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False Negative Rate of Sentinel Lymph Node Biopsy (SLNB) in Breast Cancer Patients after Neoadjuvant Chemotherapy

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ABSTRACT

Background: Managing the axilla in patients with node-positive breast cancer who converted to node-negative after neoadjuvant chemotherapy is a challenging issue. We aimed to analyze the false negative rate (FNR) of SLNB after neoadjuvant chemotherapy (NAC) in this group of patients.

Methods: In this cross-sectional study, we reviewed the results of SLNB and ALND in 368 breast cancer patients who underwent neoadjuvant chemotherapy from 2015 to 2019. The study included patients with pathologically proven axillary lymph nodes undergoing NAC. We collected the data from the Breast Diseases Research Center of Tehran University of Medical Sciences.

Results: The average age of the patients was 46.58±10.91. Of all the patients, 205 (55.7%) had positive SLN in the histologic analysis after surgery, while 163 (44.3%) had negative results. The study also revealed that the FNR of SLNB was 9.8% (n=16). Our results showed that SLN had 86.55% sensitivity and 100% specificity in detecting the involved nodes. Furthermore, after multivariable analysis, we observed that the higher number of ALND dissections was associated with a higher FNR OR=1.21, 95% CI: 1.01-1.45); while the higher number of SLN excisions was linked with a lower FNR (OR=0.42; 95% CI: 0.18-0.97).

Conclusion: After NAC in breast cancer patients with positive lymph nodes, SLNB is feasible with a low FNR; the latter is correlated with the number of nodes removed during the procedure.

INTRODUCTION

Sentinel Lymph Node biopsy (SLNB) has become a standard technique for axillary staging in early breast cancer. It has replaced complete axillary lymph node dissection due to an accuracy rate above 90% in predicting axillary lymphatic involvement. A false negative SLNB is defined when the sentinel lymph nodes (SLN) are reported to be negative in the histological assessment, but other axillary nodes harbor cancer cells.

According to a meta-analysis of 183 articles involving 9306 patients, the false-negative (FN) rate (FNR) of SLNB ranged from 4.6% to 16.7%[1], with an average of 7.5%.[2] A prospective multi-center study

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showed that different factors like tumor size, location, and surgeon experience can affect the rate of FNR 3, and patients who undergo neoadjuvant chemotherapy (NAC) before SLNB may have a higher FNR. 4 This may be due to several factors. First, NAC can cause the lymphatic pathways to be altered due to the formation of granulation tissue, fat necrosis and fibrosis; therefore, the mapping agent might be delivered to a non-sentinel node in the axilla. Second, the tumor emboli or cellular materials could block the lymphatic channels. 5 Third, while NAC may cause regression of the tumor in some SLNs, it may not do so in other nodes. Therefore, a negative SLN could be found even though there are other involved nodes in the axilla.

Some studies have reported no difference in the FNR of SLNB in patients treated with NAC compared to those who had upfront surgery.6 However, it should be kept in mind that chemotherapy can alter the lymphatic pathways by fibrosis or tumor emboli, and that finding a sentinel node without treatment effects after NAC in a patient with a previously pathologic positive node may imply a false negative result. 7

With the increasing use of NAC, it has become essential for every breast care unit to analyze its institutional accuracy and compare it with international standards. This study aimed to investigate the false negative (FN) rate of SLNB after NAC in patients who were initially node-positive but converted to node-negative by the treatment.

METHODS

This cross-sectional study received approval from the ethics committee of Imam Khomeini Hospital of Tehran University of Medical Sciences (Ethics No # IR.TUMS.IKHC.REC.1402.311). It was financially supported by the Vice President of Research of Tehran University of Medical Sciences under Code No# 1402-3-259-32908. The study included breast cancer patients with histologically-proven positive axillary lymph nodes who had undergone SLNB and an axillary lymph node dissection (ALND) after NAC between 2015 and 2019, and had been operated by the first author in a private center. The collected data included the patient's age at the time of surgery, pathologic tumor size, Ki67%, breast involvement side, family history of breast or ovarian cancer, type of surgery, lymphovascular invasion (LVI), and the number of extracted and involved lymph nodes in SLNB and ALND. Using the convenience sampling method, only patients with available information about the timing of chemotherapy, SLNB, and ALND were included in the study. The patients that had positive lymph nodes in their ultrasound examination after neoadjuvant chemotherapy were excluded.

All of Her-2 positive patients received TCH (Taxotere, Carboplatin, Herceptin) with or without Pertuzumab, due to insurance and drug access limitations. Luminal subtype and Triple-negative cases received ACT (Adriamycin, cyclophosphamide, Taxol) chemotherapy regimen. All of the patients underwent surgery 3 to 4 weeks after completing NAC. Patients with clipped positive lymph nodes or pre-chemotherapy were excluded. A dual tracer technique was used for all SLNBs. During surgery, the detected sentinel nodes were sent for frozen section examination. The SLNs were considered positive if the isolated tumor cells, micrometastases, or macrometastases were detected in the frozen or permanent histological exam.

ALND was performed in all patients with any residual tumor in SLN or when only one or two negative nodes were found during the operation. All the excised lymph nodes were assessed by H&E staining in the permanent histology examination.

Sample size calculation

According to most previously published studies, we estimated that the actual prevalence of FNR might not be more than 15%. With 5% precision and a type-1 error of 5%, at least 196 patients were needed in this study. During the four-year study period, 368 patients met the inclusion criteria.

Statistical analysis

The SPSS software (version 18, IBM Inc. NY) was used for statistical analysis. The mean ± standard deviation for continuous variables and percentage for categorical variables have been reported. Continuous variables and categorical variables were compared between groups using Student-T-test and Chi-square test, respectively. Sensitivity, specificity, and accuracy of SLN after NAC were calculated considering ALND results per patient using an online calculator (https://www.medcalc.org/calc/diagnostic_test.php). Multivariable logistic regression analyses were conducted considering false negative results (False/True) as the dependent variable. Independent variables included age (continuous variable), pathologic tumor size (continuous variable), Ki-67% (continuous variable), SLN and ALND excised (continuous variable), and LVI (Yes/ No). These variables were selected in the final analysis based on univariable results (P-value $\leq$ 0.2). A P-value less than 0.05 was considered significant.

RESULTS

The final analysis was conducted on 368 patients whose average age was 46.58 ± 10.91 (with a range of 18 to 79 years). The median pathologic tumor size

(mm) was 15 with a 23.5 interquartile range (IQR). The characteristics of these patients are shown in Table 1. Of the 368 patients who underwent histological analysis of their SLNs, 205 (55.7%) had positive SLN in the histologic analysis after surgery, while 163 (44.3%) had negative results. The FNR of SLN was 9.8% (n=16) as shown in Figure 1.

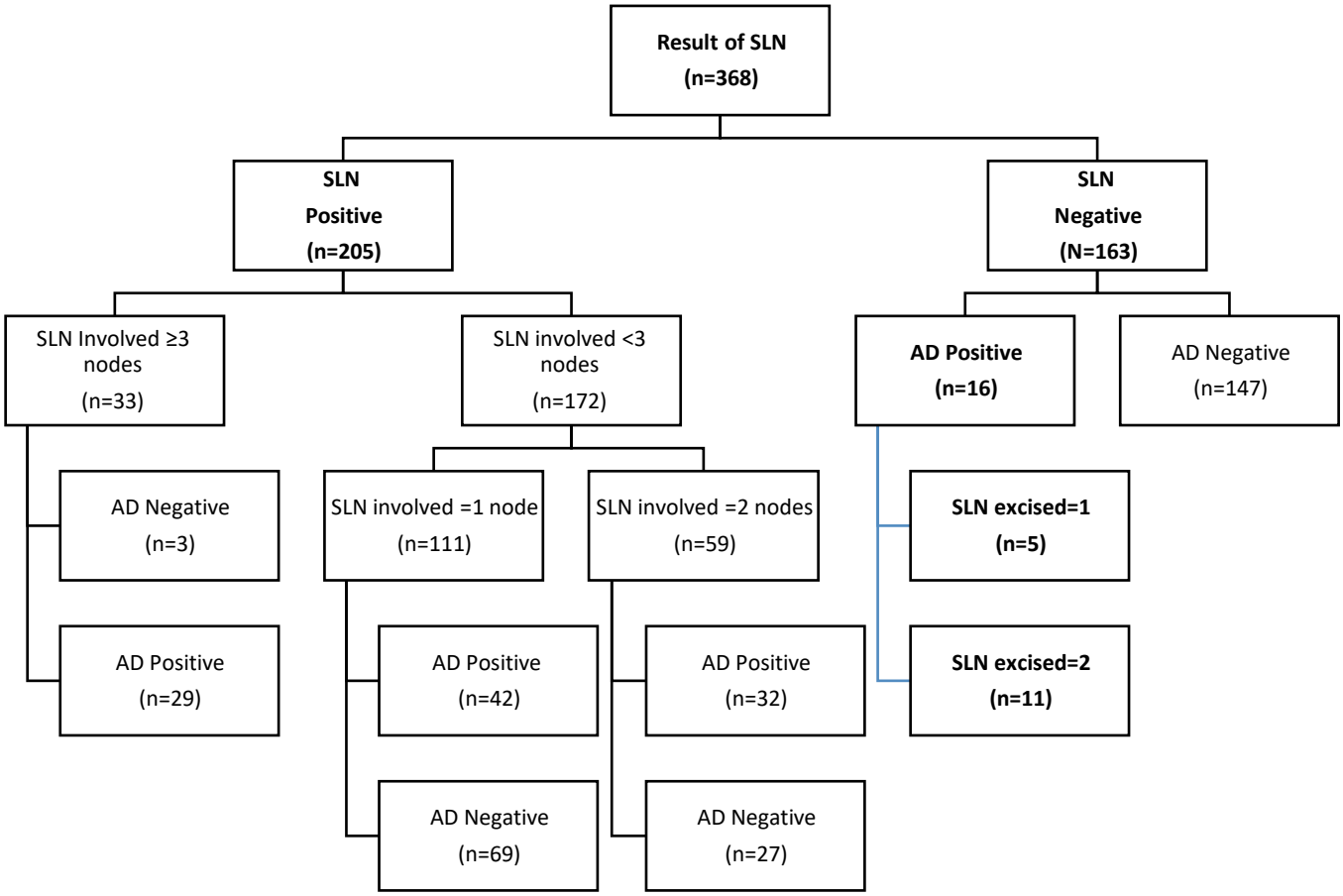

Figure 1. The results of SLN (Sentinel lymph node dissection) and AD (Axillary Dissection).

Among the 16 cases with FN results, five had one involved node while the rest had 2 involved nodes (Figure 1) in ALND. Table 2 shows the sensitivity, specificity and accuracy of SLN after NAC. The results of crude and adjusted analysis about the effective pathologic factors on FNR were reported in Table 3. According to the final analysis, the higher number of ALND dissections were associated with a higher FN (Odds ratio; OR=1.21, 95% CI: 1.01-1.45); while the higher number of SLN excisions was linked with a lower FN rate (OR=0.42; 95% CI: 0.18-0.97).

DISCUSSION

Our study revealed that 9.8% of breast cancer patients with pathologically proven positive axillary nodes experienced a false negative SLNB after NAC. Small-scale studies evaluating SLNB after NAC in patients with biopsy-proven cN1 have shown various results.[4,8]

The GANEA study [9] examined the safety of SLN biopsy in a large number of patients with early breast cancer after NAC. The study included 419 women and the false negative rate was found to be 9.4% in node-negative and 15% in node-positive patients. The overall FNR was 11.5%. Also, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial[10] included both cN0 and cN1 disease and reported an SLN FNR of 10.7% after chemotherapy.

Three large trials in Europe, USA, and Canada evaluated the FNR of SLNB after NAC in women initially presenting with biopsy-proven node-positive breast cancer. [11-13]

The SENTINA study in Europe [11] was conducted in 103 different centers in Germany and Austria and

evaluated 1737 patients who underwent NAC. In this study, SLNs were identified in 80.1% of the patients who converted from CN+ to YCN0 after NAC, and FNR was 14.2%. The FNR was 24.3% when only one SLN was removed, and it dropped to 18.5% when two SLNs were found.

Table 1. Baseline characteristics of 368 breast cancer patients.

Variable	(mean ± SD)/ Number (percentage)
Age (yrs)	46.58 ± 10.91
Involved breast	
Right	170 (46.2%)
Left	198 (53.8%)
Family History of BC or OC	
Yes	158 (42.9%)
No	210 (57.1%)
Metastasis	
Yes	56 (15.2%)
No	312 (84.8%)
Type of surgery	
BCS	116 (31.5%)
BCS + Oncoplastic	34 (9.2%)
Mastectomy	202 (54.9%)
Others	13 (3.5%)
Pathologic Type	
IDC	320 (87%)
DCIS	8 (2.2%)
ILC	13 (3.5%)
Unknown	27 (7.3%)
LVI	
Yes	167 (45.4%)
No	73 (19.8%)
Unknown	128 (34.8%)

BC= Breast cancer; OC= Ovarian cancer; BCS= Breast conserving surgery; IDC= Invasive ductal carcinoma; DCIS= Ductal carcinoma in situ; ILC= Invasive lobular carcinoma; LVI= Lymphovascular invasion.

ACOSOG Z1071 from America (the Alliance trial) [12] recruited 756 women from 136 institutions, of whom 649 had SLNB and ALND following NAC. The FNR was 12.6%, which means that positive nodes were found in ALND despite the presence of negative SLN(s) in 39 patients.

The SNFNAC study in Canada [13] recruited 153 patients, and the SLNs were assessed by immunohistochemistry (IHC). Any size of metastases including isolated tumoral cells was considered positive, and the FNR decreased from 13.3% to 8.4% by using IHC.

When only one SLN is removed, FNR tends to be high. Patients with only one SLN constitute 31% of patients in SENTINA, 20.4% in ALLIANCE, and 26.5% in SN FNAC. In a subgroup of patients with at least three SLNs removed, the FNR decreased to 8.6% in SENTINA and 9.1% in the ALLIANCE trial. In our study, all of the patients with only one or two SLN(s) underwent ALND because of the probability of a high FNR. Only patients with three negative SLNs were spared from ALND.

In line with the above trials, a meta-analysis by Nijnatten [14] showed that FNR was worse if only one SLN was removed compared to two or more SLNs (23.9% vs 10.4%). In addition to harvesting more than one SLN and IHC assessment of the SLNs, the use of dual tracer during SLNB and clipping or marking the positive nodes before NAC could decrease the FNR.

In a meta-analysis by Tee *et al.* [15], 1921 breast cancer patients were included. The FNR of SLNB using a dual tracer was 11% compared with 19% with a single tracer. The FNR was 20% when only one SLN was removed, and dropped to 12% and 4% when two and three SLNs were harvested, respectively. Similarly, a recent study showed that removing three or more SLNs after NAC in breast cancer patients decreased the FNR from 19.1% to 8.7%. [16]

Table 2. Sensitivity, specificity, and accuracy of SLN after NAC in pathologically proven axillary lymph nodes.

TP	FP	FN	TN	Sen (95% CI)	Spec (95% CI)	Accuracy (95% CI)
103	0	16	147	86.55 (79.09-92.12)	100 (97.52-100)	93.98 (90.42-96.52)

TP= True negative; FP= False positive; FN= False negative; TN= True negative; Sen= Sensitivity, Spec= Specificity, CI=Confidence interval.

We used dual mapping in all of our patients, but we excluded the patients who had undergone targeted axillary dissections, because marking or clipping involving axillary lymph nodes is not done routinely in many centers before or during NAC.

All SLNs in our study were examined by H&E, and IHC was used only in a minority with suspicious H&E results. In comparison with other studies, our FNR was lower than expected, especially considering our inclusion criteria that enrolled only patients with one or two negative SLNs. The subgroup analysis of the 14 patients with FNR considering the number of SLNs had no significant results.

Our FNR is very close to the value reported in Lazar's study which found an identification rate of 93.13% with a FNR of 7.4% for SLNB after NAC in 102 breast cancer patients in a tertiary single center. [17]

We found a relation between a larger post-NAC residual tumor in the primary site and FNR. This

association was also detected by Ozmen in 2009 in a study on 77 locally advanced breast cancer patients who had received NAC, where a higher FNR was found in patients with tumors larger than 2 cm. [18]However, this finding must be considered with caution because of the small sample size, especially given the previous studies that showed an indirect association between tumor size and the FNR of SLNB. [3, 19] Future studies with larger sample sizes could clarify this association.

Table 3. Result of binary logistic regression analysis of effective variables on negative result of SLN (False /True).

Variables	Crude OR (95%CI)	P-value	Adjusted OR (95% CI)	P-value
Pathologic Tumor-size	1 (0.99-1.01)	0.90	1.02 (0.99-1.06)	0.25
Ki67	0.97 (0.94-1)	0.06	0.99 (0.95-1.03)	0.53
SLN- Excised	0.52 (0.30-0.89)	0.02	0.41 (0.17-0.98)	0.04
ALN- Excised	1.09 (0.99-1.21)	0.07	1.20 (1.02-1.42)	0.03
LVI (Yes/No)	2.01 (0.62-6.56)	0.25	0.69 (0.15-3.24)	0.64

OR= Odds Ratio; CI= Confidence Interval; SLN= Sentinel Lymph Node; ALN= Axillary Lymph Node; LVI= Lymphovascular Invasion.

The strength of our study is that all operations were performed by a single experienced surgeon, which ensures the similarity of referred patients for NAC and could eliminate the impact of surgical skills on the rate of FNR. This study is valuable because most previous studies were conducted in developed countries, and the few studies that were conducted in developing countries including Iran, had a very small sample size.

Our study had some limitations, including the small sample size and its retrospective nature. The number of false negative results (fourteen patients) is not sufficient for any subgroup analysis. The association between FNR and tumor subtype and receptor status and other histologic factors was not statistically significant.

CONCLUSION

In conclusion, SLNB after NAC in previously node-positive patients is feasible and accurate with a low FNR. According to our study, when deciding to spare ALND in the presence of a negative SLNB in the neoadjuvant setting, the size of the residual tumor, i.e., the response of the primary tumor to systemic therapy, should be considered.

ETHICAL CONSIDERATIONS

This cross-sectional study received approval from the ethics committee of Imam Khomeini Hospital of Tehran University of Medical Sciences (Ethics No # IR.TUMS.IKHC.REC.1402.311).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None.

DATA AVAILABILITY

All data relevant to the study are included in the article.

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