RESEARCH ARTICLE

# Effect of Neoadjuvant Chemotherapy on Axillary Lymph Node Positivity and Numbers in Breast Cancer Cases

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## Abstract

**Background: The aim of this study is to compare the numbers of axillary lymph nodes (ALN) taken out by dissection between patients with breast cancer operated on after having neoadjuvant chemotherapy (NAC) treatment and otherswithout having neoadjuvant chemotherapy, and to investigate factors affecting lymph node positivity. Materials and Methods: A total of 49 patients operated due to advanced breast cancer after neoadjuvant chemotherapy and 144 patients with a similar stage of the cancer having primary surgical treatment without chemotherapy at the general surgery clinic of Ondokuz Mayıs University Medicine Faculty between the dates 01.01.2006 and 31.10.2012 were included in the study. The total number of lymph nodes taken out by axillary dissection (ALND) was categorized as the number of positive lymph nodes and divided into <10 and ≥10. The variables to be compared were analysed using the program SPSS 15.0 with P<0.05 accepted as significant. Results: Median number of dissected lymph nodes from the patient group having neoadjuvant chemotherapy was 16 (16-33) while it was 20 (5-55) without chemotherapy. The respective median numbers of positive lymph nodes were 5 ( 0-19) and 10 (0-51). In 8 out of 49 neoadjuvant chemotherapy patients (16.3%), the number of dissected lymph nodes was below 10, and it was below 10 in 17 out of 144 primary surgery patients. Differences in numbers of dissected total and positive lymph nodes between two groups were significant, but this was not the case for numbers of <10 lymph nodes. Conclusions: The number of dissected lymph nodes from the patients with breast cancer having neoadjuvant chemotherapy may be less than without chemotherapy. This may not always be attributed to an inadequate axillary dissection. More research to evaluate the numbers of positive lymph nodes are required in order to increase the reliability of staging in the patients with breast cancer undergoing neoadjuvant chemotherapy.**

**Keywords:** Breast cancer - neoadjuvant chemotherapy - axillary lymph nodes - dissection

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## Introduction

The effective choice of the treatment of breast cancer is surgery. However, NAC takes the place of surgery at the first treatment in order to allow breast protective treatment in patients with locally advanced breast cancer (LABC) that cannot be operated and in selected phase IIIA patients. Axillary lymph node dissection (ALND) is implemented for the patients with breast cancer for diagnosis and treatment, and it is also the most important prognostic factor in disease-free survival, staging and the planning of adjuvant systemic treatment (Gogia et al., 2014). For axillary staging in LABC, level 1-2 or level 1-2-3 dissection should be implemented. It is necessary to take out at least 10 lymph nodes to provide the accuracy of the pathologic staging (Thain et al., 1998; Somner et al., 2004).

LABC is considered for the patients with Stage IIB (T3, N0. M0) and IIIA, B, C breast cancer. Starting the treatment with chemotheraphy for LABC has become a current issue to provide far disease-free survival in addition to local disease-free survival, and NAC has been the first treatment for LABC for the last 20 years (Chaves et al., 2010; Khokher et al., 2010; Goel et al., 2011).

Altough it has been demonstrated before that NAC reduces the number of ALN related to tumor and lower the clinical stage, it is not clear it reduces the total number of ALN taken out for pahologic staging. Opposite results has been obtained from the related studies. In the present study, we aim to assess the total number of ALN taken out by ALND of the patients implied NAC and primary surgery and the factors that may affect the number.

## Materials and Methods

In this study, the records of the 193 patients operated for breast cancer at Ondokuz Mayıs University Medical Faculty, General Surgery Clinic between the

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dates 01.01.2006 and 31.10.2012 has been studied retrospectively. American Joint Committee on Cancer 2002 system criteria has been used for staging the patient (Greene et al., 2002). 49 of the patients was in the group having NAC. Patients in NAC group were examined in detail during chemotheraphy implementation, applied control breast MR and Response Evaluation Criteria in Solid Tumors (RECIST) was employed to evaluate the response during chemotheraphy (Keam et al., 2013). After the patients became operable modified radical mastectomy (MRM) was applied. If there is no palpable lymph node at level 3, standard level 1-2 axillary dissection is applied in our clinic. The patients having breast protective surgery (BPS) after treatment were excluded from the study, and it was tried to obtain a homogenous group including only the patients applied MRM. A comparison group was formed separating 144 patients with operable breast cancer not having NAC among the patients. There were patients applied SLNB and ALND completed in the study group, and sentinel and non-sentinel lymph nodes were added to the total ALN number.

Factors of which efficiency would be searched are; age, menapause status, size of the tumor, stage, grade, histopathological type of the tumor, hormon receptor status, LVI existence, number of the lymph nodes taken out and number of the pathological/reagent lymph nodes taken out, number of <10 and ≥10 lymph nodes, the size of the biggest metastatic lymph node, size of the tumor before chemotheraphy and pathological response.

Data was recorded using Statistical Program for Social Science (SPSS) 15.0 version. Chi-square test was used to compare qualitative data, Mann-Whitney-U test was used to compare numeric data. P<0.05 was determined as significance level.

## Results

3 of the patients given NAC were at stage IIB (6.1%), 21 were at stage IIIA (42.9%) and 25 were at stage IIIB (51%) breast cancer when established diagnosis. There was palpable lymph node in axilla before treatment. Protocols containing doxorubicin 50 mg/kg, docetaxel 75 mg/kg (AT) for 42 patients, 5-fluorouracil 500 mg/kg, doxorubicin 50 mg/kg, cyclophosphamide 500 mg/kg (FAC) for 4 patients and doxorubicin 50 mg/kg, cyclophosphamide 500 mg/kg (AC) for 3 patients were implied every 21 days. MRM was applied for the patients recieved response clinically, the treatment was carried fort he patients who did not give at the least partial response. Patients received 2-6 cure of chemotheraphy depending on the response obtained.

The average age of the patients included in the study was found as 50 (23-85). It was recognised that there was no age difference among the patients in the NAC group and primary surgery group according to univariate analysis (p=0.588).

In NAC group, there were 24 premenopausal patients (49%) and 25 postmenopausal patients (51%), and in primary surgery group there were 56 premenopausal patients (38.9%) and 88 postmenopausal patients (61.1%). It was found that menopausal state had no difference in both groups (p=0.463).

The average tumor size in NAC group was assessed

**Table 1. Characteristics of Patients**

| Property of patients | NAK | Primary surgery |
|---|---|---|
| Menopausal status | | |
| Pre | 24 (%49) | 56 (%38.9) |
| Post | 25 (%51) | 88 (%61.1) |
| Right or Left ALND | | |
| Left | 24 (%49) | 64 (%44.4) |
| Right | 25 (%51) | 79 (%55.6) |
| The median size of tumor | 2.75 (0-12) | 3.6 (0.3-13.5) |
| Pathological tumor stage | | |
| T0 | 7 (%14.3) | --- |
| T1 | 21 (%42.9) | 37 (%25.7) |
| T2 | 15 (%30.6) | 77 (%53.5) |
| T3 | 4 (%8.2) | 27 (%18.7) |
| T4 | 2 (%4) | 3 (%2.1) |
| Pathological lymph node stage | | |
| N0(0) | 6 (%12.2) | 2 (%1.4) |
| N1(1-3) | 14 (%28.5) | 29 (%20.2) |
| N2(4-9) | 22 (%44.8) | 58 (%40.2) |
| N3(10+) | 7 (%14.5) | 55 (%38.2) |
| Clinical stage | | |
| II A | --- | 51 (%26) |
| II B | 3 (%6.1) | 86 (%45) |
| III A | 21 (%42.9) | 47 (%24) |
| III B | 25 (%51) | 10 (%5) |
| Histopathological diagnosis | | |
| İnvasive ductal carcinoma | 44 (%89.8) | 127 (%88.2) |
| İnvasive lobular carcinoma | 2 (%4.1) | 6 (%4.2) |
| Mixed(ductal+lobular) | 1 (%2) | 6 (%4.2) |
| Others | 2 (%4.1) | 5 (%3.4) |
| Histological grade | | |
| 1 | 7 (%14.3) | 13 (%9) |
| 2 | 23 (%46.9) | 73 (%50.7) |
| 3 | 19 (%38.8) | 58 (%40.3) |
| Lymphovascular invasion | | |
| Yes | 30 (%61.2) | 95 (%34) |
| No | 19 (%38.8) | 49 (%66) |
| The median number of axillary lymph nodes | 16 (6-33) | 20 (5-55) |
| The median number of positive lymph nodes | 5 (0-19) | 10 (0-51) |
| The median number of negative lymph nodes | 11 (0-33) | 10 (0-52) |
| Number of lymph nodes | | |
| <10 | 8 (%16.3) | 17 (%11.8) |
| ≥10 | 41 (%83.7) | 127 (%88.2) |
| Estrogen receptor | | |
| Positive | 29 (%59.2) | 107 (%74.3) |
| Negative | 20 (%40.8) | 37 (%25.7) |
| Progesterone receptor | | |
| Positive | 22 (%44.9) | 81 (%56.3) |
| Negative | 27 (%55.1) | 63 (%43.7) |
| CerbB2 | | |
| Positive | 21 (%42.9) | 81 (%56.3) |
| Negative | 28 (%57.1) | 63 (%43.7) |

as 2.755±2.896 ( 0-12 cm) and in primary surgery group 3.613±2.235 (0.3-13.5 cm). It was determined that tumor size in NAC group was smaller (P≤0.01). The average tumor size had been 5.532±2.617 (2.5-12 cm) and it was found that the size decreased after treatment and it was found significant (P≤0.01).

While residual tumor was not detected pathologically in 7 patients (14.2%) after NAC, ALN metastasis was observed in 6 patients (12.2%). It was determined that total clinical response developed in 5 patients (10.2%), nearly total clinical response in 6 patients (12.2%), partial clinical response in 27 patients (55.1%), stable disease in 9 patients (18.4%) and progression in 2 patients (4.1%) at the follow-up of 49 patients during the treatment process. Lymph node negative rate in axilla was significantly higher in patients recieved total pathological response from the tumor (P≤0.01).

Pathological features of the patients were examined and the staging was made depending on the size of the focus of the invasive cancer at the definitive surgical specimen. Accordingly, NAC group had smaller average tumor size, lower pathological tumor stage and lower pathological lymph node stage that primary surgery group (P≤0.01). It was determined that two groups did not differ in terms of histological type of the tumor (P=0.522).

Pathological tumor grades of the patients: in 20 patients (10.3%) grade 1, in 96 patients (49.7%) grade 2, in 77 patients (39.8%) grade 3. It was determined that pathological tumor grade was not different between the two groups (P=217).

While LVI was positive in 79 patients of 193 patients (40.9%), it was negative in 114 patients (59.1%). LVI existence in NAC group was significantly high (P<0.01).

It was found that there was no significant difference between the two groups in terms of estrogen receptor status (P=0.567), progsterone receptor status (P=0.59), C-erb-B2 status (P=0.263) and triple negative status (P=0.611).

Total ALN number taken out during ALND: the average number was 16 (6-23) in NAC group and 20 (5-55) in primary surgery group. A significant difference was determined between the two groups in terms of total lymph nodes number (P<0.001).

Number of positive lymph nodes: the average number was 5 (0-19) in NAC group and 10 (0-51) in primary surgery group. It was observed that positive lymph nodes number was fewer in NAC group (P<0.001).

Fewer than 10 lymph nodes were taken out from 8 patients (16.3%) out of 49 patients in NAC group, and fewer than 10 lymph nodes were taken out from 17 patients (11.8%) out of 144 patients in primary surgery group. Difference between two groups was not significant (P=0.57).

Follow-up period in our study was median 36 months (6-72). Distant organ metastases was found in 20 patients (10.3%). Distant organ metastases was found respectively in bones, lungs, brain, liver and more than one organ. Axillary recurrence was determined in 15 patients (7.7%). There was no difference between the groups in terms of distant organ metastases (p=0.899) and axillary recurrence (p=0.651).

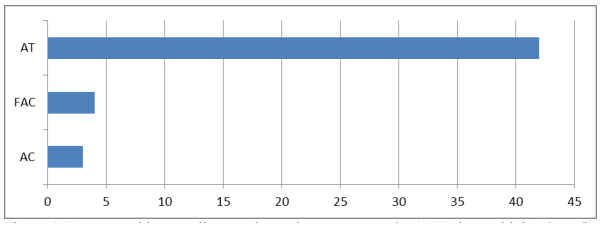


**Figure 1. Drugs used in Neoadjuvant Chemotherapy Protocols.** (AT: doxorubicin 50mg/kg, docetaxel 75 mg/kg, FAC: 5-fluouracil 500 mg/kg, doxorubicin 50 mg/kg, cyclophosphamide 50 mg/kg, AC: doxorubicin 50 mg/kg, cyclophosphamide 50 mg/kg)

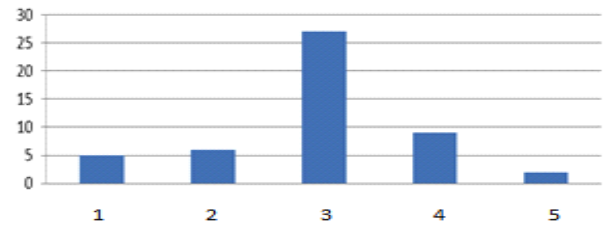


**Figure 2. Frequency of Clinical Response to Neoadjuvant Chemotherapy.** (1: complete response, 2 near complete, 3: parial response, 4: stable disease, 5: progressive disease)

## Discussion

LABC was tried to be cured via surgery and radiotheraphy primarily until 1980s but response for the treatment and survival was low. After Fisher claimed that breast cancer was a systemic disease and revealed that it could be controlled by chemotheraphy, systemic treatments for LABC came into prominence primarly, and local control, disease-free survival and survival average rates increased (Yu et al., 2013). The objective of NAC is to remove the microscopic systemic disease, provide the curative treatment to be done, observe the response of tumor to chemotheraphy and that medicine can be changed without causing toxicity in case of resistance.

Local and systemic recurrence risk is high in LABC. ALN involvement is the most significant indicator of prognosis in breast cancer and it takes part to determine the treatment to be implied when staging the disease. It is suggested that at least 10 lymph nodes to be taken out for adequate axillary staging (Thain et al., 1998; Somner et al., 2004). It is stated that the number of ALN of the patients implied ALND after NAC is significantly fewer than the number in the patients having surgery without chemotheraphy (Neuman et al., 2006; Belanger et al., 2008). In our batch the number of ALN taken out in NAC group was significantly fewer than the primary surgery group, and this is accordant with the literature. Also the state of the number of lymp nodes taken out of ALND samples being fewer than 10 did not demonstrate a significant difference although the number of lymph nodes taken out of NAC group was more. The state of the number of ALN being abound creates high risk for local recurrence development (Meric et al., 2000). The median

value of the number of pathological ALN in NAC group was 5 (0-19) and 10 (0-51) in primary surgery group, and this was found significant and compatible with the literature. Negative lymph nodes were similar in both groups (11% and 10%). Clinical response can be obtained between 60-80% via NAC, but pathological complete response rate varies between 10-20% (Apffelstaedt et al., 2003). In our study, pathological complete response rate obtained from tumor and axilla was 14% and compatible with the literature. Kuerer et al. state that 75% of the patients obtained pathological complete response in tumor also gave complete response in axilla (Kuerer et al., 1998). In our study, it was determined that 4 out of 7 patients obtained pathological complete response in tumor (57%) gave complete response also in axilla. There is a directly proportional relation between the responses of tumor and axilla metastases obtained after NAC in LABC. The average tumor size and the number of lymph nodes before NAC decreased significantly in our study and this is compatible with the literature.

Various mechanisms were proposed that NAC could be the reason of the decreasing of the number of tumors taken out (Newman et al., 2003; Kurio et al., 2006). In microscopic examination of primary tumor and ALNs of the patients recieving NAC, it was found that there was an increased fibrosis stromal response in tumor and tissues around it and also histiocyte cumulation. Accordingly, it is stated that NAC can reduce the number and size of ALN causing lymphocytic toxicity, complete fibrotic involution and obliteration in tumor metastases in ALNs. Another possibility is the opinion that NAC has a cytotoxic effect on lymphocytes that formed a large proportion of lymph node cortex and that it can directly obliterate lymph nodes (Neuman et al., 2006).

It is expected the response to chemotheraphy to be great since the cell proliferation is fast in the patients having high grade of tumor. The rate of pathological comlete response increases in high grade tumors and the chance to obtain complete response in patients with grade 3 tumor is about three times more (Colleoni et al., 2000). In our study no difference determined between the low and high grade tumors in terms of the response to pathological and axillary tumor.

Althogh there are studies to demonstrate the relationship of C-erbB-2 gene expression with local recurrence, survival without metastasis and ALN involvement, no relationship is determined with ALN metastasis in the study of Brotheric et al. (1995) and similar studies (Brotherick et al., 1995). Makris et al. propose that the response rate of the patients having positive c-erbB-2 to chemotheraphy is lower (Makris et al., 1997). No significant difference found between the two groups in terms of c-erbB-2 positivity in our study. While no relationship is determined between estrogen receptor existence and ALN involvement in many studies searching the relationship between axillary lymph nodes and hormone receptors, it is demonstrated that disease-free survival of the patients with ER (+) is longer than the ones with ER (-) (Clark et al., 1988). Knight et al. state the ER negativity as independent prognostic factor in terms of early recurrence (Knight et al., 1977). Althogh Giani et al. present progsterone receptor as a useful factor for for ALN metastasis (Giani et al., 1989), Colleoni et al. state that pathological complete response rate to chemotheraphy in ER/PR negative patients is higher (Colleoni et al., 2000). There is no significant difference between two groups in our study.

Another indicator to point the risk of ALN metastasis is LVI existence. Rahusen et al. examine 1228 patients and set that LVI existence is a predictive factor affecting ALN positivity (Rahusen et al., 2001). There is a significant difference between ALN metastasis and LVI in our study.

In some studies it is stated that as the age of the patient increases, ALN number decreases (Schaapveld et al., 2004). Such relationship is not found in our study. Thus, age is not considered as the reason of taking out fewer lymph nodes in NAC group.

When tumor and nodal staging examined; pathological tumor and pathological node staging in NAC group was significantly lower than that of the primary surgery group and this is compatible with the literatüre (Belanger et al., 2008).

LABC patients are constituted a high risk group in terms of local/zonal and systemic recurrence. It is stated that systemic metastasis rate is 5-10% in LABC in related studies; in LABC patients in our batch systemic metastasis rate is 10.2% and this is compatible with the literature. In literature local recurrence rate is stated between 7.9% and 34%; this rate is 7.7% in our batch and this is compatible with the literature. Neuman et al. state that axillary recurrence is not determined in the patients during their 72-month follow up after taken out lymph nodes under 10 and they proposed that the surgical technique they applied is sufficient (Neuman et al., 2006). In our study axillary recurrence is not observed in any patients recieved NAC and taken out lymph nodes under 10 during their 36-month follow up.

Belenger et al. find a little difference between the patients recieved NAC and had primary surgery in terms of the number of lymph nodes taken out by axillary dissection, but determine lymph nodes under 10 in significantly more patients received NAC (Belanger et al., 2008). Neuman et al. (2006) do not find a difference in terms of the total number of lymph nodes taken out, they determine lymph nodes under 10 in significantly more patients received NAC (Neuman et al., 2006). Boughey et al. (2014) state that the average number of lymph nodes is more in NAC group than primary surgery group and the rate of determining rate of lymph nodes under 10 in both groups is equal in their study (Boughey et al, 2014). They stated that the reason of their contrast with other authors is that their surgical technique and histopathological examination is more comprehensive. The number of lymph nodes taken out from NAC group was found significantly fewer in our study, but, although the number of patients fewer than lymph nodes taken from in NAC group was more, there wasn't a significant difference.

In conclusion, 4 factors affecting ALN number taken out in both group were found significant. These are: NAC, tumor stage, tumor size and LVI existence. Total number of lymph nodes taken out and positive lymph

nodes can be more in patients with breast cancer having NAC than the ones not having NAC. This state should not be always attributed to insufficient ALND, and it should be considered that NAC can reduce the number of ALN. Even so, its effect on prognosis and staging in patients with invasive breast cancer is not certain. More studies to evaluate the number of lymph nodes after NAC is needed in order to increase the reliability related to staging in breast cancer patients.

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