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RESEARCH ARTICLE

HOW COULD NODE-POSITIVE BREAST CANCER PATIENTS BENEFIT FROM POST-NEOADJUVANT CHEMOTHERAPY SLNB ADOPTING ACOSOG Z1071 END RECOMMENDATIONS

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ABSTRACT

Introduction: axillary lymph node status is one of the most significant prognostic factors that guide treatment strategy in breast cancer. Patients with advanced tumor or axillary nodal metastasis could benefit from neoadjuvant chemotherapy (NAC) resulting in down-staging of the disease. Sentinel lymph node biopsy (SLNB) in patients with axillary nodal disease is debated regarding its identification rate (IR) and false negative rate (FNR). American College of Surgeons Oncology Group (ACOSOG) conducted a large trial to assess SLNB in such patients and it showed depressing outcome resulting in proposition of some recommendations and modification in their methodology when SLNB to be carried out. In this study we adopt ACOSOG Z1071 recommendation to assess SLNB in post-NAC node-positive breast cancer patients. **Methods:** This study included 42 breast cancer patients with pathologically proved nodal metastasis. SLNB carried out in patients who showed clinical negative nodes after NAC. Three or more SLNs was mandatory to continue the assigned management pathway, while less than 3 nodes or failure to identify any SLN shift the patient to axillary lymph node dissection (ALND). Detailed evaluation of SLNs and nodes yielded from ALND was done and data interpreted to show how far such patient could benefit from such procedure and if any could spared ALND. **Results:** From 42 patients included in the study clinical conversion rate after NAC to negative axilla was 78.6%. 33 patients underwent SLNB with identification rate of 84.8%. Three or more SLNs were identified in 20 patients. 24% of patients subjected to SLNB were spared axillary dissection. On final evaluation of all retrieved nodes in all limbs of the study we assumed that neoadjuvant chemotherapy resulted in pathological complete response in 35% of our studied group. **Conclusions:** SLNB following NAC in node-positive patients is feasible and can be a future standard of care with some modification in methodology adopting recommendations released from large concerned trials.

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INTRODUCTION

Neoadjuvant chemotherapy (NAC) considered as a typical treatment for locally advanced breast cancer, inoperable breast cancer, or that showed metastatic lymph nodes. Lately it was integrated in the treatment of early breast cancer, especially in triple negative disease and human epidermal growth factor receptor 2 (HER2) enriched (Mieog *et al*., 2007; Fisher *et al*., 1998; Palma *et al*., 2015). NAC grants *in vivo* testing of chemotherapeutic effect, eradicates micro metastasis and help down-staging the disease, allowing conservative surgery in previously unsuitable patients (Wolmark *et al*., 2001).

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Axillary management was always one of the main critical issues in managing breast cancer patients regarding local control and indicating prognostic features of the disease. With evolution of sentinel lymph node biopsy (SLNB) technique, it became a standard measure in clinically node negative early breast cancer. Many recent researches have shown nodal pathological complete response in nearly 40% of patients with positive nodal disease after NAC, which is varied according to tumor biology reaching up to 49% and 74% in triple negative and HER2-positive disease, respectively (Hennessy *et al*., 2005; Von Minckwitz *et al*., 2012; Dominici, 2010; Boughey, 2014). Depending on the remarkable rate of node conversion along with the success of SLNB technique in patients with negative axill a, the motivation for carrying out SLNB after neoadjuvant chemotherapy in patients who initially showed node-positive disease has expand (King, 2015). Those patients may be spared the axillary lymph node dissection (ALND) and its possible complications as lymphedema, shoulder joint

dysfunction, and sensory problems at the arm pit (The American Society of Breast Surgeons, 2010). Although that the current standard of care is doing ALND in all patients with biopsy-proven axillary metastasis prior to NAC (Hennessy *et al*., 2005; Shen, 2007), many recent studies were carried on to assess the SLNB following NAC in patients with initially proved to have positive nodal disease. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial main endpoint was a false negative rate FNR of 10% or less. Conversion from clinically positive axilla (cN+) to clinically negative (cN-) was not a must, but at least 2 SLNs had to be retrieved to be incorporated in estimating the FNR. Identification rate was 93%. The FNR when ≥2 SLNs retrieved was 13% and this did not match the pre-defined 10% rate to consider the procedure successful. In further analysis, a remarkable reduction in the FNR was seen when dual method for mapping was employed (dual method FNR 11% versus 20% with single agent, p=0.05) and when 3 or more SLNs were removed (FNR 9% ≥3 SLNs, 21% 2 SLNs, p=.007) (Boughey, 2013).

The SENTINA study was a multi-centers trial where patients were aligned according to clinical assessment of axillary nodes both pre- and post-chemotherapy using clinical examination and US. Histologic proof of nodal metastases was not mandated. Unlike ACOSOG Z1071 only patients with complete clinical axillary response was included. SLN identification rate was 80%, (88% dual radiolabelled colloid and blue dye versus 77% radiolabelled colloid only). The overall FNR was 14%; (9% for dual mapping versus 16% for radiolabelled colloid only). with removal of 3 or more SLNs the FNR was 7%, while with 2 nodes removed it was 19% and 24% with only one SLN retrieved (p=0.008) (Kuehn *et al*., 2013).Another study, the Sentinel Node Biopsy Following Neo adjuvant Chemotherapy (SN FNAC) with comparable design and a defined optimal identification rate of 90% with a FNR of ≤10%. Immunohistochemistry (IHC) was added to the routine pathologic examination. Results showed identification rate of 88% and an 8% FNR when isolated tumor cells (ITCs) were considered node positive.

The FNR was raised to 13% on considering ITCs as node negative (Boileau *et al*., 2015). Although the ACOSOG Z1071, SENTINA and SN FNAC trials were considered as negative trials as their primary goal to identify false negative rate (FNR) of SLNB was higher than proposed (10% was set to be the cutoff). Yet they indicate some recommendations at the end result that could be considered as refinement of the methodology if SLNB is to be undertaken in node-positive breast cancer patients who received neoadjuvant chemotherapy (NAC). These recommendations mainly advocate the use of dual-method in identifying SLNs and retrieval of 3 or more nodes as these measures reduce the FNR. Also ACOSOG Z1071 trial recommend clipping of the initially positive axillary node before starting NAC and effort to be made to remove this node along with all SLNs and if a clip was not placed or it cannot be identified at least 2 and ideally 3 sentinel nodes are advised to identified and removed. Immunohistochemistry (IHC) staining of sentinel nodes is to be considered as it will lower the FNR. In our study we adopt the ACOSOG Z1071 recommendation with some modification that were applied to all our patients including enrolling only patient showed clinical conversion to negative axilla, use of dual method to identify SLNs and retrieval of at least 3 nodes to continue in the study.

PATIENTS AND METHODS

During the period from June 2015 to June 2019, selected patients with breast cancer presented to surgery department, Kuwait cancer control center, Kuwait and surgery department, faculty of medicine, Suez Canal University, Ismailia, Egypt. Those patients diagnosed as having invasive duct carcinoma stage II, IIIA and IIIB with proved positive nodal metastasis by mean of image guided FNAC or core biopsy. The axilla was clinically assessed by clinical examination and US and was biopsied if showed suspicious nodal features in the form of lost hilar fat, thickened or markedly hypoechoic cortex or round shape. All patient received neoadjuvant chemotherapy; anthracycline based, anthracycline plus cyclophosphamide (AC) and taxane, AC and taxane with trastuzumab if Her-2-neu positive. Clinical response was assessed regarding the tumor and nodes as response in the form of complete remission (CR) and partial remission (PR), or no response in the form of Stable disease(SD) and progressive disease (PD). Patients with stable or progressive disease were excluded from the study.

All patients showed response to neoadjuvant chemotherapy (42 cases) were enrolled in the study and underwent either mastectomy or conservative breast surgery in the form of wide local excision of palpable mass or excision of tumor site in case of complete remission after wire localization. Management of the axilla was determined for each patient after discussion in MDT and applying the approved treatment protocols at both centers, also it was tailored to meet the NCCN guidelines and adapting recommendations published by ACOSOG Z1071 trial (dual method for SLNB encouraged with at least 3 nodes retrieved to minimize false negative rate). Patients' informed consents were obtained after full explanation of the benefits and possible risk and the need for follow up program. Patients showed clinical nodal PR (9 cases) (palpable or still showed US suspicious features) were subjected to axillary lymph node dissection (ALND) and patient showed clinical CR for axilla (33 cases) were subjected to SLNB.(Figure 1 showed flow chart of management). SLNB was done using dual method,blue dye (Patent blue) plus radiolabelled colloid in all cases.(Figures 2 -5). Lymphatic mapping was performed using technetium 99mTc -labeled sulfur colloid (TSC) injected 1 hour before surgery and retroareolar injection of 1–2 ml of isosulfan blue dye (Patent Blue V 2.5% Guerbet laboratories, France) 5-10 min before skin incision.

Intraoperatively, we usually started with retrieval of SLNs via separate axillary incision unless it was decided before hand to do mastectomy when we started with elevation of upper skin flap and went to the axilla through its lateral end to search for the SLNs then go back to complete mastectomy. In cases subjected to conservative breast surgery, WLE was done after identification of SLNs and sending them to frozen section examination.SLN identification was done using both visual identification of blue colored nodes and following any colored lymphatic along with usage of hand held gamma probe (Gamma Finder® II, World Of Medicine AG, Germany) any node gave reading of at least 10% of the index SLN was considered a sentinel node. Patients showed positive SLNs by frozen section examination or failed to identify at least 3 SLNs were subjected to ALND. Detailed examination and interpretation of nodal status for the 33 patients underwent SLNB were documented regarding both SLNs and non-SLNs.

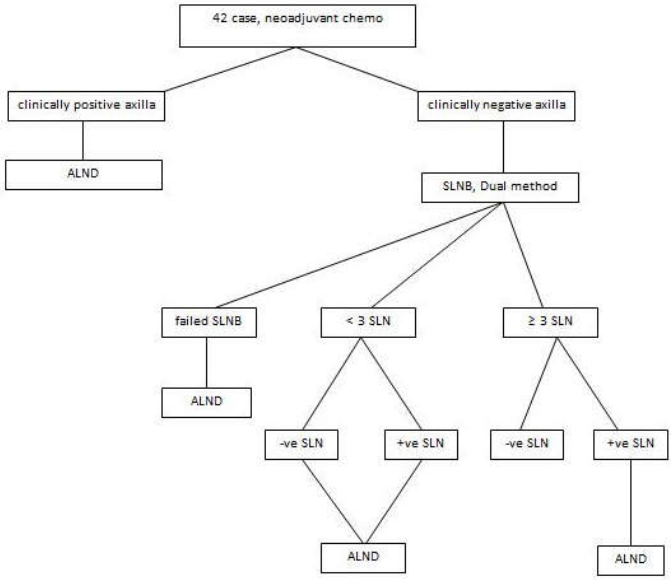

Fig. 1. Diagrammatic flow chart showing the way of management of axillae after receiving neoadjuvant treatment

Fig. 2. Photo showing blue colored SLN in axilla

Fig. 3. Photo showing blue colored lymphatics and SLN in axilla

Table 1. Baseline patients' characteristics

		Frequency	Percentage
Age (years)	≤ 50 years old	21	50%
	>50 years old	21	50%
	Mean ± SD	50.71 ± 8.74	
	Range	33 – 72	
Initial TNM stage	T2N1	18	42.9%
	T2N2	8	19%
	T3N1	9	21.4%
	T3N2	3	7.1%
	T4N1	3	7.1%
	T4N2	1	2.4%
Post-NAC TNM	T0N0	3	7.1%
	T1N0	16	38.1%
	T2N0	14	33.3%
	T2N1	5	11.9%
	T3N1	3	7.1%
	T4N1	1	2.4%

Table 2. Management plan characteristics

		Frequency	Percentage
Breast management (42 Pts)	Mastectomy	5	11.9%
	Wire loc + WLE	3	7.1%
	WLE	34	81%
Axillary management (42 Pts)	SLNB	8	19%
	Failed SLNB+ ALND	5	11.9%
	SLNB+ALND	20	47.61%
	ALND	9	21.42%
Number of SLNs (33 Pts)	0	5	7.1%
	1	6	38.1%
	2	2	33.3%
	3	15	11.9%
	4	5	7.1%
	Mean ± SD	2.27 ± 1.35	

Table 3. Lymph node status after pathological examination

		Negative	Positive	Total
Post-NAC clinical N1 (9 patients)	ALND	1	8	9
Post-NAC clinical N0	Failed SLNB+ ALND	1	4	5
(33 patients)	SLNB< 3 +ALND	5	3	8
	SLNB ≥ 3	8	12	20

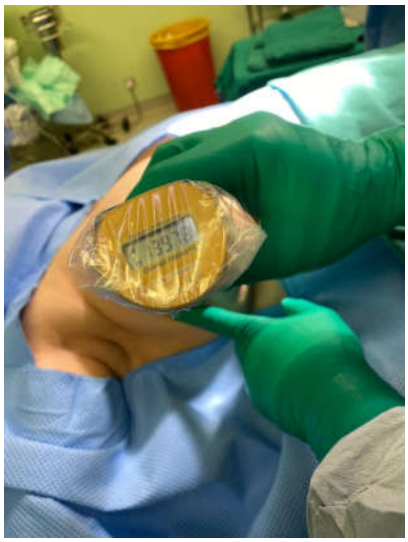

Fig. 4. Photo showing using gamma probe getting the reading before opening the axilla

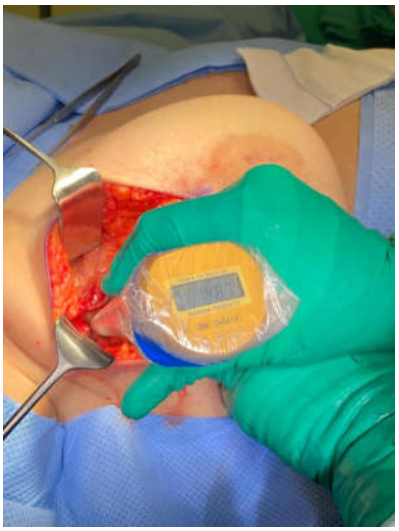

Fig. 5. Photo showing using gamma probe in locating SLN in axilla

All patients who considered having negative axilla after SLNB and spared ALND were put under regular follow up by means of clinical examination, axillary US assessment and FDG-PET scan if clinically indicated. This follow up ranged between 12-40months.

RESULTS

The study included 42 participants who had breast cancer with pathologically proven node positive axilla. The mean age was 50.7 years (range 33-72). The clinical stage of the disease ranged between T1-4, N1-2with N1 representing 71.43% (30 patients) and N2 28.57%. Regarding breast management 34 patients (81%) underwent wide local excision, 3 patients had wire localization and WLE, while 5 patients underwent mastectomy. 33 patients (78.6%) showed axillary conversion to clinical N0 after NAC and were subjected to SLNB, while 9 patients (21.4%) revealed clinically residual nodal disease and underwent ALND that revealed pathologically positive node in 8 patients and pCR in only 1 patient. In 20 patients from the 33 patients who underwent SLNB, 3 or more SLNs were identified while less than 3 nodes were identified in 8 patients, giving a whole identification rate (IR) of 84.8% and a mean number of 2.67 of retrieved nodes (Table).

SLNB was failed in five patients (15.2%) who underwent ALND where it revealed pathologically positive nodes in 4 patients while the fifth showed pCR. All patients with less than 3 SLNs underwent ALND where 5 of them showed pCR and 3 patients showed positive nodes. From the 20 patients who their SLNB yield 3 or more node, positive SLNs identified in 12 while only 8 patients showed negative SLNs and spared ALND giving a percentage of 24% and those patient were put to regular follow up using clinical examination, US assessment and FDG-PET scan if clinically indicated and this follow up ranged between 12-40 months (mean 25.5 months) with no evidence of loco regional recurrence. Tracking the flow chart of the adopted procedure in our study, we can summarize the following results: The IR of SLNB was 84.8%, and the pCR could be assumed to occur in 15 patients from the overall study sample with a percentage of 35%. With SLNB, 8patients (24%) out of 33 were spared ALND.

DISCUSSION

Evaluation of axillary nodal status is a critical prognostic factor in patients with breast cancer and its determination helps in designing treatment protocols. In patients presented with large tumor size or metastasis to axillary nodes neoadjuvant chemotherapy may be considered to downstage the disease facilitating conservative surgery. Precise assessment of axillary nodal involvement following NAC is important; yet, dissecting all nodes to assess for residual disease

exposes patients to some surgical morbidity and, potentially, some will benefit. To parry the complications resulted from ALND, it is better to recognize nodal disease with the less invasive procedure such as SLNB that results in lower morbidity (Veronesi, 2003). This study was conducted to clarify the role of SLNB in patients proved to have node positive breast cancer and received NAC with the assumption that earlier studied tested the same issue may need some modifications or incorporation of multiple recommendations from these studies that may abolish drawbacks resulted in each of them on its own. It is well known that SLNB in node-negative patients is a standard procedure now, while it is not the same for node positive patients where ALND still considered the standard of care. Many studies indicated that NAC resulted in clinical nodal conversion from positive to negative, ACOSOG Z1071 showed a conversion rate of 83% (Boughey, 2013). In our series of 42 patients the clinical nodal conversion rate was 78.6% and this could be comparable if we consider the big difference in studied population size. ACOSOG Z1071 carried out their SLNB procedure on all enrolled patients after NAC regardless of their new clinical nodal status, but at its end results the researchers recommended not to perform the procedure on patients with clinically residual nodal disease (Boughey, 2013). In our study we follow such recommendation omitting 9 patients with clinically palpable axillary nodes after chemotherapy and their pathological examination after ALND showed metastasis to 8 of them with only one patient showed pCR. In our study the identification rate of SLN was 84.8% using dual mapping method and this is comparable to what was reported in SENTINA trial by Kuehn T and his colleagues where they find a SLN identification rate of only 80%, with improvement on the use of dual radiolabelled colloid and blue dye compared to radiolabelled colloid alone (88% versus 77%) (Kuehn, 2013). The mean number of retrieved SLNs in our series was 2.67 nodes (range 1-4) and this is comparable to other studies where SLNB undertaken after NAC for positive axilla. False negative rate is a crucial output that resulted in non-recognition of SLNB as a standard procedure in nodal positive patients and every effort is to be paid to lower this rate to minimum following recommendations of earlier large scale trials. From these trials ACOSOG Z1071, SENTINA and SN FNAC, FNR found to be 10.8%, 8.6% and 5.2% respectively when using dual mapping method. Also when more than 2 SLNs were identified the FNR for these studies in order found to be 12.6%, 9.6% and 4.9% (16).So, we assume that our FNR reproducing theses 2 measures in considering SLNB will be of comparable results. Shen J *et al*, reported that Anthracyclines and taxane-based NAC have been shown to clear nodal metastasis in nearly 30% to 40% of patients (11).The current study showed an assumed pCR in 15 patients representing 35% of our studied population. Conducting SLNB in 33 patients with post-NAC clinically axillary conversion using dual method and mandating retrieval of more than 2 SLNs resulted in sparing 8 patients from ALND representing 24% of candidate patients.

Conclusion

SLNB is a useful option after NAC in patients initially proved to be node-positive breast cancer, given the high node-conversion rate. Although the FNR is presumed to be higher than desired with theoretical chance to increase local recurrence, still it has no effect on chemotherapy decision-making, and mostly will not influence the overall survival. Yet, there are multiple measures that can be adopted to increase its precision: Selecting patients who show high probability to give nodal complete response after chemotherapy namely triple negative and HER2 positive. Also patients with normal axillary US following NAC and those who show good metabolic response on FDG-PET scan if available. Using dual mapping increase the yield of SLNs reducing FNR, and retrieval of 3 or more SLNs when possible with clipping of the initial positive node or marking it with radioactive seeds and making every effort to include it in the excised SLNs. Finally pathological evaluation of the SLNs and assigning positivity may be refined to include ITC and micro metastasis using IHC.

Conflict of interest: None.

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