


Management of the axilla with sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer

A single-center study

Suleyman Ozkan Aksoy, MD^{a,*} , Ali İbrahim Sevinc, MD^a, Mücahit Ünal, MD^a, Pınar Balcı, MD^b, İlknur Bilkay Görkem, MD^c, Merih Guray Durak, MD^d, Ozden Ozer, MD^e, Recep Bekiş, MD^f, Büşra Emir^g

Abstract

The neoadjuvant chemotherapy (NAC) is the gold standard initial treatment of the locally advanced breast cancer (LABC). However, the reliability of methods that used to assess response the NAC is still controversial. In this study, patients with LABC who underwent NAC were evaluated retrospectively. The assessment of response to NAC and the effect of axillary approach were investigated on LABC course.

The study comprised 94 patients who received NAC with an LABC diagnosis between 2008 and 2020. In our center, magnetic resonance imaging, ultrasonography, and ¹⁸F-flouro deoxyglucose positron emission tomography/computed tomography, and, for some patients, fine-needle aspiration biopsy of suspicious axillary lymph nodes have been performed to assess the effects of NAC. Patients with positive hormone receptor status received adjuvant hormonotherapy, and those with human epidermal growth factor receptor 2 gene expression were treated with trastuzumab. Adjuvant radiotherapy was applied to all patients undergoing breast conserving surgery. Radiotherapy was applied to the peripheral lymphatic areas in the clinical N1 to N3 cases regardless of the response to NAC.

The clinical response to the NAC was found that partial in 59% and complete in 19% of the patients. However, 21.2% of the patients were unresponsive. The mean of lymph nodes that excised with the procedure of sentinel lymph node biopsy (SLNB) was 2.4 (range 1–7). In 22 of the 56 patients who underwent SLNB, axillary dissection (AD) was added to the procedure upon detection of metastasis in frozen section examinations. There was no difference between the SLNB and AD groups regarding overall survival (OS; $P = .472$) or disease-free survival (DFS) rates ($P = .439$). However, there were differences in the OS ($P < .05$) and DFS ($P = .05$) rates on the basis of the LABC histopathological subtypes.

The study found that a relationship between molecular subtypes and LABC survival. However, the post-NAC axillary approach had no effect on OS or DFS. Therefore, multiple imaging and interventional methods are needed for the evaluation of NAC response. In addition, morbidity can be avoided after AD by the use of SLNB in cN0 patients.

Abbreviations: ¹⁸F-FDG PET/CT = ¹⁸F-flouro deoxyglucose Positron emission tomography/computed tomography, AD = axillary dissection, Adjht = adjuvant hormonotherapy, ADRT = adjuvant radiotherapy, ADRT = adjuvant radiotherapy, BCS = breast conserving surgery, CI = confidence interval, DFS = disease-free survival, ER = estrogen-receptor, FNAB = fine-needle aspiration biopsy, FNR = False negative rate, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemical, LABC = locally advanced breast cancer, LNs = lymph nodes, LRR = locoregional recurrence, MRI = magnetic resonance imaging, NAC = neoadjuvant chemotherapy, OS = overall survival, pCR = pathological complete response, PR = progesterone-receptor, RT = radiotherapy, SLNB = sentinel lymph node biopsy, TNBCs = triple negative breast cancers, US = ultrasonography.

Keywords: breast cancer, locally advanced, sentinel node, survival

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^aDepartment of General Surgery, ^bDepartment of Radiology, ^cDepartment of Radiation Oncology, ^dDepartment of Pathology, ^eDepartment of Oncology, ^fDepartment of Nuclear Medicine, Faculty of Medicine, Dokuz Eylül University, ^gDepartment of Biostatistics, Faculty of Medicine, Katip Celebi University, İzmir, Turkey.

* Correspondence: Suleyman Ozkan Aksoy, Department of General Surgery, Faculty of Medicine, Dokuz Eylül University, Mithatpasa Street, no:1606, Inciralti, Balçova, Izmir 35340, Turkey (e-mail: suleyman.aksoy@yahoo.com).

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1. Introduction

The locally advanced breast cancer (LABC) contains of heterogeneous tumor types ranging from tardily progressive to aggressive tumors.

The current approach is the use of systemic neoadjuvant therapies before definitive surgery. Chemotherapy is the most frequently applied neoadjuvant therapy. However, neoadjuvant hormonal therapy can also be used, especially in the postmenopausal luminal breast cancer subgroups.^[1,2] Neoadjuvant systemic treatments have many advantages, including the amenability of inoperable tumors to surgery, the early control of systemic disease, the elimination of micrometastasis, and the possible prolongation of survival.^[3,4]

Neoadjuvant chemotherapy (NAC) can yield favorable responses in all tumor sizes. This is the case for all breast cancer subtypes, for example, triple negative breast cancers (TNBCs) and human epidermal growth factor receptor 2 (HER2)-positive breast cancers.^[5] In immunohistochemical (IHC) examinations, the tumor subtypes are the most important markers for NAC response. Current studies have shown that the pathological complete response (pCR) rates to NAC are lower in only the estrogen-receptor (ER)- and progesterone-receptor (PR)-positive cases detected in IHC studies. The tumors that overexpress HER2 are known to be biologically more aggressive, and the current HER2-targeted therapies have been effective. Hormonal therapy has been used as an adjuvant therapy, especially in ER- and/or PR-positive patients. However, they can also be used as neoadjuvant therapies in some postmenopausal patients or for whom NAC is not appropriate.^[1,2]

The generally accepted opinion expressed in recent evaluations of the response to NAC has been that the variations in the response rates are associated with the molecular subtype of the tumor. Specifically, pCRs were found to be related to prognosis.^[5-7] NAC is the gold standard initial treatment of the LABC. However, the reliability of methods that used to assess response the NAC is still controversial. Sentinel lymph node biopsy (SLNB) is the standard treatment approach to the evaluation of the axillary region in clinically lymph node (LN)-negative (cN0) patients before the application of NAC. In 40% of clinically axillary LN-positive (cN1-cN2) cases, a complete clinical response is obtained after NAC. However, the administration of SLNB is still debatable.

False negative rates (FNRs) have been found to be associated with the use of the double method (dye + radiocolloid) and the number of excised LNs detected in studies for SLNB, as confirmed by post-NAC axillary dissections (ADs). With the excision of 2 or more LNs, the FNR decreases.^[8] In addition, the NAC response assessment methods can reduce FNRs, thereby increasing the reliability of SLNBs. Magnetic resonance imaging (MRI), ultrasonography (US), and ¹⁸F-fluoro deoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) have been used to evaluate the response to NAC in our center that Dokuz Eylul University, faculty of Medicine. In addition, some patients undergo US-guided fine-needle aspiration biopsy (FNAB) of the suspicious axillary LN(s). This is followed by surgical and subsequent adjuvant treatments.

In the present study, patients who were diagnosed with and treated for the indication of LABC were evaluated retrospectively. The assessment of response to NAC and the effect of axillary approach were investigated on LABC course.

2. Materials and methods

Patients with histopathologically confirmed LABC diagnoses between 2008 and 2020 were retrospectively evaluated. The exclusions were the following: presence of inflammatory or metastatic breast carcinoma, history of breast cancer, treatment outside the center, and unavailable treatment and/or follow-up data.

Upon the establishment of the histopathologic diagnoses of all patients on the basis of Tru-Cut or excisional biopsy results, treatments were planned (Fig. 1). The patients were evaluated in the multidisciplinary breast council of Dokuz Eylul University Faculty of Medicine, which included a breast surgeon, a radiology specialist with expertise in breast radiation, a medical oncologist, a radiation oncologist, and a breast pathologist.

In accordance with the Dokuz Eylul Breast Tumor Group protocol, the breast masses were evaluated by US, mammography, and/or MRI. Distant disease was assessed through thoracoabdominal CT and/or ¹⁸F-FDG PET/CT. The cases were subjected to consecutive anthracycline- and taxane-based systemic chemotherapy regimens. The responses were evaluated by breast MRI at the end of the fourth cycle. US and ¹⁸F-FDG PET/CT were used for the axillary response and assessment of distant disease. FNAB was also applied to the suspicious LNs detected in axillary imaging. The plans of surgical treatment were based on evaluations of final imaging and FNAB results at the breast council. The indications for mastectomy after neoadjuvant therapy were established on the basis of inappropriate breast-tumor ratios, tumor multicentricity, and patient requests for mastectomy. On the basis of the results of the FNABs performed on the suspicious LNs, SLNB was indicated for the patients with axillary clinically node-negative and those without metastasis.

For lymphoscintigraphy, 0.8 mCi Tc-99m (a nanocolloid material) was injected subdermally into the 4 quadrants of breast and/or around and inside the tumor mass 2 to 4 hours before surgery. Scintigraphic images were obtained. Patients with minimal involvement, as detected by scintigraphic evaluation, also received intradermal or subdermal injections of 5 mL methylene blue or isosulfan blue in the periareolar and peritumoral areas during surgery. The location of the SLNs was determined with the help of a gamma probe. All patients undergoing breast conserving surgery (BCS) received adjuvant radiotherapy (ADRT) to the breast. In the clinical N1 to N3 cases, radiotherapy (RT) was applied to the peripheral lymphatic areas regardless of the NAC response.

Postmastectomy RT was applied to all clinical T3 to T4 and N1 to N3 patients who underwent mastectomy regardless of the NAC response, and ADRT was administered to the chest wall and peripheral lymphatic areas. In peripheral lymphatic irradiation, ADRT was delivered to the Level III and supraclavicular lymphatic areas of the patients who had undergone full AD. The pCR was ascertained. ADRT was applied to the DI to DIII axillary lymphatics and supraclavicular lymphatic areas of the patients who had not previously undergone ADs and/or those in whom PRs were identified in the axillary area after NAC. The ADRT was prescribed as conventional fractional daily doses of 2 Gy in 25 fractions, with a total tumor dose of 50 Gy directed to the breast chest wall and/or peripheral lymphatic areas. In patients with clinical skin involvement or epidermal ulceration (T4b), ADRT was administered as an additional 10 Gy dose that amounted to a 60 Gy skin dose.

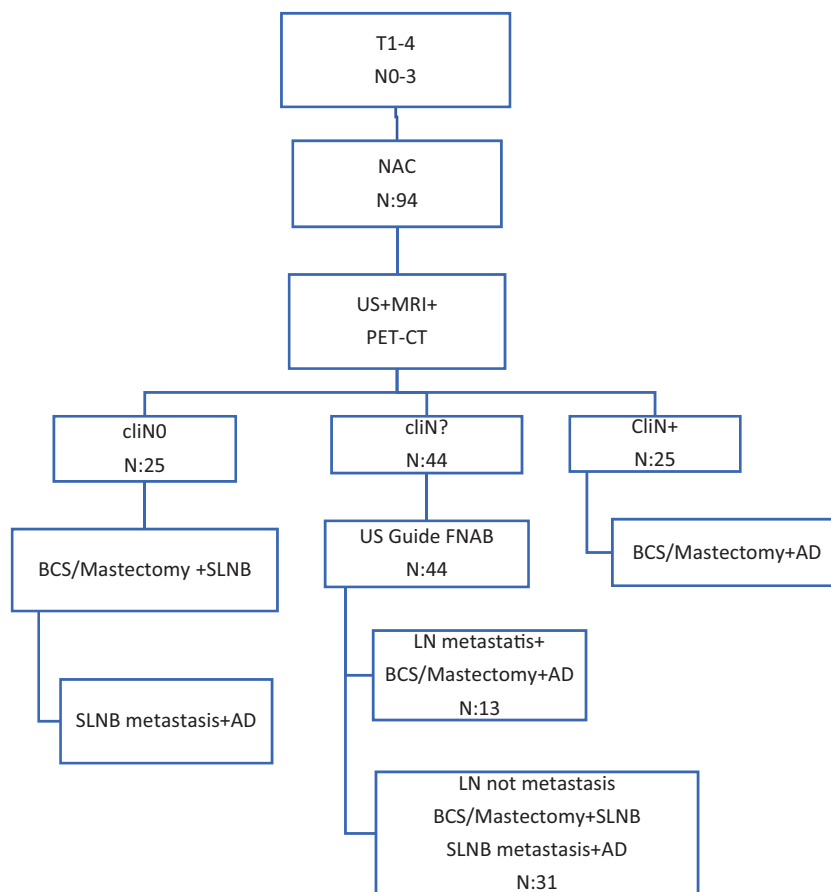


Figure 1. Summary of the patient groups and treatment flowchart.

The treatment options included in-field techniques, 3-dimensional conformal RT, and intensity-modulated RT. In all patients under 65 years old with left breast tumors, deep inspiration breath holds were used to reduce the radiation dose exposed by the heart, especially the left descending coronary artery, whenever possible (mean heart dose < 26 Gy, V25 < 10%).^[9]

The data related to the clinical and pathological evaluations, pre-NAC imaging tests, histopathologic types, molecular subtypes (ER, PR, HER2, and Ki-67 status), NAC schemes and number of cycles delivered, clinical response rates to NAC, applied surgeries, pathological stages, pathological response rates, ADRT, locoregional recurrence (LRR), and overall survival (OS) and disease-free survival (DFS) rates were obtained from the patient files. A pCR was defined as the absence of residual invasive disease in the breast or axillary LNs. The present study used the St. Gallen Consensus Panel 2011 definitions^[10] for IHC-based subtyping: luminal A (ER + and/or PR + / HER2- / Ki67 < 14%), luminal B (ER + and/or PR + / HER2- / Ki67 > 15%), HER2-enriched (ER- and PR- / HER2 +), and triple-negative (ER- and PR- / HER2-). An approval was received from the institutional manager and departments that related to study.

2.1. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v.25, Inc., Chicago, IL). Descriptive statistics are presented as count (n), percent (%), mean ±

standard deviation () and median with 25 to 75th quartiles (Median (Q₁-Q₃)). The Shapiro Wilk test was used and a histogram and Q-Q plot were examined to assess the data normality. Levene test was used to assess the variance homogeneity. Two-sided Mann-Whitney *U* test and Kruskal-Wallis test were applied to compare the differences between groups for continuous variables. Comparison between categorical groups were made using the Pearson Exact Chi-Squared test. The Kaplan-Meier method and log-rank test were used to analyze OS and disease free survival according to Age, NAC response, Molecular subtypes and Axillary operation type categories. A *P* value of less than .05 was considered statistically significant.

3. Results

The present study comprised 94 patients who received NAC and LABC diagnoses (Stages 2A–3C, cT1–T4, cN0–N3, M0) at the center between 2008 and 2020. The demographic data indicated that the average age of the patients was 50 (31–82) years. The tumor originated in the right breast in 59.5% of the cases; 23.4% of the patients had multifocal tumors (Table 1).

In 84 (89%) of the patients, histopathologic diagnosis was made by Tru-Cut biopsy and clip marking. Simultaneously, FNAB of suspicious axillary LNs was performed in 22 of these cases. In 10 (11%) patients in whom the breast lesions could not be marked for technical reasons, the diagnosis was based on the histopathologic examination of the tumor mass extirpated with

Category	Number	Percentage
Age (mean ± SD)	50.8±10.1	
Tumor localization		
Right	56	59.5
Left	38	40.5
Tumor		
Single	72	76.6
Multiple	22	23.4
Diagnosis method		
Trucut	62	66.0
excision	10	10.6
Trucut+FNAB (LN)	22	23.4
Estrogen Receptor Status		
Positive	73	77.7
Negative	21	22.3
Progesterone receptor status		
Positive	58	61.7
Negative	36	38.3
HER2 receptor status		
Positive	33	35.1
Negative	61	64.9
Classification		
Luminal A	16	17
Luminal B	57	60.6
HER2 positive	10	10.6
Triple-negative	11	11.7
Histology		
IDC	52	55.3
ILC	15	15.9
IMC	9	9.5
Mixed ILC/IDC	20	21.2
Lymphovascular invasion		
Positive	48	51.1
Negative	46	48.9

FNAB=fine-needle aspiration biopsy, HER2=human epidermal growth factor receptor 2, IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, IMC=invasive meduller carcinoma, LN=lymph node.

the appropriate surgical margin. Histopathologic diagnosis was made through invasive ductal carcinoma and/or invasive lobular carcinoma in 76.5% of the patients. The IHC examinations detected ER positivity in 77.7% of the patients, PR positivity in 61.7%, and TNBC in 11.7%. Metastasis was not detected in any of the scans. The center breast council evaluated the cases, and NAC was applied. The average time between NAC initiation and surgery was 5.5 months (range 2–10). Imaging control was performed with US, MRI, and ¹⁸F-FDG PET/CT for the patients who had completed NAC. The clinical evaluation found a partial response to NAC in 59% of the cases, a complete response in 19%, and a lack of response in 21.2% (Table 2). In this assessment of the NAC response, the axillary LNs were found to have a better response than the primary tumors (26% cN0, 21% cT0).

SLNBs were performed on 25 patients for whom the clinical evaluation of the axillary region indicated a complete response (cN0) without metastasis. The evaluation was based on the results of the FNABs of the suspicious axillary LNs. During the SLNBs, 1 LN in 6 patients and 2 or more LNs in 50 patients (mean 2.3, range 1–7) were excised. In 22 of the 56 patients who underwent SLNB, AD was performed upon detection of metastasis in frozen section examinations. Patients with luminal A (17%) and luminal B (60%) breast cancer, as detected in

postoperative histopathologic examinations, were treated with hormonotherapy. Trastuzumab was administered to patients with HER2 gene expression (10.8%). Peripheral lymphatic irradiation was performed in 91 patients with cN1 to cN3 at initial diagnosis. ADRT was applied to the breast in all 65 patients who received BCS and to 26 of the 29 patients who underwent mastectomy. The subgroup characteristics in the histopathologic evaluation are summarized in Table 2.

The average follow-up period was determined as 28 (range 5–139) months. The mean follow-up time for the SLNB group was shorter (mean 20.6±14.6; range 3–65 months) than the mean time (mean 33±20; range 4–159 months) for the AD group ($P=.002$). LRR was observed during the follow-up of 6 (6.4%) patients who had undergone either mastectomy ($n=3$) or BCS ($n=3$).

In the AD group, LRR was observed in the breast in 3 patients and in the axillary region in 1 patient. Three of these AD patients who experienced LRR received BCS and RT to the breast and the peripheral lymphatic area concurrently. LRR was observed in 2 patients who underwent SLNB. One of these patients had undergone BCS, and the other, mastectomy followed by RT. In addition, 4 (66%) of the patients who manifested LRR were younger than 50 years. In 3 patients, distant metastases were found: in the bone in 2 patients and in the brain in 1 patient. LRR was detected in one of the patients with bone metastasis.

During follow-up period 6 patients were dead. The mean DFS of the patients was 27.6 months (range, 3–159±20std), whereas the mean OS was 28.0 months (range, 3–159±19). Factors affecting survival rates were analyzed. There was no significant difference in both OS ($P=.472$) and DFS ($P=.439$), between patients with SLNB only and AD. Similarly, neither age of the patients nor evaluation of response to chemotherapy had influence on survival rates (Table 3).

Impact of molecular subtypes of invasive tumors on survival rates were analyzed. The mean OS in luminal A group was 27.9 months (95% confidence interval [CI]: 18.8–32.1), in luminal B group it was 30.7 months (95% CI: 24.5–36.8), in HER2 positive group 16.7 months (95% CI: 8.76–24.6), and in TNBC group 24.7 months (95% CI: 19.9–37.4). On the other hand, the mean DFS in luminal A group was 28.2 months (95% CI: 17.7–31.3), in luminal B group it was 30.4 months (95% CI: 22.4–36.6), in HER2 positive group 15.2 months (95% CI: 8.34–23.7), and in TNBC group 24.1 months (95% CI: 17.8–35.4). Nevertheless, luminal A and luminal B groups of patients showed the best OS and DFS rates, while HER2 positive group had the worst survival rates. Therefore, it was concluded that molecular subtypes of breast cancer had significance in both OS ($P=.00$) and in DFS ($P=.05$) of patients (Figs. 2 and 3).

4. Discussion

NAC has become the standard treatment protocol in LABC; however, there is no consensus on its evaluation or the posttreatment surgical approaches. The LABC is a very large group that contains heterogenous clinical subtypes; thus, controversies about treatment are inevitable. The difficulties on management to LABC are that how to evaluate of responses NAC and to plan subsequent surgery. Some of the difficulties in the evaluation of the response to NAC are the result of the partial deficiencies of imaging modalities. US is frequently used in post-NAC evaluations of the axillary region; however, it has a diagnostic accuracy of 62% to 65%.^[11,12]

Table 2**Clinicopathological characteristics of patients.**

Variable	Age		P	Axillary operation type			Molecular subtypes of breast cancer				P
	<50 N (%)	>51 N (%)		SLNB N (%)	AD N (%)	P	Lum A N (%)	Lum B N (%)	HER2 N (%)	TNBC N (%)	
NAC before cN			.099			.010					.218
N0	2 (4)	1 (2.3)		3 (9)	0 (0)		0 (0)	3 (5)	0 (0)	0 (0)	
N1	15 (30)	24 (54)		16 (47)	23 (38)		9 (56)	20 (35)	4 (40)	6 (54)	
N2	30 (60)	18 (40)		14 (41)	34 (56)		7 (43)	32 (56)	6 (60)	3 (27)	
N3	3 (6)	1 (2.3)		1 (3)	3 (5)		0 (0)	2 (5.59)	0 (0)	2 (18)	
NAC before cT			.542			.001					.706
T1	14 (14)	15 (34)		3 (9)	26 (43)		7 (43)	16 (28)	4 (40)	2 (18)	
T2	22 (44)	17 (38)		21 (62)	18 (30)		7 (43)	23 (40)	4 (40)	5 (45)	
T3	10 (20)	11 (25)		7 (20)	14 (23)		2 (15)	14 (24)	1 (10)	4 (36)	
T4	4 (8)	1 (2.3)		3 (9)	2 (3)		0 (0)	4 (7)	1 (10)	0 (0)	
Multifocal			.663			.507					.097
yes	12 (24)	8 (18)		9 (26)	11 (18)		6 (37)	13 (22)	0 (0)	1 (9)	
no	38 (76)	36 (81)		25 (73)	49 (81)		10 (62)	44 (77)	10 (100)	10 (90)	
Clinic response			.946			.541					.407
Not	11 (22)	9 (20)		9 (26)	11 (18)		1 (6)	13 (22)	2 (20)	4 (36)	
Partial	29 (58)	27 (61)		20 (59)	36 (60)		10 (62)	36 (63)	5 (50)	5 (45)	
complete	10 (20)	8 (18)		5 (15)	13 (21)		5 (31)	8 (14)	3 (30)	2 (18)	
NAC after cN			.027			.648					.059
N0	10 (20)	15 (34)		11 (32)	14 (23)		2 (12)	14 (14)	4 (40)	5 (45)	
N1	13 (26)	3 (6.8)		4 (11)	12 (20)		2 (12)	12 (21)	2 (20)	0 (0)	
N2	27 (54)	25 (56)		19 (56)	33 (55)		12 (75)	30 (52)	3 (30)	6 (54)	
N3	0 (0)	1 (2.3)		0 (0)	1 (2)		0 (0)	1 (2)	1 (10)	0 (0)	
NAC after cN			.299			.336					.155
T0	7 (14)	6 (14)		5 (15)	8 (13)		3 (19)	4 (7)	3 (30)	3 (27)	
T1	7 (14)	5 (11)		6 (17)	6 (10)		1 (6)	8 (14)	1 (10)	2 (189)	
T2	27 (54)	24 (55)		20 (58)	31 (51)		10 (62)	32 (56)	4 (40)	5 (45)	
T3	6 (12)	5 (11)		2 (6)	9 (15)		2 (13)	7 (13)	1 (10)	1 (9)	
T4	3 (6)	4 (9)		1 (3)	6 (10)		0 (0)	6 (10)	1 (10)	0 (0)	
pN			.001			.001					
N0	20 (40)	15 (34)		34 (100)	1 (1.6)		4 (25)	15 (26)	7 (70)	9 (81)	
N1	19 (38)	19 (43)		0 (0)	38 (63)		9 (56)	25 (43)	2 (20)	2 (19)	
N2	10 (20)	9 (20)		0 (0)	19 (32)		3 (18)	17 (30)	0 (0)	0 (0)	
N3	1 (2)	1 (2)		0 (0)	2 (3.3)		0 (0)	0 (0)	1 (10)	0 (0)	
pT			.312			.331					.079
T0	10 (20)	8 (18)		5 (15)	13 (22)		5 (31)	8 (14)	3 (30)	2 (18)	
T1	8 (16)	5 (11)		6 (17)	7 (12)		1 (6)	7 (12)	0 (0)	5 (45)	
T2	22 (44)	24 (55)		17 (50)	29 (48)		9 (56)	30 (52)	4 (40)	3 (27)	
T3	6 (12)	3 (7)		3 (9)	6 (10)		1 (6)	6 (10)	1 (10)	1 (9)	
T4	4 (8)	4 (9)		3 (9)	5 (8)		0 (0)	6 (10)	2 (20)	0 (0)	
LRR			.681			1					.176
Yes	4 (8)	2 (4.5)		2 (6)	4 (7)		0 (0)	3 (5)	2 (20)	1 (9)	
No	46 (92)	42 (95)		32 (94)	56 (93)		16 (100)	54 (94)	8 (80)	10 (91)	
Exitus			1			1					.028
yes	3 (6)	3 (6.8)		2 (6)	4 (7)		1 (6)	1 (3)	2 (30)	2 (18)	
No	47 (94)	41 (93)		32 (94)	56 (93)		15 (93)	56 (97)	8 (70)	9 (82)	

Pearson Exact Chi-Squared test.

AD = axillary dissection, HER2 = human epidermal growth factor receptor 2, LRR = locoregional recurrence, Lum = luminal, NAC = neoadjuvant chemotherapy, SLNB = sentinel lymph node biopsy, TNBCs = triple negative breast cancers.

Previous evaluations have indicated that MRI has the best accuracy rates and positive predictive value in the evaluation of the treatment response of breast tumors.^[13,14] However, the results were not the same for MRI of the axillary region. Several studies have reported low negative predictive values of 38% to 47%.^[15–17] In addition, the time between chemotherapy and morphological response was 4 to 6 weeks, and determining fibrosis from the live tumor residue was difficult. The presence of scars, edema, and inflammatory reactions post-chemotherapy could lead to the misclassification of chemo-sensitive tumors as

unresponsive.^[18] In 1993, Wahl et al demonstrated tumor response by measuring changes in tumor FDG standardised uptake values with treatment based on serial FDG PET/CT imaging. Subsequent studies have shown that the pathological response to NAC in LABC can be accurately predicted by ¹⁸F-FDG PET/CT after the fourth course of NAC in the early period.^[19–21]

Partial FDG uptake is predictive of residual disease. However, the absence of FDG uptake is not a reliable indicator of complete pathological response.^[22,23] This is especially true for axillary

Table 3
Kaplan–Meier means, standard deviations and 95% confidence interval for Survival time (months) of patients.

	Overall survival (mo)				Diseases free survival (mo)			
	Mean	Std.	95% CI	P	Mean	Std.	95% CI	P
Age				.703				.610
<50	142.15	9.54	123.4–160.8		137.548	10.36	117.2–157.8	
>51	49.21	2.00	45.2–53.1		52.161	1.932	48.3–55.9	
Clinic response				.422				.853
Not	47.8	3.13	41.7–54.0		48.917	3.234	42.5–55.2	
Partial	145.9	8.80	128.7–163.2		145.069	8.282	128.8–161.3	
Complete	61.3	3.54	54.3–68.2		60.818	3.987	53.0–68.6	
Molecular subtypes				.00				.05
Luminal A	27.19	3.24	18.8–32.1		28.21	3.121	17.7–31.3	
Luminal B	30.7	3.05	24.5–36.8		30.4	3.214	22.4–36.6	
HER2	16.7	3.52	8.76–24.6		15.2	3.01	8.34–23.7	
TNBC	24.73	3.92	19.9–37.4		24.1	3.74	17.8–35.4	
Axillary operation type				.472				.439
SLNB	54	6.98	40.3–67.7		56.355	6.086	44.4–68.2	
AD	144.8	6.96	131.1–158.5		139.402	9.859	120–158.7	

The Kaplan–Meier method and log-rank test were used to analyze overall survival and disease free survival according to age, NAC response, molecular subtypes and axillary operation type categories. AD= axillary dissection, HER2=human epidermal growth factor receptor 2, SLNB=Sentinel lymph node biopsy, TNBCs=triple negative breast cancers.

node disease because FDG has a low sensitivity in displaying microscopic disease. Therefore, the evaluation of the NAC response with only a single imaging modality may give erroneous results. In the present study, 3 imaging methods were used for each patient to reduce the FNRs. In addition, axillary FNAB was performed on the patients who could not be evaluated precisely with US. SLNBs were performed on a total of 56 patients: 25 (29.7%) cN0 patients and 31 (32.9%) patients whose FNABs could not reveal the presence of tumor cells. Approximately 70% of the patients exhibited a clinical response to NAC; however, only 20% achieved pCR.^[24,25] The results confirmed those of previous studies. A partial response was detected in 78.7% of patients, and a pCR was detected in 9.1% of the patients.

In our study group, 41.6% of the patients did not have axillary macrometastases after NAC. This was similar to the rates (37%–41%) reported in the National Surgical Adjuvant Breast and Bowel Project B-18 and American College of Surgeons Oncology Group study Z1071 series. Breast cancer patients with clinical type T1 to T4, N1 to N2, and M0 who received NAC were found to have FNRs of 12.6% to 14.2% in prospective multicenter studies that were designed similar with our study. In retrospective single-center evaluations of post-NAC SLNB, the FNRs were reported to be 5% to 20%.^[26–29] Breast cancer patients with clinical type T1 to T4, N1 to N2, and M0 who received NAC were found to have FNRs of 12.6% to 14.2% in prospective multicenter studies that were designed similar with our study. All

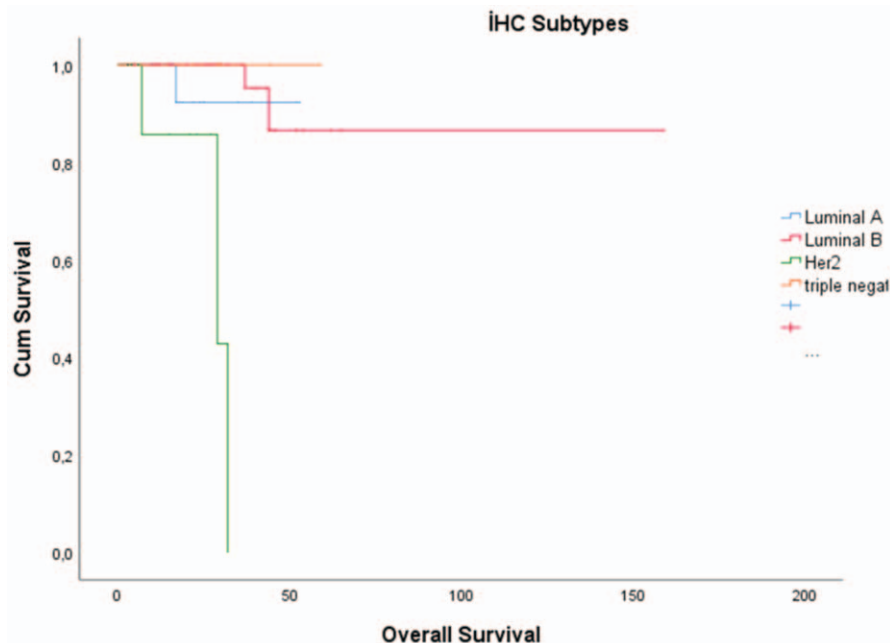


Figure 2. Overall Survival for immunohistochemical subtypes.

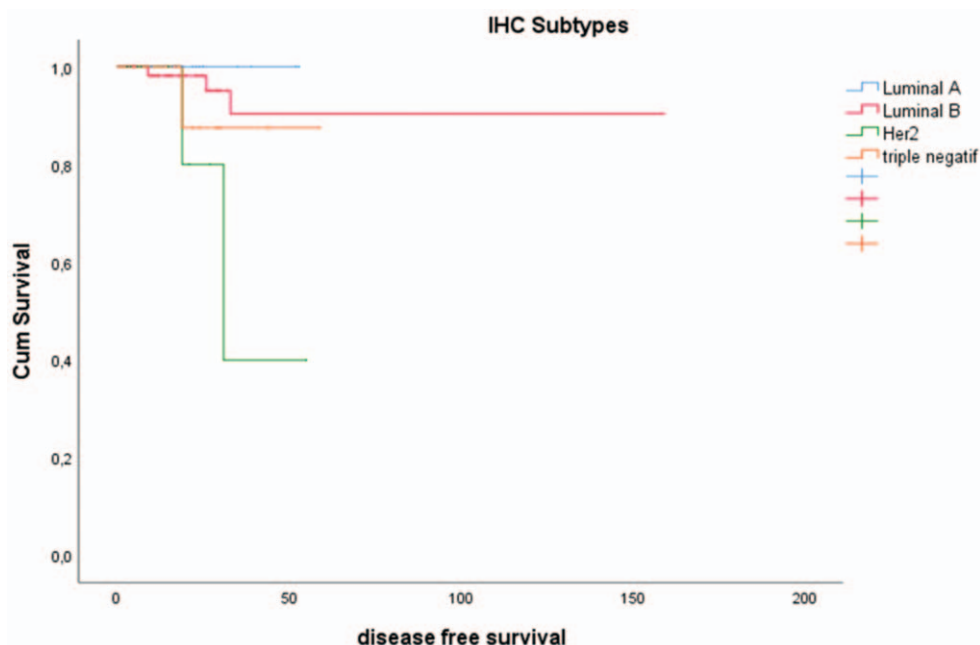


Figure 3. Disease free Survival for immunohistochemical subtypes.

of these studies emphasized the importance of the surgical technique, the application of double dyes, and the extraction of a large number of SLNs.^[11,30–32]

A recent meta-analysis highlighted the superior accuracy of pre-NAC SLNB with the removal of clip-marked nodes.^[33] In the present study, 44 patients with suspicious LNs detected through radiological examinations underwent US-guided FNAB because of the lower FNRs produced by this approach. However, AD was not performed on all the patients; thus, the FNRs cannot be provided.

According to the molecular subtypes, the incidence rates, as per Peru's classification, are as follows: 30% to 40% in luminal A tumors, 20% to 30% in luminal B tumors, 12% to 20% in HER2 overexpressing tumors, and 15% to 20% in TNBC.^[34] In the present study, the incidence rate (17%) of luminal A tumors was lower than that reported in previous studies; however, the incidence rate (60%) of luminal B tumors was higher. As was found in previous studies, the molecular subtypes were associated with both survival and pathological response.^[35]

In the American College Of Surgeons Oncology Group study Z1071 study, the pCR rates were 45.4% in the HER2-positive cancer group, 38.2% in the TNBC group, and only 11.4% in the hormone receptor-positive group. Through HER2-targeted therapy, the treatment response of patients with HER2-positive tumors has significantly improved.^[36,37] In the present study, the highest pCR rate, 30%, was detected in the HER2-positive group. Considering that approximately 2-thirds of the study population was hormone-receptor positive, the pCR rates of 18% in the triple-negative group and 17.8% in the luminal group were in accordance with the results of previous studies.^[31]

In the present study, the patients were followed up for an average of 29 months. The follow-up time for the patients in the AD group was longer than that for the SLNB group. The difference of follow-up periods in 2 groups was associated with the high number of patients with an indication of AD in the early phases of the study. LRR was observed in 6 patients within an

average follow-up period of 22 months (range 9–33). Kim et al^[38] reported LRR in only 1 of 31 patients who underwent post-NAC SLNB. They found no survival difference in the AD group during an average follow-up period of 19.5 months. Park et al^[39] applied only SLNB to 28 patients who underwent post-NAC cN0. During an average follow-up period of 37 months, no difference was found in the DFS of these patients and those who underwent AD. In the present study, 66% of the patients who experienced LRR were in the AD group. However, as was found in previous studies, there was no statistically significant difference in the DFS rates of the AD and SLNB groups ($P = .439$).

The European Organisation for Research and Treatment of Cancer 10994/BIG 1-00 study focused on patients with large operable tumors or LABC. The patients received NAC. No significant correlation was found between LRR and age.^[40] In the present study, patient age, older or younger than 50 years, did not have a significant effect on LRR and DFS.

In the present study, the IHC subtypes were found to influence DFS ($P = .05$). The luminal B group had the longest DFS (average, 30 months; 95% CI: 22.4–36.6), and the HER2 tumor group had the shortest (average, 15.2 months; 95% CI: 8.34–23.7). In a previous study, longer DFS (HR, 0.15; 0.09–0.27) and OS (HR, 0.08; 0.03–0.22) were reported in patients with HER2-enriched tumors.^[6] Another study also found a higher OS in patients with HER2-enriched subtype tumors; however, there was no difference in DFS.^[41] In the present study, the patients with HER2-enriched subtype tumors had the worst DFS rates ($P = .05$) and OS rates ($P < .05$); however, they had the highest pCR rates.

Another finding of this study was the lack of a significant effect of the response to NAC assessment on either OS ($P = .45$) or DFS ($P = .85$). Despite there are no universally accepted criteria for the effects of the NAC response on outcomes, pCR has been found to have effect on survival.^[6,42–44]

More studies are needed to evaluate the prognostic roles of pCR and partial response.

The OS and DFS rates of patients with luminal molecular subtype were significantly better compared to both HER2 and TNBC subtypes ($P=.00$). Endocrine therapy, in which estrogen inhibits tumor growth, is the primary systemic therapy in hormone-receptor positive breast cancer. Standard endocrine therapy consists of antiestrogen medication, which is administered peroral daily for 5 years. This medication may vary according to the presence of menopause. In 2 important studies, the prognostic significance of HR status in HER2 positive breast cancer patients was evaluated, and detected that HR positive group had approximately 40% better OS and DFS rates compared to HR negative group during 4 year follow-up period.^[45,46] In this study, we also showed the positive effects of endocrine therapy on survival in luminal group of patients. Nowadays, the prognosis of HER2 positive breast cancer has recovered significantly due to HER2 targeted therapies, and many institutions do report similar favorable prognosis as HR positive breast cancer.^[36,47] However, due to limited number of patients with LABC, our HER2 positive patients who were treated with NACT had poor prognosis, particularly when compared to luminal group of patients. Nevertheless, triple-negative breast cancer patients have poor prognosis, possibly because of lack of targeted receptor therapy, such as ER, PR and HER2.^[48,49]

Another important conclusion derived from the study data was the lack of a significant difference in the OS ($P=.472$) and DFS ($P=.432$) of the SLNB-only and AD-treated groups. These findings might support the hypothesis that SLNB administered after a good post-NAC assessment would not have an effect on the risk of axillary failure and poor prognosis. However, this assumption needs to be evaluated with prospective randomized long-term studies.

This study has some limitations. First, it has a retrospective design. Second, it is a single-center study with relatively few patients.

In conclusion, post-NAC evaluation is very important in LABC because of biological and anatomical differences. The molecular subtypes were found to be associated with survival. However, the post-NAC axillary approach had no effect on either OS or DFS. Therefore, multiple imaging and interventional methods should be applied to the evaluation of the response to NAC. In addition, AD morbidity can be avoided by the use of SLNB for cN0 patients.

Author contributions

Data curation: Mücahit Ünal, İlknur Bilkay Görkem, Merih Guray Durak, Ozden Ozer.

Formal analysis: Ozden Ozer, Büşra Emir.

Investigation: Merih Guray Durak.

Methodology: Pınar Balcı, İlknur Bilkay Görkem, Merih Guray Durak.

Resources: Ozden Ozer.

Supervision: Ali İbrahim Sevinc, Pınar Balcı, İlknur Bilkay Görkem, Recep Bekiş.

Writing – review & editing: suleyman ozkan aksoy.

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