Neoadjuvant Chemotherapy and Axillary Lymph Nodes: Factors Affecting Lymph Node Yield in Patients Undergoing Axillary Node Dissection

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Abstract

Aim: This study aims to investigate the impact of neoadjuvant chemotherapy (NAC) on the number of lymph nodes dissected during axillary lymph node dissection (ALND) in breast cancer patients, a topic of significant debate among surgeons and pathologists.

Methods: We conducted a retrospective analysis of 440 breast cancer patients who underwent surgery between January 1, 2018, and December 31, 2020. Patients were categorized into two groups based on NAC administration. We collected demographic, clinical, and pathological data, focusing on the total and malignant lymph node counts.

Results: Among the 440 patients, 124 received NAC, while 316 did not. The mean number of lymph nodes removed was 18.1 in total, with 17.2 in the NAC group and 18.5 in the non-NAC group (P = 0.17). No significant differences were observed in the number of malignant lymph nodes between the two groups (P = 0.73). However, multivariate analysis indicated that NAC significantly influenced the total number of lymph nodes dissected (P = 0.05). Additionally, lymphovascular invasion (LVI) was found to significantly impact the number of malignant lymph nodes.

Conclusions: Our findings suggest that NAC is associated with a reduced number of lymph nodes dissected during ALND in breast cancer patients. These results indicate that the standard guideline of removing at least 10 lymph nodes may require reconsideration for patients undergoing NAC. Further studies are needed to clarify the implications of these findings for staging and treatment protocols.

Keywords: *Neoadjuvant chemotherapy; axillary dissection; lymph node retrieval*

1. Introduction

The status of lymph node metastasis is one of the most important prognostic factors affecting recurrence and survival in breast cancer. Many factors affect the number of lymph nodes removed during axillary dissection[1,2]. One of these is undoubtedly receiving neoadjuvant chemotherapy (NAC). In cases where axillary dissection is performed for accurate staging, removal of at least 10 lymph nodes is recommended[1]. Nevertheless, there is ongoing debate concerning the validity of this number in patients receiving NAC. The goals of NAC include downstaging the cancer, making surgery less invasive, and minimizing surgery-related complications. It is already established that NAC reduces the number of positive, i.e., metastatic, lymph nodes[3-6]. However, the effect of NAC on axillary dissection, and particularly the total number of lymph nodes removed remains controversial. Both surgeons and pathologists suggest, based on their clinical experience, that in these cases axillary dissection becomes more difficult and the number of lymph nodes removed decreases. Nevertheless, there are limited studies in the literature addressing this issue and supporting this view. A study by Belanger et al reported significantly fewer lymph nodes were harvested during surgical dissection in patients receiving NAC. This was attributed to the lymphocytic toxicity and fibrotic effects of NAC on both the axillary tissue and the lymph nodes[2,3]. The data obtained by Erbes et al. supported these findings[5]. In contrast, Boughey et al reported that NAC had no effect on the total number of lymph nodes dissected[4]. To date, the literature does not demonstrate a consensus on the impact of NAC on axillary dissection or on the quantity of lymph nodes removed. The purpose of this study was to examine how NAC influences the number of lymph nodes removed during axillary dissection—an area frequently discussed by surgeons and pathologists, but one that has received limited attention in published research. At the same time, the effect of many pathologic and clinical factors other than NAC on the number of total and malignant lymph node will also be addressed in this study.

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2. Materials and Methods

Study Setting and Ethical Considerations

This retrospective study was carried out in the Department of General Surgery at the Gaziantep City Hospital. Prior to initiating the research, approval was obtained from the Scientific Research Ethics Committee of the Health Sciences University (Approval Date: 11/08/2023, Protocol Number: 15-5). As this was a retrospective study using anonymized patient data, the requirement for individual informed consent was waived by the Ethics Committee. The research procedures adhered to the ethical standards established by the institutional research committee and complied with the principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical guidelines.

Eligibility Criteria and Patient Selection

Patients included in the study were those who underwent surgery with a diagnosis of breast cancer between January 1, 2018 and December 31, 2020. Participants were eligible if they were over 18 years old, had been diagnosed with unilateral breast cancer, and had received level I or II axillary lymph node dissection (ALND). Patients excluded from the study included those younger than 18 years, individuals with bilateral or metastatic breast cancer, those who did not undergo complete ALND (i.e., patients who had only a sentinel lymph node biopsy or excisional biopsy), and individuals presenting with simultaneous involvement of axillary lymph nodes at levels I, II, and III. Participants in the study were categorized into two groups based on whether they received NAC treatment.

Outcomes

Demographic, clinical, and pathological data were collected from patient files, including details on surgical approaches, clinical and pathological stage of disease, histological subtype, tumor size, lymphovascular invasion (LVI) and perineural invasion (PNI), multicentricity, margin status, presence of ductal carcinoma in situ (DCIS), pathological complete response (PCR), number of dissected lymph nodes, metastasis, ratio of malignant to total lymph nodes, as well as estrogen, progesterone, and C-erbB-2 receptor status. The primary objective of the study was to evaluate differences in the number of surgically excised total and malignant lymph nodes between patients who received NAC and those who did not. Secondary objectives included assessing the impact of variables other than NAC on the quantity of lymph nodes removed during surgery.

Statistical Analysis

To assess differences in measured variables between groups, the Mann-Whitney U test was performed. For categorical variables, the relationships and differences were analyzed using the chi-square test and Fisher's exact test as appropriate. The associations between total and malignant lymph node counts and the examined variables were evaluated using multivariate linear regression analysis. Pearson correlation was employed to determine whether multicollinearity existed among the variables, and no multicollinearity was identified. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as a P value less than 0.05.

Table 1

Demographic and Clinical Data

	All patients (n = 440, 100%)	NAC group (n = 124, 28.2%)	Non-NAC group (n = 316, 71.8%)	P
Age (year)	59.4 (13.2)	57.5 (13.1)	60.2 (13.1)	.06
<40	29 (6.6%)	11 (8.9%)	18 (5.7%)	
41-65	267 (60.7%)	80 (64.5%)	187 (59.2%)	
>65	144 (32.7%)	33 (26.6%)	111 (35.1%)	
Tumor type				.06
Invasive ductal CA	371 (84.3%)	102 (82.2%)	269 (85.1%)	
Invasive lobular CA	30 (6.8%)	15 (12.1%)	15 (4.7%)	
Mixed type	14 (3.2%)	2 (1.6%)	12 (3.8%)	
Mucinous CA	7 (1.6%)	0	7 (2.2%)	
Solid papillary CA	7 (1.6%)	1 (8.1%)	6 (1.9%)	
Other	11 (2.5%)	4 (3.2%)	7 (2.2%)	
Stage				.72
1	52 (11.8%)	17 (13.7%)	35 (11.1%)	
2A	120 (27.3%)	31 (25%)	89 (28.2%)	
2B	102 (23.2%)	25 (20.2%)	77 (24.4%)	
3A	106 (24.1%)	35 (28.2%)	71(22.5%)	
3B	8 (1.18%)	2 (1.6%)	6 (1.9%)	
3C	52 (11.8%)	14 (11.3%)	38 (12.02%)	
4	0	0	0	
T				< .001
T1	103 (23.4%)	37 (29.8%)	66 (20.9%)	
T2	270 (61.4%)	57 (46%)	213 (67.4%)	
T3	49 (11.1%)	12 (9.7%)	37 (11.7%)	
T4	18 (4.1%)	18 (14.5%)	0	
N				.23
N0	131 (29.8%)	40 (32.2%)	91 (28.8%)	
N1	165 (37.5%)	39 (31.4%)	126 (39.9%)	
N2	92 (20.9%)	32 (25.8%)	60 (19%)	
N3	52 (11.8%)	13 (10.5%)	39 (12.3%)	

NAC: neoadjuvant chemotherapy, CA: carcinoma

Table 2
Pathological Data

	All patients	NAC group	Non-NAC group	P
Tumor diameter (mm)	29.6 (19.6)	25.4 (19.5)	31.22 (19.4)	.005
Grade				.26
1	41 (9.3%)	16 (12.9%)	25 (7.9%)	
2	288 (65.5%)	79 (63.7%)	209 (66.1%)	
3	111 (25.2%)	29 (23.4%)	82 (26%)	
Estrogen receptor %	57.7 (38.9)	71.1 (33.6)	52.4 (39.6)	< .001
Progesterone receptor %	35.8 (35.3)	42.2 (36.1)	33.3 (34.8)	.02
C-erbB-2				.27
0	200 (45.5%)	63 (50.8%)	137 (43.4%)	
1	41 (9.3%)	10 (8.1%)	31 (9.8%)	
2	96 (21.8%)	29 (23.4%)	67 (21.2%)	
3	103 (23.4%)	22 (17.7%)	81 (25.6%)	
Lymphovascular invasion	219 (49.8%)	66 (53.2%)	153 (48.4%)	.36
Ki67	23 (18.4)	18.2 (14.4)	21.7 (16.8)	.001
Multicentric tumor	87 (19.8%)	33 (26.6%)	54 (17.1%)	.03
Perineural invasion	153 (34.8%)	38 (30.6%)	115 (36.4%)	.52
Surgical margin positivity	11 (2.5%)	1 (8.1%)	10 (3.2%)	.3
Ductal carcinoma in situ	89 (20.2%)	29 (23.4%)	60 (19%)	.3
Pathological complete response	31 (7%)	31 (25%)	0	< .001
Dissected LNs, total n	18.1 (8.7)	17.2 (8.3)	18.5 (8.7)	.168
Dissected LNs, n ≥ 10	392 (89.1%)	104 (83.9%)	288 (91.1%)	.03
Dissected, n < 10	48 (10.9%)	20 (16.1%)	28 (9.9%)	.03
Number of malignant LNs	4.2 (7)	4.2 (6.7)	4.2 (7.03)	.73
Lymph node ratio	0.2 (0.27)	0.18 (0.24)	0.21 (0.28)	.59

NAC: neoadjuvant chemotherapy, LN: lymph node

Table 3
Pathological Data

	All patients	NAC group	Non-NAC group	P
Surgeon's specialty				< .001
Breast-specific	284 (64.5%)	112 (90.3%)	172 (54.4%)	
General	156 (35.5%)	12 (9.7%)	144 (45.6%)	
Surgical procedure				.12
Lumpectomy and axillary dissection	15 (3.4%)	3 (2.4%)	12 (3.8%)	
Modified radical mastectomy	414 (94.1%)	115 (92.7%)	299 (94.6%)	
Subcutaneous mastectomy Axillary dissection and implant	11 (2.5%)	6 (4.8%)	5 (1.6%)	

NAC: neoadjuvant chemotherapy

3. Results

The study included 440 patients who had breast cancer surgery at our clinic; 124 received NAC, and 316 did not. All the patients were women. The mean age was 59.4 years. According to the evaluation of the T classification, T2 tumors were most common overall (n = 270, 61.4%). T2 tumors were the most identified in both the NAC group (46%) and the non-NAC group (67.4%). When the groups were compared, T1 and T4 tumors were detected more frequently in the NAC group, while T2 tumors were predominantly observed in the non-NAC group (P < 0.001). N1 was the most frequent N category overall (n = 165, 37.5%). N0 tumors predominated in the NAC group, whereas N1 tumors were more frequent in the non-NAC group (*P* = 0.23). No significant differences between groups were found for age, sex, tumor type, stage, or N classification. The details of this data are presented in Table 1.

Among the patients evaluated, 64.5% underwent surgery performed by breast-specific surgeons, while 35.5% were operated on by general surgeons. In the NAC group, 90.3% of patients were treated by breast-specific surgeons, compared to 54.4% in the non-NAC group (*P* < 0.001). LVI was observed in 53.2% of patients within the NAC group and 48.4% in the non-N*AC* group (P = 0.36). PNI was present in 30.6% of NAC patients and 36.4% of non-NAC patients (P = 0.52). The most prevalent pathological grade in both groups was Grade 2 (P = 0.26). Most of the C-erbB-2 scores in both groups were 0 (P = 0.27). Surgical margin positivity was identified in 8.1% of the NAC group and 3.2% of the non-NAC group (P = 0.3). DCIS concomitant with carcinoma was detected in 19% of NAC patients and 23.4% of non-NAC patients (P = 0.3) (Table 2).

Within the NAC group, PCR was achieved in 25% of cases. The average number of total lymph nodes removed across the entire cohort was 18.1, with 17.2 in the NAC group and 18.5 in the non-NAC group (P = 0.17). Across all patients, the average count of malignant lymph nodes was 4.2, with no statistically significant difference between the two groups (P = 0.73). The overall lymph node ratio was 0.2, with values of 0.18 and 0.21 noted in the NAC and non-NAC groups, respectively (P = 0.59) (Table 3).

Multivariate Linear Regression Analysis

Potential factors influencing the total and malignant lymph node counts - including age, surgeon specialty, tumor type, neoadjuvant chemotherapy (NAC), tumor stage, T and N classification, multicentricity, PNI, DCIS focus, and LVI - were assessed using linear regression analysis. Among these variables, only NAC demonstrated a statistically significant impact on the total quantity of lymph nodes removed (P = 0.05). In the regression model, NAC was associated with a reduction of approximately 2 lymph nodes in the total yield ($\beta = -2.04$). (Table 4). Additionally, LVI was found to significantly influence the number of malignant lymph nodes dissected. Specifically, cases with LVI had a mean number of malignant lymph nodes dissected that was 0.26 higher than those without LVI (*P* = 0.016; Table 4).

Table 4

Linear regression analysis of factors affecting the number of total and malignant lymph nodes dissected

Characteristic	Total Regression coefficient (β)	P	Malignant Regression coefficient (β)	P
Estrogen receptor	-0.025	.06	0.001	.64
Progesterone receptor	0.021	.13	0.002	.25
C-erbB-2	0.455	.18	-0.011	.78
Lymphovascular invasion	-0.081	.93	0.259	.016
Perineural invasion	-1.162	.19	0.099	.36
DCIS	0.497	.67	0.021	.88
Tumor type	1.086	.46	0.404	.06
Tumor diameter	-0.010	.84	-0.004	.53
Ki67	-0.034	.18	0.004	.23
Multicentric tumor	-0.814	.42	0.061	.62
Neoadjuvant chemotherapy	-2.04	.05	-0.130	.31
Surgeon's specialty (breast-specific)	1.577	.13	-0.025	.84

4. Discussion

To ensure accurate staging and treatment of breast cancer, at least 10 lymph nodes should be removed during axillary dissection[1]. Inadequate dissection may result in inaccurate staging. Increased disease-free survival has been observed in patients with at least 10 lymph nodes in the ALND specimen, aligning with guidelines[7,8]. One of the many factors affecting lymph node yield during axillary dissection is LVI status. In a study involving 1,228 patients, Uyan et al. identified a significant association between axillary lymph node metastasis and LVI[9]. Rahusen et al. found that LVI could predict axillary lymph node positivity[10]. In our study, regression analysis demonstrated a positive correlation between LVI, and the number of malignant lymph nodes removed during dissection (r = 0.259, p = 0.016).

According to Uyan et al., factors such as NAC, tumor stage, tumor size, and LVI play significant roles in determining lymph node counts[9]. Additional studies have highlighted other variables including age, hormone receptor status, BMI, and the surgeon's expertise. In our study, we observed that age did not impact lymph node count in either group, which aligns with the results reported by Uyan et al[4,9]. Breast cancer subtypes did not significantly affect lymph node yield in our study, consistent with prior research[2,9].

C-erbB-2 expression and ER/PR positivity also showed no significant impact on lymph node count in our analysis, aligning with previous findings[11,12]. However, PR positivity has been associated with limited lymph node involvement in some studies[13]. In this study, although ER and PR levels were found to be higher in NAC received patients, this finding did not demonstrate a statistically significant effect.

In a large case series comprising approximately 57,000 patients, PCR and the primary tumor's receptor status independently predicted the presence of fewer than 10 lymph nodes in the ALND specimen. In other words, patients who received NAC and had fewer than 10 dissected lymph nodes were found to have lower rates of ER and PR positivity[14]. In this current study, although both ER and PR levels were higher in the NAC group, none of these parameters had a significant effect on the quantity of total and malignant lymph nodes dissected, according to regression analysis. Although ER and PR levels differed significantly between the NAC and non-NAC groups, these variables did not show an independent association with lymph node yield in multivariate analysis.

A study examining the impact of PNI on prognosis found significantly higher rates of vascular invasion, axillary lymph node involvement, and PR positivity in patients with PNI compared to those negative for PNI[15]. Our analysis revealed no significant difference between the NAC and non-NAC groups regarding PNI. Moreover, PNI did not significantly influence the number of total or malignant lymph nodes dissected.

It has been reported that lymph node metastasis rarely occurs in DCIS cases without an invasive component identified during standard pathological evaluation[16]. For DCIS associated with invasive carcinoma, thorough axillary lymph node examination and surgical dissection, if necessary, are recommended. Some researchers have also observed sentinel lymph node metastasis in isolated DCIS cases and recommend sentinel lymph node sampling not only in invasive cancer cases but also in isolated DCIS[17]. In the present study, there was no statistically significant difference in the incidence of DCIS with invasive cancer between the NAC and non-NAC groups. Additionally, the presence of DCIS was found to have no significant effect on the total or malignant lymph node numbers dissected.

A large-series study has demonstrated a linear relationship between tumor diameter and the proportion of cases with positive lymph node[18]. Another study showed a correlation between tumor size and lymph node metastasis, except in luminal A and B subtypes[19]. Seidman et al. reported that the mean size of the invasive focus in the breast was larger among patients with lymph node involvement (6.5 mm vs. 14.3 mm, *P* = 0.0001)[20]. However, tumor diameter did not affect the count of total or malignant lymph nodes dissected, aligning with literature suggesting no association between tumor diameter and the number of dissected lymph nodes.

According to Li et al., the Ki-67 index serves as an independent prognostic marker for survival in patients with one to three positive nodes (N1)[21]. Similarly, Yin et al. observed that elevated Ki-67 levels (over 20%) were linked to a greater likelihood of lymph node metastasis[22]. Numerous studies have shown that Ki-67 values tend to decrease following NAC[23,24]. In our research, we found that the Ki-67 index was higher among patients who had not received NAC, and this supports the view that NAC reduces Ki-67 levels. However, we did not find any association between the Ki-67 index and the total number or malignancy of lymph nodes dissected.

Previous studies stated that the metastasis of lymph node occurs more frequently in patients with multicentric and multifocal tumors[25]. Andea et al. reported similar rates of regional lymph node metastasis for both unifocal and multifocal breast carcinoma cases[26]. In our study, we detected multicentric tumors more often in the NAC group. This may be attributed to the trend toward using less invasive alternatives, such as breast-conserving surgery, after NAC in multicentric tumors. Nonetheless, our findings indicate that multicentricity does not significantly influence the number of total or malignant lymph nodes removed.

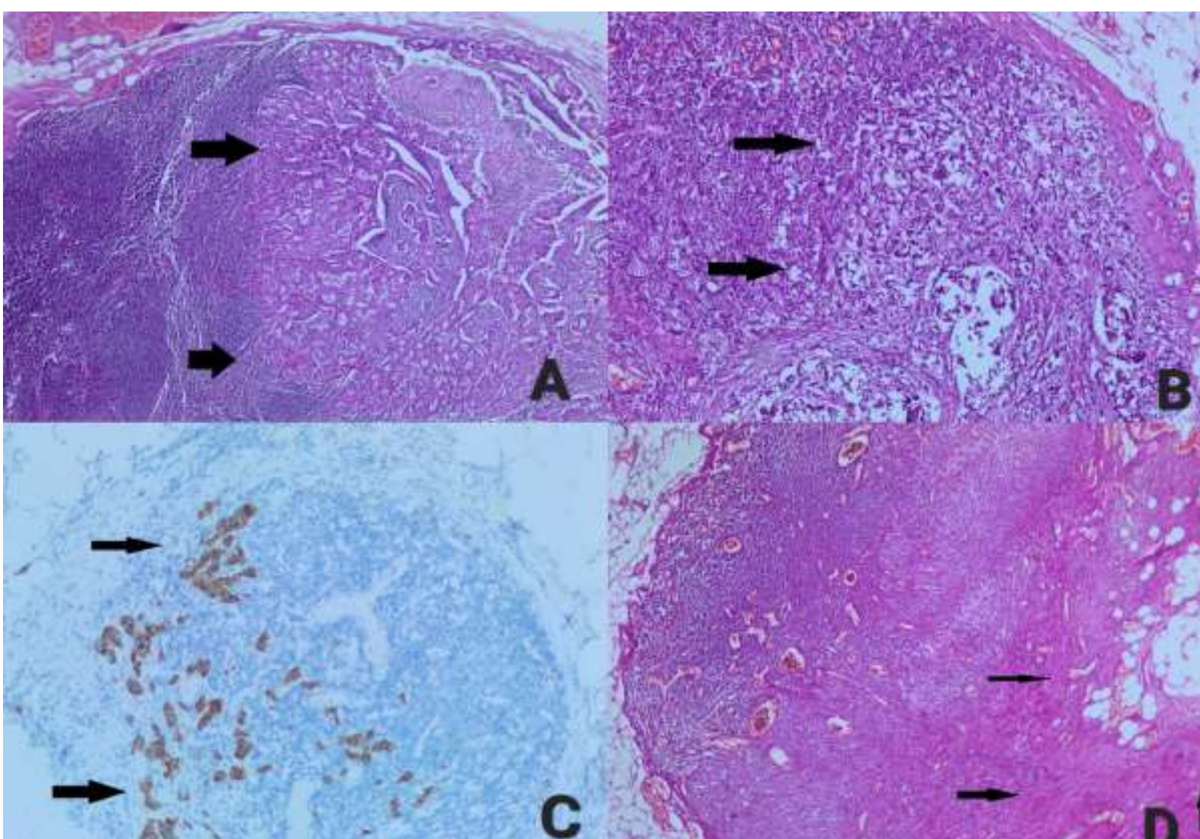
The surgeon's experience and specialty also play a role in effective lymph node removal during axillary dissection. Studies have shown that oncological surgeons achieve better outcomes[27]. Hoffmann noted that in institutions with specialized breast disease units, the proportion of cases with fewer than ten lymph nodes removed dropped from 5.8% to 0.5% [28]. In our cohort, most patients receiving NAC were managed by breast-specialist surgeons, who typically work in multidisciplinary teams, potentially increasing NAC usage. Despite this, regression analysis revealed no significant impact of the surgeon's specialty on the number of lymph nodes dissected.

Neoadjuvant Chemotherapy (NAC) is one of the most debated factors affecting the quantity of total and malignant lymph nodes removed, with no consensus currently established in the literature. While some studies report that fewer lymph nodes are retrieved in patients who received NAC (Mean: 10.0 vs. 12.5; P=0.002)[2] , with higher rates of cases yielding fewer than 10 nodes[2,3,14], other researchers have found no statistically significant difference in the total number of removed lymph nodes between NAC and non-NAC groups[3,27,29,30]. Conversely, a few reports even observed that more nodes were retrieved in NAC cases[27]. These contradictory findings highlight the complex and inconsistent effect of NAC on lymph node dissection outcomes.

In our study, the average number of dissected lymph nodes was 18.1, with means of 17.2 in the NAC group and 18.5 in the non-NAC group. This numerical difference was not found to be statistically significant. However, regression analysis indicated that NAC was the only significant factor affecting the node count, demonstrating a negative correlation. This negative association can be explained by the known mechanism that NAC may directly destroy lymph nodes by exerting a cytotoxic effect on the lymphocytes, which constitute a large portion of the lymph node cortex[5]. The main effects of NAC on lymph nodes include fibrosis, lymphocytic toxicity, and obliteration. These specific histopathological changes were also observed in the pathological sections of some patients receiving NAC in our study (See Figure 1).

Figure 1

Histopathological examination of lymph nodes in patients in the NAC group



Carcinoma metastasis in lymph node that did not receive NAC: HEX200 (A). Carcinoma metastasis in lymph node that received NAC: HEX200 (B). In the case in B, the immunohistochemical pan-cytokeratin positivity of the carcinoma cells: panCKX200 (C). Diffuse fibrosis and lymphoid depletion in a non-metastatic lymph node that received NAC: HEX200 (D)

5. Conclusion

Although the exact mechanism has not yet been established, many studies have shown that the number of total and/or malignant lymph nodes dissected in breast cancer patients is reduced in cases receiving NAC. This situation cannot always be attributed to inadequate ALND due to poor surgical quality; it should be considered that the presence of NAC may also reduce the number of excised lymph node. Some authors have suggested that the generally accepted limit of 10 lymph nodes for ALND in breast cancer should be changed for patients who have received NAC, and that this information should be included in the relevant guidelines. To increase the reliability of staging in patients with breast cancer, there is a clear need for further studies to evaluate the number of dissected lymph nodes following NAC.

Statement of ethics

The study received ethical approval the Scientific Research Ethics Committee of the Health Sciences University (Approval Date: 11/08/2023, Protocol Number: 15-5) and was conducted in accordance with the principles of the Declaration of Helsinki

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

Concept (MEU, EÖ), Design (ET, SY), Data Collection and/or Processing (MEU, EÖ), Analysis and/or Interpretation (ET,SY)

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