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SENTINEL LYMPH NODE BIOPSY AFTER NEOADJUVANT CHEMOTHERAPY IN PREVIOUSLY CLINICALLY NODE POSITIVE AXILLA OF BREAST CANCER

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ORIGINAL ARTICLE

Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in Previously Clinically Node-positive Axilla of Breast Cancer

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Abstract

Background: **The invasiveness and possible morbidity of axillary lymph node dissection (ALND), the conventional strategy for assessing lymph node health for the past century, have brought into doubt the procedure in the last 15 years.**

Aim: **This study aims to assess the possibility of avoiding the morbidity of an ALND by staging an axilla using sentinel lymph node biopsy (SLNB) following neoadjuvant therapy (NAT) in previously diagnosed node-positive axillas in cancer of the breast.**

Patients and methods: **This prospective cohort research intends to involve a total of 50 participants. All of these women have breast cancer that has spread to their lymph nodes. These individuals will be recruited in a prospective cohort study that will performed from April 2021 to March 2023 at the Department of Surgery of the Al-Azhar University Hospitals in Cairo, Egypt.**

Results: **Patients in this research had an average age of 47.6 years and were all females with early-stage breast cancer with no history of other malignancies or lymphadenopathy.**

Conclusion: **When both radioactive colloid and blue dye are utilized to identify the sentinel lymph node (SLN), the detection rate is higher, and FNR after neoadjuvant chemotherapy (NAC) is better, allowing for the possible omission of axillary dissection following a positive SLN. It has been debated whether or not depending on SLNB following neoadjuvant chemotherapy is acceptable for women who arrive with clinically positive nodes. When identifying SLNs in these individuals with two agents, FNRs are likewise reduced to the 10 % range or below. The FNR is constantly below 10 % when three or more SLNs are found, and this trend holds true regardless of the starting point.**

Keywords: Axillary lymph node dissection, Breast cancer, Chemotherapy

1. Introduction

In women, breast cancer has a higher prevalence rate than any other invasive cancer. As for invasive malignancies in women, it makes up 22.9 % of all cases and 16 % of the total. Breast cancer is the second leading cause of cancer-related mortality in females, accounting for 18.2 % of all cancer deaths globally[1] (see Figs. 3–7).

Thirty-five percent of all cases of cancer managed at the National Cancer Institute in Egypt have been brought on by breast cancer. Unfortunately, most cases are not discovered until it is too late to do anything about them.[2]

Axillary dissection is a surgical technique employed to locate, evaluate, or remove lymph nodes by incising the axilla. The axilla is often dissected out as part of breast cancer staging and therapy. The only individuals who should undergo an axillary dissection are those who have preoperatively established axillary disease or who have had a sentinel node biopsy that was positive.[3]

Treatment of breast cancer with neoadjuvant therapy (NAT) is now standard practice since it has

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been shown to have the same level of efficacy as adjuvant treatment. The benefits include less extensive surgery due to a reduced disease load and the ability to determine an individual tumor's chemosensitivity.[4]

Downstaging of tumors has been reported at near-94 % rates in recent years; more importantly, pathological complete response (PCR) is achieved by 20–40 % of patients following neoadjuvant chemotherapy (NAC). The prognosis and overall survival of cases with a pathologic complete response are improved.[5]

In instances with node-negative axillae, axillary lymph node dissection (ALND) has been substituted by SLN biopsy, and those who have low-load illness in the SLNs can avoid an ALND without affecting oncologic findings. ALND had been performed in situations with node-positive axillas. In the past 10 years, the indications for NAT have broadened to encompass individuals with illnesses that can be operated on. Additionally, the rate of PCR following NAT has grown with the introduction of targeted medicines. This is due to the fact that patients are responding better to the targeted treatments. In patients who have clinically negative nodes, neoadjuvant SLN performed following NAT is practical as well as precise. Additionally, in an attempt to reduce the morbidity associated with ALND, it was investigated in a variety of randomized prospective investigations in participants who have clinically positive axilla.[6]

2. Patients and methods

From April 2021 to March 2023, participants from the Department of Surgery at Al-Azhar University Hospitals in Cairo, Egypt, will be involved in a prospective cohort research. Pre- and postoperative assessments will be performed on all patients utilizing the same methodology. The ethical committee's approval will be obtained. Every individual will be asked to sign a permission form after having their questions answered about the procedure, its advantages, and any potential intra- and postoperative hazards.

2.1. Inclusion criteria

Individuals who are able to tolerate general anesthesia and are among the ages of twenty and seventy have had positive axillary lymph nodes confirmed by fine-needle aspiration biopsy (FNAB) before receiving NAC and have since transformed to having clinically and radiologically negative lymph nodes in the axillary area as a result of receiving NAC.

2.2. Exclusion criteria

Individuals with lymphadenopathy for reasons besides breast cancer, individuals who have radiologically positive axillary lymph nodes following NAC, participants who have lymphadenopathy for reasons outside breast cancer, and females with organ metastases due to breast cancer.

All of the participants had complete clinical evaluations, including exams of the breasts and axillae, and extensive medical and family histories. In addition to the standard blood and urine tests [complete blood count (CBC), coagulation profile, liver and kidney functions, and renal blood sodium], electrocardiogram (ECG), sonomammography (both breasts and axillae), and CT (pelvis and abdomen, chest) were performed. Fine-needle aspiration biopsy and cytology (FNABC) of radiologically + ve axillary L.Ns were also performed.

2.3. Chemotherapy

At the end of the six cycles of doxorubicin and taxane NAC that each case had, we performed a second breast ultrasound to confirm that the patient had achieved a radiologically negative axilla (complete radiological response).

2.4. Preoperative

Every individual gave their informed consent after being given a thorough explanation of the procedures' potential benefits and risks.

2.5. Intraoperative

Following the removal of the SLN (number three to four lymph nodes), the participant underwent SLNB utilizing one cm of patent blue dye administered retro-areolar at 3, 6, 9, and 12 o'clock. Next, the participant received massage for 15–20 min for the entire breast to enable the dye to move from the retro-areolar plexus of Sappey to the SLN at the axilla. Finally, the participant had been referred to the pathologist for both the during-surgery frozen and after-surgery paraffin histopathological examinations, followed by the formal axillary clearance completion.

2.6. Postoperative

Hospitalization for a period of 24 h–48 h, followed by a follow-up after 1 week to learn the results of the histological investigation of the SLN, then 2 weeks to have the drain removed, and finally 6 months of

antibiotics that are effective throughout a broad spectrum. During the operation, a surgical site suction drain was inserted, and it remained in place for 7–14 days. This was performed by clinical evaluation.

2.7. Statistical analysis

Information was compiled, checked, coded, and put into IBM's Social Science Statistical Package (SPSS) Version 23. When possible, numerical information was shown in parametric form, including mean, standard deviation, and range. Quantitative and percentage representations of qualitative factors were also provided. When the predicted count in a given cell was less than 5, only then did we use the χ^2 test or the Fisher exact test to compare the two groups' qualitative data. When comparing 2 groups based on quantitative data with a parametric distribution, the Independent *t*-test was used.

A receiver-operating characteristic curve (ROC) was used to evaluate the qualitative diagnostic precision of paraffin sections (axilla) and frozen sections, using a paraffin section SLN as the gold standard. We used a 95 % confidence interval and an acceptable error of 5 %.

3. Results

Fifty women, with average age of 47.6 years, were involved in our study; all of them had been diagnosed with early-stage breast cancer and had no additional malignancies or lymphadenopathy.

Table 1 shows that the mean age of the cases 47 years and positive family history in 66 % of patients denoting family history is strong risk factor (Figs. 1–7and Tables 2–6) (see Fig. 2).

Table 7 shows a high statistical significance regarding the negative results of SLN in the frozen section in relation to the results of axilla in paraffin section.

There is no distinction among the outcomes of being positive or negative for SLNs as well as additional lymph nodes in axillary clearance, according to the conclusion of formal axillary clearing, which has been performed to evaluate the safety as well as precision of SLNB. This was discovered after the completion of formal axillary clearance (Table 8).

Table 9 Shows that 70 % of patients were HER 2neu and triple -ve who respond well to NAC.

Table 1. Displays demographic data about the individual, including age, family history, and which side of the body the tumor is located.

	No. = 50
Age (y)	
Mean ± SD	47.60 ± 13.41
Range	22–68
Family history	
Negative	17 (34.0 %)
Positive	33 (66.0 %)
Tumor side	
Right	31 (62.0 %)
Left	19 (38.0 %)

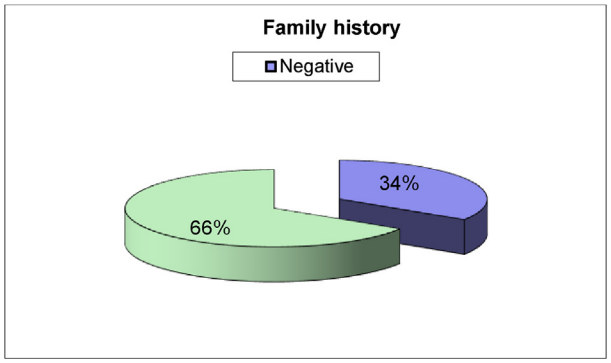

Fig. 1. Shows family History of the studied patients.

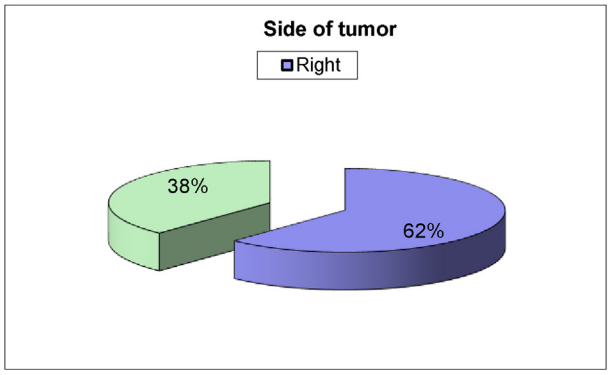

Fig. 2. Indicates the tumor side among these individuals investigated.

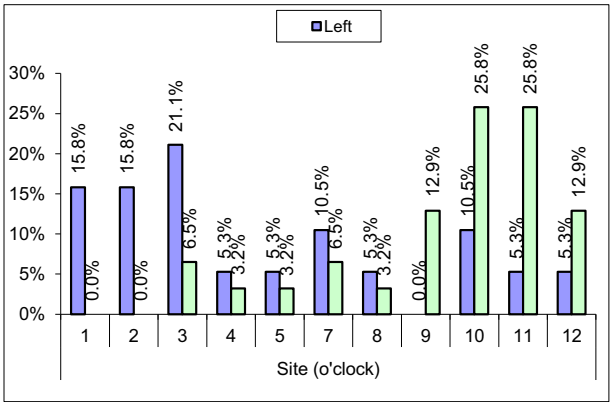

Fig. 3. The tumor's site among the examined cases.

4. Discussion

The most frequent invasive cancer among women is breast cancer. When it comes to cancer, women

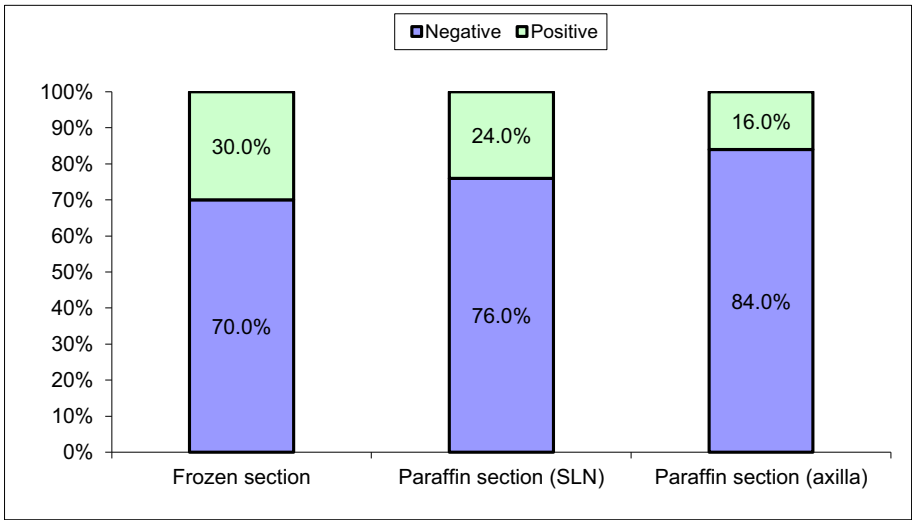

Fig. 4. Indicates the results of frozen and paraffin sections (sentinel lymph node and axilla) between the examined participants.

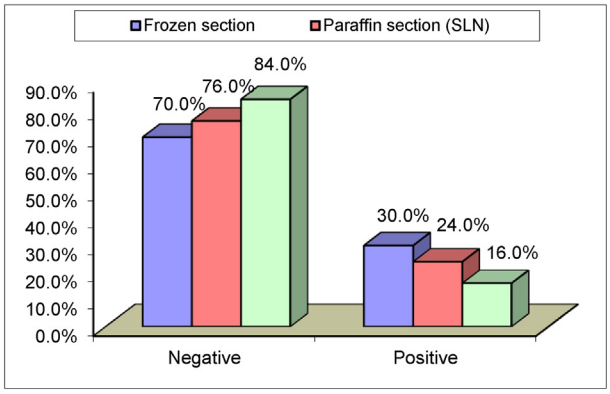

Fig. 5. Shows a comparison of the examined participants' sentinel lymph node and axilla tissue utilizing a frozen section, a paraffin section, and each of the sections.

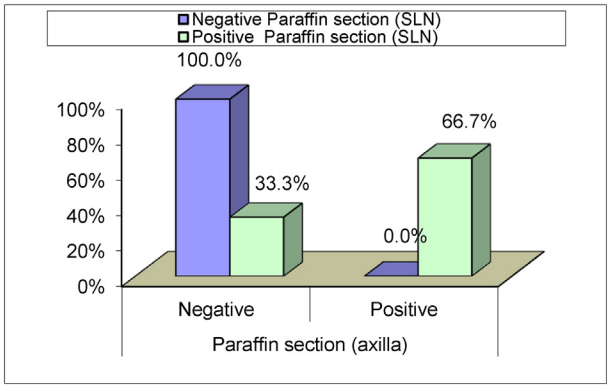

Fig. 7. Illustrates the relationship between paraffin section (sentinel lymph node) and paraffin section (axilla) in the investigated individuals.

account for 22.9 % of invasive cases and 16% of the total. With an estimated 18.2 % of all cancer fatalities occurring in women, breast cancer is the second highest cause of cancer-related death worldwide.[1]

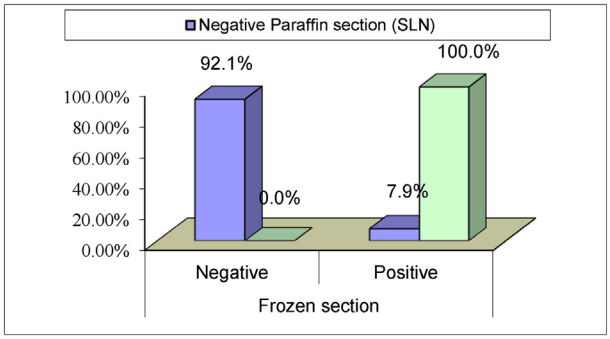

Fig. 6. Illustrates the relationship between paraffin section (sentinel lymph node) and frozen section in the investigated individuals.

Fifty individuals with axilla-positive clinical and pathological breast cancer diagnoses were included in our investigation. All of them had six rounds of chemotherapy followed by an ultrasound of the breast to confirm a negative axillary node (complete radiological response).

Our study comprised fifty participants with ages varying from 22 to 68 years old (average age: 47.6 years). The average age of a breast cancer patient, in accordance with the American Cancer Society, is 50 years.[7]

Sixty-six percent of our sample size of 33 individuals had a positive family history. Yet, according to the American Cancer Society, favorable family histories were found in more than seventy percent of breast cancer cases.[7]

The research found that 38 % of individuals who have breast cancer have tumors on their left side,

Table 2. Displays the tumor's site among the examined cases.

Site	Left No. (%)	Right No. (%)
1	3 (15.8 %)	0
2	3 (15.8 %)	0
3	4 (21.1 %)	2 (6.5 %)
4	1 (5.3 %)	1 (3.2 %)
5	1 (5.3 %)	1 (3.2 %)
7	2 (10.5 %)	2 (6.5 %)
8	1 (5.3 %)	1 (3.2 %)
9	0	4 (12.9 %)
10	2 (10.5 %)	8 (25.8 %)
11	1 (5.3 %)	8 (25.8 %)
12	1 (5.3 %)	4 (12.9 %)

Table 3. Displays tumor parameters and the patient's weight.

	No. = 50
Size of breast mass (cm)	
Mean ± SD	3.23 ± 0.64
Range	1.5–4.2
BIRADS	
4	32 (64 %)
5	18 (36 %)
PT. weight	
Mean ± SD	77.84 ± 8.22
Range	57–90

Table 4. Illustrates number of sentinel lymph node.

	Frequency	Percent
Number of SLN		
3	28	56 %
4	22	44 %

Table 5. Illustrates the outcomes of paraffin section, frozen section, sentinel lymph node, and axilla analysis among the individuals that were evaluated.

	No. = 50
Frozen section	
−ve	35 (70.0 %)
+ve	15 (30.0 %)
Paraffin section (SLN)	
−ve	38 (76.0 %)
+ve	12 (24.0 %)
Paraffin section (axilla)	
−ve	42 (84.0 %)
+ve	8 (16.0 %)

whereas 62 % of individuals who have breast cancer have tumors on their right side.

Our findings, indicating tumors most frequently arise in the upper outer quadrant (between ten and eleven o'clock on the right breast and from two to three o'clock on the left breast), are in line with those of another research which found that tumors most frequently arise in these locations.[8]

According to the results, the diameters of these masses vary widely, from 1.50 to 4.20 cm on average. In addition, 64 (64 %) patients were classified as BIRADS 4, whereas 36 % (18 patients) were classified as BIRADS 5. The average patient weighs 77.84 kg, with a range of 57–90 kg.

After injecting 1 cm of patent blue dye retro-areolar at 3, 6, 9, and 12 o'clock, participants received a massage of the whole breast for 15–20 min in order to help the dye go from the retro-areolar plexus of Sappey to the SLN in the axilla.

The SLN (lymph nodes 3–4) is removed during surgery and transferred to the pathologist for intraoperative frozen and subsequent paraffin histological analysis.

The number of SLN in this research was three lymph nodes in 28 individuals with a percentage of 56 % and four lymph nodes in the other 22 participants with a percentage of 44 %.

It is estimated that in up to 60 % of all instances and in over 90 % of individuals who carry only micrometastatic illness, the SLN is the only tumor-bearing node. As a result of these findings, it has been proposed that individuals with +ve SLNB in fewer than three lymph nodes may not require full ALND. This is due to the fact that the requirement for systemic therapy has been proven, and it looks like there is very little likelihood of an axillary recurrence.[9]

Paraffin sections of SLN indicated −ve lymph nodes in 38 individuals (76%) and +ve lymph nodes in 12 individuals (24 %), while frozen sections demonstrated −ve lymph nodes in 35 individuals (70 %) and +ve lymph nodes in the other 15 individuals (30 %).

There were early worries that frozen section assessment would use more of the sample compared with cytological evaluation, but new evidence is emerging demonstrating that it is enough, and maybe superior, for assessing the burden of nodal tumors during surgery. According to a review of the available literature, the reliability of H and E staining and immunohistochemistry on SLNs performed on frozen sections ranges from 73 % to 96 %.[10]

An independent predictor of chemotherapy response, hormone receptor (HR) status, has been recognized for quite some time. In accordance with the findings of our study, people who had a +ve HER 2 neu status and a triple -ve status responded better to NAT treatment. Those individuals who had an HR+/HER2 tumor had a lower likelihood of obtaining a PCR, but they still had a great prognosis overall. On the other hand, those participants who had an HR−/HER2 tumor only had an excellent prognosis if they achieved a PCR. We discovered that 18 patients have a positive result for HER 2 neu,

Table 6. Compares frozen and paraffin sections (sentinel lymph node and axilla) of the investigated subjects.

	Frozen section	Paraffin section (SLN)	Paraffin section (axilla)	Test value[a]	*P*-value	Sig.
−ve	35 (70.0 %)	38 (76.0 %)	42 (84.0 %)	2.758	0.252	NS
+ve	15 (30.0 %)	12 (24.0 %)	8 (16.0 %)			

P greater than 0.05: nonsignificant (NS); *P* less than 0.05: significant (S).
P less than 0.01: highly significant (HS).
[a] χ2Chi-square test.

Table 7. Displays all variables influencing the positivity and negativity of the paraffin section of sentinel lymph node.

	Paraffin section (SLN)		Test value	*P*-value	Sig.
	Negative No. = 38	Positive No. = 12			
Age (y)					
Mean ± SD	47.42 ± 13.64	48.17 ± 13.23	−0.166•	0.869	NS
Range	22–68	32–65			
Family history					
Negative	15 (39.5 %)	2 (16.7 %)	2.114*	0.146	NS
Positive	23 (60.5 %)	10 (83.3 %)			
Side of tumor					
Right	25 (65.8 %)	6 (50.0 %)	0.965*	0.326	NS
Left	13 (34.2 %)	6 (50.0 %)			
Breast mass size (cm)					
Mean ± SD	3.18 ± 0.68	3.37 ± 0.49	−0.875•	0.386	NS
Range	1.5–4.2	2.3–4.2			
BIRADS					
4	24 (63.2 %)	8 (66.7 %)	0.049*	0.825	NS
5	14 (36.8 %)	4 (33.3 %)			
PT weight					
Mean ± SD	77.42 ± 8.42	79.17 ± 7.78	−0.637•	0.527	NS
Range	57–89	69–90			
6	36 (94.7 %)	5 (41.7 %)			
Number of SLN					
3	21 (55.3 %)	7 (58.3 %)	0.035*	0.852	NS
4	17 (44.7 %)	5 (41.7 %)			

Table 8. Demonstrates the correlation between paraffin sections (sentinel lymph node), frozen sections, and paraffin sections (axilla) between the subjects investigated.

	Paraffin section (SLN)		Test value	*P*-value	Sig.
	Negative No. = 38	Positive No. = 12			
Frozen section					
Negative	35 (92.1 %)	0	36.842	0.000	HS
Positive	3 (7.9 %)	12 (100.0 %)			
Paraffin section (axilla)					
Negative	38 (100.0 %)	4 (33.3 %)	30.159	0.000	HS
Positive	0	8 (66.7 %)			

Table 9. Shows biological classification of patients.

	Patients' number (50) (percentage)
Luminal A	8 (16 %)
Luminal B	7 (14 %)
HER 2neu	18 (36 %)
Triple −ve	17 (34 %)

which corresponds to a percentage of 36 %, and another 17 cases have a result of triple negativity, which corresponds to a percentage of 34 %.[11]

SLN detection rates and FNRs can be improved by utilizing a dual tracer consisting of a radiolabeled colloid and a patent blue dye, which will enhance the number of detected SLNs.[12]

The limited sample size, the short time periods of follow-up, and the sole usage of patent blue dye as opposed to radiolabeled colloid are some other drawbacks of our research.

The majority of women who satisfy certain requirements (T1–2 tumor, 1–2 positive lymph nodes, lack of prior NAT, and those whose breast conservation operation with the entire breast irradiation is planned) should not have ALND. Instead, they should have breast-conserving surgery with whole-breast irradiation. The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) each released their own versions of these guidelines in the years 2014 and 2015, correspondingly. They only advocate completing ALND for people who have greater than 20 positive lymph nodes in their bodies.[13]

Before NAT, axillary lymph node metastases in cancer of the breast were initially identified surgically using magnetometer guidance to identify the specified lymph node. Using a 1.5-mm surgical marker made of stainless steel, the magnetic seed is a cutting-edge medical device. It can be detected by a magnetometer (Sentimag, Endomag, Cambridge, UK), which will inform you of the marker's location and the direction it is facing. By using this method, it is possible to identify the marked node, analogous to detecting a radioactive iodine seed, without having to worry about the regulatory issues that go along with it. They speculate that magnetic seed tagging of positive lymph nodes before NAT might facilitate easy and accurate surgical identification of the marked node.[14]

4.1. Conclusion

Even if an individual meets the criteria for ALND omission, we recommend that a multidisciplinary team decide whether ALND should be skipped following a positive SLNB. The radiologist, by detecting positive axillary nodes during preoperative imaging; the surgeon, by removing more sentinel nodes and clinically suspicious nonsentinel nodes; the pathologist, by indicating a high risk of nonsentinel node metastasis; and the medical oncologist and radiotherapist, by requesting the total number of positive nodes for adjuvant treatment decisions. Because arm lymphatic drainage is more difficult to identify and preserve than breast SLNB, it is likely to need a longer learning curve than breast SLNB. This disparity is reflected in the difference in detection rates and lymphatic drainage dissection described in previous articles (71 % vs. 47 %).[15]

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Conflicts of interest

No conflict of interest.

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