

Evaluation of the effect of neoadjuvant chemotherapy on tumor and axillary lymph nodes in locally advanced breast cancer: a study of 50 patients

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Abstract Objective: The purpose of the study was to correlate between effect of pre-neoadjuvant chemotherapy (NACT) and post-NACT clinical, sonographic and pathologic features of the tumor and axillary lymph nodes (ALNs) and to raise the possibility of applying the concept of sentinel lymph node biopsy (SLNB) in patients with initially positive ALNs before NACT. **Methods:** A prospective study of 50 female patients with locally advanced breast cancer (LABC) with clinically palpable and cytologically (under ultrasonographic guidance) positive ALNs. All patients received NACT and then referred for ultrasonographic assessment of the axilla regarding any detectable sonographic criteria of metastatic deposits in ALNs as well as the tumor size in relation to its pre-chemotherapy size. All patients were then subjected either to modified radical mastectomy or breast conserving surgery. The clinical, sonographic and pathological response of the tumor and the ALNs were documented, classified and correlated with each other. **Results:** Patients' mean age was 47.7 ± 9.1 years. The mean clinical tumor size was 6.7 ± 1.4 cm; stage IIIA that was presented in 32 patients (64%) and IIIB was presented in 18 patients (36%). Chemotherapy was given for a median of 4 cycles. there was reduction of the mean clinical tumor size from 6.7 ± 1.4 cm to 4.3 ± 2.7 cm ($P < 0.001$). Clinical response was complete in 5 (10%) tumors, complete pathological tumor response (post-neoadjuvant) was detected in 8 (16%) of patients. Complete clinical nodal response (post-neoadjuvant) in 23 (46%) axillae, on sonographic assessment of the axilla, response was complete in 17 (34%) axillae. Complete pathological nodal response occurred in 16 (32%) axillae. Out of 17 axillae that showed complete sonographic response 11 axillae showed complete pathological nodal response ($P < 0.001$). **Conclusion:** Formal axillary lymph node dissection can be avoided and replaced by SLNB post NACT in patients with LABC with metastatic ALNs if there were complete clinical and sonographic criteria of nodal response as well as complete pathological tumor response.

Key words locally advanced breast cancer (LABC); neoadjuvant chemotherapy (NACT); axillary nodes

Breast cancer is the most frequently diagnosed cancer, the most common lethal neoplasm in women and the second leading cause of cancer death [1]. The term "locally advanced breast cancer (LABC)" is commonly associated with stage III cancer. It also refers to a tumor that is > 5 cm (about 2 inches) in size. Tumor down staging by pre-operative neoadjuvant chemotherapy (NACT) in patients with LABC allows breast conservation in women who were previously candidates for mastectomy [2]. A complete clinical response which is traditionally assessed on basis of tumor size was reported to significantly improve disease free survival [3]. Given the advances in the effi-

ciency of NACT in reducing the size of the primary to the extent of complete gross/microscopic resolution in some cases, it is expected to assume the same response in the axilla [4]. Many studies have assessed clinical response of axillary nodes to NACT. Some studies have demonstrated complete histopathological response following NACT. Yet only few have addressed the issue of omitting of axillary dissection in a particular subset of patients following NACT [5]. There is a reasonable survival rate of breast cancer patients' post neo-adjuvant chemotherapy and mastectomy that warrants starting looking for avoiding the complications of an undue axillary dissection. If there is a tool that can reliably predict the state of the axilla in this subset of patients, then an unnecessary evacuation can be

avoided [6]. Controversies exist about the role of sentinel lymph node biopsy (SLNB) after NACT. Although complete axillary downstaging occurs in up to 20%–30% of the patients, however, sentinel node biopsy after NACT is not recommended in patients with initial axillary nodal involvement and complete axillary response after NACT and clinical trials are required to identify patients with initial axillary metastatic involvement who could avoid an axillary dissection after systemic therapy [7]. On the other hand, Schwartz GF *et al.* stated that SLNB after NACT was feasible in virtually all patients and accurately selected patients who required complete level I and II axillary dissection. NACT frequently downstages the axilla, converting patients with N1–N2 lymph node (LN) status to N0 status and also avoiding full axillary dissection in these patients [8]. This study will evaluate the response of ALNs to NACT and correlates it with the response of the primary tumor, in a trial to avoid complete ALN dissection in selected cases with predicted complete pathological response to NACT, and thus, opening a path for the possibility of safe application of sentinel LN biopsy in patients with initially positive nodes before NACT.

Materials and methods

This prospective study included 50 female patients presented to the Department of Surgical Oncology, National Cancer Institute, Egypt, between January 2010 and December 2013 with LABC (stage IIIA, IIIB). All patients were subjected to complete metastatic work-up to exclude distant metastases and had cytologically proven positive ipsilateral ALNs for cancer cells. Clinical staging and ultrasonographic assessment of the primary tumor and ipsilateral axillary nodes were done before starting NACT.

Clinical staging

Clinical staging of the tumor was done and the surface area of the primary tumor was calculated as the product of the two longest perpendicular diameters. Clinical staging of ALN was done according to the 7th edition of the American Joint Committee on cancer staging [4].

Radiological assessment of axilla

Ultrasonographic examination of the axilla was done using GE (USA). RT-3600 equipment with 7.5 MHz transducer probe. The sonographic characteristics of ALNs were documented. The ultrasonographic diagnostic criteria that have been used to identify abnormal metastatic LNs were:

Nodal shape, including longitudinal to transverse axis ratio of less than 2. Nodes considered suspicious when they had two diameter enlargements imparting a rounded appearance to the LN, and poor central hilum, absence

of a fatty hilum and eccentricity of the nodal cortex Together with nodal size greater than 20 mm [9].

Abnormal morphology of the cortex, particularly concentric or eccentric thickening to more than 2 mm, focal doubling of the cortical thickness [10–11]. The normal cortical thickness of a LN was 1 to 2 mm, and an abnormal LN generally had a thickness greater than 2.3 mm [12].

We defined complete sonographic response of the axilla (negative axilla by ultrasound) as the absence of any detectable sonographic criteria of metastatic deposit in ALNs that were mentioned above.

NACT regimens

FEC regimen (5-fluorouracil dose 500 mg/m², epirubicin 100 mg/m², cyclophosphamide dose 500 mg/m² dose) was given to 41 patients (FEC 100 in 30 patients and FEC 75 in 11 patients) and FAC regimen (5-fluorouracil dose 500 mg/m²; doxorubicin dose 50 mg/m²; cyclophosphamide dose 500 mg/m² dose) to 9 patients. Chemotherapy was given for a median of 4 cycles (range from 3 to 6 cycles). Then they were evaluated clinically for response. All the patients were reassessed clinically and radiologically for feasibility of surgery 21 days after the completion of the third cycle of chemotherapy. Patients underwent surgery within one month after completion of last cycle of chemotherapy.

Assessment of response

After completion of NACT, ultrasound (US) assessment of axilla adopting the same US criteria previously used to detect metastatic ALN pre-chemotherapy. The clinical, sonographic response of the tumor and the ALNs were documented and classified as per the WHO criteria [13]. Complete response (CR) meant disappearance of all known disease, partial response (PR) as decrease a 50% decrease in the sum of the products of the perpendicular diameters from baseline, confirmed at 4 weeks and no response where 50% decrease in size could not be demonstrated.

Surgery

Either modified radical mastectomy or conservative breast surgery were done to all patients according to the response to NACT and patients' preference.

Pathological assessment

Surgical mastectomy specimens were all grossly inspected thoroughly for tumor size, site, gross necrosis and fibrosis, multiplicity, local tumor extension, and different surgical margins. Haematoxylin and eosin slides of each case were prepared from each formalin fixed paraffin block for proper evaluation of pathologic response of tumor as well as LNs. Additional one positively charged slide was prepared from each case with microscopically

proved negative nodes for staining with pan cytokeratin (Dako, Denmark, mouse monoclonal antibody, clone AE1/AE3, ready to use).

Pathological response in the surgically resected specimen was based on microscopic examination of multiple sections from the breast and ALNs according to: 1. primary tumor was evaluated according to Miller and Payne scoring system [14]. Miller-Payne System: Grade 1: no change or some alteration to individual malignant cells, but no reduction in overall cellularity (no pathological response). Grade 2: a minor loss of tumor cells, but overall cellularity still high; up to 30% loss (pathological PR, pPR). Grade 3: between an estimated 30% and 90% reduction in tumor cells. Grade 4: a marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; -90% loss of tumor cells (almost pathological CR, pCR). Grade 5: no malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastotic stroma remains, often containing macrophages; however, ductal carcinoma in situ may be present. 2. LN status was evaluated according to National Surgical Adjuvant Breast and Bowel Project scoring system [15]. pCR: no histological evidence of invasive tumor cells. No pCR: histological evidence of invasive disease of any extent. Complete pathological response: was defined as grade 5 according to Miller-Payne. Partial pathological response: was defined as grades 3 and 4 according to Miller-Payne. No pathological response as grade 1 according to Miller-Payne.

Studied parameters

The clinical, sonographic and pathological response of the tumor and the ALNs were documented, classified and correlated with each other. The response of the tumor and the axilla were correlated with various patients' characteristics and analyzed. Clinical breast tumor size and axilla assessment were obtained before any treatment by physical examination.

Statistical analysis

Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., standard deviation (SD) or median and range as appropriate. Qualitative data Chicago, USA). Numerical data were expressed as mean and were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Evaluation of different diagnostic methods versus pathological results (considered as the gold standard) was done and presented as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. A $P < 0.05$ was considered significant.

Results

This study included fifty female patients with LABC with positive metastatic ALNs proved by cytological examination, and received NACT, then radiological and clinical assessment of the primary tumor and metastatic LNs were done between January 2010 and December 2013. This was followed by modified radical mastectomy in 41 patients (82%) and breast conserving surgery in 9 patients (18%).

Patients' characteristics

Patients' mean age was 47.7 ± 9.1 years; 28 patients (56%) were postmenopausal. Tumor was in the right breast in 29 patients (58%), and in the left breast 21 patients (42%; Table 1).

Tumor characteristics

The mean clinical tumor size was 6.7 ± 1.4 cm; the commonest tumor, node, metastases (TNM) stage initially was stage IIIA that was detected in 32 patients (64%) and stage IIIB in 18 patients (36%; Table 2). The initial mammographic finding of the tumors breast imaging reporting and data system (BIRADS score) was mainly BIRADS in 42 patients (84%) and all ALNs showed malignant criteria with axillary US assessment before starting chemotherapy (Table 3). The commonest histological subtype of breast cancer encountered initially was invasive duct carcinoma (IDC) in 46 patients (92%), the grade was mainly of grade II in 46 patients (92%), and regarding receptors status; estrogen (ER) was positive in 25 patients (50%), progesterone was positive in 28 patients (56%) and human epidermal growth factor receptor 2 (HER2/neu) was (+3) only in 4 patients (8%; Table 4).

NACT

NACT was given for a median of 4 cycles. Then they were evaluated clinically for response. The mean number of CTH cycles was 4.1 ± 1 (Table 5).

Assessment of breast tumor response to NACT

Clinical response

Following NACT, there was reduction of the mean clinical tumor size from 6.7 ± 1.4 cm to 4.3 ± 2.7 cm ($P < 0.001$). Clinical response was CR in 5 patients (10%), PR in 22 patients (44%) and stationary disease in 23 patients (46%). No patients showed progressive disease during/after NACT. Clinically the breast tumor diameter was ranging from 2 to 5 cm (T2) in 19 patients (36%) and TNM stage was mainly (IIB) in 15 patients (30%; Table 6).

Pathological response

Following NACT, there was a pathological primary tumor response in 40 patients (80%) ranging from mild therapeutic (grade 2) response in 20 patients (40%) to

Table 1 Patient's characteristics

Characteristics	<i>n</i>	%
Total	50	100
Age (years)		
Mean ± SD	47.7 ± 9.1	
Median (range)	48 (24–66)	
Menopausal status		
Postmenopausal	28	56
Premenopausal	22	44
Laterality		
Right	29	58
Left	21	42

Table 2 Tumor characteristics

Characteristics	<i>n</i>	%
Total	50	100
Tumor size (cm)		
Mean ± SD	6.7 ± 1.4	
Median (range)	6 (5–12)	
T stage		
T0	0	
T1	0	
T2	0	
T3	32	64
T4	18	36
N stage		
N0	0	
N1	47	94
N2	3	6
TNM stage		
IIIA	32	64
IIIB	18	36

Table 3 Initial radiological assessment of breast tumors and ALNs

Item	<i>n</i>	%
Initial mammogram (BIRADS score)		
IV	4	8
V	42	84
VI	4	8
Axillary US		
Non-malignant LNs	0	
Malignant LNs	50	100

complete therapeutic response in 8 patients (16%; Table 7). There were no major variations between histological subtypes or grade assessment preoperatively and postoperatively ($P > 0.05$). One tumor that was preoperatively diagnosed as ILC, diagnosed postoperatively as IDC. Two tumors were diagnosed preoperatively as grade II but postoperatively as grade III (Table 8).

Assessment of axillary nodal response to NACT

Clinical response

Table 4 Pathological criteria of the tumors

Item	<i>n</i>	%
Histologic subtypes		
IDC	46	92
ILC	4	8
Grade		
I	2	4
II	46	92
III	2	4
ER receptor status		
Negative	25	50
Positive	25	50
PR receptor status		
Negative	22	44
Positive	28	56
HER2/neu		
0	31	62
1	12	24
2	3	6
3	4	8

ILC: invasive lobular carcinoma

Table 5 NACT regimens

Item	<i>n</i>	%
NACT regimen		
FEC	41	82
FAC	9	18
Number of NACT cycles		
3.00	13	26
4.0	28	56
6.0	9	18
Mean ± SD	4.1 ± 1.2	

Complete clinical nodal response (N0) in 23 patients (46%), 26 patients (52%) had clinically mobile ipsilateral metastatic ALN (N1) and only one patient (2%) had matted ipsilateral ALNs (N2; Table 9).

Radiological response

On sonographic assessment of the axillae, response was complete in 17 patients (34%) and 33 patients (66%) still showed residual metastatic disease (Table 9).

Pathological response

Complete pathological nodal response occurred in 16 patients (32%) and no pathological complete nodal response in 34 patients (68%) from whom 27 (79%) patients had nodal capsular rupture (Table 9).

The mean number of dissected ALNs was 18 ± 5.7 (range: 9–35, median: 18) and the mean number of positive ALNs 4.5 ± 5.3 (range: 0–22, median: 2).

Correlation of the clinical response of ALNs to the pathological nodal response

Out of 23 axillae that showed clinical complete nodal response only 10 axillae showed complete pathologi-

Table 6 Post NACT characteristics

Characteristics	<i>n</i>	%
Total	50	100
Tumor size (cm)		
Mean ± SD	4.3 ± 2.7	
Median (range)	3.5 (0.0–11)	
Post NACT T stage	50	100
T0	5	10
T1	6	12
T2	19	38
T3	15	30
T4	5	10
Post NACT TNM stage		
IA	6	12
IB	5	10
IIA	9	18
IIB	15	30
IIIA	10	20
IIIB	5	10

Table 7 Post NACT pathological tumor response

Pathological tumor response	<i>n</i>	%
Grade 1 (poor)	10	20
Grade 2 (mild)	20	40
Grade 3 (moderate)	9	18
Grade 4 (marked)	3	6
Grade 5 (complete)	8	16

cal nodal response. Correlation of clinical assessment of ALNs versus pathological results showed that the sensitivity of clinical assessment was 60.0%, specificity was 62.5%, PPV was 77.8%, NPV was 41.7% and accuracy was 60.8% ($P=0.135$; Table 10).

Correlation of sonographic response of ALNs to pathological response

Out of 17 axillae that showed complete sonographic response 11 axillae showed complete pathological nodal response and 6 cases showed no complete pathological response. Correlation of US response of ALNs versus pathological results showed that the sensitivity US assessment of ALNs was 82.9%, specificity was 68.8%, PPV was 85.3%, NPV was 64.7%, accuracy was 78.5% ($P < 0.001$; Table 11).

Pathological nodal response and pathological tumor response

From the 8 breast tumors that showed complete pathological response 7 axillae also showed complete pathological nodal response with PPV is 29%, NPV: 93%, Sensitivity: 70%, and specificity: 73% ($P < 0.001$; Table 12).

Table 8 Histological subtypes and grade after NACT

Item	<i>n</i>	%
Post NACT histologic subtype		
IDC	47	94
ILC	3	6
Post NACT tumor grade		
I	2	4
II	44	88
III	4	8

Table 9 Clinical, radiological and pathological nodal responses to NACT

Item	<i>n</i>	%
Post NACT N stage		
N0	23	46
N1	26	52
N2	1	2
Post NACT axillary US		
Non-malignant	17	34
Malignant	33	66
Pathological nodal response		
No pCR	34	68
pCR	16	32
Capsular rupture (positive axillae)		
Positive	27	79.4
Negative	7	20.6

Pathological nodal response and NACT regimen

In the current study there were nodal pCR in 14 out of 41 axillae that received FEC, and nodal pCR in 2 out of 9 axillae that received FAC (Table 13).

Discussion

LABC encompasses tumors with a broad range of biological behaviors. This category includes tumors that are large and/or have extensive regional LN involvement without evidence of distant metastatic disease at initial presentation. Seventy-five percent of patients LABC have clinically palpable axillary or supraclavicular LNs at the time of diagnosis^[2]. All patients in this study, initially had palpable ipsilateral ALNs (N1, N2) which were all confirmed to be metastatic by US guided FNAC, inspite the sensitivity of US guided FNA is highly dependent on the size of the metastatic deposit^[16].

Many standard chemotherapy regimens exist for the adjuvant and neoadjuvant treatments of breast cancer. The Early Breast Cancer Trialists' Group established the superiority of anthracycline-based chemotherapy regimens^[17] which were administered for all patients in this study, with expert recommendations are to administer four to six cycles as long as there is no disease progression^[18]. In the post neoadjuvant setting, the primary tu-

Table 10 Correlation of clinical response of ALNs to pathological nodal response [n (%)]

Clinical nodal response	Pathological nodal response		Total	P
	No pCR	pCR		
N+ (No cCR)	21 (77.8%)	6 (22.2%)	27 (100%)	0.135
N0 (cCR)	13 (56.5%)	10 (43.5%)	23 (100%)	
Total	34	16	50	

cCR: clinical CR

Table 11 Correlation of sonographic response of ALNs to pathological nodal response [n (%)]

Post NACT axillary US	Pathological nodal response		Total	P
	No pCR	pCR		
Malignant LNs (No CR)	28 (84.8%)	5 (15.2%)	33 (100%)	< 0.001
Non-malignant LNs (CR)	6 (35.3%)	11 (64.7%)	17 (100%)	
Total	34	16	50	

Table 12 Pathological nodal response and pathological tumor response

Nodal pCR	Primary tumor pathological response (n)		Total (n)
	No CR (grade 1–4)	CR (grade 5)	
Total	42	8	50
No pCR	33	1	34
pCR	9	7	16
P	P < 0.001	P < 0.001	

Table 13 Pathological nodal response and NACT regimen

Pathological nodal response	NACT regimen (n)		Total (n)	P
	FEC	FAC		
No pCR	27	7	34	0.699
pCR	14	2	16	
Total	41	9	50	

mor was re-evaluated clinically and pathologically after surgery which was either conservative breast surgery or modified radical mastectomy; in addition the ALNs were also re-evaluated clinically, sonographically and pathologically.

Post neoadjuvant pCR of the primary tumor was found in 16% of patients which coincides with the results of Bonnefoi H *et al.* 2014 as they reported 18% pCR [19]. PCR was detected in 32% of ALNs which was confirmed by thorough histopathological examination using H&E in addition to immunohistochemistry, this was a much higher percentage than the 12% pCR reported in the breast and axillary specimens by Kuerer *et al.* [20].

The ability of high-resolution axillary US to predict pathologic LN status specifically in patients with locally advanced breast tumors which received NACT was studied; the PPV of post chemotherapy axillary US compared to physical examination was 83% versus 93%, and the NPV was 52% versus 58% [21]; in the current study, considering pathological results of axillary lymph node dissections as the control parameter, ultrasonography was found to be better than clinical examination in the assessment of

axillary nodes and their response to NACT with sensitivity 82.9% versus 60%; specificity 68.8% versus 62.5%, PPV 85.3% versus 77.8%, NPV 64.7% versus 41.7%, and accuracy rate was 78.5% versus 60.8% respectively ($P < 0.001$). In a correlation between sonographic response of ALNs and pathological response (control parameter), out of 17 axillae that showed complete sonographic response 11 axillae showed complete pathological nodal response and 6 cases showed no complete pathological response ($P < 0.001$).

Regarding that a pathologic complete primary tumor response was predictive of a complete ALN response ($P < 0.01$) [20] as also proved by this study, and regarding the highly significant sonographic detection rate of complete pathological nodal response ($P < 0.001$), we can assume that axillary lymph node dissection can be omitted in patients with LABC who received NACT and proved to have clinically and sonographically free axillae as well as complete pathologic response of the primary tumor. However SLNB could be used as a safer option as confirmation of pCR of the primary tumor on Frozen section is questionable inspite an accuracy of 91.2%, a sensitivity of 78%, and a specificity of 100% [22].

Conclusion

Current chemotherapeutic regimens are, to some extent, capable of eradicating cancer cells from the ALNs. Ultrasonographic assessment is better and more accurate than clinical examination in the assessment of ALNs and their response to NACT. Axillary lymph node dissection can be omitted in patients with LABC who received NACT and proved to have clinically and sonographically free axillae as well as complete pathologic response of the primary tumor. However SLNB could be used as a safer option as confirmation of pCR of the primary tumor on Frozen section is questionable.

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