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EVALUATION OF THE AXILLARY NODAL STATUS POST NEO-ADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED FEMALE BREAST CANCER PATIENTS

By

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ABSTRACT

Background: Breast cancer is the most common neoplasm among women in the majority of the developed countries, accounting for one-third of newly diagnosed malignancies. Given the efficiency of neo-adjuvant chemotherapy (NACT) in reducing tumor size, it is logical to assume the same response in axilla.

Objective: Our propose was to assess axillary lymph nodes (ALNs) response to NACT using clinical, ultrasound (US) or pathological examinations of sentinel lymph node biopsy (SLNB) or ALN dissection (ALND).

Patients and methods: This prospective study included 100 female patients with locally advanced breast cancer (LABC) with clinically palpable or US detectable ALNs. True cut biopsy of primary tumor and fine needle aspiration cytology (FNAC) of ALNs were performed before NACT. Clinical and US response of ALNs was assessed. Surgical local control started with SLNB then ALND in all patients followed by appropriate mastectomy procedure. Primary tumor, SLNB and ALND specimens were submitted for pathological examination. Negative SLN by hematoxylin and eosin (H&E) were subjected to immunohistochemical (IHC) section.

Results: Clinical, US and pathological complete response (pCR) to NACT were encountered in 47.1%, 33.3% and 31.4% of patients, respectively. The sensitivity of clinical, radiological, SLNB in predicting pCR were 60%, 82.9%, and 94.1% respectively. US was better than clinical examination in response assessment with accuracy of 78.5% versus (vs.) 60.8%, respectively ($p<0.001$). SLNB was more sensitive than clinical examination in predicting pCR with accuracy of 94.9%. The detection rate of SLN was 76.5%.

Conclusions: pCR post NACT is high enough to make axillary conservation worthwhile. US and SLNB can assess and predict nodal response with accepted accuracy rate and SLNB is feasible after NACT.

Keywords: Sentinel lymph node, complete response, Axillary lymph nodes.

INTRODUCTION

Breast cancer is a heterogeneous disease, comprising various histological types, with distinct clinical presentations and underlying molecular signatures. NACT of early breast cancer has many advantages both for patients and for the rich track of clinical, translational, and scientific research that can be carried out. Published evidence confirms a reduction in mastectomy rates with increasing use of neo-adjuvant therapy both on a population and individual trial basis *(Kuehn et al., 2013)*.

The relationship between pathological response and longer-term outcome in women with early breast cancer receiving neo-adjuvant systemic therapy is highly complex and its' dependencies are multifactorial. A meta-analysis of neo-adjuvant breast cancer trials and a meta-regression of trials data have confirmed in just short of fifteen thousand women the robust relationship between achieving a pCR and improved longer-term outcomes on an individual patient level *(Houssami et al., 2011)*.

Systemic or local treatment decisions may be based on axillary status at presentation (pre-NACT). Pre-NACT SLNB is not recommended because assessment of nodal response in the axilla, a very important determinant of survival post-NACT, is unreliable after excision of a positive node (Killelea et al., 2015). This position should be balanced against the accuracy of SLNB post-NACT. Post-NACT SLNB is strongly recommended *(Fisher et al., 2010)*.

So, to obtain maximum information about the axillary status pre-NACT for systemic or local treatment decisions, routine ultrasound of the regional nodal basins is strongly encouraged diagnosis of clinically or radiologically abnormal lymph nodes (LNs) by FNAC is strongly recommended before NACT. Clip placement into the biopsied node may improve the accuracy of post-NACT SLNB. However, in clinically node-negative patients, it may be that pre-therapeutic sentinel LNs (SLNs) status may determine systemic or local treatment in some cases *(American Joint Committee on Cancer, 2010)*.

The use of NACT in women with locally advanced breast cancer can reduce the tumor size and improve the rates of breast conserving surgery. The degree of pCR to NACT has been shown to correlate with long-term prognosis, although the precise definition of pCR varies across different studies. Patients with high grade or triple negative tumors have higher pCR to cytotoxic therapy and, conversely, failure to achieve pCR clearly results in poor long-term outcomes *(Bear et al., 2019)*.

In addition, the utility of markers, such as estrogen receptors (ER) and progesterone receptors (PR) status in the neo-adjuvant setting, is not clear, although human epidermal growth factor receptor2 (HER2) gene amplification is associated with better response to neo-adjuvant anti-HER2 therapy (Bleicher et al., 2013). Given the heterogeneity of breast cancer at a phenotypic and molecular level and the fact that only 15 to 20% of patients achieve a pCR, biomarkers that accurately predict a survival benefit from NACT remain a pressing and unmet clinical need *(Buzdar et al., 2010)*.

The aim of this study was to evaluate the ALNs pathologically by axillary evacuation after NACT and to estimate disease free survival with pCR in breast cancer cases.

PATIENTS AND METHODS

A prospective study included 100 female patients presented to Surgical Oncology Department Al-Azhar University and Ismailia Oncology Teaching Hospitals between October 2017 and September 2020 with locally advanced breast cancer and cytological

positive ALNs. All patients had received NACT and referred for mastectomy.

Inclusion Criteria:

- Operable, unifocal, non-inflammatory, large breast tumor.
- Infiltrative carcinoma was diagnosed before treatment by core needle biopsy.
- Pathologically proven positive nodes by FNAC from ALNs.
- Patient had received NACT. NACT was proposed to enable the patient to be eligible for breast-conserving surgery).

Exclusion Criteria:

- Pregnancy.
- Metastatic disease.
- Previous excisional biopsy or lumpectomy.
- Multifocal or multicentric disease.
- Local recurrence after previous treatment.
- Inflammatory cancer.
- Premature interruption of NACT Due to cancer progression.
- Patients known to be allergic to patent blue dye.

Before Starting Chemotherapy:

Initial evaluation:

Initial evaluation of the patients included: Complete history and physical examination. Complete blood count and chemistry. Chest x ray. Pelviabdominal US. Bone scan. Echocardiography. Bilateral breast mammography with complementary US of the breast and axilla. True cut biopsy from breast tumor. FNAC from clinically and radiologically positive ALNs.

FNAC was done to establish the presence of metastases in all patients.

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 ALNs was done according to American Joint Committee of Cancer (AJCC, 7th edition) staging score. (5)

Radiological assessment of axilla: US examination of the axilla was done using GE_RT3600 equipment with 7.5 Mega Hertz (MHz). Transducer probe the sonographic characteristics of ALNs were documented. The US diagnostic criteria that have been used to identify abnormal metastatic LNs.

Treatment regimens: In the current study, patients received the chemotherapy regimens that were FEC in 82 patients (FEC 100 in 60 patients & FEC 57 in 22 patients) and FAC in 18 patients. Chemotherapy was given for median of 4 cycles (range from 3 to 6 cycles). Then they were evaluated clinically for response.

Chemotherapy regimens were given as follow:

- F (5 Fluorouracil) dose 500mg/m2.
- E (Epirubicin) dose 100mg/m2.
- A (Doxorubicin) dose 50mg/m2.
- C (Cyclophosphamide) dose 500mg/m2.

All the patients were reassessed clinically and radiologically for feasibility of surgery 21 days after the completion of

the fourth cycle of chemotherapy. Patients underwent surgery within one month after completion of last cycle of chemotherapy.

SLNB (Figure 1):

The mastectomy procedure was started with SLNB. SLN identification was performed using patent blue dye injection. The patient was prepped and draped in the operating room, injection sites were superficial around the tumor (peritumoral), subareolar, peri-areolar, left to the discretion of the participating surgeons.

About 2-3 mL of patent blue was injected under general anesthesia after injection breast massage was performed for 10 minutes. Axillary fascia is entered through a transverse axillary incision and blunt dissection was performed until a blue-stained lymphatic tract or node was visualized. The blue lymphatic vessel was dissected into the axilla until the first LNs was encountered. All blue LNs and any LNs at the end of a blue lymphatic channel are removed and designated as SLNs. After excision of SLNs, all patients underwent a level 1 and II axillary lymphadenectomy, followed by the appropriate mastectomy procedure as dictated by each patient's condition individually.

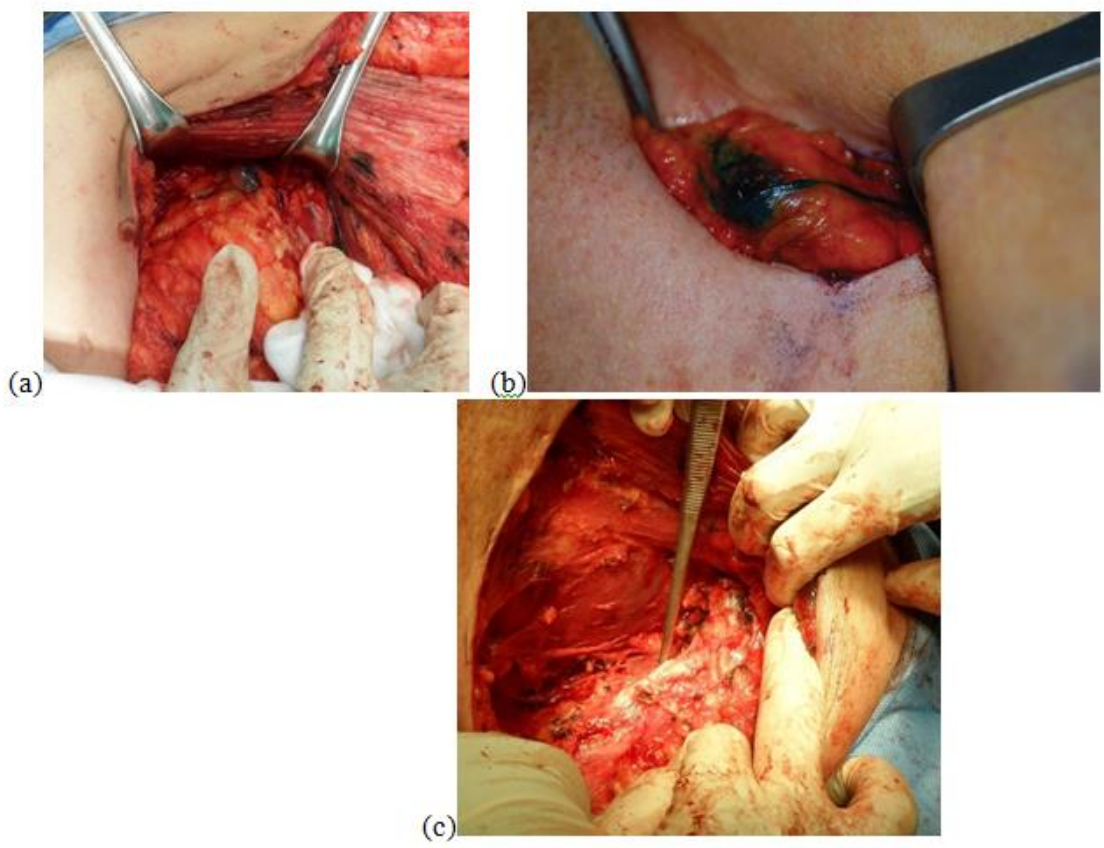

Figure (1): (a) Exploration of axilla after dye injection. (b) Visualization of blue-stained lymphatic tract. (c) Identification & excision of blue stained lymph nodes.

Pathologic Analysis:

For each case, the diagnostic core biopsy was examined for determination of tumor type according to WHO classification Histological grading was evaluated according to Nottingham combined histologic grade (Elston-Ellis modification of the Scarff Bloom Richardson grading system).

Three positively charged slides were prepared from representative tumor block of each core and stained with primary monoclonal antibodies against ER (Dako, mouse monoclonal, clone 1D5, ready to use), PR (Dako, mouse monoclonal, clone PgR 636, ready to use, HER2/neu (Dako, rabbit polyclonal, dilution 1:250), using avidin-biotin-based detection method.

Statistical methods:

Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data 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) and negative predictive value (NPV), and accuracy. A p-value <0.05 was considered significant.

RESULTS

Seventy-six (76%) patients had modified radical mastectomy and twenty-four (24%) patients had breast conserving surgery according to primary tumor chemotherapy response. Patient's mean age was 47.7±9.0 years; fifty-six (56%) patients were postmenopausal. Tumor was in right breast in fifty-eight (58%) patients, and only two female patients (2%) had bilateral breast cancer.

One-hundred patients were enrolled; two of them had bilateral breast cancer so there were 102 tumors. The mean clinical tumor size was 6.7±1.4cm; the commonest TNM stage initially was stage IIIA that was presented in 64 (62.7%) tumors **(Table 1)**.

Table (1): Patients and baseline tumor characteristics

Patients' characteristics	Total patients (n=100)
Age	
Mean ±SD	47.7±9.0
Median (range)	48 (24-66)
Menopausal status	
Post menopause	56 (56%)
Premenopausal	44 (44%)
Laterality	
Right	58 (58%)
Left	40 (40%)
Bilateral	2 (2%)
Tumors' characteristics	**Total tumors (n=102)**
Tumor size	
Mean ±SD	6.7±1.4
Median (range)	6 (5-12)
T stage	
T3	64 (62.7%)
T4	37 (37.3%)
N stage	
N1	96 (94.1%)
N2	6 (5.9%)
TNM stage	
IIIA	64 (62.7%)
III B	38 (37.3%)

SD: standard deviation, TNM: tumor, node, metastases.

The initial mammographic finding of the tumors (BI-RADS SCORE) was mainly score (V) in 84 (82.4%) tumors and all ALNs showed malignant criteria with axillary US assessment before starting chemotherapy (Table 2). The commonest histological subtype of breast cancer encountered initially was invasive duct carcinoma (IDC) in 92 (90.2%) tumors, the grade was mainly of grade II in 92 (90.2%) tumors, and regarding receptors status; ER was positive in 50 (49.0%) tumors, PR was positive in 56 (54.9%) tumors and HER2/neu was (+3) only in 8 (7.8%) tumors **(Table 2)**.

Table (2): Initial radiological and pathological characteristics of tumors and axillary lymph nodes

Radiological characteristics	Total tumors (n=102)
BI-RADS Score IV	8 (7.8%)
BI-RADS Score V	84 (82.4%)
BI-RADS Score VI	10 (9.8%)
Axillary US (malignant LNs)	102 (100.0%)
Pathological characteristics	
IDC	92 (90.2%)
ILC	8 (7.8%)
Unclassified carcinoma	2 (1.96%)
Grade	
Grade I	6 (5.9%)
Grade II	92 (90.2%)
Grade III	4 (3.9%)
ER status	
Negative	52 (51%)
Positive	50 (49.0%)
PR status	
Negative	64 (45.1%)
Positive	56 (54.9%)
HER2/neu	
0	64 (62.7%)
1	24 (23.5%)
2	6 (5.9%)
3	8 (7.8%)

BI-RADS: breast imaging reporting and data system, US: ultrasound, LN lymph node, IDC: invasive duct carcinoma, ILC: invasive lobular carcinoma, ER: estrogen, PR: progesterone, HER2/neu: human epidermal growth factor receptor 2.

In the current study, patients received the standard of care chemotherapy regimens that was FEC, in 82 patient (FEC 100 in 60 patients & FEC 75 in 22 patients) and FAC in 18 patients. Chemotherapy was given for a median of 4 cycles. The mean number of chemotherapy cycles was 4.1±1.2 (26 patients received 3 cycles, 56 patients 4 cycles, 2 patients 5 cycles and 16 patients 6 cycles).

Following NACT, there was reduction of the mean clinical tumor size from 6.7±1.4cm to 4.3±2.3 cm with significant p value <0.001. Clinical response was CR in 10 (9.8%) tumors, partial response in 44 (43.1%) tumors and stationary disease in 48 (47.1%) tumors and there was no patient showed progressive disease under NACT. Clinically the breast tumor diameter was ranging from 2 to 5 cm (T2) in 38 (37.3%) tumors and (TNM) stage was mainly (IIB) in 30 (29.4%) **(Table 3)**. There was pathological primary tumor response in 80 (78.4%) tumors ranging from mild therapeutic response in 40 (39.2%) tumors to pCR in 16 (15.7%) tumors **(Table 3)**.

Table (3): Clinical and pathological response of tumors after NACT

Clinical response	Total tumors (n=102)
Tumor size (mean ±SD)	4.3±2.3
T stage	
T0	10 (9.8%)
TI	14 (13.7%)
T2	38 (37.3%)
T3	30 (29.4%)
T4	10 (9.8%)
TNM stage	
IA	14 (13.7%)
IB	10 (9.8%)
IIA	18 (17.8%)
IIB	30 (29.4%)
IIIA	19 (19.6%)
IIIB	10 (9.8%)
Pathological response (Miller grade)	
Grade 1 (poor)	22 (21.6%)
Grade 2 (mild)	40 (39.2%)
Grade 3 (moderate)	18 (17.6%)
Grade 4 (marked)	6 (4.9%)
Grade 5 (compete)	16 (15.7%)

NACT: neoadjuvant chemotherapy, TNM: tumor, node, metastases, SD: standard deviation.

The mean number of the total dissected ALN was 36±5.7 and the mean number of non-SLNs were 30.8±5.6. Non SLN were positive in 52 (51%) axillae and negative in 50 (49%) axillae **(Table 4)**.

Table (4): Non SLN status

Number of total dissected ALN	Total tumors (n=102)
Mean ±SD	36±5.7
Median (range)	36 (9-35)
Number of total Positive ALN	
Mean ±SD	9±5.3
Median (range)	4 (0-22)
Number of Non SLN	
Mean ±SD	30.8±5.6
Median (range)	30 (7-32)
Non SLN status	
Positive	52 (51)
Negative	50 (49)

SLN: sentinel lymph node, ALN: axillary lymph node, SD: standard deviation.

Out of 64 axillae with positive SLN, there were 46 axillae with positive non SLN and in 18 axillae non SLN were negative. So, SLN were the only positive nodes in 18 cases. Out of 14 axillae with negative SLN there were 4 axillae with positive non SLN. The false-negative rate was defined as the ratio of the number of axillae with a false-negative case of SLNB (4 axillae) to the number of axillae with at least one involved node (>2 mm), SLN or not, (68 axillae) among patients with at least one detected SLN. So, the false negative rate in the current study was 5.8%. Correlation of SLNB assessment of ALN versus pathological results (considered as the gold standard) showed that sensitivity of SLNB was 94.1%, specificity was 100.0%, PPV was 100.0%, NPV was 71.4%, accuracy was 94.9% with highly significant (p<0.001) **(Table 5)**.

Table (5): Correlations between SLN and non SLN status, clinical N response, sonographic nodal response, pathological tumor response, capsular rupture status, and pathological nodal response

		SLN status		Total	P value
		Positive	Negative		
Non SLN status	Positive	46 (92.0%)	4 (8.0%)	50 (100.0%)	0.075
	Negative	18 (64.3%)	10 (35.7%)	28 (100%)	
Post NACT N	Positive	42 (87.3%)	6 (12.5%)	48 (100.0%)	0.396
	Negative	22 (73.3%)	8 (26.7%)	30 (100.0%)	
Post NACT axillary US	Malignant LNs	54 (93.1%)	4 (6.9%)	58 (100.0%)	0.075
	Non-malignant LNs	10 (50%)	10 (50%)	20 (100.0%)	
pCR	No pCR	62 (86.1%)	10 (13.9%)	72 (100.0%)	
	pCR	2 (33.3%)	4 (66.7%)	6 (100.0%)	
Capsular rupture status	Positive	50 (96.2%)	2 (3.8%)	52 (100.0%)	0.003
	Negative	14 (53.8%)	12 (46.2%)	26 (100.0%)	
Pathological nodal response	No CR	64 (94.1%)	4 (5.9%)	68 (100.0%)	<0.001
	CR	0 (0.0%)	10 (100.0%)	10 (100.0%)	
Total		64	14	78	

SLN: sentinel lymph node, NACT: neoadjuvant chemotherapy, Post NACT N: post chemotherapy lymph node status, US: ultrasound, LNs: lymph nodes, pCR: pathological complete response, CR: complete response.

Identification of SLN was positive for non SLN status in 50 tumors while it was negative for non SLN status in 28 tumors **(Table 6)**.

Table (6): Correlations between identification of SLN and non SLN status, and capsular rupture status

		Identification of SLN		Total	P value
		Identified	Unidentified		
Non SLN status	Positive	50	2	52	0.001
	Negative	28	22	50	
Capsular rupture status	Positive	52	2	54	<0.001
	Negative	26	22	48	
Total		78	24	102	

SLN: sentinel lymph node.

DISCUSSION

Present study documented complete axillary conversion from cytologically positive LNs into negative in 31.4% of patients following NACT. Pathological complete response of cytologically positive axillary LNs following NACT was documented in various studies varying from 23% up to 36%. Other studies have reported conversion of clinically involved axilla to a pathologically negative status in 25% to 38% of patients following NACT. The nodal metastasis was not cytologically documented before administering chemotherapy in these studies *(Beatty et al., 2011* and *Classe et al., 2011)*.

Documentation of metastasis in ALNs before initiation of chemotherapy, as done in present study, is essential to demonstrate complete pathological response following NACT. Clinically palpable nodes cannot be assumed be metastatic all the time. In current study, we observed that twelve patients who had clinically palpable nodes did not have metastasis.

In the current study there was nodal pCR in 28 out 82 axillae (34.1%) that received FEC and pCR in 4 out of 18 axillae (22.2%) that received FAC. The higher pCR with FEC can be explained by the higher dose of the Epirubicn compared to doxorubicin (75 or 100 mg vs.50 mg).

Pathological response rate is improved with induction of other effective chemotherapy regimens, including taxanes. Taxanes added either concurrently or in sequence to anthracycline-based regimens and showed increased response rates in the neo-adjuvant setting. Recently Trastuzumab was added to various NACT regimens in several phase II trials. Large phase Ill resulted in pCR rates ranging from 12% to 76%. The addition of gemcitabine or capecitabine to anthracycline- and taxane-based regimens are under investigation *(Guarneri et al., 2010)*.

NACT in current study 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. The optimal duration of NACT has not been established. More prolonged duration, typically six rather than three or four cycles of NACT has generally resulted in higher pathologic complete

response (pCR) rates *(VonMinckwitz et al., 2012)*.

Expert recommendations are to administer four to six cycles of NACT, if there is no disease progression. Although the optimal timing is unknown, some prefer completing the course of chemotherapy before surgery rather than dividing it between the preoperative and postoperative setting, to increase the chance of pCR and breast conservation *(Gralow et al., 2010)*.

In the current study, considering pathological results of ALND as the gold standard, US was found to be better than clinical examination in the assessment of ALN and their response to NACT with sensitivity 82.9% vs. 60%; specificity 68.8% vs. 62.5% PPV 85.3% vs. 77.8% NPV 64.7% vs. 41.7% and accuracy rate was 78.5% vs. 60.8% respectively (p <0.001).

Other study comparing clinical examination, US and mammography concluded that US was the best single non-invasive method of assessing the extent of nodal involvement. The sensitivity and specificity of US for detection of ALNs have been reported to range from 56% to 73% and 70% to 90%, respectively *(Santamaria-Barria et al., 2019)*.

In our study the high sensitivity of axillary US could be attributed to using US criteria of metastatic deposits and the definition of US CR as the absence of any detectable US criteria of metastatic deposit in ALNs that were mentioned earlier (patients and method section).

In other study, they considered the axilla to be positive only if it contained frankly metastatic nodes, visualized as ovoid or lobulated, well demarcated, hypo echoic nodes (>5 mm), and considered to be negative for disease when it was reported to be without any visible adenopathy or to contain echogenic, fat replaced nodes. Previous studies reported that a negative axilla by clinical examination and US after induction chemotherapy still had 48% to 53% chance of being pathologically positive *(Santamaria-Barria et al., 2019)*.

The study examined the accuracy of US-guided FNA for indeterminate and suspicious ALNs in the initial staging of breast cancer. They found that the sensitivity of US-guided FNA was highly dependent on the size of the metastatic deposit. When the metastatic deposit was <0.25 mm, the sensitivity was 16%; if the metastasis was >1.5 cm, the sensitivity increasecf4 to 88% *(Alkuwari and Auger, 2010)*.

Based on this study, US with FNA cytology is better than US alone and physical examination in evaluating the axilla. The specificity is high, and false-positive cases are rare. Furthermore, although a cytologically positive LN accurately determines ALN status, a cytologically negative LN does not. The use of other imaging modalities in the preoperative staging of the axilla has been explored. Preoperative magnetic resonance imaging (MRI) of the axilla was performed, and ALN metastases was identified with a sensitivity, specificity, and accuracy of 83% 90%, and 88%, respectively *(Kvistad et al., 2010)*.

Using 2-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan has been shown to accurately

detect breast primary tumors. It has been adopted as a reliable means of staging the whole body in patients with various malignancies, and there has been growing interest in its use in predicting ALN status in patients with breast carcinoma. Several studies examined FDG-PET in predicted ALN status; the sensitivity, specificity, PPV, and NPV were 61%, 80%, 62%, and 79%, respectively. They found that the accuracy of detecting axillary metastases was improved with the presence of positive lesions, intense lesions, smaller size of the patient, and larger size of the tumor. They concluded that FDG-PET is currently not a suitable substitute for ALND in the assessment of ALNs in breast cancer patients *(Avril et al., 2010).*

Current study showed that SIN detection rate using single method (patent blue dye injection) was 76.5%, considering the pathological result of AIND as the gold standard the Sensitivity of SLNB in predicting ALNs response after NACT was 94.1%, specificity was 100.0%, PPV was 100.0%, NPV was 71.4%, a false negative rate of 5.8%, accuracy was 94.9% with highly significant p value <0.001.

The detection rate in this study was 76.5%, some of the reported series have detection rate up to 100%. The pooled results of detection rates published in a recent meta-analysis of SLNB after NACT, ranging from 72% to 100% *(Classe et al., 2011).*

We attributed the relatively low rate of detection in the current study to the fact that only one technique was used, namely patent blue dye injection.

The methods of SLN detection have an impact on both the detection rate and the false-negative rate. In our prospective series, we used only one method in other study the detection rate was 87.6% with the combined methods and 78.1% with blue dye alone *(Mamounas et al., 2011).*

False-negative rate assessment requires both an SLNB and a complete level I to II lymphadenectomy *(Classe et al., 2011).* In the current study the false-negative rate was 5.8% while in recent meta-analysis of SLNB after NACT it was 12% and 9.8% in results of National Surgical Adjuvant Breast and Bowel Project B32 trial and this low figure of false negative rate in our study may be attributed to small patient number *(Krag et al., 2012).*

To reduce the SLNB false-negative rate after NACT, some proposed an axillary intraoperative US assessment after SLNB to explore the non-sentinel region for additional suspicious LNs, reducing the false-negative rate from 9.6% to 1.39%. In the case of patients treated for an early breast cancer, a positive preoperative PET imaging showing suspicious ALNs may indicate a lymphadenectomy rather than a SLNB, with a high specificity limiting the false-negative rate. The impact of pre-therapy ALN assessment on false-negative rate remains controversial. The false-negative rate from the National Surgical Adjuvant Breast and Bowel Project B-27 trial did not differ for patients with clinical N0 disease as compared with those with clinical N1 disease *(Mamounas et al., 2011).*

In a study of patients with SLNB and axillary lymphadenectomy with suspicious ALNs, there was no difference in false-negative rate and accuracy when comparing the group of patients treated

with NACT to the group of patients treated without NACT *(Lee et al., 2010)*.

The correlation between the false-negative rate and the pathologic response to treatment is rarely studied. In a series of patients with pretreatment biopsy-proven axillary metastasis, they demonstrate a high SLNB accuracy after a complete or partial pathologic response to NACT *(Newman et al., 2011)*.

The high false-negative rate observed with a series of patients with pretreatment biopsy-proven axillary metastasis may be linked to the lack of IHC analysis. An examination of SLNs by serial sectioning and IHC staining significantly increases the detection rate of micro-metastasis, which could reduce the rate of false-negative cases.

In the current study all negative SLN by H&E were subjected to IHC pathological examination none of them showed micro-metastatic disease.

In the case of NACT, a false-negative SLN does not lead to a risk of inadequate systemic treatment, because chemotherapy has already been performed. Systemic adjuvant treatment will not be modified by the axillary pathologic results.

A false-negative result may impact decision about postsurgical irradiation, particularly concerning the LN area as axillary, supraclavicular, or internal mammary areas. The potential risk of under treatment because of lack of LNs area radiotherapy remains controversial. The risk of microscopic invasion of the supraclavicular LNs exceeds 15% in the case of four and more involved ALNs. However, in our series, the SLN was the only involved node in 18 (17.6%) axillae, and in the case of the two patients with false-negative SLN results, one patient had only one involved node and the 2nd patient had two involved nodes.

Present study documented complete pathological axillary conversion in 31.4% of patients following NACT which is a high percentage regarding pathological response of breast tumor that can be Improved with marvelous advances in NACT making trial of conservation of axilla post NACT worthwhile. The pathological response in current study is a real one that is confirmed by meticulous pathological examination using H&E and IHC. Axillary predictors studied in present study showed collectively high sensitivity and specificity in accurately predicting axillary status post NACT with low false negative rate. The detection and false-negative rates of SLNB did not differ from those obtained in the case of early breast cancer without NAC, thus demonstrating the feasibility and accuracy of SLNB after NACT.

We suggest that formal ALND can be avoided post NACT in patients with LABC with cytologically proven metastatic ALN if there were complete clinical, sonographic response and negative SLNB post NACT.

REFERENCES

1. **Alkuwari E and Auger M.:** Accuracy of fine-needle aspiration cytology of axillary lymph nodes in breast cancer patients: a study of 115 cases with cytologic-histologic correlation. Cancer, 114:89-93.
2. **American Joint Committee on Cancer (AJCC) (2010):** Cancer Staging Manual, 7th edition, Edge SB, Byrd DR, Compton CC (Eds), Springer-Verlag, New York 2010; Pp. 347-362.

3. **Avril N, Dose J, Jänicke F, Bense S, Ziegler S, Laubenbacher C, Römer W, Pache H, Herz M, Allgayer B, Nathrath W, Graeff H and Schwaiger M. (2010):** Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. J Clin Oncol., 14:1848-57.

4. **Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, Brown AM, Robidoux A, Margolese R, Kahlenberg MS, Paik S, Soran A, Wickerham DL and Wolmark N. (2019):** Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. Clin Oncol., 24: 2019-27.

5. **Beatty JO, Precht LM, Lowe K and Atwood M. (2011):** Axillary-conserving surgery is facilitated by neoadjuvant chemotherapy of breast cancer. Am J Surg., 197(5):637-42.

6. **Bleicher RJ, Kioth DD, Robinson D and Axelrod P. (2013):** Inflammatory cutaneous adverse effects of methylene blue dye injection for lymphatic mapping/sentinel lymphadenectomy. J Surg Oncol., 99:356.

7. **Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D and Hortobagyi GN. (2010):** Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and Epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol., 23: 3676-85.

8. **Classe JM, Bordes V, Campion L, Mignotte H, Dravet F, Leveque J, Sagan C, Dupre PF, Body G and Giard S. (2011):** Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study. J Clin Oncol., 27(5):726-32.

9. **Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A and Margolese RG. (2010):** Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-27. Clin Oncol., 15:2483-93.

10. **Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, von Minckwitz G, Buzdar AU, Smith IE, Symmans WF, Singh B and Winer EP. (2010):** Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol., 26: 814.

11. **Guarneri V, Frassoldati A and Giovannelli S. (2010):** Primary systemic therapy for operable breast cancer: a review of clinical trials and perspectives. Cancer Lett., 248: 175-182.

12. **Houssami N, Ciatto S and Turner RM (2011):** Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. Ann Surg., 254: 243–251.

13. **Killelea BK, Yang VQ, Mougalian S, Horowitz NR, Pusztai L and Chagpar AB. (2015):** Neo-adjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the National Cancer Database. J Am Coll Surg., 220:1063–9.

14. **Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, Weaver DL, Miller BJ, Jalovec LM, Frazier TG, Noyes RD, Robidoux A, Scarth HM, Mammolito DM, McCready DR, Mamounas EP, Costantino JP and Wolmark N. (2012):** Technical outcomes of sentinel- lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: Results from the NSABP B-32 randomized phase Ill trial. Lancet Oncol., 8:881-888.

15. **Kuehn T, Bauerfeind I and Fehm (2013):** Sentinel-lymph-node biopsy in patients with

breast cancer before and after neo-adjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncology, 14: 609–618.

16. **Kvistad KA, Rydland J, Smethurst HB, Lundgren S, Fjøsne HE and Haraldseth O. (2010):** Axillary lymph node metastases in breast cancer: preoperative detection with dynamic contrast-enhanced MRI. Eur Radiol., 10:1464-71.
17. **Lee S, Kim EY, Kang SH, Kim SW, Kim SK, Kang KW, Kwon Y, Shin KH, Kang HS, Ro J and Lee ES. (2010):** sentinel node identification rate, but not accuracy, is significantly decreased after pre-operative in axillary node- positive breast cancer patients. Breast Cncer Res Treat., 102:283-8.
18. **Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, Bear HD, Caldwell CB, Walker AP, Mikkelson WM, Stauffer JS, Robidoux A, Theoret H, Soran A, Fisher B, Wickerham DL and Wolmark N. (2010)**: Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: Results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol., 23:2694-2702.
19. **Newman EA, Sabel MS, Nees AV, Schott A, Diehl KM, Cimmino VM, Chang AE, Kleer C, Hayes DF and Newman LA. (2011):** Sentinel lymph node biopsy performed after neoadjuvant chemotherapy is accurate in patients with documented node-positive breast cancer at presentation. Ann Surg Oncol., 2011; 14:2946-2952.
20. **Santamaria-Barria JA, Stern S, Khader A, Garland-Kledzik M, Scholer AJ, Fischer T and Bilchik A. (2019):** Changing Trends in Industry Funding for Surgical Oncologists. Ann Surg Oncol., 26(8):2327-2335.
21. **VonMinckwitz G, Untch M, Blohmer JU and Costa SD. (2012):** Definition and impact of pathologic complete response on prognosis after neo-adjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol., 30: 1796-1804.

تقييم حالة العقدة الإبطية بعد العلاج الكيميائي المساعد الجديد في مرضى سرطان الثدي الإناث المتقدمين محليًا

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خلفيـــة البحـــث: ســرطان الثــدي هــو الــورم الأكثــر شــيوعًا بــين النســاء فــي غالبيــة البلــدان المتقدمــة، ويمثــل ثلــث الأورام الخبيثــة التــي تــم تشخيصــها حــديثًا. بــالنظر إلــى كفــاءة العــلاج الكيميــائي المســاعد الجديــد (NACT) فــي تقليــل حجــم الــورم، فمن المنطقي افتراض نفس الاستجابة في الإبط.

الهــدف مــن البحــث: تقيــيم إســتجابة الغــدد الليمفاويــة الإبطيــة للعــلاج الكيميــائي المســاعد الجديــد باســتخدام الفحوصــات الســريرية أو بالموجــات فــوق الصــوتية أو المرضــية لخزعــة العقــدة الليمفاويــة الحارســة أو تشــريح العقــدة الليمفاويــة الإبطية.

المرضـــى وطـــرق البحـــث: تضــمنت هــذه الدراســة المســتقبلية 100 مريضــة مصــابات بســرطان الثــدي المتقــدم محليًــا مــع العقــد اللمفاويــة الإبطيــة التــي يمكــن إكتشــافها ســريريًا أو يمكــن اكتشــافها فــي الموجــات فــوق الصــوتية تــم إجــراء خزعــة حقيقيــة مــن الــورم الأولــي وعلــم الخلايــا بــالإبرة الدقيقــة للغــدد الليمفاويــة الإبطيــة قبــل العــلاج الكيميــائي المســاعد الجديــد. تــم تقيــيم الاســتجابة الســريرية والموجــات فــوق الصــوتية لتقيــيم الغــدد الليمفاويــة الإبطيــة. بــدأ الــتحكم الموضــعي الجراحــي بخزعــة العقــدة الليمفاويــة الحارســة ثــم تشــريح العقــدة الليمفاويــة الإبطيــة فــي جميــع المرضــى متبوعًــا بــإجراء استئصــال الثــدي المناســب. تــم تقــديم عينــات مــن الــورم الأولــي وخزعــة العقــدة الليمفاويــة الحارســة وعينــات تشــريح العقــدة الليمفاويــة الإبطيــة للفحــص المرضــي. تعرضــت العقــدة الليمفاويــة الخــافرة السلبية بواسطة الهيماتوكسيلين ويوزين لقسم كيميائي مناعي.

نتـــائج البحـــث: تمـــت مواجهـــة الاســـتجابة الســـريرية والموجـــات فـــوق الصـــوتية والمرضـــية الكاملـــة للعـــلاج الكيميـــائي المســـاعد الجديـــد فـــي 47.1٪ و 33.3٪ و 31.4٪ مـــن المرضـــى علـــى التـــوالي. كانـــت حساســـية الخزعـــة الســـريرية والإشـــعاعية والعقـــدة الليمفاويـــة الحارســـة فـــي التنبـــؤ بالاســـتجابة المرضـــية الكاملـــة 60٪ و 82.9٪ و 94.1٪ علـــى التـــوالي. كانـــت الموجـــات فـــوق الصـــوتية أفضـــل مـــن الفحـــص الســـريري فـــي تقيـــيم الاســـتجابة بدقـــة 78.5٪ مقابـــل (مقابـــل) 60.8٪ علـــى التـــوالي. وكانـــت خزعـــة العقـــدة الليمفاويـــة الحارســـة أكثـــر حساســـية مـــن الفحـــص الســـريري فـــي التنبـــؤ بالاســـتجابة المرضـــية الكاملـــة بدقـــة 94.9٪. كـــان معدل الكشف عن العقدة الليمفاوية الحارسة 76.5٪.

الاســـتنتاج: الإســـتجابة المرضـــية الكاملـــة بعـــد العـــلاج الكيميـــائي المســـاعد الجديـــد عاليـــة بمـــا يكفـــي لجعـــل الحفـــاظ علـــى الإبـــط مفيـــدًا. يمكـــن لخزعـــة العقـــدة الليمفاويـــة الخـــافرة والموجـــات فـــوق الصـــوتية تقيـــيم الاســـتجابة العقديـــة والتنبـــؤ بهـــا بمعـــدل دقـــة مقبـــول، كمـــا أن خزعـــة العقـــدة الليمفاويـــة الخـــافرة ممكنـــة بعـــد العـــلاج الكيميائي المساعد الجديد.

الكلمـــات الدالـــة: العقـــدة الليمفاويـــة الحارســـة، الاســـتجابة الكاملـــة، العقـــد الليمفاويـــة الإبطية.