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Evaluation of Sentinel Lymph Node Biopsy after Neoadjuvant Therapy for Breast Cancer Patients with Positive Axillary Nodes: A Multicenter Study

Sherif M. Elkaffas[1], Emad M. Abdelrahman[1], Eman Ibrahim Elgendy[2], Salah-El-din Sayed Omar Semary[3], Refaat S. Salama[1]

Departments of [1] General Surgery, [2] Pathology, Faculty of Medicine, Benha University, Egypt

[3] Pathology Department, Faculty of Medicine, Al-Azhar University, Dameitta, Egypt

Corresponding Author: Emad M. Abdelrahman, Email: emadshan301@gmail.com**,**

Tel: O1226763986, **ORCID:** https://www.orcid.org/0000-0001-6066-2215

ABSTRACT

Background: With the advancement of breast cancer treatment, sentinel lymph node biopsy (SLNB) might take the place of conventional axillary lymph node dissection (ALND) in many clinical scenarios.

Objective: The current study aimed to evaluate SLNB in patients with early-stage breast cancer (BC) whose axilla shown complete clinical and radiological response after neoadjuvant chemotherapy (NAT).

Patients and Methods: The study included 96 patients with early BC and positive axilla showing complete clinical and radiological response after neoadjuvant therapy,and underwent SLNB before performing axillary lymph node dissection. Both specimens were examined by frozen section (for SLNB) and paraffin (for both specimens).

Results: The mean age of the patients was 47.6 ±13.41 years. No significant difference was present when comparing the results of the frozen section of SLN, the paraffin section of SLN, and the paraffin section of the axilla as regards % of +ve and -ve cases. The specificity, negative predictive value, and accuracy between the frozen section and paraffin section (axilla) taking the paraffin section (SLN) as a gold standard were insignificant while the sensitivity of the frozen was significantly higher while the positive predictive value of the paraffin section (axilla) was significantly higher.

Conclusion: SLNB can replace ALND in breast cancer patients with +ve axillary nodes without affecting the oncologic safety.

Keywords: Breast cancer, SLNB, ALND, Neoadjuvant therapy

INTRODUCTION

Breast cancer (BC) is the most frequent type of cancer in women worldwide presenting around 18-23 % of all malignancies in females and 18.2% of all cancer-related deaths worldwide. First of all, unfortunately, this disease's therapy is complicated by its late detection [(1)].

During axillary lymph node dissection (ALND), the axilla is explored, and axillary lymph nodes are located and removed. For many years, axillary dissection was thought to be the gold standard method for managing and staging the axilla in BC patients [(2)].

Sentinel-node biopsy (SLNB) was introduced, and it revolutionized the way axillary surgery was done since it allowed for axillary staging with far lower morbidity and consequences than with normal ALND. These days, axillary dissection is only performed in cases where sentinel node biopsy results are positive or where preoperative axillary metastases have been verified. It is considered overtreatment of at least 60% of node-negative patients to use ALND as the main therapeutic option in patients with positive lymph nodes and to execute ALND in all those individuals [(3)].

With a demonstrated efficacy comparable to adjuvant treatment, the applications and value of neoadjuvant therapy (NAT) for breast cancer have grown [(4)]**.** The ideal time for SLNB is still up for debate, though. Axillary clearance is still advised in all cases where neoadjuvant therapy (NAT) was used to downstage breast cancer lesions, with the exception of situations in which a sentinel node biopsy results in a negative result prior to the initiation of neoadjuvant chemotherapy [(3)]**.**

Following NAT, pathological complete response (PCR) has been established in 20–40% of cases, and this percentage continues to rise with the use of targeted therapies. These outcomes are ultimately linked to improved prognoses and overall survival [(5)]**.**

While several writers considered the SLNB to be a valid staging evaluation of the axilla following NAT [(6,7)]**.** Some studies still advise against using this method [(3)]**.**

Our study's goal was to determine whether SLNB, as opposed to standard ALND, may be used to treat axilla in breast cancer patients who demonstrate PCR following NAT.

PATIENTS AND METHODS

The current retrospective study was conducted between October 2021 to March 2024, in the Department of General Surgery at Benha University Hospitals. Patient selection was done through the multi-disciplinary team in the breast unit and every case was discussed individually.

The current study included 96 female patients with early stages of BC (cT1/cT2) and +ve axillary lymph nodes (cN1/2) rendered cN0 after NAT. All patients included in the study were ASA-I or II.

In compliance with the adopted protocol for cases of early breast cancer, 4 - 6 cycles of NAT were received then the breast Sono mammography was repeated to ensure a

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radiologically negative axilla (complete radiological response).

Intraoperatively, patients underwent SLNB using 1 cm of patent blue dye injected retro areolar at 3, 6, 9, 12 o'clock (**Figure 1**) then massage to the whole breast was done for 15-20 minutes. After identification and removal of SLN (number 3-4 lymph nodes) within the context of the predetermined oncoplastic procedure for the patient during the MDT meeting (whether via the same incision or a separate incision at the axilla), intraoperative frozen section and postoperative paraffin histopathological examination (**Figure 2, 3**) were done. Formal axillary clearance (AC) was then done to assess the safety and accuracy of SLNB. A suction drain was left in the axilla.

Figure 1: Injection of the dye.

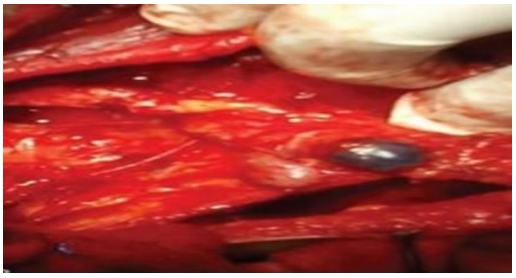

Figure 2: identification of the SLN.

Figure 3: Dissection of the SLN.

Five main Diagnostic Parameters of Frozen and Paraffin sections were assessed: Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV), and **diagnostic accuracy**.

Outcomes and follow-up:

The primary outcome was proper management of patients with breast cancer on the basis of oncological safety and minimal postoperative complications.

The secondary outcome was to detect the accuracy of frozen section in comparison with the paraffin section analysis to avoid unnecessary dissection with its subsequent complications.

The postoperative reviewing of the patients was performed in the outpatient clinic after one week and two weeks for assessment of the presence of postoperative complications and to plan the adjuvant therapy then reviewing was performed monthly for 3 months. Complications were recorded and assessed. The drain was removed when drain efflux was less than 50 cc/24 hours.

Ethical approval:

The current study was conducted after approval of the Ethical and Research Committee at Benha University. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki). Informed written consent was obtained from all included patients.

Statistical Analysis

Sample size:

Using G-power 3.1 software (Universities, Dusseldorf, Germany), a sample size of 96 was taken into consideration with a power of 80% and an effect size of 0.7.

Qualitative parameters were expressed as frequency with percent and were compared by chi^2 test. Quantitative factors were reported using mean and standard deviation (SD). The statistical package used was SPSS-21 (Statistical Package for the Social Sciences, version 21, Armonk, NY: IBM Corp, USA). spearman linear correlation between the quantitative variables—that is, the positive and negative cases in the paraffin section SLN and the cases in the frozen section (SLN) and the paraffin section (axilla)—was measured using the rank correlation coefficient (r). The P value of less than or equal to 0.05 was designated as the significance level.

Five main Diagnostic Parameters of Frozen and Paraffin sections were assessed: Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV), and **diagnostic accuracy**.

RESULTS

The current study included 96 female patients with early stages BC (T1, T2) and +ve axillary lymph nodes (cN1/2) who were rendered cN0 after neoadjuvant therapy. The mean age was 47.6 ±13.41 years. Positive family history was present in 67.7% of cases. 69.8 % of the tumors were in the upper outer quadrant. The mean tumor size was 3.23± 0.64 cm. Other sociodemographic data and tumor characteristics were reported in **table 1.**

Table 1: Sociodemographic data and tumor characteristics

Variables		**N= 96**
Mean age	Mean ±SD (years)	47.6 ±13.41
BMI	Mean ±SD (kg/m^2)	30.7± 2.89
Family history		
• Negative	n (%)	31 (32.3%)
• Positive	n (%)	65(67.7%)
BIRADS classification		
• 4	n (%)	63 (65.6%)
• 5	n (%)	33 (34.4%)
Tumor side		
• Right	n (%)	59 (61.5%)
• Left	n (%)	27(38.5%)
Tumor location		
Upper outer quadrant	n (%)	67 (69.8%)
Lower outer quadrant	n (%)	17(17.7%)
Upper inner quadrant	n (%)	8 (8.3%)
Lower inner quadrant	n (%)	4 (4.2%)
Tumor size	Mean ±SD (cm)	3.23± 0.64
Pathological tumor type		
Invasive ductal carcinoma **(Figure 4)**	n (%)	76 (79.2%)
Invasive lobular carcinoma **(Figure 5)**	n (%)	20 20.8%)
TNM classification		
• T1	n (%)	51(53.1%)
• T2	n (%)	43 (46.9%)
• N1	n (%)	54 (56.25%)
• N2	n (%)	41 (43.75%)
• M0	n (%)	96 (100%)
Biological classification		
• Luminal A	n (%)	15(15.65%)
• Luminal B	n (%)	13 (13.55)
• HER 2 neu	n (%)	36 (37.5)
• Triple negative	n (%)	32(33.3)
Neoadjuvant chemotherapy	n (%)	96(100%)
Number of SLN		
• 3	n (%)	52 (54.1%)
• 4	n (%)	44(45.9%)

There was no statistical difference, comparing the results of frozen section of SLN, paraffin section of SLN and paraffin section of axilla as regards % of +ve and -ve cases **(Table 2).**

Table 2: Comparison between frozen section and paraffin section (SLN and axilla)

	Frozen section (SLN)	Paraffin section (SLN)	Paraffin section (axilla)	P-value
Negative	67 (69.8%)	73 (76%)	80 (83.4%)	
Positive	29 (30.2%)	23 (24%)	16 (16.7%)	0.087

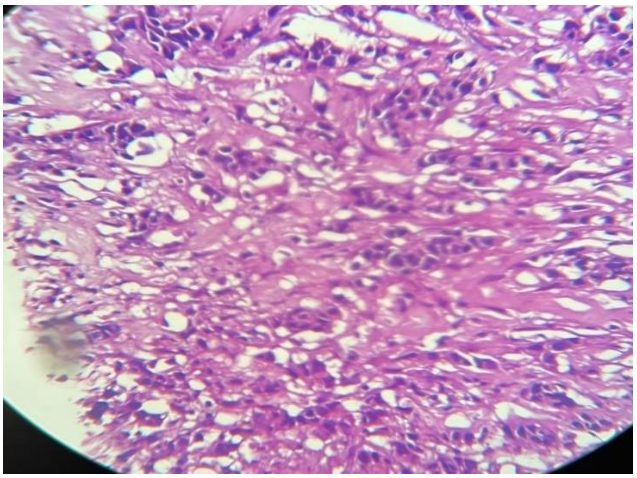

Figure 4: Invasive duct carcinoma with a +ve resection margin (H&E, 20x).

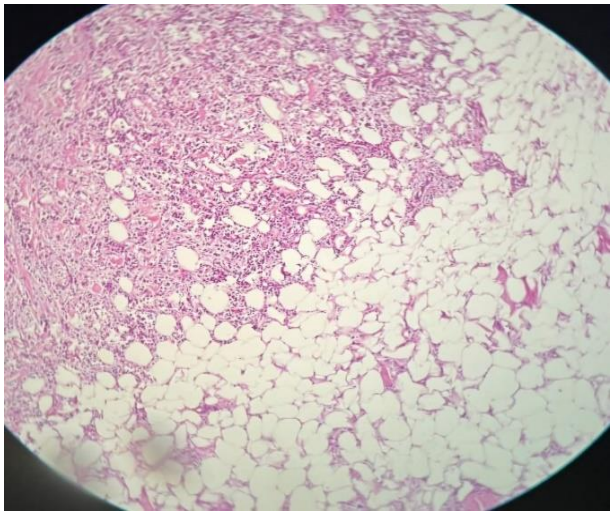

Figure 5: infiltrating lobular carcinoma with a negative resection margin (H&E, 10x).

Table 3 shows a strong positive correlation between positive and negative cases in the paraffin section SLN the frozen section (SLN) and between the paraffin section SLN and paraffin section (axilla).

Table 3: Correlation paraffin section SLN with frozen section and paraffin section (axilla) among the patients taking the paraffin SLN as gold standard

		Paraffin section SLN		**r**
		Negative	**Positive**	
		No. = 73 (76%)	No. = 23(24%)	
Frozen section (SLN)	**Negative**	65 (69.8%) **True -ve**	2 (0%) **False -ve**	0.913
	Positive (Figure 6)	8 (6.25%) **False +ve**	21 (24%) **True +ve**	
Paraffin section (axilla)	**Negative**	76 (76%) **True -ve**	4 (7.4%) **False -ve**	0.837
	Positive	2 (0%) **False +ve**	14 (16.7%) **True +ve**	

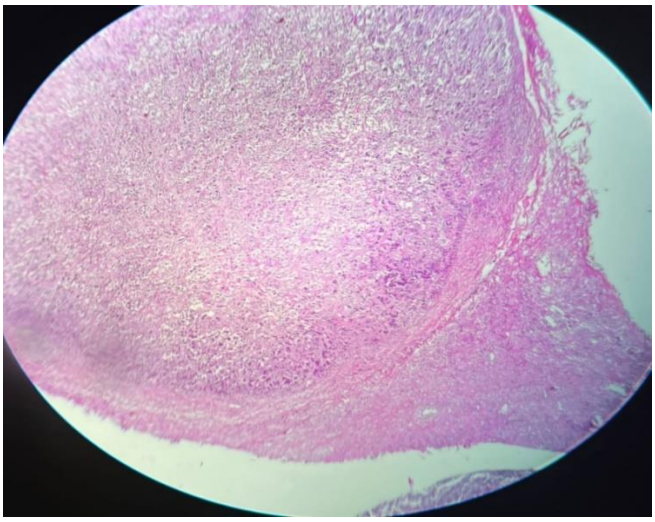

Figure 6: sentinel lymph node involved by metastatic lobular carcinoma (H&E, 10x).

The specificity, NPV, and accuracy between the frozen section and paraffin section (axilla) taking the paraffin section (SLN) as a gold standard were insignificant. At the same time, the sensitivity of the frozen was significantly higher while the PPV of the paraffin section (axilla) was significantly higher **(Table 4).**

Table 4: Diagnostic accuracy of frozen section (SLN) and paraffin section (axilla) taking paraffin section (SLN) as a gold standard.

Variable	Frozen section	Paraffin Axilla	P value
Sensitivity	91.3%	77.8 %	0.001*
Specificity	89%	97.4%	0.072
PPV	72%	87.5 %	0.001*
NPV	97%	95 %	0.21
Accuracy	89.6%	93.8 %	0.35

*: Significant.

DISCUSSION

Worldwide, BC is the most common 1ry cause of cancer-related deaths in women representing 22.9% of all invasive cancer cases [(1)]. SLNB after NAT can be employed to prevent the non-therapeutic ALND linked to increased morbidity and complications in 30 to 40% of individuals radiologically demonstrating CR following NAT. The mean age of the patients in the present study was 47.6± 13.41 years, and 69.8% of the included patients, the tumor was allocated in the upper outer quadrant. This is comparable to the American Cancer Society's published data, which states that the mean age of breast cancer 50 years, with about 70% of them falling into "the upper outer quadrant" [(8,9)]. The SLN is the lone tumor-bearing node in 60% of overall cases and in 90 % of individuals with only micrometastatic disease. These findings have raised the possibility that in certain cases with a +ve SLNB in fewer than 3 nodes, completion of ALND may not be required because systemic therapy is clearly required and the probability of an axillary recurrence seems to be minimal [(10)].

Numerous investigations have demonstrated that the data on the assessment of frozen sections is becoming better, indicating that the intraoperative evaluation of nodal tumor load is adequate, if not superior. Few concerns are about that it takes up more specimen than cytological examination. The accuracy of frozen section analysis in conjunction with H&E staining and immunohistochemistry on SLN ranges from 73 to 96%, according to an examination of numerous published data [(11)]. The results of the classical axillary dissection, which was completed to evaluate the safety and accuracy of SLNB, were sent for paraffin section and showed a slight difference but still statistically insignificant between the results of positivity and negativity of both SLNs and the remaining lymph nodes after ALND. Of the 96 patients in the current study, 76% had negative lymph nodes, and the remaining 24% had positive lymph nodes.

Several variables influence the accuracy and success of sentinel lymph nodes. When combined, using a dual tracer that combines a radiolabeled colloid with a patent blue dye, enhances the number of SLNs discovered and decreases false negative findings. Recent guidelines recommend completing ALND only for patients with more than 2 +ve LNs. Most women who meet specific criteria, such as having a T1-2 tumor, 1-2 +ve LNs, no prior NAT, and planned Breast-conserving surgery with whole breast irradiation, should not undergo ALND [(12-15)].

The advice that micrometastases at SLNB should no longer be suggested for ALND is not yet supported in certain areas. Regardless of the type of breast surgery offered, the St. Gallen Consensus Conference (2011) took a more cautious stance and recommended that micrometastases in a single SLN should not be a cause for ALND. According to ASCO practice guidelines, individuals with micrometastatic and even 1-2 macro metastatic positive SLNs can now forego the ALND [(16)]. In contrast, the Consensus of SLN in Mammary Carcinoma was issued by the Venezuelan Mastology Society. In all cases of macrometastasis, it suggested executing ALND; in cases of micrometastasis, it leaves the choice up to each working group.

One of the cornerstones in the clinical practice is the sensitivity and specificity of the frozen section, in the present study it was reported to be 91.3% and 89% respectively and this was different with a recent meta-analysis conducted by **Elshanbary *et al.*** [(17)] who reported a sensitivity of 74.7% and a specificity of 99.4%. This is assumed to be due to inclusions of many researches in their meta-analysis with different inclusion criteria and different sample sizes. Also, the current result reported higher sensitivity and NPV than what was reported by **Arora *et al***. [(18)], who described the sensitivity, and NPV

of 81.25% and 92.73%, although the same study reported higher specificity and PPV than what was reported in the present study. This can be explained as the standard NAT applied to the patients in the present study changed clearly the numbers of true and false +ve and -ve cases with subsequent change in all parameters of the assessment.

In the present study taking in consideration the paraffin SLN as a gold standard, there was no significant difference between the specificity, NPV or even the accuracy between the paraffin axilla and the frozen SLN. Even the frozen SLN reported higher sensitivity than the paraffin axilla confirming the standard guideline that don't recommend ALND

Our findings indicate that SLNB is acceptable in cN1/2 patients who were rendered cN0 after NAT, particularly in patients with no residual disease in the breast, because SLN status retains its expected prognostic role, and even in cases with residual disease, because ALND has no effect on outcomes.

This study has several limitations. A bigger sample size would have been advantageous to corroborate the results of our result regarding the accuracy of SLNB.

CONCLUSION

SLNB can replace ALND in breast cancer patients with +ve axillary without affecting the oncologic outcomes and acceptable false negative results and avoiding the complications of ALND particularly in cases with clinical and radiological complete response (c/rCR) following neoadjuvant therapy (NAT).

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REFERENCES

1. **Łukasiewicz S, Czeczelewski M, Forma A *et al.* (2021):** Breast cancer-epidemiology, risk factors, classification, prognostic markers, and current treatment strategies-An updated review. Cancers (Basel), 13(17): 4287-94.
2. **Ibrahim A, Khaled H, Mikhail N *et al.* (2014):** Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol., 2014:437971.
3. **Canavese G, Bruzzi P, Catturich A *et al.* (2016):** Sentinel lymph node biopsy versus axillary dissection in node-negative early-stage breast cancer: 15-year follow-up update of a randomized clinical trial. Ann Surg Oncol., 23(8):2494-500.
4. **Esserman L, Berry D, De Michele A *et al.* (2012):** Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL--CALGB 150007/150012, ACRIN 6657. J Clin Oncol., 30(26):3242-9.
5. **Shin H, Han W, Moon H *et al.* (2013):** Breast-conserving surgery after tumor downstaging by neoadjuvant chemotherapy is oncologically safe for stage III breast cancer patients. Ann Surg Oncol., 20(8):2582-9.
6. **Rubio I (2016):** Sentinel lymph node biopsy after neoadjuvant treatment in breast cancer: Work in progress. Eur J Surg Oncol., 42(3):326-32.
7. **Kuehn T, Bauerfeind I, Fehm T *et al.* (2013):** Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol., 14(7):609-18.
8. **DeSantis C, Ma J, Jemal A (2019):** Trends in stage at diagnosis for young breast cancer patients in the United States. Breast Cancer Res Treat., 173(3):743-747.
9. **Rummel S, Hueman M, Costantino N *et al.* (2015):** Tumour location within the breast: Does tumour site have prognostic ability? E cancer medical science, 13(9):552-9.
10. **Jeruss J, Winchester D, Sener S*et al.* (2005):** Axillary recurrence after sentinel node biopsy. Ann Surg Oncol., 12(1):34-40.
11. **Rahman M, Mohammed S (2015):** Breast cancer metastasis and the lymphatic system. Oncol Lett., 10(3):1233-1239.
12. **Coufal O, Zapletal O, Gabrielová *et al.* (2018):** Targeted axillary dissection and sentinel lymph node biopsy in breast cancer patients after neoadjuvant chemotherapy - a retrospective study. Rozhl Chir., 97(12):551-557.
13. **García-Moreno J, Benjumeda-Gonzalez A, Amerigo-Góngora M *et al.* (2019):** Targeted axillary dissection in breast cancer by marking lymph node metastasis with a magnetic seed before starting neoadjuvant treatment. J Surg Case Rep., 4(11):344-9.
14. **Huober J, von Minckwitz G, Denkert C *et al.* (2010):** Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat., 124(1):133-40.
15. **Lyman G, Temin S, Edge S*et al.* (2014):** American Society of Clinical Oncology Clinical Practice. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol., 32(13):1365-83.
16. **Esposito E, Sollazzo V, Di Micco R *et al.* (2016):** Can axillary node dissection be safely omitted in the elderly? A retrospective study on axillary management of early breast cancer in older women. Int J Surg., 33(1):114-8.
17. **Elshanbary A, Awad A, Abdelsalam A *et al.* (2022):** The diagnostic accuracy of intraoperative frozen section biopsy for diagnosis of sentinel lymph node metastasis in breast cancer patients: a meta-analysis. Environ Sci Pollut Res Int., 29(32):47931-47941.
18. **Arora A, Chauhan N, Saini S *et al.* (2019):** Is there a role of frozen section of sentinel lymph node in patients with early breast cancer for the management of axilla in India: a prospective study. Int Surg J., 6(6):2126-2132.