Retrospective study to assess axillary management and oncological outcome after neoadjuvant chemotherapy for patients with breast cancer

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Intro
duction Preoperative chemotherapy (NAC) has been recognized as the standard of care for patients with locally advanced breast cancer and recently for some patients with stage II and chemoresponsive subtypes (HER2 and TNBC). Lymph node (LN) status is the most important prognostic factor in patients who receive neoadjuvant therapy. Patients who have a positive LN by fine-needle aspiration (or core needle biopsy) before neoadjuvant therapy usually undergo completion axillary dissection at the time of primary tumor resection. Axillary lymph node dissection has been the standard treatment of the axilla after NAC for many years. Sentinel lymph node biopsy (SLNB) as an alternative can reduce the extent of axillary surgery without compromising the prognostic and predictive value of axillary staging.

Aim
The aim of this work was to primarily evaluate the effect of neoadjuvant chemotherapy on axillary nodal status. The secondary objective was to evaluate the percentage of patients who are eligible for SLNB after neoadjuvant chemotherapy.

Patients
This retrospective study was conducted by collecting data during the period from October 2019 to July 2021. The study included 64 patients who had biopsy-proven locally advanced breast cancer with clinically or radiologically positive axillary LNs, had been receiving neoadjuvant chemotherapy at the Clinical Oncology Department, and underwent surgery after neoadjuvant therapy at the surgical oncology unit of Alexandria Main University Hospital.
Exclusion criteria were as follows:
Patients with early-stage breast cancer.
Patients with metastatic stage IV breast cancer.
Patients unfit for neoadjuvant therapy.
Patients who refused neoadjuvant therapy.
Patients aged less than 18 years or more than 75 years.
Patients with clinically and radiologically negative axilla.

Methods
Data were collected retrospectively to assess the oncological and surgical outcomes after completing NAC.
The files of 450 patients were reviewed, and only 64 patients were eligible patients to be included in our study.

Results
Complete pathological response (ypT0ypN0) was found in six of the 64 patients in our study.
Four patients were triple-negative and two patients were HER2-enriched biological subtype.
One patient was T1, one patient was T2, one patient was T3, and three patients were T4.
One patient was N1, four patients were N2, and one patient was N3.

Conclusion
Post-neoadjuvant ultrasound is essential for assessment of axillary response.
Approximately 44.4% of patients with negative post-neoadjuvant axillary ultrasound can avoid unnecessary ALN clearance.
Accurate axillary staging is the cornerstone for omission of axillary clearance after neoadjuvant among patients.

Our recommendations
Further prospective studies with large sample sizes to assess the false-negative rate and feasibility of SLNB after neoadjuvant chemotherapy are needed.

SLNB can be performed for patients showing post-neoadjuvant clinical and radiological axillary response if we can discover a technique with an acceptable false-negative rate for SLNB in post-neoadjuvant patients.

Keywords:
locally advanced breast cancer, neoadjuvant chemotherapy, sentinel lymph node

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Introduction

Locally advanced breast cancer (LABC) refers to large (≥5 cm) invasive tumors with varying degrees of involvement of skin and/or chest wall (T3 and T4) or large or matted (N2 and N3) regional lymph nodes (LNs). It includes all patients with clinical stage III, which is further classified as IIIA (T3N1M0 and T3N2M0), IIIB (T4N0M0, T4N1M0, and T4N2M0), and IIIC (T3N3M0 and T4N3M0) according to AJCC Staging System. LABC also includes some patients in stage IIB (T3N0) [1].

Preoperative chemotherapy (NAC) is recognized as the standard of care for patients with LABC and for some patients with stage II and chemoresponsive subtypes (HER2 and TNBC). Although the effectiveness of therapy can be assessed according to clinical, radiological, or pathological response, the pathological complete response (pCR) is the most predictive parameter for survival. pCR is considered when there is complete eradication of locoregional disease both clinically as well as pathologically. Residual disease in the axilla after NAC has been associated with poor prognosis [2].

Axillary staging is an important component of the surgical procedure performed in patients with breast cancer. This was initially performed as axillary lymph node dissection (ALND). No difference in regional control, disease-free survival, and overall survival was found between sentinel lymph node biopsy (SLNB) and ALND in patients with clinically negative nodes [3]. With the omission of unnecessary ALND, patients have less complications [4].

ALND has been the standard treatment of the axilla after NAC for many years. Axillary staging after NAC is considered more meaningful in predicting locoregional recurrence than the axillary staging before NAC. It can be used to guide adjuvant locoregional treatment. SLNB as an alternative can reduce the extent of axillary surgery without compromising the prognostic and predictive value of axillary staging. Argument against the application of post-NAC SLNB is that the lymphatic drainage alteration after NAC could decrease the SLN identification rate and increase the false-negative rate (FNR) [5–7].

The SLN identification rate and FNR of SLNB after NAC are less satisfactory in patients with pretreatment positive nodes. However, in a subset of patients, the accuracy of SLNB in this setting has been reported to be similar with that in patients without NAC. Patients who achieve a pCR to NCT have better prognosis compared with those with residual invasive disease in the breast or LNs at the completion of NCT. This is especially true for triple-negative and HER2-amplified breast cancer, where pCR is associated with improved survival. However, the overall FNR is still a concern, and axillary node dissection remains a standard option in the management [8,9].

Prospective trials evaluating the accuracy of SLND after neoadjuvant chemotherapy in clinically node-positive patients have been completed. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial reported a FNR of 12.6% for SLND in patients with cN1 disease who had at least two SLN removed. While the trial did not meet its prespecified success threshold of 10%, subgroup analyses revealed that technical aspects of SLND could lower the FNR. The European SENTinel NeoAdjuvant (SENTINA) trial and the Canadian Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) trial corroborated these findings. Techniques such as use of dual tracers (blue dye and radioisotope) and removal of more than two SLNs were shown to lower the FNR in all three trials [10–12].

Aim

The aim of this work was to evaluate the effect of neoadjuvant chemotherapy on axillary nodal status and also to evaluate percentage of patients who are eligible for SLNB after neoadjuvant chemotherapy.

Patients

This retrospective study was conducted on 64 patients who had biopsy-proven LABC with clinically or

radiologically positive axillary LNs, who received neoadjuvant chemotherapy at the Clinical Oncology Department, and underwent surgery after neoadjuvant therapy at the surgical oncology unit of Alexandria Main University Hospital. The study was accepted by Alexandria University Ethical Committee. Consent was obtained from each patient to be included in this study, stating that the study is a research, and the details of the procedure and the potential benefits and complications were announced.

Exclusion criteria:

The following were the exclusion criteria:

(1) Patients with early-stage breast cancer.
(2) Patients with metastatic stage IV breast cancer.
(3) Patients with unfit for neoadjuvant therapy.
(4) Patients who refused neoadjuvant therapy.
(5) Patients aged less than 18 years or more than 75 years.
(6) Patients with clinically and radiologically negative axilla.

Methods

Data were collected retrospectively to assess the oncological and surgical outcomes after completing NAC. The collected data were as follows:

(1) All data had been collected for every patient regarding age and tumor size, nodal status, and metastasis staging (clinical TNM description):
    (1) Clinically: by examination of both breasts and palpation of any palpable axillary LNs.
    (2) Radiologically:
        (1) Based on ultrasound of both breasts and mammogram (tumor size and location) and/or MRI if done.
        (2) Ultrasound description of LNs (normal, suspicious, and malignant).
        (3) FNA or core needle biopsy from breast mass.
        (4) FNA from suspicious axillary LNs if done.
        (5) Degree of clinical response in primary tumor (complete, partial, or no response).
        (6) Clinically palpable LNs.
        (7) Axillary ultrasound description of LNs (normal, suspicious, and malignant).
        (8) Data regarding the type of breast surgery.
        (9) Postoperative histopathology included the following:
            (a) Pathologic (pTNM) description.
            (b) Total number of excised LNs.
            (c) Number of positive LNs with micrometastases and macrometastases.
            (d) Extranodal invasion.
            (e) Lymphovascular invasion.
            (f) Postoperative complications.

This study was conducted retrospectively by collecting data during period from October 2019 to July 2021 on 64 female patients who were admitted to the Surgical Oncology Unit of Alexandria Main University Hospital with a diagnosis of LABC.

Demographic data

Age

The mean age was 50.02 ± 8.89 years (Table 1).

Menstrual history

(1) A total of 64 (37.5%) patients were premenopausal and 12 (62.5%) patients were postmenopausal (Table 2).

Medical comorbidities

(1) A total of 11 patients experienced diabetes mellitus, 10 patients had hypertension, and three patients were cardiac patients. Only one patient experienced hepatitis B virus and one patient experienced osteoarthritis (Table 2).

Tumor status

(1) The majority of patients had tumors in the upper outer quadrants (71.9%).

Table 1 Distribution of the studied cases according to age (years) (*N*=64)

Age (years)	*n* (%)
<50	33 (51.6)
50–60	24 (37.5)
>60	7 (10.9)
Minimum–maximum	32.0–79.0
Mean±SD	50.02 ± 8.89
Median (IQR)	49.0 (44.0–54.50)

IQR, interquartile range.

Table 2 Distribution of the studied cases according to history (*N*=64)

History	*n* (%)
Menstrual history	
Regular	24 (37.5)
Menopausal	40 (62.5)
Medical history	
DM	11 (17.2)
HTN	10 (15.6)
Osteoarthritis	1 (1.6)
HBV	1 (1.6)
Cardiac	3 (4.7)
Family history	0

DM, diabetes mellitus; HBV, hepatitis B virus; HTN, hypertension.

(2) TNM staging: two patients were T1, 24 were T2, 22 were T3, and 16 patients were T4.
(3) A total of 25 patients were N1, 33 patients were N2, and six patients were N3 (Table 3).

Histopathology and tumor grade

(1) A total of 61 patients were diagnosed with infiltrating ductal carcinoma, two patients had infiltrating mammary carcinoma, and one patient had infiltrating mucinous carcinoma.
(2) One patient had grade I tumor, 35 patients had grade II, and 28 patients were grade III (Table 4).

Biological subtype

(1) Overall, 31.3% of patients were luminal A, 28.1% were luminal B, 21.9% were triple negative, and 18.8 were HER2 enriched (Table 5).

Table 3 Distribution of the studied cases according to tumor status and TNM (*N*=64)

	n (%)
Tumor location	
UOQ	46 (71.9)
Central	7 (10.9)
UIQ	6 (9.4)
LIQ	3 (4.7)
LOQ	2 (3.1)
Tumor size (cm)	
<2	2 (3.1)
2–<5	33 (51.6)
≥5	29 (45.3)
TNM staging	
T	
T1	2 (3.1)
T2	24 (37.5)
T3	22 (34.4)
T4	16 (25.0)
N	
N1	25 ((39.1)
N2	33 (51.6)
N3	6 (9.4)
M	
M0	64 (100.0)

Table 4 Distribution of the studied cases according to histopathology and grade (*N*=64)

	n (%)
Histopathology	
Infiltrating ductal carcinoma	61 (95.3)
Infiltrating mammary carcinoma	2 (3.1)
Infiltrating mucinous carcinoma	1 (1.6)
Grade	
I	1 (1.6)
II	35 (54.7)
III	28 (43.8)

Axillary nodal status

(1) A total of 41 patients who underwent ultrasound of the axilla before neoadjuvant therapy were malignant and 23 were suspicious.
(2) Only 16 patients were biopsied by fine-needle biopsy of axillary LN before neoadjuvant.
(3) No patients had clipping of pathological axillary LNs (Table 6).

Neoadjuvant chemotherapy

(1) A total of 11 patients had adriamycin-cyclophosphamide-based therapy and 53 patients had adriamycin-cyclophosphamide plus taxane-based neoadjuvant chemotherapy (Table 7).

Response to neoadjuvant chemotherapy

(1) Twelve patients had no residual tumor on ultrasound basis.
(2) Two patients showed progressive response, 11 showed stable response, 43 showed partial response, and eight showed complete clinical response.
(3) Twelve patients had clinically palpable axillary LNs after neoadjuvant therapy.
(4) Axillary ultrasound was normal in 45 (70.3%) patients, suspicious in eight (12.5%) patients, and malignant in 11 (17.2%) patients (Table 8).

Table 5 Distribution of the studied cases according to biological subtype (*N*=64)

Biological subtype	*n* (%)
Luminal A	20 (31.3)
Luminal B	18 (28.1)
Triple negative	12 (18.8)
HER2 enriched	14 (21.9)

Table 6 Distribution of the studied cases according to axillary status (*N*=64)

Axillary status	*n* (%)
Ultrasound of axilla before neoadjuvant	
Malignant	41 (64.1)
Suspicious	23 (35.9)
Biopsied axilla	
No	48 (75.0)
Yes	16 (25.0)
Clipped axilla	
No	64 (100.0)
Yes	0

Table 7 Distribution of the studied cases according to neoadjuvant chemotherapy type (*N*=64)

Neoadjuvant chemotherapy type	*n* (%)
AC only	11 (17.2)
AC+TAX	53 (82.8)

Pathological TNM

(1) Six patients revealed no tumor (T0).
(2) Axillary response showed complete axillary LN response (pN0) in 21 patients.
(3) A total of 28 patients were pN1, 13 were pN2, and two patients were pN3 (Table 9).

Number of excised lymph nodes

(1) The mean number of excised LNs was 13.38 ± 5.57. The median was 12.0 (10.0–15.0) (Table 10).

Pathological complete response (ypT0ypN0)

(1) Complete pathological response (ypT0ypN0) was found in six patients out of the 64 patients in our study.
(2) Four patients were triple negative and two patients were HER2-enriched biological subtypes.

Table 8 Distribution of the studied cases according to response (*N*=64)

Response	*n* (%)
Residual tumor size	
Vanished	12 (18.8)
<2	11 (17.2)
2–<5	35 (54.7)
≥5	6 (9.4)
Degree of clinical response	
Progressive	2 (3.1)
Stable	11 (17.2)
Partial	43 (67.2)
Complete	8 (12.5)
Clinically palpable LNs	12 (18.8)
Ultrasound axilla post-neoadjuvant	
Normal	45 (70.3)
Malignant	11 (17.2)
Suspicious	8 (12.5)

LN, lymph node.

Table 9 Distribution of the studied cases according to pTNM (*N*=64)

pTNM	*n* (%)
pT	
0	6 (9.4)
1	19 (29.7)
2	32 (50.0)
3	7 (10.9)
pN	
0	21 (32.8)
1	28 (43.8)
2	13 (20.3)
3	2 (3.1)
pM	
0	64 (100.0)

(3) One patient was T1, one patient was T2, one patient was T3, and three patients were T4.
(4) One patient was N1, four patients were N2, and one patient was N3.
(5) One patient received AC and five patient received AC+taxanes (Table 11).

Pathological complete response

Of 64 patients included in our study, six (9.37%) patients showed pCR (ypT0ypN0).

Correlation between pathological complete response (PCT) and clinical TNM

Our results support limited correlation between PCT and clinical TNM of the tumor, with high *P* value (Table 12).

Correlation between biological subtype and pathological complete response

There is a strong correlation between triple-negative and HER2-enriched biological subtypes and pCR to neoadjuvant chemotherapy according to our results (Table 13).

(1) Complete pathological axillary response (ypN0).

Correlation between ypN0 and pre neoadjuvant clinical TNM

(1) Complete axillary response was found in 10 patients with preneoadjuvant N1 tumors, 10 patients with preneoadjuvant N2 tumors, and one patient whose preneoadjuvant LN stage was N3 (Table 14).

Table 10 Descriptive analysis of total number of excised lymph nodes and number of positive lymph nodes with micrometastasis or macrometastasis (*N*=64)

	Minimum–maximum	Mean±SD	Median (IQR)
Total number of excised LNs	5.0–35.0	13.38 ± 5.57	12.0 (10.0–15.0)
Number of positive LNs with micro or macrometastasis	0.0–32.0	3.38 ± 5.53	2.0 (0.0–4.50)

LN, lymph node.

Table 11 Correlation between complete pathological axillary response (ypN0) and breast pathological response (ypT) (*N*=64)

ypT	*N*	pN_0 [*n* (%)]	χ^2	^{MC}P
0	6	6 (100.0)		
1	19	4 (21.1)		
2	32	10 (31.3)	13.162*	0.002*
3	7	1 (14.3)		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories. *Statistically significant at *P* value less than or equal to 0.05.

Table 12 Relation between PCT (ypT0N0) with clinical TNM (*N*=64)

	N	PCT (pT0N0) [*n* (%)]	χ^2	^{MC}P
T				
T1	2	1 (50.0)		
T2	24	1 (4.2)	5.992	0.085
T3	22	1 (4.5)		
T4	16	3 (18.8)		
N				
N1	25	1 (4.0)		
N2	33	4 (12.1)	1.912	0.341
N3	6	1 (16.7)		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories.

Table 13 Relation between PCT (ypT0N0) with biological subtype (*N*=64)

Biological subtype	*N*	PCT (ypT0N0) [*n* (%)]	χ^2	^{MC}P
Luminal A	20	0		
Luminal B	18	0	9.866*	0.003*
Triple negative	12	4 (33.3)		
HER2 enriched	14	2 (14.3)		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories. *Statistically significant at *P* value less than or equal to 0.05.

Table 14 Relation between ypN0 with clinical TNM (*N*=64)

	N	pN_0 [*n* (%)]	χ^2	^{MC}P
T				
T1	2	1 (50.0)		
T2	24	5 (20.8)	3.045	0.375
T3	22	9 (40.9)		
T4	16	6 (37.5)		
N				
N1	25	10 (40.0)		
N2	33	10 (30.3)	1.240	0.544
N3	6	1 (16.7)		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories.

Correlation between ypN0 and tumor histopathology and grade

(1) Complete axillary response group patients were all diagnosed with infiltrating ductal carcinomas.
(2) The complete axillary response was found in the only one patient with grade I tumor, 34.3% of patients with grade II tumor, and 28.6% of patients with grade III tumors (Table 15).

Correlation between ypN0 according to biological subtype

(1) Complete axillary response was found in three (15%) patients of the luminal A group, four (22.2%) patients of the luminal B group, and seven (58.3%) patients of the triple-negative group (Table 16).

Table 15 Relation between pN0 with histopathology and grade (*N*=64)

	N	pN_0 [*n* (%)]	χ^2	^{MC}P
Histopathology				
IDC	61	21 (34.4)		
IMC	2	0	1.137	0.701
Infiltrating mucinous carcinoma	1	0		
Grade				
I	1	1 (100.0)		
II	35	12 (34.3)	2.146	0.388
III	28	8 (28.6)		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories.

Table 16 Relation between ypN0 with biological subtype (*N*=64)

Biological subtype	*N*	pN_0 [*n* (%)]	χ^2	^{MC}P
Luminal A	20	3 (15.0)		
Luminal B	18	4 (22.2)	8.920*	0.028*
Triple negative	12	7 (58.3)		
HER2 enriched	14	7 (50.0)		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories. *Statistically significant at *P* value less than or equal to 0.05.

Table 17 Relation between ypN0 with residual tumor size (*N*=64)

Residual tumor size	*N*	ypN_0 [*n* (%)]	χ^2	^{MC}P
Vanished	12	8 (66.7)		
<2	11	1 (9.1)	11.172*	0.008*
2–<5	35	12 (34.3)		
≥5	6	0		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories. *Statistically significant at *P* value less than or equal to 0.05.

Correlation between ypN0 and residual tumor size

(1) Complete axillary response was found in eight patients, whose tumors vanished after neoadjuvant chemotherapy (Table 17).

Correlation between ypN0 and degree of tumor response

(1) Complete axillary response was found in six patients of the eight patients who showed complete clinical response.
(2) Overall, 32.6% of the partial response group showed complete axillary response in biopsy and one patient of the stable response group showed complete axillary response (Table 18).

Correlation between ypN0 and post-neoadjuvant axillary ultrasound

(1) Complete axillary response was found in 20 (44.4%) patients of the post-neoadjuvant normal axillary ultrasound group.

Table 18 Relation between ypN0 and degree of response (*N*=64)

Degree of response	*N*	ypN_0 [*n* (%)]	χ^2	^{MC}P
Progressive	2	0		
Stable	11	1 (9.1)	9.130*	0.014*
Partial	43	14 (32.6)		
Complete	8	6 (75)		

χ^2, χ^2 test; MC, Monte-Carlo. *P*: *P* value for comparing between the studied categories. *Statistically significant at *P* value less than or equal to 0.05.

Table 19 Relation between pN0 with ultrasound of axilla after neoadjuvant (*N*=64)

Ultrasound of axilla after neoadjuvant	*N*	ypN_0 [*n* (%)]	χ^2	^{MC}P
Normal	45	20 (44.4)		
Suspicious	8	1 (12.5)	10.005*	0.004*
Malignant	11	0		

χ^2, χ^2 test, MC, Monte-Carlo.*P*: *P* value for comparing between the studied categories. *Statistically significant at *P* value less than or equal to 0.05.

(2) One patient out of eight patients whose ultrasound of the axilla was suspicious showed complete axillary response.
(3) No patient whose ultrasound showed malignant axilla after neoadjuvant exhibited complete axillary response in biopsy (Table 19).

Discussion

Taxane and anthracycline-based therapies have been reported to achieve clinically complete responses ranging from 20 to 31% [13]. There still might be residual tumor histologically in patients who achieved complete clinical response. In our study, 12 (18.8%) patients showed no palpable breast mass after NAC. Of the 12 patients, eight (12.5%) patients whose breast mass vanished also showed complete radiological response. Six (9.37%) of them showed complete pathological response (ypT0ypN0).

According to Cortazar *et al.* [14], the overall frequency of pCR was low; 22% of patients achieved ypT0. In our study, 9.4% of patients showed ypT0. Cortazar *et al.* [14] revealed that 13% achieved pCR (ypT0ypN0). In our study, pCR rate was 9.37%.

The ipsilateral axillary LN is the most common site for breast cancer metastases and is the most important prognostic factor. Although ALND is easier for staging with good regional control, it is also associated with risk of complications of breast cancer surgery. ALND remains the gold standard axillary staging procedure after chemotherapy for women who initially present with positive axillary metastases. Approximately 73% of patients undergoing ALND have complications such as nerve injury, restricted shoulder motion, arm weakness, and infections owing to the surgical technique which was referred to the number of LNs removed [15].

This is similar to Samiei *et al.* [16] who showed in their meta-analysis that the triple-negative and HER2-enriched subtypes were associated with the highest axillary pCR rate. Our study showed a statistically significant association between these biological subtypes and (pN0), with *P* value of 0.028.

A strong correlation between the breast tumor pCR and the axillary LNs pCR was proved in the study by Elamin *et al.* [17], with a highly significant association ($P<0.001$). Our study showed the same highly significant association between breast pathological response and axillary pathological response, with *P* value of 0.002.

Overall, 32.6% of the partial clinical response group showed complete axillary response in biopsy and one patient of the stable response group showed complete axillary response.

Complete axillary response was found in eight patients whose tumors were vanished after neoadjuvant chemotherapy. The *P* value for the correlation between complete axillary response and residual tumor size was 0.008.

SLNB is the standard for evaluation of axillary LN status in early-stage breast cancer with negative axillary LNs with low complication rate [18]. SLNB may now be used instead of axillary clearance in patients with clinically LN-negative LABC; however, the usage in initially clinically LN-positive patients is controversial [19].

ALND rates after NAC could be because 20–40% of LN-positive patients convert to LN negative at the time of operation [20]. Our study showed the same results in initially clinical LN-positive group, and ypN0 was determined in 32.8% of cases. This percentage of ypN0 patients in our study is eligible to be candidates for SLN biopsy after neoadjuvant chemotherapy.

A recently published study showed the potential benefits of post-NAC and preoperative axillary ultrasound to assess residual LN disease in women with LN-positive breast cancer. It showed that axillary ultrasound reduced the FNR of SLNB from 12.6 to 9.8% [21].

According to Boughey *et al.* [21], 130 (71.8%) of 181 post-neoadjuvant axillary ultrasound suspicious patients were node positive at surgery compared with 243 (56.5%) of 430 post-neoadjuvant axillary ultrasound-normal patients.

Our results showed that one (12.5%) patient out of eight patients whose ultrasound axilla was suspicious showed complete axillary response. In our study, complete clinical axillary response was found in 20 (44.4%) patients of the post-neoadjuvant normal axillary ultrasound group. We believe these patients can be offered post-neoadjuvant SLN biopsy for axillary staging. The *P* value was 0.004, which suggests a strong correlation between post-neoadjuvant axillary ultrasound and axillary pathological response. Reliability of SLNB is measured by sentinel node identification rate, which was 92.7% (ACOZOG Z1071) and 87.8% (SENTINA) in patients with initially LN positive disease [3,22].

The use of dual tracers is strongly recommended in studies discussing SLNB after NAC [8,22]. Dual mapping significantly improved the SLN identification rate [93% (ACOZOG Z1071) and 87.7% (SENTINA)] compared with single-agent mapping [88.9% (ACOZOG Z1071) and 77.4% (SENTINA)] [8,22]. However, the combined use of additional mapping agent decreased the FN rate from 16.0% (SENTINA) and 22.2% (ACOZOG Z1071) to 8.6 and 10.8%, respectively [8].

A significant relation between the number of sentinel nodes removed and the FN rate was established [23]. The FN rate was less than 10% for women who had three or more SLN removed compared with 24.3% when one harvested [8].

An evidence-based selection criterion to predict complete pathological response in the axilla after NACT in node positive breast cancer patients is possible. This may maximize the benefits of NACT in de-escalating axillary surgical treatment. According to our study, the complete axillary pathological response was associated with clinical and radiological response, negative post-neoadjuvant axillary ultrasound, triple-negative, and HER2-enriched biological subtypes. Prospective studies with larger sample size are needed.

It is worth to decide performing SLNB after NAC in both clinically negative and positive patients. Approximately 32% of the patients according to our findings can avoid unnecessary axillary LN clearance with accurate axillary staging.

An optimal technique (dual mapping, more than three nodes removed and metastatic nodes marking before NAC) should be chosen in node-positive patients to reduce the FNR and ensure the success of the procedure.

There are several limitations to our study. First, only 15 patients were biopsied with fine-needle biopsy of axillary LN before neoadjuvant. The other 48 patients did not have a biopsy-proven axillary metastasis and were diagnosed only with ultrasound. Second, ultrasound alone might be somewhat subjective. Third, as this was a retrospective study, the number of included patients was relatively small, and there were limited data available in the reports.

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Conflicts of interest
The authors have no conflicts of interest to declare.

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