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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

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ABSTRACT

Purpose: Factors affecting local outcome were evaluated in patients with clinically node-positive (cN+) breast cancer at diagnosis, who underwent sentinel lymph node biopsy (SLNB) alone after neoadjuvant chemotherapy (NAC).
Methods: Between 2004 and 2018, 303 cytopathology-proven cN (+) patients in a multicentric registry, who received NAC and underwent SLNB alone were analysed. All patients had regional nodal irradiation.
Results: Median age was 46 (23–70). Of those, 211 patients had ypN0 disease (69.6%), whereas 92 patients had ypN (+) disease including 19 (20.6%) isolated tumor cells (ITC), 33 micrometastases (35.9%) and 40 macrometastases (43.5%). At a median follow-up of 36 months (24–172), one patient (0.3%) with macrometastatic SLN was found to have locoregional recurrence as chest wall and supraclavicular LN metastases at the 60th month. Five-year disease-free survival (DFS) and disease specific survival (DSS) rates were 87% and 95%, respectively. Patients with cT3/4 (HR = 2.41, 95% CI; 1.14–5.07), non-luminal molecular pathology (HR = 2.60, 95% CI, 1.16–5.82), and non-pCR in the breast (HR = 2.11, 95% CI, 0.89–5.01) were found to have an increased HR compared to others in 5-year DFS. However, no difference could be found between ypN0 and ypN ITC and micrometastasis (HR = 1.23, 95% CI, 0.44–3.47), whereas there was a slight increase in HR of patients with ypN macrometastasis versus ypN0 (HR = 1.91, 95% CI, 0.63–5.79).
Conclusion: ALND could be avoided in meticulously selected cN (+) patients who underwent SLNB after NAC having breast and/or nodal pCR, cT1-2, or low volume residual nodal disease with luminal pathology, as long as axillary radiotherapy is provided.

Introduction

The mainstay of axillary staging in breast cancer has been the sentinel lymph node biopsy (SLNB) for more than two decades. The

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controversial issue to complete axillary lymph node dissection (ALND) faded away in patients with early breast cancer after the pioneering multicentric randomized trials reporting no differences in local recurrences or overall survival between patients having up to 2 positive SLNs with or without further surgery [1–6]. As to decrease the morbidity of surgical treatment is the major goal with oncological safety, there has been great enthusiasm to use SLNB to stage the axilla after neoadjuvant chemotherapy (NAC).

Studies examining patients with clinically node positive disease at diagnosis who undergo NAC reported rates of nodal pathologic complete response up to 50% which means avoiding axillary dissection in nearly half of the patients [7–9]. The documented false negative rate (FNR) was shown to be ranging between 8.4 and 14.2% in prospective trials including ACOSOG Z1071 (Alliance), SENTINA, and SN FNAC [10–12] and a meta-analysis [13] in concordance with our previous study reported a similar FNR of 13.7% [14]. Briefly, presenting with T1-3/cN1 disease, having 2 or more SLNs, using combined technique, and removing the clipped node as SLN or non-SLN decreased the false negative rates less than 5% [15,16] or 10% in the large prospective trials [10–12,17].

The major question to be answered regarding the performance of SLNB alone in patients who converted from node-positive disease to cN0 after NAC is the rate of axillary and locoregional recurrence [18,19]. The most recent challenge is to find out if we could omit ALND in a subgroup of patients with residual nodal disease in SLNs after NAC. The aim of the presented study is to evaluate factors affecting local recurrence and overall outcome in patients with clinically node-positive disease at diagnosis, who underwent SLNB without ALND after NAC, by using a retrospective multicentric registry.

Materials and methods

Between January 2004 and January 2018, 303 patients with cT1-4/cN1-3 disease who received NAC and underwent SLNB without ALND were finally analysed (Fig. 1). Clinical and pathological data were retrospectively collected in a multicentric registry database. The study was approved by the Istanbul University ethics committee. Axillary nodal metastases were detected by axillary ultrasonography (US) and fluorodeoxyglucose positron emission tomography/computed tomograph (FDG-PET/CT), and breast magnetic resonance imaging (MRI) in addition to physical exam as reported previously [20]. Patients were considered to have clinically axillary lymph node positivity (cN+) at diagnosis when verified as cytopatology-proven cN+ (see Fig. 2).

Following NAC, patients underwent SLNB with blue dye alone (66%) or combined blue dye and ^{99}Tc-labeled colloid injection technique (34%). Palpable suspicious lymph nodes were also considered as SLN as described before [11,21]. Intraoperative evaluation of SLNs were performed by imprint cytology and/or frozen section, and examined for final definitive pathology as reported previously [14]. SLNs containing micrometastases and isolated tumor cells (ITC) detected by H&E or cytokeratin immunochemistry (IHC) staining were considered positive according to the AJCC 8th edition. Pathologic complete response (pCR) was defined as the absence of invasive cancer both in the breast and in the axillary lymph nodes whereas presence of ductal carcinoma in situ was also considered as pCR [22]. The tumor subtypes according to the IHC staining of core biopsies before NAC were defined as follows [23]: luminal A; ER (+) or PR (+), HER2-neu (−), Ki67 < 20%; luminal B, ER (+) or PR (+), HER2-neu (+) and/or Ki67 ≥ 20%; non-luminal HER2-neu (+), ER (−) PR (−) HER2-neu (+); triple-negative, ER (−) PR (−) HER2-neu (−).

The majority of the patients (n = 252, 83.2%) received 4 cycles adriamycin (60 mg/m^2) and cyclophosphamide (500 mg/m^2) plus 12 cycles of weekly paclitaxel (80 mg/m^2). Of the remaining patients, 24 (8%) had four cycles of 5-fluorouracil (500 mg/m^2), epirubicin (100 mg/m2), and cyclophosphamide (500 mg/m^2) plus 4 cycles of docetaxel (75 mg/m^2), 2 patients with triple negative disease had docetaxel followed by carboplatine, and 25 patients (8.3%) received antracycline and taxane based chemotherapy regimens with different protocols. All patients with HER2-neu positive disease additionally received trastuzumab therapy (2 mg/kg) with taxanes, and 3 of them had also pertuzumab as anti-HER2-neu targeted therapy in addition to the trastuzumab.

Adjuvant radiotherapy (RT) was given 45–50 Gy in 25 fractions to the whole breast in patients treated with breast conserving surgery or chest wall for mastectomy, and axillary (level I-II-III) and supraclavicular lymph node regions for all patients with ypN0 and ypN + disease. RT to the mammary internal lymph nodes was

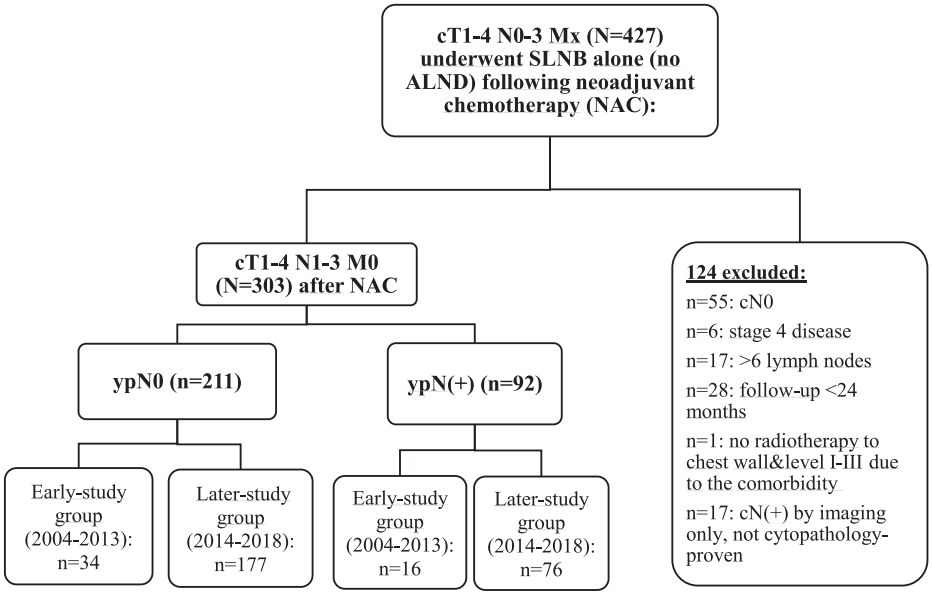

Fig. 1. Turkish multicentric Neosenti-TURK MF-18-02-study Flow chart.

delivered upon discretion of the treating radiation oncologist, and according to the tumor characteristics such as clinical stage or location. Boost RT for tumor bed was also delivered to patients treated with breast conserving surgery. Boost doses are 10–16 Gy in 5–8 fractions. RT was delivered via 2-dimensional (2D) Conventional or 3-Dimensional Conformal Radiation Therapy (3D-CRT) or Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) treatment techniques.

Following completion of RT, patients with hormone receptor positive disease received hormonotherapy including mainly tamoxifen with/without leuprolide acetate monthly for premenopausal patients and aromatase inhibitors for postmenopausal patients. Trastuzumab therapy was offered to patients with HER2 receptor overexpression for one year duration.

Statistical analysis

The statistical analysis was performed by using the statistical software program SPSS 25 (Statistical Package for Social Sciences; SPSS, IBM Corp., Armonk, NY, USA). To assess the differences between the groups, categorical variables were evaluated by Pearson Chi-Square, and Fisher's Exact Tests in two-tailed univariate analyses. Furthermore, Mann-Whitney *U* test was used to estimate the differences between nonparametric continuous variables.

Disease-free survival (DFS) was analysed by considering local and systemic metastases, and disease-specific survival (DSS) rates was analysed by considering breast cancer-related mortality. All nodal recurrences of the axillary and supraclavicular and mammaria interna region, along with breast and chest wall recurrences were accepted as local recurrence (LR), and local recurrence free survival was analysed by considering local metastases. Kaplan-Meier analyses were used for the survival curves test, and log rank test was used to compare different prognostic factors affecting outcome. Multivariate Cox regression analysis was performed to assess the hazard ratio of factors associated with prognosis that were found to be statistically significant in univariate analysis. A p value equal or less than 0.05 was considered as statistically significant.

Results

Median age of patients was 46 (23–70). Of 303 patients, 218 (71.9%) were clinically T1-2, and 85 patients (28.1%) were clinically T3-4 before receiving NAC, whereas 256 patients were cN1 (84.5%), and 47 patients were cN2-3 (15.5%) (Table 1). The majority of patients (n = 199, 65.7%) were treated with breast conserving therapy (BCT), whereas the remaining 104 (34.3%) underwent mastectomy with (n = 39) or without reconstruction.

The median number of LNs removed was 3 [1–6]. The majority of patients (n = 262, 86.5%) had 2 or more LNs retrieved in the final definitive pathology regardless of the SLNB technique (blue dye alone, n = 170, 85%, and combined technique, n = 92, 89.3%). Of ypN (+) patients (n = 92, 30.4%), 40 cases had macrometastasis (43.5%), 33 had micrometastasis (35.9%) and 19 had ITC (20.6%) in the final definitive pathology (Table 1). Of those, 70 (76.1%) had one metastatic lymph node, whereas 20 (21.7%) had 2 metastatic lymph nodes. The remaining 2 patients were found to have 3 metastatic lymph nodes with micrometastatic involvement who declined a completion axillary node dissection. Furthermore, extracapsular extension was present in only 8 patients (8.7%). All ypN (+) patients had a negative intraoperative lymph node evaluation, and axillary dissection was not performed as a decision of the patient following a discussion with the surgeon.

When ypN (+) patients were compared to the group with the ypN0 (axillary pCR), patients with ypN0 were more likely to have tumors with lymphovascular invasion, higher Ki-67 scores (≥20%), and non-luminal tumors including triple negative breast cancer or HER2-neu positivity (non-luminal tumors: ypN0, 39.6% (n = 82) vs ypN+, 14.3% (n = 13); p < 0.001). Contrastly, patients with ypN (+) were more likely to have ER or PR positive tumors that would probably cause a decreased downstaging response to NAC resulting in diminished pCR in the breast and axilla (Table 1). In logistic regression analysis, significant factors associated with axillary pCR were higher Ki-67 scores (≥20%) (OR = 2.01; CI 95%: 1.01–4.01, p = 0.046), non-luminal tumor type (OR = 2.07; CI 95%: 0.99–4.34, p = 0.055), and breast pCR (OR = 4.40; CI 95%: 2.11–9.18, p<0.001).

Outcome

Patients in the early (2004–2013, n = 50, 16.5%) and later study group (2014–2018, n = 253, 83.5%) had a median follow-up time of 95 months (24–172) and 35 months (24–72), respectively (Table 1). Furthermore, patients with ypN0 (n = 34) and ypN (+) (n = 16) in the early study group had a median follow-up of 108 months (31–172), and 86.5 months (24–167), whereas patients with ypN0 (n = 177) and ypN (+) (n = 76) in the later study group had a median follow-up of 35 months (24–72), and 34.5 months (24–72), respectively. At a median follow-up time of 36 months (24–172) for the whole cohort (n = 303), none of the patients developed an axillary recurrence. The ipsilateral breast cancer recurrence rate was found to be 3% among patients with BCT (Table 2). Furthermore, one cT2N1 patient (0.3%) with macrometastatic SLNB including extracapsular invasion was found to have locoregional recurrence including chest wall and supraclavicular region metastasis at the 60th month. No difference could be detected in the local recurrence rate after BCT, chest wall recurrence after mastectomy, regional nodal recurrence including axilla and/or supraclavicular region and systemic recurrence rates between patients with ypN0 and ypN (+) disease (Table 2).

Five-year local recurrence (LRR)-free, disease-free survival (DFS) and disease specific survival (DSS) rates were estimated as 96.6%, 86.7% and 95.3%, respectively. (Table 3). Patients with cT1/2, luminal tumors, a pCR in the breast and breast/axilla were more likely to have a better 5-year DFS rate compared to non-responders (Table 3, Fig. 2a–c). However, no difference could be found in 5-year LRR-free survival, DFS, and DSS rates between patients with a negative or positive ypN and also between those groups with ypN-negative disease versus with ypN ITC and micrometastasis versus ypN-macrometastasis (Table 3, Fig. 2d). Furthermore, patients with ER-positive and luminal type tumors were found to have a better 5-year LRFS compared to those with ER-negative or non-luminal tumors (Table 3). However, no difference could be found in other clinical and pathological parameters associated with LRFS, DFS and DSS survival rates. In multivariate Cox regression analysis, patients with cT3/4 (HR = 2.41, 95% CI; 1.14–5.07) and non-luminal pathology (HR = 2.60, 95% CI, 1.16–5.82), and non-pCR in the breast (HR = 2.11, 95% CI, 0.89–5.01) were found to have an increased HR compared to others in 5-year DFS, even though the statistical significance could not be obtained for the factor non-PCR in the breast (p = 0.089). However, no difference could be found between patients with ypN-ITC and micrometastasis versus ypN0 disease (HR = 1.23, 95% CI, 0.44–3.47), even though there was a slight increase in HR for patients with macrometastasis versus ypN0 that did not reach a statistical significance (HR = 1.91, 95% CI, 0.63–5.79) in 5-year DFS. (Table 4).

Discussion

Despite a relatively higher FNR in patients with cN (+) disease undergoing SLNB after NAC, high axillary relapses were

Table 1
Demographic and pathological characteristics of cT1-4/N1-3 patients who underwent sentinel lymph node biopsy (SLNB) with negative axillary staging after completion of neoadjuvant chemotherapy (NAC), and factors associated with axillary pathologic complete response (pCR).

	N = 303	ypN (−) (N = 211)	ypN (+) (N = 92)	
Characteristics	Total N (%)	N (%)	N (%)	*P*value
Median follow-up	36 (24–172)	36 (24–172)	37 (24–167)	0.619**
Median follow-up for patients (months)				
Early study group between 2004 and 2013	95 (24–172) (n = 50)	108 (31–172) (n = 34)	86.5 (24–167) (n = 16)	0.072**
Later study group between 2014 and 2018	35 (24–72) (n = 253)	35 (24–72) (n = 177)	34.5 (24–72) (n = 76)	0.589**
Median age(Minimum-Maximum)	46 (23–70)	46 (23–70)	44 (24–70)	0.396**
Age				0.848*
≤50	200 (66)	140 (66.4)	60 (65.2)	
>50	103 (34)	71 (33.6)	32 (34.8)	
Clinical T stage				0.075*
cT1	24 (7.9)	19 (9)	5 (5.4)	
cT2	194 (64)	126 (59.7)	68 (73.9)	
cT3	55 (18.2)	45 (21.3)	10 (10.9)	
cT4	30 (9.9)	21 (10)	9 (9.8)	
				0.079*
cT1/2	218 (71.9)	145 (68.7)	73 (79.3)	
cT3/4	85 (28.1)	66 (31.3)	19 (20.7)	
Clinical N stage				0.666*
cN1	256 (84.5)	176 (83.4)	80 (87)	
cN2	41 (13.5)	31 (14.7)	10 (10.9)	
cN3	6 (2)	4 (1.9)	2 (2.2)	
Type of Breast Surgery				0.524*
BCT	199 (65.7)	141 (66.8)	58 (63)	
Mastectomy	104 (34.3)	70 (33.2)	34 (37)	
Histopathology of core biopsy and surgical specimen				0.264*
Invasive ductal carcinoma	245 (80.9)	174 (82.5)	71 (77.2)	
Invasive Lobular carcinoma	15 (5)	8 (3.8)	7 (7.6)	
Invasive ductal&lobular carcinoma	3 (1)	1 (0.5)	2 (2.2)	
Other***	40 (13.2)	28 (13.3)	12 (13)	
Grade(n=104)				0.424*
I/II	59 (56.7)	42 (53.8)	17 (65.4)	
III	45 (43.3)	36 (46.2)	9 (34.6)	
Presence of LVI(n=153)				**0.031***
Yes	53 (34.6)	26 (28)	27 (45)	
No	100 (65.4)	67 (72)	33 (55)	
pCR (breast)				**<0.001***
Complete	124 (40.9)	108 (51.2)	16 (17.4)	
Partial	179 (59.1)	103 (48.8)	76 (82.6)	
ER(n=298)**				**<0.001***
Yes	191 (64.1)	114 (55.1)	77 (84.6)	
No	107 (35.9)	93 (44.9)	14 (15.4)	
PR(n=298)**				**<0.001***
Yes	165 (55.4)	98 (47.3)	67 (73.6)	
No	133 (44.6)	109 (52.7)	24 (26.4)	
HER2- neu(n=298)**				0.103*
Negative	196 (65.8)	130 (62.8)	66 (72.5)	
Positive	102 (34.2)	77 (37.2)	25 (27.5)	
Ki-67 expression (n=242)**				**0.004***
Negative (<%20)	49 (20.2)	25 (15)	24 (32)	
Positive (≥20%)	193 (79.8)	142 (85)	51 (68)	
Tumor Subtype (IHC) (n=289)**				**0.001***
Luminal A	27 (9.3)	15 (7.4)	12 (14.0)	
Luminal B/HER2(−)	103 (35.6)	62 (30.5)	41 (47.7)	
Luminal B/HER2(+)	65 (22.5)	45 (22.2)	20 (23.3)	
Non luminal B/HER2(+)	38 (13.1)	33 (16.3)	5 (5.8)	
Triple negative	56 (19.4)	48 (23.6)	8 (9.3)	
				<0.001*
Luminal	203 (68.1)	125 (60.4)	78 (85.7)	
Non-luminal	95 (31.9)	82 (39.6)	13 (14.3)	
Sentinel Lymph Node Methodology				0.388*
Blue Dye	200 (66)	136 (64.5)	64 (69.6)	
Combined (Blue dye and radioisotope)	103 (34)	75 (35.5)	28 (30.4)	
Number of total LN				0.782*
1	41 (13.5)	30 (14.2)	11 (12)	
2	44 (14.5)	32 (15.2)	12 (13)	
3	69 (22.8)	45 (21.3)	24 (26.1)	
4-6	149 (49.2)	104 (49.3)	45 (48.9)	
Characteristics of metastatic lymph nodes (LNs) removed	N = 92			
Isolated tumor cells	19 (20.6)	–	19 (20.6)	
Micrometastasis	33 (35.9)	–	33 (35.9)	
Macrometastasis	40 (43.5)	–	40 (43.5)	

(*continued on next page*)

Table 1 (*continued*)

	N = 303	ypN (−) (N = 211)	ypN (+) (N = 92)
Presence of extracapsular extension			
Yes	8 (8.7)	–	8 (8.7)
No	84 (91.3)	–	84 (91.3)
Number of total metastatic LN (n=92)			
1	70 (76.1)	–	70 (76.1)
2-3	22 (23.9)	–	22 (23.9)

values < 0.05 were considered statistically significant (in bold), *Chi-Square Tests*, **Mann-Whitney *U* Test.
***other: 2 metaplastic cancers, 2 musinous cancers, 1 medullary cancer, 35 unspecified invasive cancers (23 of them are pCR in breast and 12 of those are partial response in breast).
****Data was not available for ER, PR and HER2-neu staining for 5 patients, and Ki-67 stainings were not available for 61 patients, and therefore a discrimination of luminal A and B could not made in 9 patients.

Table 2
Local, locoregional and systemic recurrences in cT1-4N1-3 patients with ypN0/ypN (+) disease (N = 303).

	LN Status			
	ypN (−)	ypN (+)		
	N (%)	N (%)	Total N (%) (N = 303)	*P* value
Local recurrence after BCT[a]				0.999
Yes	4 (2.8)	2 (3.4)	6 (3)	
No	137 (97.2)	56 (96.6)	193 (97)	
Chest wall recurrence after mastectomy				0.327
Yes	0 (0.0)	1 (2.9)	1 (1)	
No	70 (100.0)	33 (97.1)	103 (99)	
Locoregional (axilla, peripheric lymphatic, mammaria interna) recurrence				0.304
Yes (supra)	0 (0)	1 (1.1)	1 (0.3)	
No	211 (100)	91 (98.9)	302 (99.7)	
Systemic recurrence				0.787
Yes	17 (8.1)	9 (9.8)	26 (8.6)	
No	194 (91.9)	83 (90.2)	277 (91.4)	

[a] **BCT:** breast conserving therapy.

interestingly not seen in published studies without ALND [9,24–27]. Our results presented in this study of 303 patients cT1-T4/cN1-3 with clinically negative axillary staging after NAC who underwent SLNB seem to be therefore encouraging. To our knowledge, this is the largest cohort cT1-4/cN1-3 with SLNB without ALND following NAC. We first report here excellent local control could be achieved even in 92 cases with a pN + without performing ALND at a median a follow-up of 36 months. In this analysis, we excluded all patients with a follow-up less than 2 year and included all patients up to 14.3 year follow-up in our database. The majority of the patients (n = 253, 83.5%) included in the later study group were operated between 2014 and 2018 after the publication of large prospective trials "SENTINA" and "ACOSOG Z1071" [10,11]. Patients in the early study group between 2004 and 2013 (n = 50, 16.5%) were found to have a median follow-up of 95 months including 16 patients with ypN+ in the final pathology. Additionally, patients with a final pathology report with >6 LNs removed but without ALND were not included into the study (Fig. 1) to exclude patients who potentially could have undergone sampling in addition to SLNB, and to evaluate the oncological safety of SLNB perfomance more accurately. Of note, ≤ 3 SLNs were removed in 51% of patients without ALND in the present study.

There are few studies regarding outcome in patients treated with SLNB alone without ALND following NAC [9,24–28]. Classe et al. recently reported one axillary recurrence among 419 patients with initial cN0 who underwent SLNB-alone with a negative SLN after NAC at median follow-up of 3 years in the French multicentric prospective study GANEA-2 [28]. Furthermore, Martelli et al. recently reported the outcome of 353 patients with cT2 cN0/1 disease who were prospectively assigned SLNB after NAC between 2007 and 2015 [26]. At a median follow-up of 9 year, none of the patients with pN0 treated with SLNB-alone developed an axillary failure with a 10-year OS and DFS of 89% and 79%, respectively. Therefore, they suggested patients with cT2 cN0/1 whose SNs are metastasis-free (pN0) after NAC could be safely offered SNLB alone without affecting OS or DFS.

Galimberti et al. from the European Institute of Oncology in Milan reported the results of 396 patients cT1-T4/cN0-2 with negative axillary staging after NAC [24]. At a median follow-up of 61 months, only one patient with a positive SLN and ypN3 disease who underwent ALND had an axillary recurrence at the 7th year, and the 5-year OS and DFS of patients with cN1/2 were 86.3% and 75.8%, respectively. In the present study cohort, the 5-year DSS and DFS were found to be 95.3% and 86.7% at a 36-month median follow-up. In concordance with all these studies, we also report here a very low locoregional recurrence rate since we do have only one cT2N1 patient developed a supraclavicular metastasis concomitant with chest wall recurrence at the 60th month having a SLN metastasis containing extracapsular extension (1/1 SLN+), and no axillary failure has been observed in our cohort at least at a 36-month median follow-up. Among patients with cN1/2 in Galimberti's study and in our study, no difference could be found in outcome between patients with ypN+ and ypN0 disease. However, these findings could be due to the short follow-up and relatively small number of patients in the ypN + SLN-only-group with selection bias such as low volume residual disease with luminal pathology in our study.

Kahler-Ribeiro-Fontana et al. from the European Institute of Oncology in Milan recently reported the 10-year follow-up results of 688 patients initially cT1-T3/cN0-2 with negative axillary staging after NAC who underwent SLNB and ALND in the case of metastatic SLN [27]. After a median follow-up of 9.2 years, axillary failure

Table 3
Clinical and pathological characteristics associated with outcome in cT1-4N1-3 patients with ypN0/ypN (+) disease.

Characteristics of patients		Five-year L-RFS		Five-year DFS		Five-year DSS	
Total (N = 303)		All = 96.6%		All = 86.7%		All = 95.3%	
	N	%	*P* value	%	*P* value	%	*P* value
Clinical Stage			0.416		**0.014**		**0.004**
cT1/2	218	96.2		90.3		97.6	
cT3/4	85	97.8		78.7		84.9	
Surgery after Neoadjuvant Treatment			0.339		0.910		0.088
Breast Conserving Surgery	199	96.1		86.6		96.3	
Mastectomy	104	97.1		86.8		94.1	
Histological type			0.776		0.787		0.453
Invasive ductal carcinoma	245	96.4		86.1		95	
Other	58	97.2		87.5		96.6	
Estrogen receptor (n=298)			**0.006**		0.144		0.614
Positive	191	98.8		90.2		96.6	
Negative	107	92.5		80.9		94	
Progesterone receptor(n=298)			0.457		0.317		0.446
Positive	165	97.4		90.2		97.7	
Negative	133	95.4		82.6		92.8	
HER2-neu (n=298)			0.191		0.646		0.960
Positive	102	94.6		84.7		94.8	
Negative	196	97.6		88.3		96.1	
Median Ki-67 expression (range) (n=242)			0.375		0.131		0.449
Negative (<%20)	49	95.2		83.4		97.4	
Positive (≥20%)	193	97.6		88.3		93.5	
Molecular Subgroup (IHC) (n=289)			0.207		0.788		0.673
Luminal A	27	100		92		100	
Luminal B/HER2(−)	103	96.6		91.6		96.3	
Luminal B/HER2(+)	65	98.4		90.5		95.7	
Non luminal B/HER2(+)	38	88.7		77.1		93.8	
Triple negative	56	97.3		84.8		93.1	
			0.020		**0.036**		0.394
Luminal	203	98.4		90.4		96.8	
Non-luminal	95	92.6		79.5		93.1	
Pathological Complete Response (breast)			0.354		0.067		0.445
Complete	124	95.1		91.5		95.4	
Partial	179	97.6		83.1		91.9	
Pathological Complete Response (axilla)			0.931		0.322		0.452
ypN-negative	211	96.8		88		96.2	
ypN-positive	92	95.8		84		93.3	
Pathological Complete Response (breast and axilla)			0.678		**0.038**		0.280
Complete	108	96		94.2		97.2	
Partial	195	97		82.3		91.4	
Type of Lymph Node Metastasis			0.965		0.410		0.775
Negative	211	96.8		88		95.8	
ITC (n = 19) and micrometastasis (n = 33)	52	97.2		85.3		92.6	
Macrometastasis	40	85.7		81.2		93.6	
Presence of extracapsular extension			0.102		0.209		0.303
Yes	8	50		72.9		94.1	
No	84	98.1		85.7		85.7	
Number of total metastatic LN (n=92)			0.420		0.897		0.288
1	70	90		84.2		91.3	
2–3	22	92.3		85.6		100	
Number of total LN			0.711		0.967		0.950
≤3	154	97.7		87.5		94	
4–6	149	95.5		85.1		96.9	

Significant p values are bold.
L-RFS: Local recurrence free survival, DFS: Disease free survival, DSS:Disease specific survival.

occurred in 1.8% of the initially cN1-2 patients and in 1.5% of the initially cN0 patients. In multivariate analysis, luminal-A pathology, ypN0 disease and breast-pCR were associated with a better outcome in the whole cohort and in patients with cN1-2 in concordance with their previous report [24] and with our present study. We similarly found that a non-luminal molecular pathology and a non-pCR in the breast were associated with an increased HR compared to others in 5-year DFS. However, no difference could be found between ypN0 and ypN ITC and micrometastasis, whereas there was a slight increase in HR of patients with ypN macrometastasis versus ypN0 (HR = 1.91, 95% CI, 0.63–5.79) that did not reach the statistical significance. This discrepancy might be due the small size of patients with ypN (+) and selection bias since the ypN0 patients were more likely to have a non-luminal pathology associated with more aggresive tumor biology such as HER2-neu (+) or triple-negative breast cancer, whereas patients with ypN (+) disease were more likely to have a luminal pathology.

Wong et al. also reported a worse outcome in cT1-4N0 patients diagnosed with an axillary pathology containing ITC or micrometastasis or macrometastasis compared to ypN0 as demonstrated in 2 cohorts from Dana Farber/Brigham and Women's Cancer Center and National Cancer Database, respectively [29]. Furthemore, results from the combined analysis of B-18 and B-27, which included nearly 3100 patients demonstrated higher LRR and

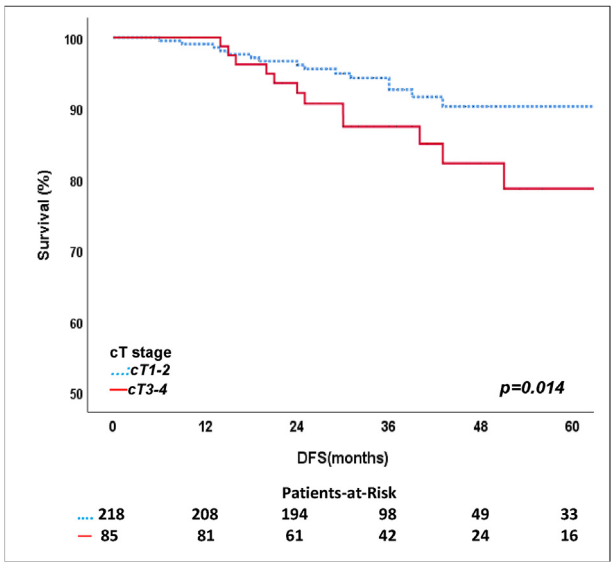

Fig. 2a. Five-year disease free survival (DFS) in cT1/2 versus cT3/4 NAC (90.3% vs 78.7%, respectively, p = 0.014).

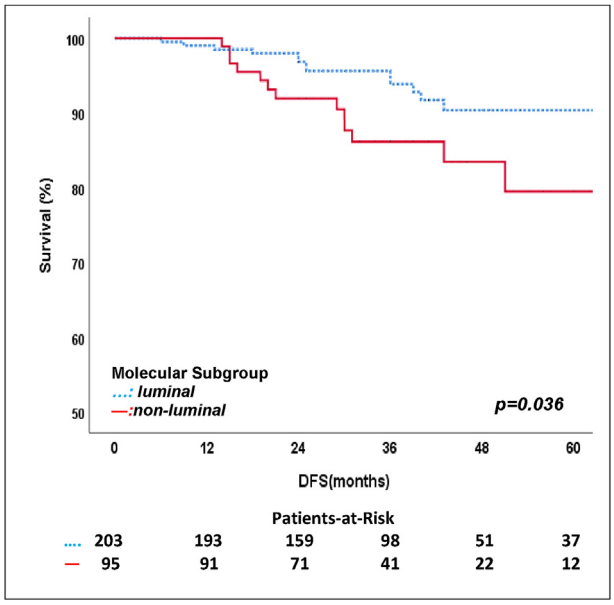

Fig. 2b. Five-year DFS in luminal versus non-luminal patients after NAC (90.4% vs 79.5%, respectively, p = 0.036).

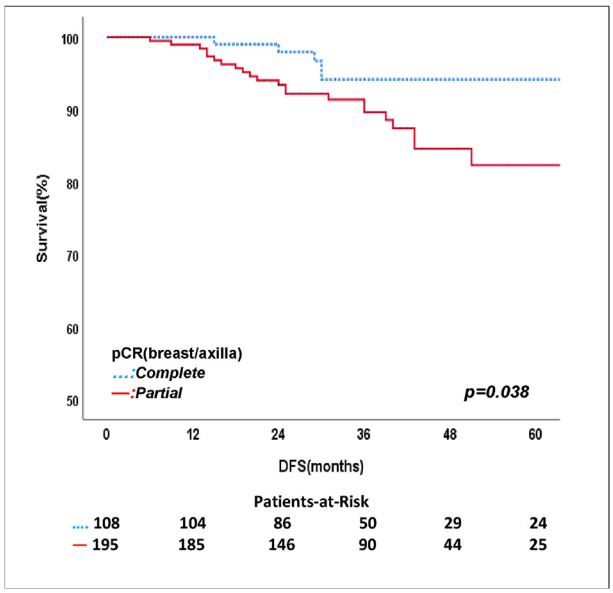

Fig. 2c. Five-year DFS in pCR (breast and axilla) versus non-pCR (breast and axilla) after NAC (94.2% vs 82.3%, respectively, p = 0.038).

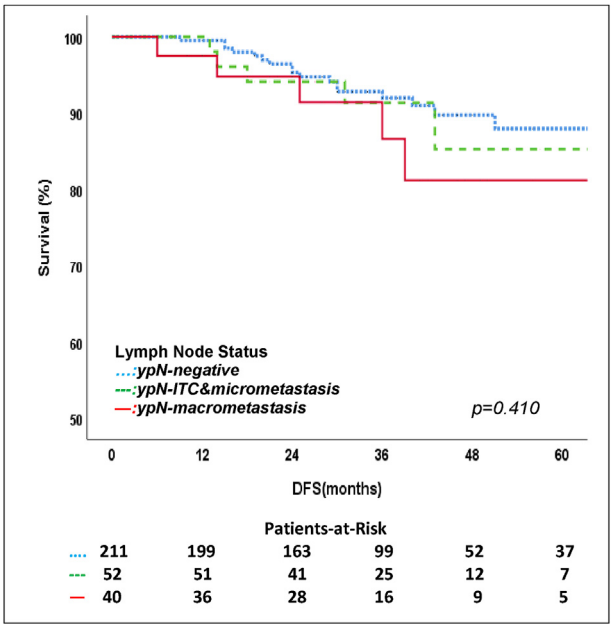

Fig. 2d. Five-year DFS in ypN-negative vesus ypN-ITC and micrometastasis vs ypN-macrometastasis patients after NAC (88% vs 85.3% vs 81.2%, p = 0.410).

worse outcomes between patients with residual disease in the nodes after NAC [30]. Of note, these studies also included patients with cN0 disease that may therefore differ from our study, and none of our patients did undergo ALND to reflect the real nodal status of our patients with ypN0 disease.

These results suggest that RT may be useful in cN1 or cN1-2 patients who become cN0 after NAC, as investigated in prospective NSABP-B51/RTOG, ALLIANCE, and TAXIS and NeoSenti-TURK MF-18-03 trials, respectively [31–34]. Our contemporary multidisciplinary management of patients with clinically node-positive disease at diagnosis provides favorable outcome with excellent local control in selected patients with either ypN (−) or low-volume residual nodal disease following NAC. Of note, the majority of our patients with ypN (+) had luminal tumor (85.7%), and received adjuvant hormonotherapy following completion of NAC and RT. Based on previous studies and our present report, ALND could be safely avoided in meticulously selected cN1-2 patients with negative axillary staging after NAC, particular in cases with breast and nodal pCR, low-volume nodal disease including ITC or micrometastasis and luminal pathology as long as adjuvant axillary RT along with systemic therapies including hormonotherapy is provided. The limitations of our study are small sample size regarding patients with ypN (+) disease and short median follow-up. We therefore have an ongoing prospective registry trial opened in Turkey "Turkish Multicentric NeoSenti-TURK MF-18-03-Study" accruing patients with node-positive disease having a negative

Table 4
Cox proportional hazards regression model assessing factors associated with disease free and disease specific survival in cT1-4 N1-3 patients with ypN0/ypN (+) disease.

	Disease Free Survival		Disease Specific Survival	
Factors	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Clinical T stage		**0.021**		**0.019**
cT1/2	Reference [1]		Reference [1]	
cT3/4	2.41 (1.14–5.07)		5.53 (1.32–23.19)	
Molecular subtypes		**0.020**		0.291
Luminal group	Reference [1]		Reference [1]	
Non-luminal group	2.60 (1.16–5.82)		2.17 (0.51–9.17)	
Pathological Complete Response (breast)		0.089		0.613
Complete	Reference [1]		Reference [1]	
Partial	2.11 (0.89–5.01)		1.46 (0.34–6.40)	
Lymph Node Status				
Negative	Reference [1]		Reference [1]	
ITC and micrometastasis	1.23 (0.44–3.47)	0.696	1.90 (0.33–10.82)	0.472
Macrometastasis	1.91 (0.63–5.79)	0.255	1.73 (0.17–18.08)	0.646

Hazard ratio (HR) are presented with their 95% confidence interval (CI) and the significant p-values are bold.

axillary staging after NAC undergoing SLNB±ALND (34).

In conclusion, longer follow-up and results of the ongoing prospective trials are required to make a more accurate algoritm for omitting ALND in patients with residual nodal disease following NAC. Therefore, ALND should still be the standard approach outside clinical trials until the results of the ALLIANCE trial randomizing ypN + after NAC to ALND vs axillary RT with a much larger cohort of patients along with other prospective trials with similar designs including TAXIS and NeoSenti-TURK are reported.

Compliance with ethical standarts

Ethics approval and consent to participate.

The study was approved by the ethical committee of Istanbul University, Istanbul Faculty of Medicine, in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration. Informed consent was obtained from all individual participants included in the study.

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Declaration of competing interest

The following authors “Neslihan Cabıoğlu, Hasan Karanlık, Nilüfer Yıldırım, Mahmut Müslümanoğlu, Güldeniz Karadeniz Çakmak, Didem Can Trabulus, Cihan Uras, Halil Kara, Baha Zengel, Ayfer Kamalı Polat, E. Yeliz Ersoy, Mustafa Tükenmez, Selman Emiroğlu, Levent Yeniay, Enver Özkurt, Kamuran İbiş, Adnan Aydıner, Vahit Özmen, Abdullah İğci” have no conflict of interest

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