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PREDICTIVE VALUE OF NEGATIVE SENTINEL LYMPH NODE BIOPSY AFTER NEO-ADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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ABSTRACT

Background: Sentinel lymph node biopsy (SLNB) is the standard conservative surgical procedure for axillary management in early breast cancer patients with clinically negative axilla. Achievement of complete response at the axilla after neo-adjuvant chemotherapy (NAC) evolving the use of SLNB in locally advanced breast cancer (LABC). **Objectives:** Evaluation of the sensitivity, false negative rate and negative predictive value of SLNB in patients with LABC that have clinically negative axilla either before or after NAC. **Methods:** A prospective study carried out on LABC patients (T3-4, N0-1, and M0) whom received NAC. All cases underwent SLNB using blue dye, followed by axillary lymph node dissection (ALND) along with surgical management of primary tumor. **Results:** The study included 67 patients, 48 of them turned to clinically negative axilla after NAC (Group A) and 19 had negative axilla before the NAC (Group B), Identification of sentinel lymph node (SLN) was achieved in 46 patients {33 in group A and 13 in group B (p=0.32)}, SLN metastasis has been detected in nine cases, {eight in group A and one in group B (p= 0.03)}, while lymph node metastasis after ALND has been observed in 12 patients {eleven in group A and one in Group B (p= 0.04)}. The sensitivity of SLNB was 80%, 78.6% and 100% for all patients, group A and group B respectively, while the false negative rate was 20%, 21.4% and 0% respectively (p= 0.00). **Conclusion:** SLNB is a valid treatment option for patients with LABC who have clinically negative axilla at presentation (before NAC), while patients who turned to be clinically negative axilla after NAC; the ALND is still the best treatment option.

KEYWORDS: Sentinel lymph node, Locally advanced breast cancer, Neo-adjuvant chemotherapy.

ABBREVIATION

ALND: axillary lymph node dissection, BCS: breast conservative surgery, IDC: infiltrating Ductal carcinoma. ILC: infiltrating lobular carcinoma, LABC: locally advanced breast cancer, MRM: modified radical mastectomy, NAC: neo-adjuvant chemotherapy, SLN: sentinel lymph node, SLNB: sentinel lymph node biopsy.

INTRODUCTION

Worldwide, breast cancer is a major health problem representing the most common cancer affecting women and the leading cause of cancer-related deaths in women under the age of 45 years.[1] In Egypt it is the second most common cancer after HCC and most common cancer in women accounting for about 17%.[2] Breast cancer in low- to middle-income countries often presents in locally advanced stage that increase breast cancer mortality in such countries.[3]

Evaluation of axillary lymph node status is essential for staging and prognosis of patient with breast cancer; and has very strong role at the time of adjuvant treatment choice.[4,5] SLNB is a standard surgical procedure for staging patients who have clinically free axillary nodes because of the much lower morbidity than ALND without compromising diagnostic accuracy and prognostic information.[6]

Locally advanced breast cancer has no uniform definition between authors, but in general includes patients with clinical stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease.[7-9] The current standard management of such disease is upfront neo-adjuvant systemic treatment followed by surgery that aim to down staging the tumor and hence increase the rate of BCS, In addition NAC provides an in vivo evaluation of chemo sensitivity to certain drugs, and assess the potential need for further adjuvant therapy.[10,11]

The standard surgical management for breast cancer patients with clinically positive axilla is ALND even after NAC and regardless response to treatment, the complications of axillary dissections include pain,

seroma formation, Shoulder stiffness and lymphedema that increase in incidence after radiation treatment, which is usually given for every case with LABC.[12]

In early breast cancer there is no doubt that SLNB is the standard surgical staging procedure for patients with clinically negative regional nodes.[13] Patients with LABC and clinically negative axilla whom treated by NAC followed by resection of primary tumor and ALND remain node-negative after chemotherapy according to a study done by Ollila et al.,[14] achievement of this observation evolving the use of SLNB in LABC, however the routine use of SLNB in LABC still a matter of controversies.[6]

If patients with LABC and clinically negative axilla managed surgically without axillary dissection, a lot of surgery related morbidity will be avoided. The aim of this work is to evaluate the use of SLNB after NAC in patients with LABC who have clinically negative axilla.

METHODS

This prospective study included female breast cancer patients with locally advanced disease (Clinical T3-T4 and either negative or positive axilla), diagnosed with true cut needle biopsy, and treated in the period between July 2011 and July 2016; patients who had distant metastatic, previous axillary surgery, other malignancy, allergic to blue dye or didn't sign the consent were excluded from the study.

All patients received NAC at the Clinical Oncology Department, Al Hussein University Hospital, either Anthracycline based regimen alone (5-Flurouracil, Epirubicin & Cyclophosphamide/or Adriamycin & cyclophosphamide) or Anthracycline based regimen followed by Taxanes (Paclitaxel or Docetaxel). During the course of chemotherapy patients subjected to clinical assessment every cycle and radiological assessment at the middle and end of chemotherapy course, patients with disease progression during treatment or flailed to achieve complete response at the axilla were excluded from the study.

Patients who had clinically negative axilla either before or after NAC were eligible to continue in this study (67 patients), all of them underwent complete clinical and radiological assessment at the end of chemotherapy, surgery was planned to be done after 3 weeks from the last chemotherapy cycle provided complete hematological recovery.

Skin sensitivity test with blue dye was done 30 minutes before anesthesia in the contralateral arm for all included patients. Immediately after anesthesia and before scrub, 5cm of Isosulphane blue was injected in and around the site of primary tumor. The first step after mastectomy or BCS was identification of axillary vein and inter-costo-brachial nerves followed by detection of sentinel lymph nodes (blue stained). Complete axillary clearance was then done for all cases followed by separation of the stained LN(s).

The following equations were used for calculation of 1) Sentinel LN detection rate [number of cases with Identified SLN/total number of cases], 2) Sentinel LN sensitivity [true positive/ (true positive + false negative) X 100], 3) Sentinel LN negative predictive value [true negative/ (true negative + false negative) X 100], and Sentinel LN false negative rate [100 - sensitivity]. Statistical analysis was performed using SPSS version 20. Data was presented in the form of numbers, percentages or median. t-test was used to detect the difference in means between groups. Statistical significance difference considered if p value was less than 0.05.

RESULTS

The median age of the studied 67 patients was 50.7 years (range 31- 65), seventeen of them were diabetic, eleven were hypertensive, and two have positive family history of breast cancer. Left sided tumor was identified in 39 patients (58.2%), while 28 patients (41.8%) were right sided. Eleven patients (16.4%) presented with central tumor, 16 (23.9%) had inner quadrants tumor, and 40 patients (59.7%) had tumor located at outer quadrants. Infiltrating duct carcinoma (IDC) was the commonest histopathological subtype (86.6%) while rest of cases was having infiltrating lobular carcinoma (ILC). Grade II, III tumors were observed in 63 (94.1%) and four (5.9%) patients respectively. Clinical tumor stage T3 and T4 were recorded for 44 and 23 patients respectively, (rest of disease characteristics are listed in table 1).

All patients received the planed NAC, 61 patients (91%) received anthracyline based regimen followed by taxanes while the remaining five patients (9%) received only anthracyline based regimen. Grade I-II hematological toxicity was recorded for 37 patients (55.2%) while grade III-IV was seen in 16 patients (23.9%). Patients who had clinically positive axilla before NAC and turned to clinically negative axilla after chemotherapy was 48 patients (group A); while patients who had clinically negative axilla at presentation were 19 (group B).

Forty six patients (68.6%) underwent MRM, and 21 (31.4%) cases underwent conservative breast surgery (CBS). Eighteen patients (26.9%) developed clinical complete remission of the primary tumor; out of them only 11 patients (16.4) developed pathological complete response at the primary tumor site.

Identification of SLN was achieved in 46 patients (68.6%); while in 23 patients (37.3%) the SLN did not stain blue. Most of the stained SLN (85.7%) were located in pectoral group. In 36 patients (out of 46 patients with detected SLN) there was only one SLN identified while in the remaining six cases more than one SLN were stained. The number of cases with identified SLN in group A and B was 33 & 13 respectively (Figure 1), with

no statistically significant difference (p= 0.34) between groups. Histo-pathological examination of the detected SLN showed metastasis in nine cases, of them eight detected in group A and only one in group B (Figure 1), this difference in SLN metastasis between the two groups was statistically significant (p= 0.03). (Table 2)

In a univariate analysis, the rate of SLN Identification did not affected significantly by any of the family history, comorbidities, tumor side, nodal stage, type of NAC, surgery type, pathology subtype, ER, PR or Her2Neu (p> 0.05); on the other hand tumor location and T stage had statistically significant effect on SLN identification rate (p= 0.010 and 0.036 respectively) (Table 3). However after multivariate analysis none of them maintained this statistical significant effect (p= 0.32 and 0.46 respectively).

All patients included in this study underwent ALND, metastasis has been detected in 12 patients (12/67), the median number (range) of excised LN was 11 (7-22) while the median number (range) of positive LN was three (1-7). In group (A) eleven patients had positive metastasis on ALND, out of them eight patients was already having metastasis in the SLN; while only one patient in group B had metastasis on ALND, this patient was having also metastasis on SLNB, the difference between group A & B in number of patients with lymph node metastasis on ALND was of significant difference (p= 0.04). (Table 2).

The sensitivity of SLNB was 80%, 78.6% and 100% for all patients, group A and group B respectively, while the false negative rate was 20%, 21.4% and 0% respectively; and negative predictive value was 94.8%, 92.5% and 100% respectively, the difference between group A and B was statistically significant in term of sensitivity, false negative rate and negative predictive (p= 0.00). (Table.2).

Table 1: Patients Demographic and Disease Characteristics.

Criteria	Number (67)	%
Median Age (Range)	**50.1 (31-65)**	
Comorbidities		
Hypertension	11	16.4%
Diabetes	17	25.4%
Family History		
Positive	2	3%
Negative	65	97%
Tumor Side		
Left	39	58.2%
Right	28	41.8%
Tumor location		
Outer	40	59.7%
Inner	16	23.9%
Central	11	16.4%
Tumor Stage		
T3	44	65.7%
T4	23	34.3%
LN Stage		
N0	19	28.4%
N1	48	71.6%
Pathological Subtype		
IDC	58	86.6%
ILC	9	13.4%
Tumor Grade		
I	0	0.0%
II	63	94. 1%
III	4	5.9%
ER Status		
Negative	18	26.9%
Positive	49	73.1%
PR Status		
Negative	16	23.9%
Positive	51	76.1%
HER 2 Neu Status		
Negative	26	38.8%
Positive	6	9.0%
NA	35	52.2%
NA: not available		

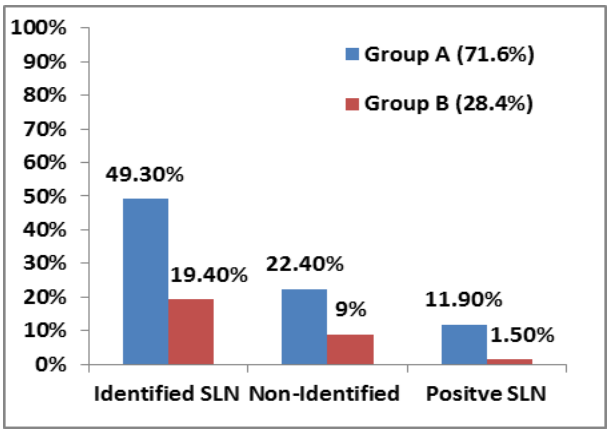

Figure 1: Distribution of Identified and Positive SLN in the 67 Patients.

Table 2: Postoperative Pathological Characteristics.

Criteria	Group A (N=48)	Group B (N=19)	P Value
Surgery Type			
MRM	32 (66.7%)	14 (73.7%)	0.65
CBS	16 (33.3%)	5.0 (26.3%)	
SLN Identification			
Yes (46)	33 (68.8%)	13 (70.6%)	0.34
No (21)	15 (31.2%)	6.0 (29.4%)	
SLN location			
Pectoral	26 (54.2%)	10 (52.6%)	0.49
Non-pectoral	7.0 (14.6%)	3.0 (15.8%)	
SLN number			
One LN	29 (60.4%)	11 (57.9%)	0.56
> one LN	4.0 (8.3%)	2.0 (10.5%)	
Metastasis in SLN			
Yes	8.0 (16.7%)	1.0 (5.3%)	0.03
No	25 (52.1%)	12 (63.1%)	
Metastasis on ALND			
Yes	11 (22.9 %)	1.0 (5.3%)	0.04
No	37 (77.1%)	18 (94.8%)	
Positive ALND Distribution			
SLN Identified	8.0 (16.7%)	1.0 (5.3%)	0.02
SLN not Identified	3.0 (6.3%)	0.0 (0.0%)	
SLN			
Sensitivity	78.6%	100%	0.00
False Negative Rate	21.4%	0.0%	0.00
Negative Predictive Value	92.5%	100%	0.00
LN: Lymph node			

Table 3: Correlation Between Different Characteristic and SLN Identification.

Characteristics	95% Confidence		P Value
	Lower	Upper	
• Family history	-0.245	0.248	0.523
• Comorbidities	-0.190	0.167	0. 614
• Tumor side	-0.230	0.458	0.121
• Tumor location	-0.800	-0.115	0.010
• T Stage	0.01791	0.50797	0.036
• N Stage	-0.24380	0.23758	0.980
• NAC type	-0.238	0.039	0.156
• Type of surgery	-0.345	0.148	0.429
• Pathology subtype	-0.099	0.263	0.370
• ER status	-0.062	0.003	0.074
• PR status	-0.194	0.059	0.065
• HER 2 neu status	-0.130	0.558	0.218

DISCUSSION

Down staging of primary breast tumor is the main goal of neoadjuvant chemotherapy, which may help in reducing the rate of radical mastectomy in patient with locally advanced disease. Many investigators tried also to treat the axilla in conservative way by limiting the axillary surgery after neoadjuvant chemotherapy by using SLNB instead of ALND that carry much more treatment related morbidity.

Neoadjuvant Anthracycline based regimen can reduce the rate of mastectomy by about 20% due to the down staging effect on the primary tumor,[15,16] adding Taxanes to Anthracycline based chemotherapy enhance the response and increase the rate of complete pathological response, but has no effect on disease free survival or overall survival, although that the NAC still independent prognostic factor.[17] All included patients in this trial received Anthracycline based chemotherapy followed by Taxanes in 52 patient, the chemotherapy convert 48 patients from clinically positive axilla to clinically negative axilla, however after axillary dissection 11 patients found to have pathologically positive axilla and 37 patients kept having pathologically negative axilla.

The absolute decrease in the mastectomy rate after NAC in patients with LABC is about 16.6%, according to a meta-analysis of 14 prospective randomized trials contained 5,500 patients, although that many patient still have to be managed with mastectomy,[18] In this study 68.6% of cases treated by MRM while the remaining patients managed by CBS.

The value of SLNB in LABC had been evaluated in a study done by Ollila et al, where patients with large breast tumor (≥5 cm) and clinically negative axilla underwent SLNB prior to neoadjuvant chemotherapy, and then axilla dissection after chemotherapy, patients with negative axilla by SLNB kept having negative axilla

after chemotherapy, this results showed high accuracy of SLNB in axillary staging for such patients and confirmed the prognostic and therapeutic implications of axillary staging by this method, although the low number of patients in this study (21patients),[14] in our trial we included patient with either clinically negative or positive axilla and SLNB had been done after the NAC, the total number of patients with clinically negative axilla was 19, only one of them had positive SLNB while the remaining 18 patients kept having no SLN metastasis and negative ALND, which is consistent with Ollila results.[14]

In a big study (included 663 patients) by the American College of Surgeons Oncology Group (ACOSOG Z1071) investigators, SLNB was done for patients with node-positive breast cancer (cN1) who received NAC, both blue dye and a radiolabeled colloid had been used for axillary mapping in most cases (79.1%), in 12.0% of cases only one SLN was excised, while in the remaining 88% of cases two or more SLNs was removed, SLN was identified in 92.9%, the false-negative rate was 12.6% when two or more SLNs were examined, and 9.1% when three or more SLNs were examined.[19] Further analysis of ACOSOG Z1071 showed improvement in the SLN identification rates if radiolabeled colloid used with blue dye (93.8%), compared with blue dye alone (78.6%).[20]

Isosulphan blue dye was used alone to map the axilla for all patients included In our study, this may explain the relative low identification rate (68.6%) in our study compared to the other published studies that examined the value of SLNB after NAC, where the reported identification rates were 78.6%,[20] 82.9%[21] 89.6%[22] and 100%.[23] The failure to identify the SLN in 31.4% of patients in current study may return in part to the lymphatic obstruct by malignant cells that prevents dye from reaching the nodes, this explain why patients with stage T4 had statistically significant lower identification rate than patients with T3 tumors (p= 0.4), which is also consistent with Carole et al findings, whom stated that the failure of SLN identification was probably due to failure of the SLN to take up the dye rather than failure of technique.[24]

SENTINA was a four-arm prospective multi-centric study, in one arm patients with clinically node-positive disease at diagnosis who converted to clinically node-negative status after NAC underwent SLNB; the false-negative rate of SLNB was 14.2% (95% CI, 9.9–19.4). However when three or more lymph nodes were removed, the false-negative rate dropped to 7.3%, the false-negative rate had also decreased from 16% to 8.6% with the addition of blue dye to radiocolloid.[25]
These previous two mega trials[19,25] had both confirmed the adding value from using blue dye and radio-colloid to decrease the false negative result of SLNB and showed direct relation between the number of excised SLN and the lower false negative rate, the majority of patients (40/46) in our trial had only one SLN excised, and relatively high false negative rate (20%) compared to SENTINA study (16%) when blue day was used alone,[25] this may be explained by the high percentage of T4 disease (34.3%) and the relative low identification rate.

Significant proportion of patients with negative SLNB after NAC will have negative metastasis in axillary nodes on ALND, however, still completion ALND is a kind of standard management in such situation.[26] Although there is new released data showing no difference in disease free survival or overall survival from omission of ALND in patients with early stage breast cancer treated with BCS if one or two lymph nodes were positive on SLNB and the radiotherapy is planned.[27]

In the current study, in patients with clinically negative axilla before NAC the SLNB had 100% sensitivity, zero false negative rates and 100% negative predictive value, although the use of blue day alone for mapping of the axilla with low identification rate, this make the SLNB very accurate method for management of the axilla in this group of patients.

CONCLUSION

Patients with locally advanced breast cancer is a heterogeneous group, surgical management of the axilla in such patients should depends on the clinical status of the axilla at first presentation, for patients with clinically negative axilla, SLNB is a good sole treatment option, while for patient with clinically positive axilla before the NAC, ALND still the more accurate method of staging based on the results of this study, however confirmation of this results needs larger trial with long term follow up to assess the rate of axillary recurrence in such patients.

Authors Discloses no Conflict Of Interest

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