

AXILLARY RESPONSE TO NEO-ADJUVAN CHEMOTHERAPY: DECREASE IN NUMBER OF LYMPH NODES

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NEO-ADJUVAN KEMOTERAPİYE AKSİLLA YANITI: LENF NODU SAYISININ AZALMASI

ÖZET

Amaç: Neo-adjuvan kemoterapi lokal ileri evre meme kanserinin standart tedavilerinden biridir. bu tedavi sonrasında yanıtı bağlı olarak aksiller doku ve lenf nodlarında değişiklikler olmaktadır. bu değişiklikler disseksiyon sonrası sonuçları etkilemektedir.

Hastalar ve Yöntem: Lokal ileri evre meme kanserli 47 hastaya neo-adjuvan kemoterapi sonrası aksilla disseksiyonu yapıldı. Kontrol grubu olarak aynı evrede olan ve NAC yapılmayan 58 hasta seçildi. Aksiller disseksiyon sonrası total ve pozitif lenf nodu sayıları arasındaki farklılık incelendi.

Bulgular: NAC sonrası ortalama lenf nodu sayısı 11,3 (4-20 arası), pozitif lenf nodu sayısı 3,6(0-15 arası) bulundu. kontrol grubunda ise 19,5(10-35 arası)ve 9,2(2-31 arası)bulundu. Hem total hem de pozitif lenf nodu sayısı için aradaki fark istatistiksel olarak anlamlı bulundu.

Sonuç: NAC sonrası aksiller doku ve lenf nodlarında oluşan değişiklikler kemoterapi yanıtı ve hastalığın prognozu açısından önemli faktördür.

Anahtar sözcükler: meme kanseri, aksiller, lenf nodu, disseksiyon, neo-adjuvan, lokal, ileri

ABSTRACT

Background: NAC (Neo-adjuvan chemotherapy) is the standard treatment method for locally advanced breast cancers. NAC is used to decrease of stage in locally advanced cancer and/or preparation for breast conserving surgery. Evaluation of patients' responses to NAC is vital for both prognosis and treatment decisions. The aim of this study was to evaluate the alterations in axillary nodes and tissues after NAC and the effect of these alterations on dissected and positive lymph node numbers.

Material and method: 47 locally advanced breast cancer patients who received neo-adjuvan chemotherapy (NAC) between 2002 and 2005 were evaluated retrospectively for their number of total and positive lymph nodes after axillary lymph node dissection. Fifty-eight breast cancer patients at same stages who did not receive NAC were selected as a control group to compare the total and positive axillary lymph node numbers.

Results: The mean number of dissected lymph nodes was 11.3 for NAC group patients (range 4 to 20) and the mean number of positive lymph nodes was 3.6 (range 0 to 15). The mean number of total lymph nodes was 19.5 (range 10 to 35) in the control group, and the mean positive lymph node number was 9.2 (range 2 to 31). The differences were statistically significant for both total number of lymph nodes and number of positive lymph nodes.

Conclusion: Alterations on axillary tissue and lymph nodes after NAC are important factors for evaluating the response to chemotherapy and determining the prognosis of disease.

Key words: breast cancer, axillary, lymph node, dissection, neo-adjuvan, local, advanced

NAC (Neo-adjuvan chemotherapy) is the standard treatment method for locally advanced breast cancers. NAC is used to decrease of stage in locally advanced cancer and/or preparation for breast conserving surgery. Evaluation of patients' responses to NAC is vital for both prognosis and treatment decisions. Axillary lymph node response in locally advanced breast cancer patients is an important prognostic factor and it needs to be evaluated together with primary tumour response. As a consequence of axillary node response to NAC, some histological alterations such as fibrosis, tumour emboli or cellular material

blockage of lymphatic may occur (1,2). After such alterations, both axillary dissection and pathological evaluation become more difficult. There is a debate on axillary response assessment, diagnostic methods and treatment choices after NAC. Conventionally, detection of less than 10 lymph nodes after axillary dissection is accepted to be insufficient but is this still true after NAC is debatable.

In this study, we evaluated the alterations in axillary nodes and tissues after NAC and the effect of these alterations on dissected and positive lymph node numbers.

Materials and Methods

A total of 47 patients who received NAC between 2002 and 2005 were included in this study. To maintain standardization, FEC regimen (Cyclophosphamide 600 mgr/m², 5-flourouracil 600 mgr/m², epirubicin 100 mgr/m²) given to patients with locally advanced cases were included in the study. Preoperatively, 17 patients had three and 30 patients had four cycles of chemotherapy. All surgical operations were carried out by 4 surgeons as standard level 2 axillary dissection. Lumpectomy-axillary dissection was performed in five patients and 42 patients underwent modified radical mastectomy after NAC. 12 patients had lumpectomy-axillary dissection and 46 patients received MRM in control group of patients. No patients received SLNB after NAC.

The mean age was 51 (range 21 to 77) in the case group and it was 51.2 years (range 24 to 72) in the control group of patients. Most of the patients and controls were in the stage 3B (60% and 57%, respectively; Table 1). Specimens were reviewed for total and positive lymph node numbers and histopathological alterations by the same pathologist. Physical examination and ultrasound examination were used for evaluations of axilla before and after NAC. Patients who did not have response to the chemotherapy by clinical and radiological means (stable disease or progression) were omitted from the study.

Two-Sample T-Test was used for statistical analysis. Jonckheere-Terpstra method was used to test for differences among the stage and operative procedures by the two groups and the Wilcoxon rank-sum test was used to test to difference in age between the two groups. $P < 0.05$ was considered statistically significant.

Results

There was no statistical differences between the case and control groups in terms of age, stage of disease and operative procedures ($p > 0.05$).

The mean number of dissected lymph nodes was 11.3 for NAC group patients (range 4 to 20) and the mean number of positive lymph nodes was 3.6 (range 0 to 15). For one patient, conglomerated lymph nodes were detected. In another patient no lymph nodes were found but had widespread malignant areas in the axillary tissue. These two patients were considered to have axillary involvement and their total and positive lymph node numbers were not counted.

The mean number of total lymph nodes was 19.5 (range 10 to 35) in the control group, and the mean positive lymph node number was 9.2 (range 2 to 31). The differences were statistically significant for both total number of lymph nodes and number of positive lymph nodes ($p < 0.01$ for number of total lymph nodes and $p < 0.01$ for number of positive lymph nodes) (Table 2).

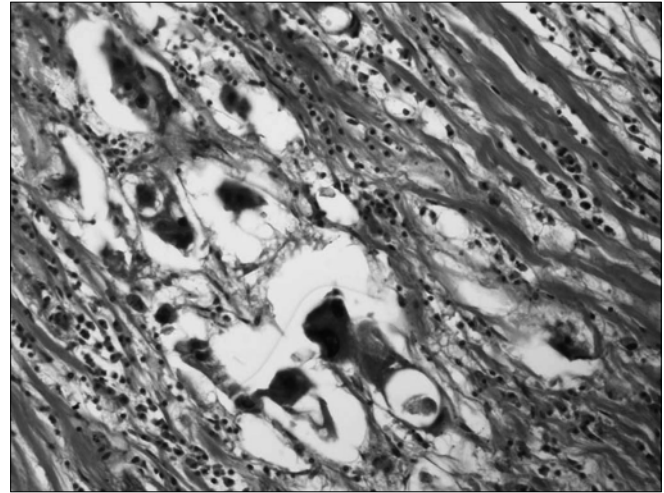


Figure 1. Changes in the axilla after NAC. (HE, 20x400)

Table 1. General Characteristics of the Patients.

	NAC	Primary Surgery
Stage 3A	19 (40%)	25 (43%)
Stage 3B	28 (60%)	33 (57%)
Mean Age	51,1	51,2
MRM	42 (89%)	46 (79%)
Lump-AD	5 (11%)	12 (21%)
Total	47 (100%)	58 (100%)

Table 2. Number of Total and Positive Lymph Nodes.

	NAC	Primary Surgery	P value
Number of Total LNs (mean)	11,3 (4-20)	19,5 (10-35)	< 0,01
Number of Positive LNs (mean)	3,6 (0-15)	9,2 (2-31)	< 0,01

Elastosis, fibrosis, hyalinisation and pycnosis were detected after NAC. Histopathologically, tumour morphology was deformed, foreign body type granulation tissue and giant cell formations were observed in the extra-capsular area. (Figure 1)

Discussion

Axillary response to NAC is equally as important as primary tumour response. These indicators are accepted to be vital for progress and prognosis of the disease. It was shown that NAC transforms positive lymph nodes to negative in a significant number of cases (1- 26). NAC causes morphologic and histopathological alterations in axillary lymph nodes, axillary tissue. (22, 23) As a consequence of such alterations, surgical and pathological difficulties as well as problems in the evaluation of the response may occur.

In a study of 58 patients who underwent mastectomy and axillary lymph node dissection after NAC total number of lymph

hodes positive lymph nodes were found to be significantly higher in patients who did not receive NAC (2). Authors stated that this decrease in total and positive lymph node numbers were as a result of response to NAC. Fibrotic response which is seen in breast and axillary tissue due to chemotherapy increases the difficulty of axillary dissection and complicates pathological evaluation (3). Another study where outcomes of patients with and without NAC were compared 17.9 lymph nodes harvested after axillary dissection in patients received NAC and 21 lymph nodes in patients who did not receive NAC, but positive lymph node numbers were similar for both groups (2.9 and 1.67, respectively)(4).

Scar tissue formation in axillary nodes was significantly higher for NAC group patients. Formation of scar tissue in axillary lymph nodes is not a frequent finding and is actually a criterion of axillary down-stage. This was mostly observed in patients who had primary tumour response. Formation of scar tissue may be a potential prognostic and predictive factor (5, 25).

Observation of lymph nodes less than 10 with axillary dissection is a result of anatomical variation or insufficient dissection. Number of lymph nodes detected with axillary dissection after NAC decreases. Increased stromal fibrosis and obliteration in lymph nodes may be observed after NAC (6). Most of the agents that are used in cancer treatment are effective for both T and B lymphocytes. Despite the lack of knowledge about chemotherapy effect on human normal lymph nodes, as a consequence of intense treatment for leukemia and tumours, vascular damage and apoptosis is suggested to be the cause of replacement of neoplastic tissue with hyaline material and cellular debris. After chemotherapy, following cellular alterations at residual tumour cells are defined as secondary to chemotherapy: increase in nuclear dimensions, pleomorphism, vacuolization, chromatin clumping. Kennedy et al showed that cytoplasmic vacuolization in residual neoplastic cells leads to histiocytoid appearance and they also reported that non-neoplastic cells in terminal ductal lobular unit and large ducts enlarge with nuclear atypia (20, 21, 24). It was thought that this type of treatment may start or accelerate normal involutinal alterations. In some of our patients we could not find malign disease in the axilla. Microscopically we have found fibrosis, pleomorphism, giant cell formation, multinucleation, picnosis, vascular dilatation, hyalinisation, elastosis, anisocaryosis, foreign body granulom, giant nucleoli and infiltration of the lymphocytes.

In our study we have found significant decrease in the number of total and positive lymph nodes after NAC. We think that revival of less than 10 lymph nodes after axillary dissection should not be considered insufficient surgery.

Ultrasonography (US) is accepted to be the most appropriate method for evaluation of axilla after NAC. Joint use of physical examination and US for evaluating lymph nodes provided better results (7). A total of 40 patients were studied after 3 regimens of NAC and 47% clinical response, 19% complete sonographic

response and 22% complete pathological response was observed. US is more sensitive than clinical findings for evaluation of axilla (8). In our study we used physical examination and US for evaluation of axilla.

Some clinics argue that lymphatic mapping will be unsuccessful due to the increased fibrosis in primary tumour and lymphatic tissues also tumour emboli or cellular material blockage of lymphatics may occur (3, 9-14).

Primary tumour response and the pathological state of axillary nodes after NAC are predictive factors for locoregional disease (15). In a study after NAC pCR was 23% for 152 patients with T1-3 tumours. In this study, axillary condition was found to be a better prognostic factor for evaluating NAC response (16). For 47 stage 2 and 3A patients, BCS and axillary dissection was applied after NAC and axillary evaluations were carried out with physical examination and US. Primary tumour response and axillary response were found to be parallel for these patients. Especially for the patients who had primary tumour response of more than 50%, axillary response increased at the same rate (17). Residual disease stage (primary tumour and axillary response) for 132 patients who underwent NAC was a significant indicator for disease-free survival (18). NAC was given to 148 stage 3A and 3B patients and a correlation was detected between primary tumour and axillary response. Especially axillary lymph node responses were found to be related with overall survival and disease-free survival (19). Pathological complete responses of primary tumour and axilla have significant effects on disease-free survival (9). Axillary response to NAC was 26% for N1 patients and 74% for N2 patients. Mean number of lymph nodes was reported to be 16. Negative ER, small size of primary tumour and response of primary tumour were all found to be correlated with axillary response. Occult metastasis rate after NAC was 10%. For axilla negative cases, 5-year disease-free survival rate was 87% while it was 51% for the cases who had residual disease in axilla (9).

Conclusion

Alterations on axillary tissue and lymph nodes after NAC are important factors for evaluating the response to chemotherapy and determining the prognosis of disease. However, number of lymph nodes detected in axillary dissection material decreases as a consequence of these alterations. This decrease is valid for numbers of both total and positive lymph nodes. The decrease in the number of lymph nodes may be an indicator for clinical response. This is increasingly important for the patients whose axillary involvement was shown to be positive clinically and radiologically. After NAC, detection of less than 10 lymph nodes with axillary dissection may not be considered as an insufficient surgery. Alterations occur in axillary morphology (granulation, histiocytosis, hyalinization, fibrosis) and this axillary response may cause granular cancerization areas in lymph nodes. As a consequence, reliability of SLNB applications after NAC may expect to be diminished.

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