Validity of sentinel lymph nodes biopsy after neoadjuvant chemotherapy in case of complete pathological response of axillary lymph nodes

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Aim
To determine the validity of sentinel lymph node (SLN) biopsy after neoadjuvant chemotherapy (NAC) in case of complete pathological response of axillary lymph node.
Patients and methods
This is a prospective study that included female patients with cancer breast who became clinically and radiologically node negative (cN0) after receiving NAC during the period of March 2016 to October 2018 in Alexandria Medical Research Institute, Alexandria, Egypt. Dual technique was used to identify the SLN followed by standard axillary lymph node dissection (ALND). Analysis of the pathological reports was used to determine the false-negative rate (FNR) of SLN.
Results
Of the 86 patients who completed the NAC and showed cN0, SLN could be identified in 76 (88.4%) patients. ALND was completed for the 76 patients, and SLNs showed false-negative results in nine (11.8%) patients. Patients in whom three or more (10.3%) SLNs could be identified showed better FNR compared with patients with two SLNs or less (16.7%).
Conclusions
SLN biopsy after NAC for patients with cN0 seems to be a reliable technique to replace ALND if certain precautions are applied. The use of a dual technique for SLN identification and determination of at least three SLNs to be the minimum number accepted is an essential requirement to be applied in this selective approach to ensure FNR within accepted range. In addition, patients should be counseled regarding benefits of the SLN biopsy technique and the possibility of failure to identify the SLN or being false negative.

Keywords:
cancer breast, neoadjuvant chemotherapy, sentinel lymph node biopsy, sentinel lymph node identification

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Introduction

Breast cancer remains the most common malignancy among women and accounts for ~32% of all cancers in women [1]. Over the past decade, there has been an evolution in the surgical management of breast cancer, with a paradigm shift toward less invasive surgery [2].

Although there are several histopathological features of breast cancer that are important to determine patient prognosis, the presence of axillary lymph node (LN) metastases remains the most important predictor of overall survival and recurrence [3,4]. It has been used to guide locoregional and systemic treatment decisions. Surgical removal of the axillary nodes facilitates staging and provides regional control in those with axillary metastasis [5].

In the past, axillary staging was accomplished through axillary lymph node dissection (ALND) [5]. However, ALND was associated with postoperative morbidity, including increased risk of infection, wound problems, pain, and lymphedema, without any therapeutic benefit in patients who are node negative [6]. Secondary lymphedema affects the quality of life of a patient and consequently leads to a considerable economic burden to the health care systems [7,8]. To avoid the complications associated with ALND, it is preferable to identify nodal disease with the less invasive sentinel lymph node (SLN) surgical procedure, which results in less morbidity [5,9].

In women with clinically node-negative (cN0) disease, SLN surgery has replaced ALND as the initial approach. Randomized trials have demonstrated that SLN surgery is technically feasible in women

presenting with cN0 disease, with identification rates exceeding 97% and false-negative rates (FNR) of less than 10% [10].

Neoadjuvant chemotherapy (NAC) is a popular sequencing strategy in the multimodality treatment of breast carcinoma [11]. The aim of NAC is to approach complete pathological response (CPR). NAC in recent studies leads to up to 40% of CPR even in the pre-NAC positive axillary LNs [12]. According to guidelines, ALND of patients with CPR is the current option, although the pathological analysis of the axillary LNs reveals pN0 in 52% [13–15]. To avoid ALND in these patients, the principle of SLN surgery (NAC) is not approved yet [5].

The aim of this study is to determine the validity of SLN biopsy after NAC in case of CPR of axillary LNs.

Patients and methods

This is a prospective study that included female patients with cancer breast who became clinically and radiologically node-negative (cN0) after receiving NAC. All patients were admitted to Alexandria Medical Research Institute, Alexandria, Egypt. The minimal sample size needed for the study was calculated to be 66 patients, using the 'G Power' program, version 3.1.3 [16], based on α of 0.05, power of 0.90, with an assumed FNR of 12% [17].

Inclusion criteria

The study included female patients who are more than 18 years old with histologically proven diagnosis of primary invasive breast cancer: clinical stage T0–T4, N0–N2, and M0 invasive according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [18]. All patients completed or were planning to undergo NAC. Axillary nodal disease, whether positive or not, was confirmed by fine-needle aspiration or core-needle biopsy before NAC.

Exclusion criteria

The following were excluded from the study: patients with advanced metastatic disease cN3 or M1, patients who did not complete the NAC, patients with incomplete response of axillary LNs after NAC, patients with failed intraoperative detection of the SLNs, and patients with a history of prior ipsilateral axillary surgery, prior SLN surgery, or excisional lymph node biopsy for pathologic confirmation of axillary status. Patients with inflammatory cancer breast were also excluded from the study.

All patients were subjected to thorough history taking and physical examination. All required laboratory and radiologic investigations were performed, and preoperative clinical staging was determined.

An informed consent was obtained from all patients regarding the surgical procedure and their participation in the study.

Surgical procedure and sentinel lymph node detection

After finishing NAC, all patients were scheduled for physical examination and axillary ultrasonography before surgery. The surgical procedure included appropriate treatment of the primary tumor, SLN detection surgery, and then ALND.

SLN detection was performed through combined injection of a radio-labeled colloid (Tc99) in the subareolar region 2 h before the surgery and blue dye (isosulfan blue or methylene blue) in the peritumor area just before the surgery, followed by massaging of the injected area. A gamma probe was used to identify radioactivity in axillary LNs. The blue-stained lymphatic channels visualized during surgery were followed to the lymph nodes where the blue dye accumulates (Figs 1 and 2). Any abnormal axillary LN(s) that were both stained blue and emitted radioactivity were identified and labeled as SLNs. ALND was then performed in the standard way, and both SLN and ALND specimens were submitted for pathological analysis.

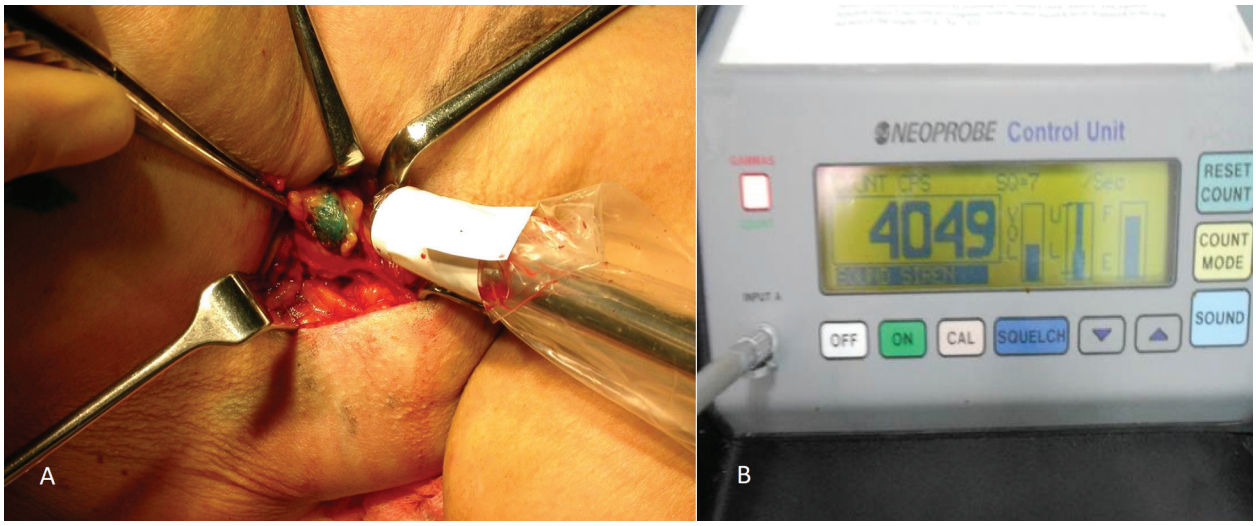
Hematoxylin and eosin staining was used for both SLN and nodes removed at ALND. SLNs were considered positive when metastases larger than 0.2 mm (per the American Joint Committee on Cancer staging system) were detected. Nodes removed at ALND were evaluated according to the standard protocol in our institution. Numbers of identified SLNs, positive and negative SLNs, number of detected LNs at ALND, and numbers of positive and negative LNs at ALND were detected and described in the pathology report.

Statistical analysis

The statistical analysis of data was done using the Statistical Package for Social Sciences (SPSS version 25; SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were applied (frequency and percentage for categorical variables, and mean and SD for quantitative variables). A statistically significant difference was considered at P values less than 0.05.

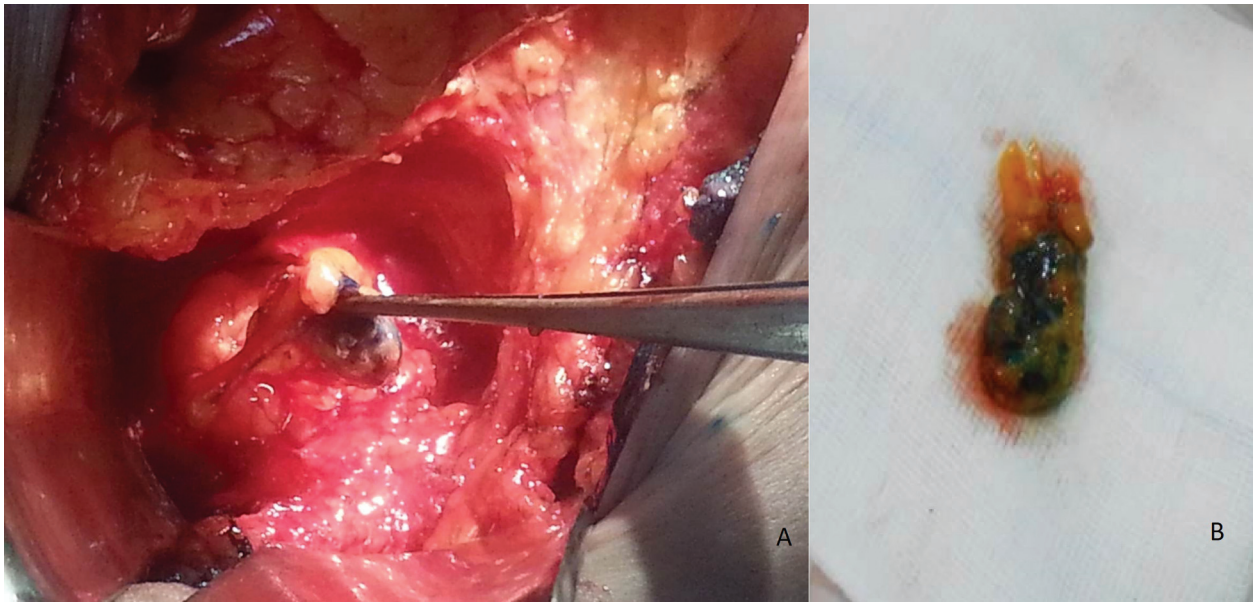
The research was approved by the Institutional Research Board of College of Medicine, Alexandria

Figure 1



Dual technique for detection of SLN(s): (a) axillary lymph node(s) that are both stained blue and emitted radioactivity are identified and labeled as SLNs and (b) high reading in the Neoprobe indicating radioactivity. SLN, sentinel lymph node.

Figure 2



(a) Intraoperative dissection of SLN(s) and (b) SLN(s) after dissection. SLN, sentinel lymph node.

University (IRB 00007555), and precautions were taken to conceal the identity of patients.

Outcomes

Primary end points

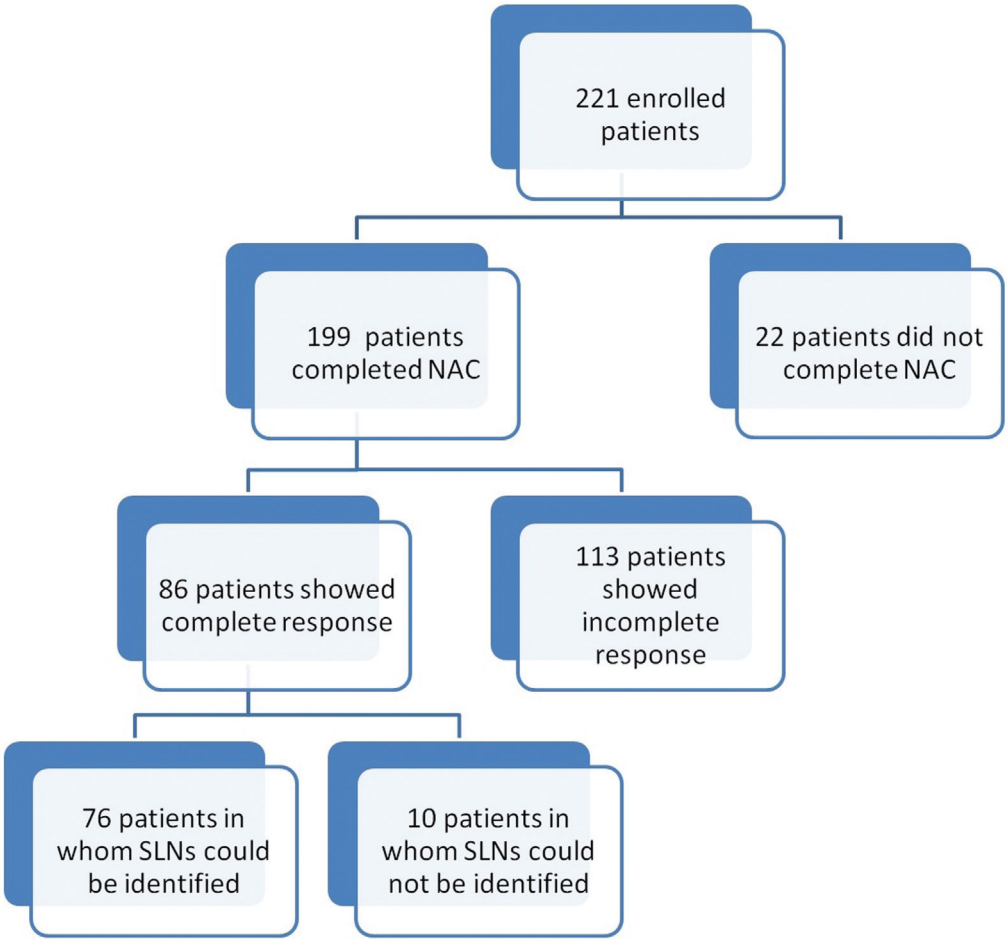
The following were the primary end points:

(1) Identification rate of SLNs detected by the surgeon intraoperatively and studied and counted by the pathologist.
(2) FNR by detection of cases in which SLNs were negative but there was a residual tumor tissue in the lymph nodes of ALND specimen detected by revising the pathologic report.

Results

The study included all female patients having breast cancer (221 patients) with clinical staging T1–T4, N0–N2, and M0 who were admitted to Alexandria Medical Research Institute during the period of March 2016 to October 2018 (Fig. 3). Twenty-two patients were excluded from the study as they did not complete the NAC. Another 113 patients were excluded owing

Figure 3



Flow of patients through the study.

to incomplete response of the axillary LNs after NAC. Ten patients were also excluded owing to intraoperative failure to identify the SLNs. Seventy-six patients fulfilled all inclusion criteria and were included in our study. The characteristics of the patients and their tumors before NAC are shown in Table 1.

Chemotherapy regimens varied, but most patients (74.6%) received anthracycline and a taxane (Table 2). The mean duration of chemotherapy was 4.3 months (1–8 months). Twenty-two patients discontinued chemotherapy and were excluded from the study: two patients owing to the progression of the disease, two patients refused to continue, whereas the other 18 patients owing to intolerance to adverse effects of the chemotherapy. They were offered an alternative treatment.

Patients who completed chemotherapy, with complete response to axillary LNs, were subjected to surgical treatment, whether partial or total mastectomy, according to the patients' condition. Details of the chemotherapy regimen, type of surgery, and the molecular subtype of the tumor are shown in Table 2.

SLNs were identified and dissected, followed by ALND in all patients. The mean number of SLNs was 3.11±1.24 LNs. However, the mean number of LNs in ALND was 13.28±2.27. FNR of the SLNs compared with the ALND was found in nine (11.8%) patients. Several factors were studied to detect their influence on the FNR. However, they did not show statistical significance. The details of true-negative and FNR among different studied variables are shown in Table 3.

Discussion

Nowadays, breast surgery has moved toward the least invasive techniques [5]. After the success of SLN technique in avoiding ALND in many patients with clinical negative node status, it became the standard care for this group of patients [19]. This led to great reduction in morbidity and improvement in the quality of life of these patients [20].

Table 1 The characteristics of the patients and the tumor before neoadjuvant chemotherapy

Characteristics	*n* (%)
Age groups (in years)	
<40	15 (19.7)
40–60	45 (59.2)
>60	16 (21.1)
BMI grades (kg/m^2)	
<25	17 (22.4)
25–30	51 (67.1)
>30	8 (10.5)
Clinical T at diagnosis	
T1	8 (10.5)
T2	42 (55.3)
T3	22 (28.9)
T4	4 (5.3)
Clinical N at diagnosis	
N0	5 (6.6)
N1	7 (9.2)
N2	64 (84.2)
Tumor site	
Upper outer quadrant	37 (48.7)
Upper inner quadrant	8 (10.5)
Lower outer quadrant	8 (10.5)
Lower inner quadrant	4 (5.3)
Central	11 (14.5)
Multicentric	8 (10.5)
Histological type	
Infiltrative ductal carcinoma (IDC)	69 (90.8)
Infiltrative lobular carcinoma (ILC)	4 (5.3)
Mixed IDC and ILC	1 (1.3)
Other types	2 (2.6)

Table 2 The chemotherapy regimens, types of surgical management, and the molecular subtypes of the tumor

Characteristics	*n* (%)
Neoadjuvant chemotherapy regimen	
Anthracycline and taxane	57 (75.0)
Anthracycline	5 (6.6)
Taxane	13 (17.1)
Other, no anthracycline and no taxane	1 (1.3)
Pathological response of the primary mass after chemotherapy	
Complete response	31 (40.8)
Partial response	45 (59.2)
Type of breast surgery after chemotherapy	
Partial mastectomy	45 (59.2)
Complete mastectomy	31 (40.8)
Molecular subtype of the tumor	
Luminal A	14 (18.4)
Luminal B	13 (17.1)
Triple-negative/basal-like	32 (42.1)
HER2-enriched	17 (22.4)

Application of the same principle of SLN technique to preserve the axilla for some patients who received NAC and became cN0 is a developing idea aiming at allowing these patients to get benefit from avoiding ALND with its consequences. However, the controversies regarding the FNR associated with the application of SNL technique after NAC are still not yet justifying it as standard care for this group of patients [5,21–23].

In our study, to improve the identification percentage of SLNs, we used the dual technique for detection of SLN(s). Boughey *et al.* [5] reported that the only factor associated with failure to identify a SLN was the type of mapping agent used, with the best results obtained using the radio-colloid with the blue dye compared with blue dye or radio-colloid alone. The better results of the dual technique were also achieved in the SENITA study [22].

In the current study, we could identify the SLN(s) in 76 patients out of 86 patients who had complete cN0 after NAC, with a success rate of 88.4%. This rate is higher than that reported in the SENITA study (80.1%) [22]. However, it is lower than what was reported in both ACOSOG Z1071 trial (92.7%) [21] and SLN identification rate reported by Krag *et al.* [24] (93%) in the 1998 publication of a multicenter validation trial of SLN surgery without NAC.

The slightly lower SLN(s) identification rate in our study could be attributed to the fact that only patients with CPR were included in our study compared with other studies that included patients with complete and incomplete pathological response. So, the rate of identification of SLN(s) in our study may be affected by the fibrosis effect of NAC that was effective and led to the CPR. We agree with Moreno *et al.* [25], who reported that tumor tissue response to NAC by its replacement by loose fibrosis is the most common pathologic event. In addition, the intensity of fibrotic change is proportional to the degree of reduction of the tumor mass.

FNR of SLN after NAC in our study was 11.8% which is comparable to FNRs in other studies [20,21]. Furthermore, it is comparable to those accepted for use of SLN biopsy in early stage breast cancer where identification rates range from 88 to 97% and FNRs of 5–12% were reported [10,26]. On the contrary, Shen *et al.* [23] reported a FNR of SLN after NAC to be as high as 25%, and accordingly, they questioned the reliability of SLN as an indicator of the presence or absence of residual disease in the axilla. We think that high FNR in their series may be attributed to the lack of a predetermined protocol dictating the method of lymphatic mapping and inaccuracy of their techniques of SLN biopsy.

Table 3 True and false-negative rates of the sentinel lymph nodes among the different studied variables

Variables	True negative [*n* (%)]	False negative [*n* (%)]	*P* value
Age groups (in years)			
<40	13 (86.7)	2 (13.3)	0.970
40–60	40 (88.9)	5 (11.1)	
>60	14 (87.5)	2 (12.5)	
BMI (kg/m^2)			
<25	14 (82.4)	3 (17.6)	0.686
25–30	46 (90.2)	5 (9.8)	
>30	7 (87.5)	1 (12.5)	
Clinical T at diagnosis			
T1	7 (87.5)	1 (12.5)	0.844
T2	38 (90.5)	4 (9.5)	
T3	19 (86.4)	3 (13.6)	
T4	12 (92.3)	1 (7.7)	
Clinical N			
N0	4 (100.0)	1 (0.0)	0.526
N1	7 (100.0)	0	
N2	56 (87.0)	8 (13.0)	
Histological type			
Infiltrative ductal carcinoma (IDC)	60 (87.0)	9 (13.0)	0.793
Infiltrative lobular carcinoma (ILC)	4 (100.0)	0	
Mixed IDC and ILC	1 (100.0)	0	
Other types	2 (100.0)	0	
Tumor site			
Upper outer quadrant	32 (86.5)	5 (13.5)	0.157
Upper inner quadrant	8 (100.0)	0	
Lower outer quadrant	6 (75.0)	2 (25.0)	
Lower inner quadrant	4 (100.0)	0	
Central	11 (100.0)	0	
Multicentric	6 (75.0)	2 (25.0)	
Neoadjuvant chemotherapy regimen			
Anthracycline and taxane	50 (87.7)	7 (12.3)	0.644
Anthracycline	5 (100.0)	0	
Taxane	11 (84.6)	2 (15.4)	
Other, no anthracycline and no taxane	1 (100.0)	0	
Pathological response of the primary mass			
Complete response	26 (83.9)	5 (16.1)	0.272
Partial response	41 (91.1)	4 (8.9)	
Molecular subtypes			
Luminal A	12 (85.7)	2 (14.3)	0.170
Luminal B	10 (76.9)	3 (23.1)	
Triple-negative/basal-like	31 (96.9)	1 (3.1)	
HER2-enriched	14 (82.4)	3 (17.6)	
Number of isolated sentinel lymph nodes			
1–2	15 (83.3)	3 (16.7)	0.360
3+	52 (89.7)	6 (10.3)	

Many factors were evaluated for their possible influence on FNR in our study. However, no significant differences in the FNR could be observed regarding age, BMI, clinical tumor size, tumor location, histopathologic type, molecular subtype, or pathological response of the primary mass. Similar results were reported by many authors [5,21,22]. Although some older studies [24,27] reported significant relation to tumor location, BMI, and old age to the identification rate of SLN and the FNR, this was not supported in our results.

In this study, it was found that the FNR was 10.3% when three or more SLNs were identified compared with 16.7% when two or less SLNs were identified. Similar results were observed in the NSABP B-32 trial [10], in which SLN surgery was performed before any chemotherapy. They reported that there was a significant decrease in the FNR as more SLNs were

resected. Furthermore, Hunt *et al*. [28] showed that the removal of fewer than 2 SLNs was associated with a higher FNR in patients with cN0 disease undergoing SLN surgery after chemotherapy. We think that these results are matching with the fact that the accuracy of any sampling test is dependent on the amount of material sampled, and consequently, the incidence of FNR decreases with identification of more SLNs.

Based on prior studies of SLN surgery reporting a 10–12% FNR following chemotherapy in patients with cN0 disease, some studies determined the 10% as a threshold of FNR for safe application of SLN biopsy techniques after NAC [17,21]. Shen *et al*. [23] concluded that SLN biopsy is technically feasible and reliable for representing the other LNs in ALND for patients who are clinically node-negative after NAC. Their justification was based on the fact that FNR for this group of patients is comparable to those accepted for use of SLN biopsy in early stage breast (5–12%).

In conclusion, we think that SLNs biopsy after NAC in case of CPR of axillary LNs is a reliable technique to replace ALND if certain precautions are applied. The use of a dual technique for SLN identification and determination of at least three SLNs to be the minimum number accepted is an essential requirement to be applied in this selective approach to ensure FNR within accepted range. In addition, patients should be counseled regarding benefits of the SLN biopsy technique and the possibility of failure to identify the SLN or being false negative and the surgical options suitable in these different conditions.

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Conflicts of interest

There are no conflicts of interest.

References

1 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, *et al.* Cancer statistics, 2005. CA Cancer J Clin 2005; 55:10–30.

2 Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347:1227–1232.

3 Huston TL, Simmons RM. Locally recurrent breast cancer after conservation therapy. Am J Surg 2005; 189:229–235.

4 Schijven M, Vingerhoets A, Rutten H, Nieuwenhuijzen G, Roumen R, Van Bussel M, *et al.* Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. Eur J Surg Oncol 2003; 29:341–350.

5 Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, *et al.* Factors affecting sentinel lymph node identification rate after neoadjuvant chemotherapy for breast cancer patients enrolled in ACOSOG Z1071 (Alliance). Ann Surg 2015; 261:547.

6 Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 2001; 92:1368–1377.

7 Eyigör S, Cinar E, Caramat I, Unlu BK. Factors influencing response to lymphedema treatment in patients with breast cancer-related lymphedema. Supp Care Cancer 2015; 23:2705–2710.

8 Tausch C, Baege A, Dietrich D, Vergin I, Heuer H, Heusler RH, *et al.* Can axillary reverse mapping avoid lymphedema in node positive breast cancer patients? Eur J Surg Oncol 2013; 39:880–886.

9 Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, *et al.* A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003; 349:546–553.

10 Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, *et al.* 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 randomised phase III trial. Lancet Oncol 2007; 8:881–888.

11 Buchholz TA, Hunt KK, Whitman GJ, Sahin AA, Hortobagyi GN. Neoadjuvant chemotherapy for breast carcinoma: multidisciplinary considerations of benefits and risks. Cancer 2003; 98:1150–1160.

12 Van J, Hage C, Velde JJ, Tubiana-Hulin M, Vandervelden C. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19:4224–4237.

13 Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, *et al.* Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384:164–172.

14 Enokido K, Watanabe C, Nakamura S, Ogiya A, Osako T, Akiyama F, *et al.* Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with an initial diagnosis of cytology-proven lymph node-positive breast cancer. Clin Breast Cancer 2016; 16:299–304.

15 Vriens BE, Keymeulen KB, Kroep JR, Charehbili A, Peer PG, de Boer M, *et al.* Axillary staging in breast cancer patients treated with neoadjuvant chemotherapy in two Dutch phase III studies. Oncotarget 2017; 8:46557.

16 Faul F, Erdfelder E, Lang A-G., Buchner A. G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39:175–191.

17 Xing Y, Foy M, Cox D, Kuerer H, Hunt K, Cormier J. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg 2006; 93:539–546.

18 Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17:1471–1474.

19 Ding J, Jiang L, Wu W. Predictive value of clinicopathological characteristics for sentinel lymph node metastasis in early breast cancer. Med Sci Monit 2017; 23:4102.

20 Tan VK, Goh BK, Fook-Chong S, Khin LW, Wong WK, Yong WS. The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after neoadjuvant chemotherapy for breast cancer—a systematic review and meta-analysis. J Surg Oncol 2011; 104:97–103.

21 Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, *et al.* Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013; 310:1455–1461.

22 Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, *et al.* Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013; 14:609–618.

23 Shen J, Gilcrease MZ, Babiera GV, Ross MI, Meric-Bernstam F, Feig BW, *et al.* Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. Cancer 2007; 109:1255–1263.

24 Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, *et al.* The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 1998; 339:941–946.

25 Moreno A, Escobedo A, Benito E, Serra JM, Gumà A, Riu F. Pathologic changes related to CMF primary chemotherapy in breast cancer. Breast Cancer Res Treat 2002; 75:119–125.

26 Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. Cancer 2006; 106:4–16.

27 Ahrendt GM, Laud P, Tjoe J, Eastwood D, Walker AP, Otterson MF, *et al.* Does breast tumor location influence success of sentinel lymph node biopsy? J Am Coll Surg 2002; 194:278–284.

28 Hunt KK, Yi M, Mittendorf EA, Guerrero C, Babiera GV, Bedrosian I, *et al.* Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg 2009; 250:558–566.