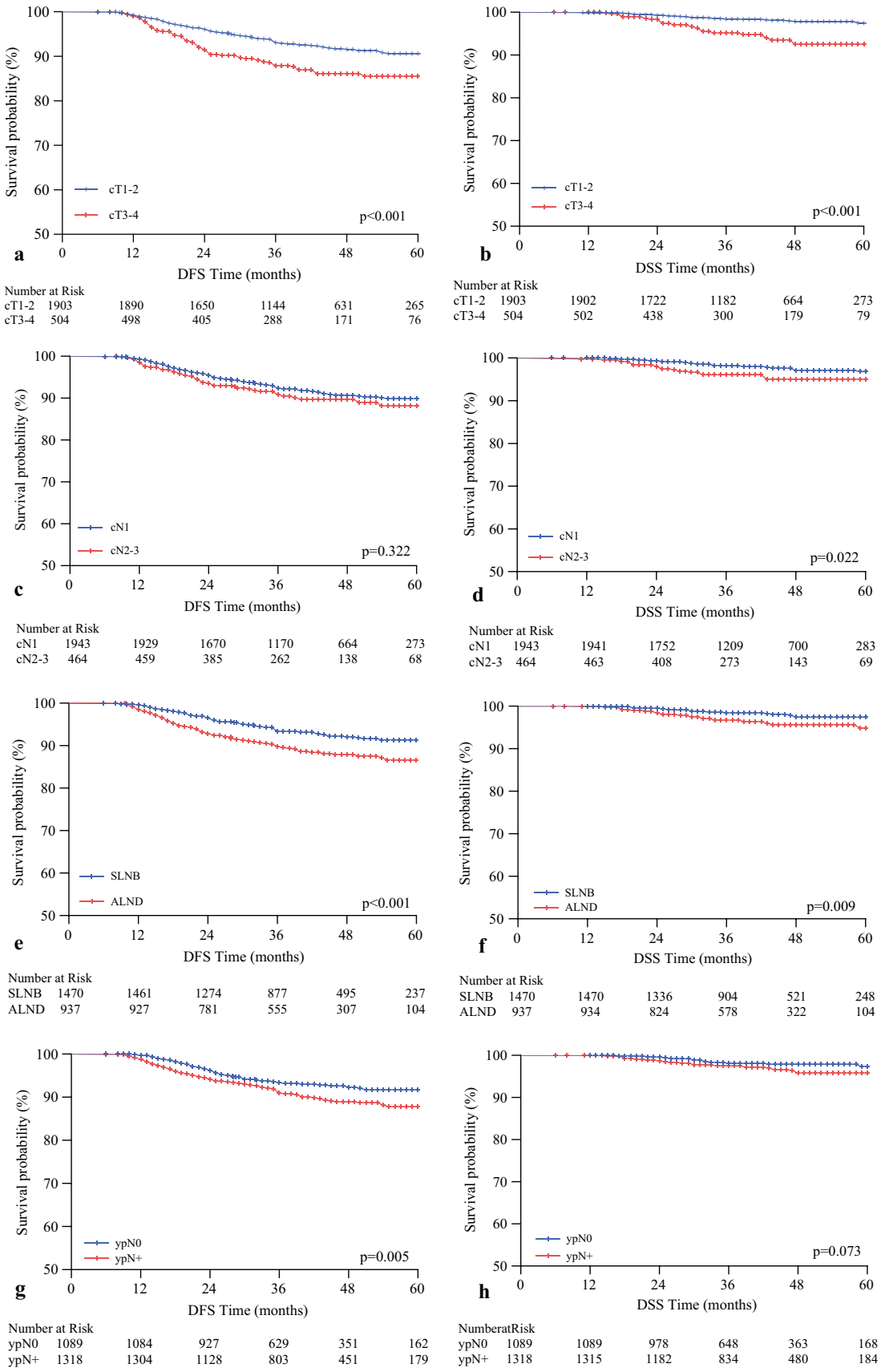


FIG. 2 Survival analyses including disease free survival (DFS) and disease specific survival (DSS)

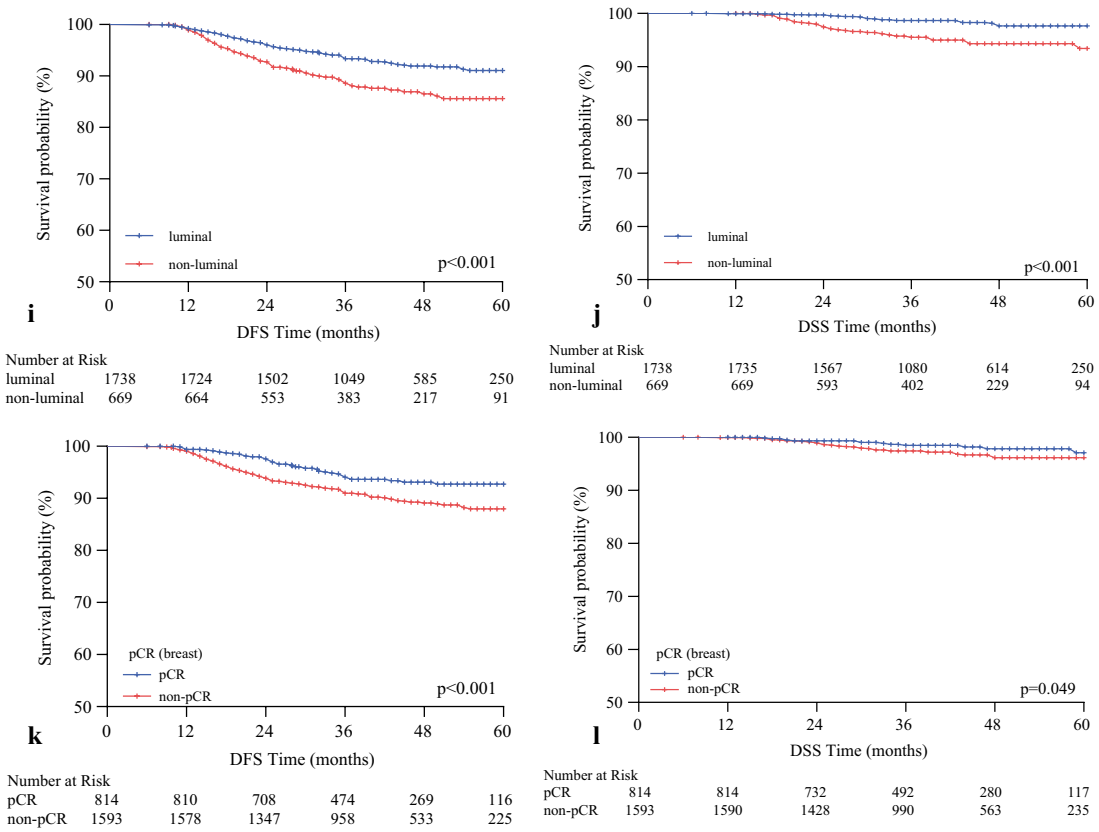


Fig. 2 (continued)

TABLE 4 Disease-free survival (DFS) and disease-specific survival (DSS) in subgroups according to the pathologic response of the axillary lymph nodes (ypN-status)

ypN-status (*n*, %)	Comparisons according to the ypN-stage	*p*-value for DFS (log-rank test)	*p*-value for DSS (log-rank test)
ypN0 (*n*=1089, 45.2%)	ypN0 vs ypN-ITC	0.425	0.128
ypN-ITC (*n*=130, 5.4%)	ypN0 vs ypN-mic	0.341	0.891
ypN-micrometastasis (*n*=254,10.6%)	ypN0 vs ypN1	0.334	0.520
ypN1 (*n*=613, 25.5%)	ypN0 vs ypN2	<0.001	0.086
ypN2 (*n*=221, 9.2%)	ypN0 vs ypN3	<0.001	<0.001
ypN3 (*n*=100, 4.2%)			
	ypN-ITC vs ypNmic	0.887	0.204
	ypN-ITC vs ypN1	0.761	0.319
	ypN-ITC vs ypN2	0.139	0.935
	ypN-ITC vs ypN3	0.048	0.162
	ypNmic vs ypN1	0.854	0.560
	ypNmic vs ypN2	0.044	0.186
	ypNmic vs ypN3	0.012	0.003
	ypN1 vs ypN2	0.004	0.298
	ypN1 vs ypN3	0.001	0.002
	ypN2 vs ypN3	0.406	0.092

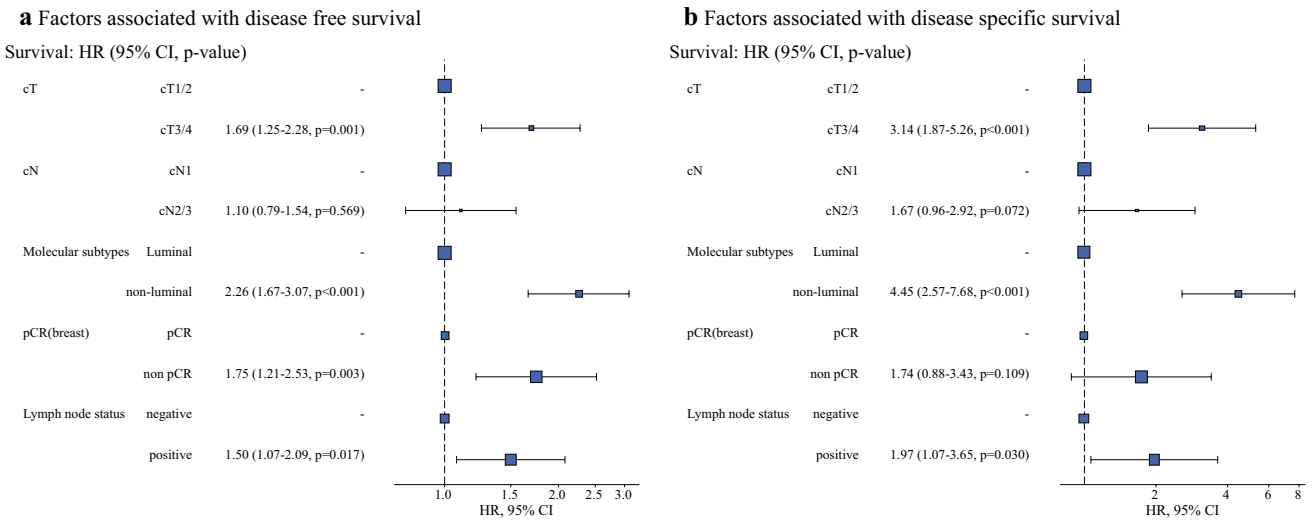


FIG. 3 Results of Multivariate Cox Regression analysis at a median follow-up of 41 months (IQR, 30-53). Cox Regression analysis (Method = Enter) *R* reference value; *HR* Hazard ratio

status (ypN-status), no significant difference was found in 5-year DFS or DSS rates among ypN0, ypN-ITC, ypNmic, and ypN1. However, ypN2 or ypN3, compared with ypN0, showed significantly lower DFS and DSS rates (Table 4).

In the multivariate Cox regression analysis related with DFS and DSS, factors, such as a cT3–4, a non-pCR in the breast or axilla, and a nonluminal pathology, were all linked with a heightened hazard ratio (HR) related to DFS. Similar associations were observed with variables, such as cT3–4 or cN2–3, a non-pCR in the breast or axilla, and a nonluminal pathology related to DSS (Fig. 3).

DISCUSSION

Axillary relapses were rarely observed in patients with cN(+) disease who underwent sentinel lymph node biopsy (SLNB) and became clinically node-negative after NAC despite high FNRs.[13–16,18] In this large registry, primarily consisting of a database collected after 2019, we found an AR rate of less than 0.5% in patients who responded to NAC and underwent SLNB, with or without ALND, over a follow-up period exceeding 3 years. Interestingly, there was no observable difference in AR or LRR rates between patients treated with SLNB or TAD and ALND. To our knowledge, this study includes the largest cohort, cT1-4/cN1-3, who underwent SLNB without ALND after NAC.

Although there is a shortage of published prospective trials with large cohorts and long-term results exceeding 5 years, retrospective studies suggest that local control of axillary surgery can be deescalated effectively in selected patients who respond positively to neoadjuvant chemotherapy (NAC). This is based on studies with shorter follow-up periods comparable to ALND.[13–24] In our previous NEOSENTITURK MF-18-02 study, a retrospective multicentre registry study that included 303 cT1-T4/cN1-3 patients treated with SLNB, we observed favorable oncological results. There were no ARs among both the 211 ypN0 and 92 ypN+ patients except for one case of supraclavicular metastasis. The median follow-up for these patients was 3 years.[18]

The current study aligns with the GANEA-2 French prospective study, which found only one AR among 419 cN0/ypN0 patients treated with SLNB-alone after NAC during an average follow-up period of 3 years.[14] In a similar vein, an analysis of 396 cT1-T4/cN0-2 patients from the European Institute of Oncology in Milan, who were tested negative for axillary staging after NAC at 61 months, only one case with ypN3(+) and mastectomy showed AR in the seventh year.[15] The 5-year overall survival (OS) and DFS rates for cN1/2 patients were 86.3% and 75.8%, respectively, while they were 96.5% and 89.6%, respectively, for DSS and DFS in this current study, with a median duration of 41 months. Furthermore, recent 10-year follow-up data from Kahler–Ribeiro–Fontana et al. of the European Institute of Oncology in Milan for 688 cT1-T3/cN0-2 patients treated with SLNB alone for ypN0 disease or ALND following SLNB for ypN(+) disease after NAC displayed extremely low AR rates less than 2%.[16]

In the present study, sentinel lymph node biopsy has been the most common procedure to stage the axilla after NAC, because only 29% of patients underwent TAD. Because clipping the suspicious node was not paid by the social security system, and owing to the lack of facilities to perform TAD in some centers in Turkey, the usage of TAD has been lower compared with other countries in Europe.[34] Of note, the majority of the patients treated with SLNB/TAD had a

mapping by blue dye alone owing to the lack of facilities to use dual tracer and/or surgeon's preference. However, the median number of lymph nodes was four in those treated with SLNB or TAD alone. Therefore, we can assume that use of single-tracer technique does not seem to be associated with high false-negative rates and worse outcome considering the favorable survival with acceptable recurrence rates in patients treated with SLNB alone as reported in our previous study MF-1802.[18]

In the recently published prospective SenTa registry study, outcomes for cT1-4N+ patients treated solely with TAD ($n = 119$) were compared against those undergoing ALND following TAD ($n = 80$). At an average 43-month follow-up, AR rates were slightly higher, at 1.4% (95% confidence interval [CI] 0–54.8) in the ALND group and 1.8% (95% CI 0–36.4) in the TAD-alone group, compared with our lower findings of 0.4% and 0.3% in the ALND and SLNB/TAD groups, respectively, over a similar average follow-up period.[23] The SenTa registry study also showed that all four patients with AR presented with concurrent locoregional recurrences; three of them also had concurrent distant metastases. Similarly, our study detected most patients with AR experiencing concurrent locoregional recurrences and one-third also having systemic recurrences in addition to the AR. In line with our current study, the SenTA study found that patients who underwent ALND following TAD had a lower DFS rate compared with those treated with only TAD (82.4% vs. 91.2%, $p = 0.04$). The lower survival rates observed in the ALND group may be attributed to the non-randomized design of both prospective registries. Patients with ALND were more likely to have residual axillary disease, as seen in the present study. Reduced AR recurrence rates might arise from variations in locoregional axillary therapy, as all patients in this study received RNI. Adjuvant radiotherapy plays a vital role in breast cancer treatment, particularly in preventing local recurrence and enhancing outcomes.[35] In the MF1802-03 cohort studies, the oncologic treatment plan consistently included adjuvant RT based on prior studies and guidelines. Patients who did not receive RNI were not included. The early results of the NSABP B51/RTOG1304 trial involving patients with cN+ disease and pCR after NAC were shared at the SABCS 2023.[25] These 5-year results revealed no significant advantage of RNI for all patients displaying exceptional responses to NAC. However, it is crucial to obtain long-term results, especially in ER-positive patients before minimizing adjuvant radiotherapy in these patient groups.

In the ACOSOG Z10 study, including of 5119 cT1-2 N0 M0 patients, factors associated with LRR were the presence of a hormone receptor-negative tumour ($p = 0.0004$) and being younger than age 50 ($p = 0.047$) in early breast cancer.[36] Of note, cT3 (compared with cT1-2) and nonpathological complete response (pCR) in the breast and axilla (compared with pCR in breast or axilla) were poor prognostic factors concerning locoregional recurrences in patients diagnosed at more advanced stages. This was concluded from a combined analysis of NSABP-18 and B-27 studies, including 3088 cT1-3N0-1 patients receiving NAC before surgery.[37]

Wong et al. found that patients with residual axillary nodal metastases, including ITCs, micrometastases, and macrometastases, showed poorer outcomes than those with ypN0. This was noted in two cohorts from Dana Farber/Brigham and Women's Cancer Center and the National Cancer Database, which studied cT1-4N0-1 patients.[38] Complementing these studies, we identified cT3-T4, non-pCR in breast or axilla, and nonluminal pathology as crucial factors predicting poor prognosis in our cohort. We are the first to report that non-pCR in the breast and nonluminal pathology were significant factors associated with both AR and LRR. Besides, being young was found to be an additional significant risk factor for AR.

The results of our study align with the European Institute of Oncology in Milan's research, which found that breast pCR, ypN0 disease, and luminal-A pathology were associated with a better patient outcome.[15] Unlike Wong et al.'s study, we found no survival difference between ypN0, ypN-ITC/micromet, and ypN1 patients. However, ypN2 or ypN3 patients exhibited poorer survival rates compared with ypN0 patients, aligning with the findings of van Nijnatten et al.[39] In the retrospective study by van Nijnatten et al., no significant difference in DFS was found between ypN0 and ypN-ITC/micromet patients (71.8% vs. 70.6%, $p = 0.978$, hazard ratio [HR] 0.92 [0.27–2.99], $p = 0.889$). However, there was a difference in ypN1-3 patients, who displayed decreased DFS compared with ypN0 patients (ypN1-2, 53.4% vs. 71.8%; $p = 0.049$, HR 1.70 [1.07–2.71], $p = 0.026$) in both univariate survival and multivariate Cox regression analyses. The recently published ICARO study showed similar outcomes between ypN0 and ypN-ITC patients.[40] These considerations should be taken into account in the forthcoming AJCC-staging classification to distinguish patients with better prognosis and to select those suitable for axillary surgery deescalation.

Moreover, there are some conflicting results reporting FNRs between 11 and 33% of intraoperative evaluation of the lymph nodes after NAC in the literature.[41,42] Importantly, the decision to omit ALND in patients with residual axillary disease should be made by a multidisciplinary team, including breast surgeons, radiation oncologists, medical oncologists, radiologists, pathologists, and nuclear scintigraphy physicians.

Almahariq et al.[17] examined patients with cT1-3N1M0 breast cancer and ypN1 disease after NAC from the NCBD database. They compared the survival of patients undergoing

SLNB (n = 304) versus ALND (n = 1313). They have reported similar outcome in a subgroup of patients with luminal-A or -B tumours or in those with a single metastatic lymph node.This suggests that ALND could be avoided in patients with minimal residual disease and favourable tumour biology.

The limitations of our study include the nonrandomized registry trial design, which encompasses some retrospective data, and a short median follow-up period of 41 months. This is particularly pertinent for patients with luminal disease, who typically exhibit recurrences after 5 years. Additionally, our reported 5-year DFS and DSS rates appear higher than those in prior studies with longer follow-ups, likely because not all of our patients have completed the 5-year mark.

CONCLUSIONS

The large, prospective registry data suggest that nodal recurrences can be detected at exceedingly low rates within 3 years postsurgery in patients with clinically node-positive disease following NAC. This is regardless of the extent of axillary surgery or nodal pathology, provided that regional nodal radiation is administered. As a result, ALND should not be the standard surgical procedure for all patients with ypN(+) disease. Patients with early nodal recurrences often show aggressive tumour biology and are prone to systemic recurrences. Hence, adjuvant systemic therapies should be considered for those with HER2(+) or triple-negative residual breast cancers postsurgery along with RNI. Further follow-up is needed to confirm the long-term safety of deescalating axillary surgery by treating with SLNB or TAD-alone, specifically in ypN(+) patients. Moreover, the outcomes of ongoing prospective clinical studies, such as A011202, TAXIS, and AXSANA,[26–28] are crucial to reinforce our findings.

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