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Omission of axillary dissection after neoadjuvant systemic treatment in initially node-positive HER2-overexpressed and triple-negative breast cancer patients: SENATURK OTHER-NAC study

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ABSTRACT

Background: More data is needed for those patients with aggressive tumor biology with a high recurrence risk for de-escalating axillary surgery in clinically N+ breast cancer. We, therefore, investigated the outcome in cN+ patients with HER2+ or triple-negative breast cancer who were treated with sentinel lymph node biopsy alone following neoadjuvant systemic treatment.

Material and methods: Clinically N+ patients ($cT_{1\text{-}4}N_{1\text{-}3}M_0$) with HER2+ and triple-negative breast cancer at admission and downstaged to cN_0 with neoadjuvant systemic treatment were included in the study. All patients were treated with sentinel node biopsy alone without further axillary dissection but followed by regional nodal irradiation.

Results: Of 259 patients, the pathologic complete response rate was 47.1 %. Overall, 171 (66 %) patients had HER2+ and 88 (34 %) had triple-negative cancer. Of 56 ypN+ patients, the lymph node metastases were macrometastases in 24 (42.9 %) patients. After a median follow-up of 46 months, irrespective of ypN status, isolated axillary, locoregional, and distant recurrence rates were 0.8 %, 2.7 %, and 7.7 %, respectively. Recurrence and disease-specific death rates were not different between HER2+ and triple-negative cancer as well as ypN_+ and ypN_0 patients. Advanced cT stage ($cT_{3\text{-}4}$) was the only significant factor associated with poor disease-free and disease-specific survivals.

Conclusion: Irrespective of the final ypN status and tumor subtype, omission of axillary dissection resulted with low axillary recurrence rate in initially cN+ HER2+ and triple-negative breast cancer patients who were downstaged to cN_0 with neoadjuvant systemic treatment and did not receive axillary dissection.

1. Introduction

There is an ongoing discussion on determining the optimal approach for managing axilla in patients with node-positive (cN+) breast cancer (BC), with options including limited axillary surgery, increased use of radiotherapy (RT), or a combination of both [1]. Roughly 30% of individuals diagnosed with early-stage BC receive neoadjuvant systemic treatment (NST), especially if they present with cN+ disease along with

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Table 1
Demographic, histopathologic and clinical characteristics of the study cohort.

	n = 259
Age; *median years (IQR)*	*46 (38–55)*
Age; *n (%)*	
<50 years old	154 (59.5)
≥50 years old	105 (40.5)
Menopausal status	
Premenopausal	159 (61.4)
Postmenopausal	100 (38.6)
Histological type; *n (%)*	
Invasive cancer (NST)	237 (91.5)
Others	22 (8.5)
Tumor subtype; *n (%)*	
HR-/HER2+	65 (25.1)
HR+/HER2+	106 (40.9)
Triple-negative	88 (34)
Clinical T stage at admission; *n (%)*	
T_{1-2}	197 (76.1)
T_{3-4}	62 (23.9)
Clinical N stage at admission; *n (%)*	
N_1	211 (81.5)
N_{2-3}	48 (18.5)
Ki67 expression level; *median % (IQR)*	40 (23–66)
Type of breast surgery; *n (%)*	
Breast-conserving surgery	165 (63.7)
Mastectomy	94 (36.3)
SLNB mapping technique; n (%)	
Blue dye only	201 (77.6)
Combined/dual agent	58 (22.4)
Number of retrieved SLN; *median number (IQR)*	4 (2–5)
Number of retrieved SLN; *n (%)*	
1	31 (12)
2-3	97 (37.4)
≥4	131 (50.6)
pCR at breast; *n (%)*	
Yes	122 (47.1)
No	137 (52.9)
ypN status after NST; *n (%)*	
ypN_0	203 (78.4)
ypN_+	56 (21.6)

SLN; sentinel lymph node, pCR; pathological complete response, NST; neo-adjuvant systemic treatment.

Table 2
Characteristics of sentinel lymph node involvement in ypN + patients.

	n = 56
Largest metastasis size at SLNs; *n (%)*	
Isolated tumor cells	11 (19.6)
Micrometastasis	21 (37.5)
Macrometastasis	24 (42.9)
Number of metastatic SLNs; *n (%)*	
1	37 (66.1)
2	11 (19.6)
≥3	8 (14.3)
Extracapsular invasion; *n (%)*	
Present	8 (14.3)
Absent	48 (85.7)
Metastatic to total number of SLN ratio; *n (%)*	
≤33 %	30 (53.6)
>33 %	26 (46.4)

SLN; sentinel lymph node.

those presenting with locally advanced BC at the initial diagnosis [2].

Obtaining a pathologic complete response (pCR), defined as the absence of tumor infiltration in the breast and lymph nodes (ypT_0 and ypN_0) after NST, is associated with a favorable prognosis and enhanced survival [3–5]. The subtype and stage of BC are the primary factors that impact the probability of attaining a pCR [6]. Neoadjuvant systemic treatment has potentially improved the pCR rates from 41 % to 64.8 % in patients diagnosed with HER2-overexpressed (HER2+) and triple-negative (TN) BC with the addition of new agents such as immunotherapy [7–9]. Furthermore, axillary pCR rates in HER2+ BC patients were found to be as high as 74 % [10]. However, NST may reduce the identification of sentinel lymph nodes (SLN) resulting in a decreased identification rate and a high false negative rate (FNR) [11, 12]. Retrieval of 3 or more SLNs, using dual tracer for mapping and targeted axillary dissection (TAD) which is defined as removal of the marked lymph node in addition to SLNs were shown to decrease the FNR [11–13].

Emerging evidence from published reports indicates that for certain patients with cN+ BC, omitting axillary dissection (AD) after SLNB may be a safe approach, especially for those who respond favorably to NST [14–23]. However, more data is needed for patients with HER2+ and TN BC that are considered aggressive tumors with poor survival rates [23, 24]. Therefore, in this study, we assessed the clinical outcomes of HER2+ and TN BC patients with histologically proven metastatic node involvement at admission who were clinically downstaged with NST and underwent SLNB as the only axillary surgical procedure regardless of the SLN involvement.

2. Material and methods

2.1. Cohort description & study design

HER2+ and TN BC patients who had histologically proven axillary node involvement at admission and were downstaged to cN_0 after NST were within the scope of the study. The study was planned to use a retrospective design with a single cohort. Data was collected from 9 institutions in Turkiye. The current cohort partly includes patients recruited to other multicentric collaborative registry studies.

Ethical approval was obtained from Istanbul University, Istanbul Faculty of Medicine Ethics Board for Clinical Studies (2023/1175, June 23, 2023).

2.2. Inclusion & exclusion criteria

Patients who were 18 years or older and had HER2+ and TN BC with stages $cT_{1-4}\ N_{1-3}\ M_0$ at admission were included in the study. All patients had histology-proven nodal involvement at admission. All patients received and completed NST according to their tumor subtype and institutional protocols. Only those patients who were downstaged to clinical N_0 with NST and underwent successful SLN mapping were included in the cohort. Patients treated with SLNB alone, regardless of the pathological findings at retrieved SLNs, were included in the study. Patients who underwent further completion AD were excluded.

All male patients and female patients with pregnancy-associated, inflammatory, bilateral BCs, or invasive cancers at other sites, and systemic metastases were excluded. Patients who remained as cN+ after NST determined by physical examination (PE) and axilla US were also excluded.

2.3. Outcomes

Primary outcomes were to measure the isolated axillary (IAR), loco-regional (LRR), and distant recurrence (DR) rates in the whole cohort. As secondary outcomes, we compared subgroups for IAR, LRR and DR rates according to their ypSLN status (ypN_0 vs ypN_+) and tumor subtypes (HER2+ vs TN BC). Among other secondary outcomes were the 5-year disease-free (DFS) and disease-specific survival (DSS) rates in the whole cohort and the independent factors for both.

2.4. Endpoints

Isolated axillary recurrence was regarded as the disease relapse in the ipsilateral axilla. LRR was defined as events in the chest wall, remaining breast, both axilla, and other regional lymph node basins

Table 3
Recurrences according to the tumor subtype and axillary disease response to NST.

	Total	Tumor subtype			ypN status		
		HER2+	TN	*p*	ypN_0	ypN_+	*p*
	n = 259	n = 171	n = 88		n = 203	n = 56	
Any recurrence	26 (10)	16 (9.4)	10 (11.4)	0.611	20 (9.9)	6 (10.7)	0.849
Isolated axillary recurrence; *n (%)*	2 (0.8)	0 (0)	2 (2.3)	0.115	1 (0.5)	1 (1.8)	0.386
Loco-regional recurrence; *n (%)*	7 (2.7)	4 (2.3)	3 (3.4)	0.692	5 (2.5)	2 (3.6)	0.647
Distant recurrence; *n (%)*	20 (7.7)	13 (7.6)	7 (8)	0.920	16 (7.9)	4 (7.1)	0.999
Time to first recurrence; *median months (IQR)*	*30 (16–43)*	34 (23–45)	18 (14–30)	**0.014***	30 (17–45)	28 (14–38)	0.465
Disease-specific death; *n (%)*	12 (4.6)	8 (4.7)	4 (4.5)	0.999	10 (4.9)	2 (3.6)	0.999

such as infraclavicular, supraclavicular, and internal mammary regions. DR was defined as any metastatic recurrence at distant sites/organs. Disease-specific death (DSD) was regarded as any death due to breast cancer progression.

2.4.1. Procedures & treatments

Clinical and pathological assessments: Assessment at admission and after NST in breast and axilla was done by physical exam (PE) and relevant imaging tools (*Supplement*).

Neoadjuvant systemic treatment: All patients received NST regimens according to the individual institutional protocols. None of the patients received neoadjuvant endocrine treatment (*Supplement*).

Sentinel lymph node biopsy: All patients underwent lymphatic mapping either with a single tracer as blue dye injection or a dual tracer combining the blue dye with ^{99}Tc-labeled colloid injection technique. The decision for the mapping technique was made in study centers according to the availability of relevant isotopes and the discretion of the operating surgeon. Intraoperative pathological assessment (IPA; i.e. Frozen section, touch print) of the retrieved SLNs was done in most centers. As the general practice, if SLN was found to be tumor-positive at IPA, level I-II AD was the principle management at the index operation. In cases in whom IPA was not available or their SLNs were found to be tumor-negative at IPA, their axilla was not cleared during index surgery. On the other hand, in cases whose SLNs were found to be metastatic at the pathological assessment on permanent sections after surgery, the patients either underwent AD at a second session or AD was omitted and RT was administered to the axilla. In this setting, some patients did not choose to undergo a completion AD after shared decision-making despite being found to have ypN + disease. Therefore, these patients constituted the ypN + subgroup of our current cohort.

Adjuvant radiation treatment: All patients received RT either to the whole breast or chest wall according to the breast surgery type with regional nodal irradiation (RNI) including level I-II axilla.

Adjuvant/extended systemic treatment: Patients received adjuvant or extended systemic treatment according to the institutional protocols and their tumor subtype (*Supplement*).

2.5. Study variables

Data for variables including patient age, menopausal status, tumor histology, tumor and nodal stages at admission, response to NST at the breast, pathological findings at initial core and FNA biopsies as well surgical specimens at definitive surgery after NST including estrogen (ER), progesterone (PR) receptors, HER2 and Ki67 expressions, findings at SLNs such as number of retrieved and metastatic SLNs, breast surgery type and mapping technique for SLNB were retrieved from patient files retrospectively. Also, the disease outcomes such as IAR, LRR, DR and DSD events and their timings were collected from hospital files or health authority registries. Categorizations of pathological findings and their definitions were provided in the *Supplement*.

2.6. Statistics

Software of SPSS 26 (Statistical Package for Social Sciences; IBM Corp., Armonk, NY, USA) was used in the statistical analyses. Nonparametric continuous variables were analyzed by the Mann-Whitney *U* test to investigate the differences between groups. Categorical variables were evaluated with Fisher's exact test or Pearson's chi-squared test in two-tailed univariate analyses to determine the associations between different variables. DFS was estimated considering the local and distant metastases. DSS was calculated considering the DSD events. DFS and DSS were estimated by using Kaplan Meier survival analyses, whereas GraphPad Prism Version 8 (GraphPad Software San Diego, California, USA) was used to generate the survival curves. Log-rank test was used to determine the differences between different variables in survival analyses. Cox regression analysis was performed to calculate the hazard ratios associated with survival for those variables that were found to be significant in the log-rank test. A p-value of less than 0.05 was considered significant. Due to a low number of events, multivariate Cox regression analysis was not performed.

3. Results

The study included 259 patients who underwent surgery between 2010 and 2021.171 (66 %) patients had HER2+ and 88 (34 %) had TN BC. Median patient age was 46 years. Most patients had $cT_{1\text{-}2}$ (n = 197; 76.1 %) and cN_1 (n = 211; 81.5 %) disease at admission. After NST, pCR at breast was reported in 122 (47.1 %) patients. Median number of retrieved SLN was 4 (IQR, 2–5). In 203 (78.4 %) patients, sampled SLNs were tumor-free, in the rest (n = 56; 21.6 %), at least one SLN was involved with tumor. Patient demographics and their clinical and pathological findings are provided in detail in Table 1.

Of 56 ypN_+ patients, SLN involvement was with macrometastases in 24 (42.9 %), micrometastases in 21 (37.5 %), and ITC in 11 (19.6 %) patients. Details of pathological findings in patients with ypN + disease are provided in Table 2.

At a median follow-up time of 46 months (IQR 34–63), overall 26 (10 %) patients had recurrence and median time to first recurrence was 30 (16–43) months. 12 (4.6 %) patients died due to breast cancer. Overall, 2 (0.8 %) patients had IAR, 7 (2.7 %) had LRR, and 20 (7.7 %) had DR (Table 3). 25 (9.7 %) patients had recurrences at a single site. Only 1 (0.4 %) patient had combined LRR and DR. All 2 axillary recurrences were ipsilateral and isolated (see Table 4).

There was no IAR in HER2+ BC patients. 2 patients who had IAR were of TN subtype. However, IAR, LRR, DR, and DSD rates were statistically similar in HER2+ and TN BC patients. Only, time to first recurrence was significantly shorter in TN BC patients (18 [14–30] months) compared to that of patients with HER2+ BC (34 [23–45] months; *p: 0.014*; Table 3).

IAR, LRR, DR, DSD rates, and time to first recurrence were similar in ypN_0 and ypN_+ patients (Table 3).

In univariate (Table 4) and multivariate analysis, advanced cT-stage ($cT_{3\text{-}4}$) was found to be the only significant factor associated with both decreased DFS ($cT_{1\text{-}2}$: 92.1 % vs $cT_{3\text{-}4}$: 75.3 %, HR: 3.27 [95%CI

Table 4
Univariate analysis of demographic, clinical, and histopathologic variables for disease-free (DFS) and disease-specific survivals (DSS) in the total cohort.

	DFS			DSS		
	Event	5-year (%)	p-value	Event	5-year (%)	p-value
All	26/259	88.2		12/259	94.8	
Age			0.912			0.377
<50 years	16/154	89.2		6/154	96.9	
≥50 years	10/105	86.5		6/154	91.6	
Menopausal status			0.833			0.283
Premenopausal	16/159	89.6		6/159	97	
Postmenopausal	10/100	85.5		6/100	90.1	
Histological type			0.593			0.208
Invasive cancer (NST)	23/237	88.8		10/237	94.8	
Others	3/22	81.5		2/22	81.6	
Tumor subtype			0.785			0.746
HR-/HER2+	7/65	85.9		2/65	96	
HR+/HER2+	9/106	91		6/106	94.2	
Triple-negative	10/88	87		4/88	94.6	
Clinical T stage at admission			**0.002***			**0.036***
cT_{1-2}	13/197	92.1		6/197	96.2	
cT_{3-4}	13/62	75.3		6/62	85.3	
Clinical N stage at admission			0.126			0.095
cN_1	24/211	86.5		12/211	93.6	
cN_{2-3}	2/48	95.8		0/48	100	
Type of breast surgery			0.424			0.996
Breast-conserving surgery	19/165	86.8		8/165	94.4	
Mastectomy	7/94	90.8		4/94	95.5	
Number of retrieved SLN			0.855			184
1	4/31	88		3/31	91.1	
2-3	10/97	88.5		6/97	91.4	
≥4	12/131	88		3/131	97.7	
pCR at breast			0.184			0.214
Yes	10/129	91.7		4/129	96.2	
No	16/130	84.6		8/130	90.7	
ypN status after NST			0.765			0.738
ypN_0	20/203	88.5		10/203	95.2	
ypN_+	6/56	87		2/56	93.5	
Largest metastasis size at SLNs			0.486			0.810
Isolated tumor cells	0/11	100		0/11	100	
Micrometastasis	3/21	81.5		1/21	92.3	
Macrometastasis	3/24	85.4		1/24	92.3	
Number of metastatic SLNs			0.452			0.544
1	3/37	88.8		2/37	89.6	
2	1/11	88.9		0/11	100	
≥3	2/8	75		0/8	100	
Extracapsular invasion			0.956			0.482
Present	1/8	87.5		0/8	100	
Absent	5/48	86.4		2/48	91.9	
Metastatic to total number of SLN ratio			0.214			0.681
≤33 %	2/30	92.8		1/30	94.4	
>33 %	4/26	78.5		1/26	91.7	

1.51–7.09], $p = 0.002$) and DSS (cT_{1-2}: 96.2 % vs cT_{3-4}: 85.3 %, HR: 3.17 [95%CI 1.02–9.90], $p = 0.036$). Kaplan-Meier survival curves of DFS and DSS were similar according to tumor subtypes and T stages of patients at admission (Fig. 1).

4. Discussion

Considering the poor prognostic factors for BC patients undergoing surgery after NST, we investigated the outcome in initially node-positive HER2+ and TN BC patients who were treated with SLNB-alone without AD. Here, we report a very low IAR (<1 %) and low LRR rates (<3 %) in a highly selected cohort of cN + patients treated with a combination of SLNB-only and RNI following NST after a median follow-up (FU) of 3.8 years. Moreover, patients with ypN+ axilla who did not undergo AD had similar disease outcomes when compared to those with complete response in axilla. Also, the IAR, LRR, DR, and DSD rates were not different in HER2+ and TN BC patients. We only found that in TN BC patients the first recurrence was developed significantly earlier compared to HER2+ BC patients. Furthermore, having a clinically advanced T-stage at admission was found to be the only poor prognostic factor associated with increased risk for poor DFS and DSS.

Of note, 21.6 % (n = 56) of the present cohort with HER2+ and TN BC had ypN+ disease and these patients did not undergo AD. Of those with ypN+, 43 % had macrometastases. Here in this study, we found no difference in outcomes between ypN_0 and ypN+ disease regarding IAR, LRR and DR rates, DFS, and DSS. Recently published reports similarly demonstrated very low rates of axillary and LRR in selected ypN + patients with $cT_{1-4}N_{1-3}$ disease at the initial presentation if they had limited axillary involvement after NST and were treated with RNI [18,25,26].

There are few studies regarding long-term outcome in patients treated with SLNB-alone without AD following NST [18,23,27,28]. Martelli et al. reported that none of the 77 patients with cT_2 cN_{0-1} ypN_0 disease, who were treated with SLNB-alone after NST, developed an axillary recurrence after a median FU of 6 years [27]. They further analyzed 353 consecutive cT_2 cN_{0-1} patients who had only SLNB between 2007 and 2015. At a median FU of 9 years, 10-year OS and DFS did not differ significantly between the patients who only underwent SLN when it was tumor-free and those who had AD after SLN was found to be positive. No axillary recurrence was reported in the SLNB-only group [28].

Kahler-Ribeiro-Fontana et al. recently analyzed the 10-year follow-up results of 688 patients initially cT_{1-3} cN_{0-2} treated with SLNB for ypN_0 disease and AD for ypSLN + disease after NST [23]. After a median FU of 9.2 years, axillary recurrence developed in 1.8 % of the initially cN_{1-2} patients. In multivariate analysis, both luminal and non-luminal HER2-positivity and TN subtypes were associated with a worse overall survival. In the retrospective NEOSENTI-TURK MF18-02 study, 303 cN+ patients receiving NST underwent SLNB-alone with RNI. Of those, 70 % of patients had ypN_0 disease. Among those with ypN + disease, 56.5 % of patients had isolated tumor cells (ITC) or micrometastases and 43.5 % had macrometastases. Five-year DFS and DSS rates were 87 % and 95 %, respectively. As a similar finding from the study of Kahler-Riberio-Fontana et al., patients with cT_{3-4}, non-luminal tumor,

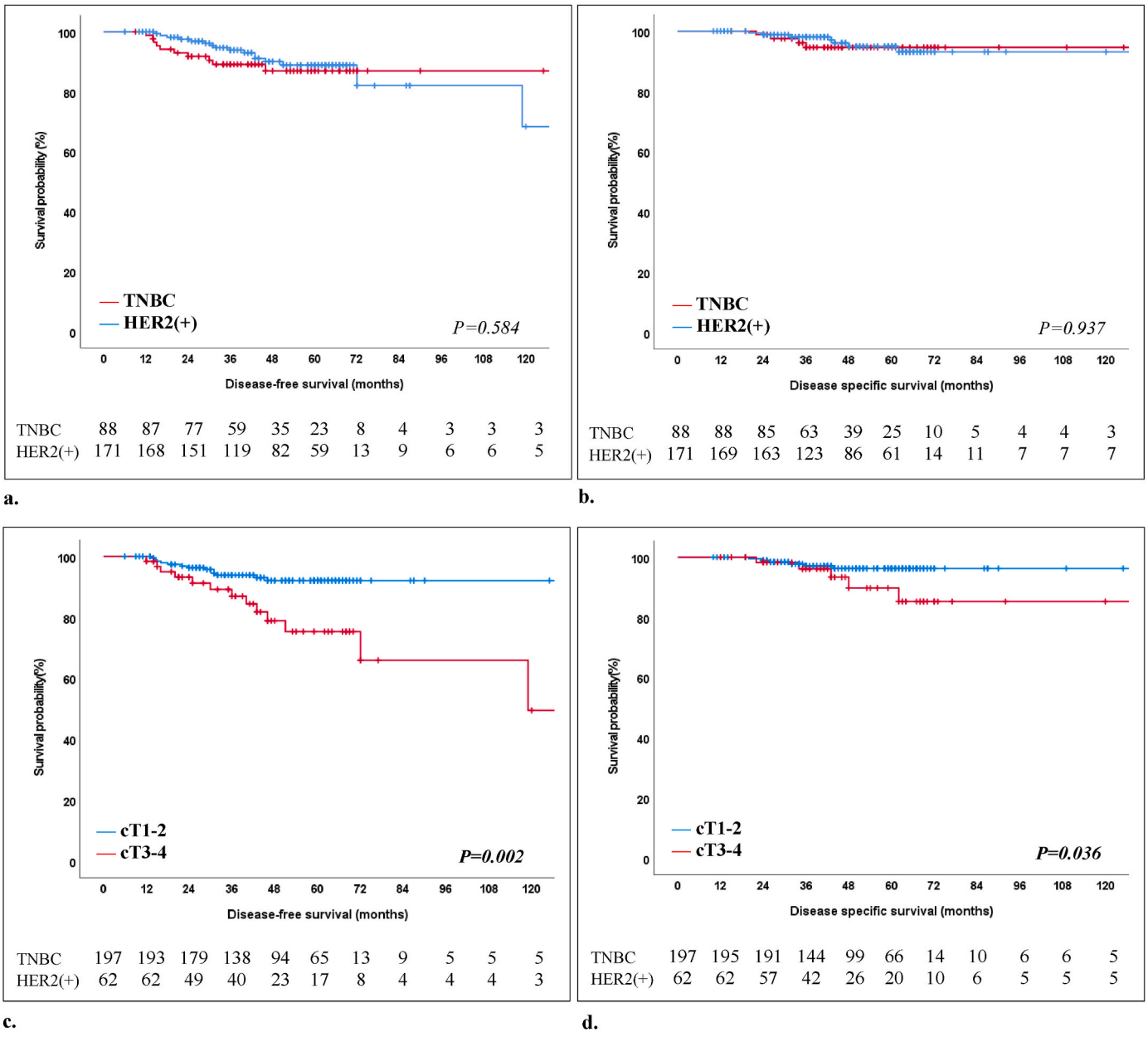

Fig. 1. Kaplar-Meier survival curves of the study cohort.
a. Disease-free survival (DFS) of patients with HER2+ and triple-negative breast cancer
b. Disease-specific survival (DSS) of patients with HER2+ and triple-negative breast cancer
c. Disease-free survival (DFS) of patients with cT_{1-2} vs cT_{3-4} breast cancer
d. Disease-specific survival (DSS) of patients with cT_{1-2} vs cT_{3-4} breast cancer.

and non-pCR in the breast were found to have an increased risk of recurrence [18].

Furthermore, a recent registry study form Germany including 2698 cN+ patients undergoing NST included 2204 patients who had AD, SLNB-alone or TAD. After a 2-year median FU, 3 year-invasive DFS was 69.7 % in AD group, 76.6 % in SLNB with ≥3 SLNs removed, 76.7 % in SLNB with <3 SLNs removed, and 78.7 % in TAD group. Multivariate Cox regression analysis indicated ypN+, TN subtype, and ypT_{3-4} as poor prognostic factors associated with increased risk for poor iDFS [24]. All these studies indicated non-luminal biology (including HER2+ and TN BC subtypes) as a poor prognostic factor.

Finally, the OPBC-04/EUBREAST-06 analyzed a total of 1144 patients from 11 countries and 25 centers [29]. Of those, in 58.2 % of patients SLNB using dual tracer as the mapping technique was done, whereas others underwent TAD. 93 % of patients had N_1 disease and 54 % had HER2+ BC. Overall, the 5-year rates of any axillary, LRR, and any invasive recurrence were 1.0 %, 2.7 %, and 10 %, respectively. Of note, the 3-year cumulative incidence of axillary recurrence did not differ between TAD and SLNB.

All these findings indicate that AD could be avoided in meticulously selected cN+ patients who underwent SLNB after NST having breast and/or nodal pCR, cT_{1-2}, as long as RNI is provided. The similar outcome between ypN_0 and ypN+ might have been due to the selection bias since the ypN_0 patients were more likely to have a non-luminal pathology associated with more aggressive tumor biology such as HER2+ or TN BC, whereas patients with ypN+ disease were more likely to have a luminal pathology as in the present study cohort in concordance with the previous NEOSENTI-TURK MF18-02 study [18]. Of note, all the

patients received RNI in the present cohort and both NEOSENTI-TURK MF18-02 and 18-03 studies regardless of the presence of residual nodal disease [18,26,30].

The strength of the present study is a multicentre study with a relatively long-term outcome of a cohort with aggressive tumor biology including HER2+ and TN BC which are underrepresented subgroups in big trials.

The limitations of our study are its retrospective nature, small sample size regarding patients with ypN + disease, and short median follow-up. Also, we did not compare our findings to those in patients who underwent AD due to ypN+ disease which is accepted as the standard of care. However, in our cohort, we found very low axillary recurrence even in patients who did not undergo AD despite having ypN+ disease. Therefore, with our findings, the relevance of such a comparison might be questioned.

Ongoing prospective randomized trials including NSABP-B51/RTOG, Alliance A011202, and TAXIS and prospective registry studies including NEOSENTI-TURK MF-18-03 and AXSANA will further highlight whether the omission of AD could be safe in node-positive BC including those with aggressive tumor biology [18,30–35].

In conclusion, the omission of AD could be considered in upfront cN+ patients with an aggressive tumor pathology as long as a complete clinical response to NST is achieved and RNI is administered. Even in HER2+ and TN BC patients with ypN+ disease confirmed by SLNB, the axillary recurrence rates were low with no further AD. Nevertheless, long-term results of the prospective trials with larger sample sizes are pending to support our findings.

Compliance with ethical standards

The ethical review board of Istanbul University, Istanbul Faculty of Medicine approved the study that it is in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration.

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Declaration of competing interest

The following authors N Cabıoğlu, H Karanlık, A İğci, C Uras, O Dülgeroğlu, G Karadeniz Çakmak, A Sezer, G. Gürleyik, M Tükenmez, S Bademler, M Müslümanoğlu, E. Özkurt, N. Yıldırım, Ü. Uğurlu, H. Balbaloğlu S. Emiroğlu, V. Özmen, BM Güllüoğlu' have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.109642.

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