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ORIGINAL ARTICLE

Sentinel lymph node biopsy does not apply to all axillary lymph node-positive breast cancer patients after neoadjuvant chemotherapy

Wen-kai Ge[1,2], Ben Yang[2], Wen-shu Zuo[2], Gang Zheng[2], Ying-qi Dai[1], Chao Han[1], Li Yang[2] & Mei-zhu Zheng[2]

1 School of Medicine and Life Sciences, University of Jinan, Shandong Academy of Medical Sciences, Shandong Cancer Hospital, Jinan, China
2 Department of Surgery II, Shandong Breast Center of Prevention and Treatment, Shandong Cancer Hospital, Jinan, China

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Correspondence
Wen-shu Zuo, Department of Surgery II, Shandong Breast Center of Prevention and Treatment, Shandong Cancer Hospital, Jinan, Shandong 250117, China.
Tel: +86 531 67626822
Fax: +86 531 87984783
Email: cjcpt@public.jn.sd.cn

Wen-kai Ge and Ben Yang are co-authors of this article.

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Abstract

Background: The aim of this study was to investigate the feasibility of sentinel lymph node biopsy (SLNB) after neoadjuant chemotherapy (NAC) in breast cancer patients with confirmed axillary nodal metastases.

Methods: We enrolled 51 patients with breast cancer who received NAC. All patients were proven to have axillary nodal metastases by histopathology biopsy prior to NAC. They all underwent SLNB before breast surgery, and complete axillary lymph node dissection immediately followed.

Results: The identification rate for SLNB was 87.5% (84/96); the false negative rate was 24.5% (12/49). The clinicopathological factors were not significantly correlated with the identification and false negative rate of the SLNB. Lymphatic mapping, blue dye or radionuclide methods tended to decrease the identification rate of SLNB ($P = 0.073$). Clinical nodal status before NAC has a trend to increase the false-negative rates of the SLNB ($P = 0.059$). For patients with N1 clinical axillary lymph nodal status, the identification rate was 93.9%, and the false negative rate was 5.9%, compared with N2-3 patients with 73.9% and 38.9%, respectively.

Conclusions: SLNB is feasible for the patients whose axillary lymph nodal status before NAC is N1. However, for N2-3 patients, SLNB cannot be used as an infallible indicator of non-SLN status.

Introduction

The wide use of sentinel lymph node biopsy (SLNB) as an alternative to axillary lymph node dissection is an important advance in the treatment of patients with early-stage breast cancer. For breast cancer patients who have received neoadjuvant chemotherapy (NAC), axillary lymph node dissection (ALND) is still the standard treatment method. SLNB has been widely adopted as a treatment method for patients who have not received NAC, however, the use of SLNB in patients who have received NAC is controversial. Over the past years, multiple studies have been conducted to identify the feasibility and accuracy of SLNB after NAC. Some studies suggest that SLNB would have a lower detection rate and a higher false negative rate if it was used in NAC patients, and would not accurately reflect the status of non-SLNs.[1,2] It has been suggested that chemotherapy may interfere with the anatomy and physiology of the lymphatics and this may reduce the accuracy of SLNB.[3,4] However, many studies, including some meta-analyses, suggest that SLNB is an accurate predictor of the histopathologic status of axillary lymph nodes.[5–9] However, all of these studies did not distinguish or exclude patients who were suspected or proven to harbour axillary metastases before receiving NAC. Studies have reported that NAC can make the most of axillary lymph node status down staging. Chemotherapy containing anthracyclines and taxanes can reach a response rate of 40%,[10–12] which potentially implies that those patients may not require ALND because the axillary lymph nodes are clinically and pathologically negative. Could SLNB accurately predict the staging of the axillary lymph node after NAC? Is SLNB feasible for patients with positive axillary lymph nodes? In this study, we enrolled patients who had confirmed axillary lymph node metastases by ultrasound-guided fine-needle

aspiration (FNA), to analyze the feasibility of SLNB for axillary lymph node-positive breast cancer patients after NAC.

Materials and methods

Patient population

This single center study was conducted at the Shandong Tumor Hospital. Between 2008 and 2012, 51 patients with breast cancer were enrolled in accordance with the following criteria: (i) IIA-IIIB stage breast cancer patients; (ii) pathological diagnosis clearly confirmed breast cancer; (iii) patients who had confirmed positive axillary lymph node by ultrasound-guided FNA; (iv) without anti-cancer therapy before treatment; (v) received NAC before surgery; and (vi) SLNB and different levels of ALND were a component of their surgical treatment. The basic clinical data of the patients is shown in Table 1.

Table 1 Patient and tumor characteristics

Clinicopathological factors		Number of patients ($n = 51$)	%
Age	Range	25–68	—
	Median	47.8	—
Tumor localization	Upper outer	19	37.3%
	Upper inner	9	17.6%
	Lower outer	6	11.8%
	Lower inner	5	9.8%
	Central	12	23.5%
Histological type	Invasive ductal carcinoma	39	76.5%
	Invasive lobular carcinoma	9	17.6%
	Composite carcinoma	3	5.9%
Tumor classification	T1	9	17.6%
	T2	23	45.1%
	T3	11	21.6%
	T4	8	15.7%
Clinical nodal status	N1	28	54.9%
	N2	16	31.4%
	N3	7	13.7%
Clinical AJCC stage	IIA (T1N1M0)	7	13.7%
	IIB (T2N1M0)	19	37.3%
	IIIA (T1-3N1-3)	13	25.5%
	IIIB (T4N1-2)	7	13.7%
	IIIC	5	9.8%
ER	(–)	22	43.1%
	(+)	29	56.9%
PR	(–)	24	47.1%
	(+)	27	52.9%
HER-2	(–)	21	41.2%
	(+)	17	33.3%
	(++)	8	15.7%
	(+++)	5	9.8%

AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Study design

The preoperative clinical axillary nodal status was assessed by palpation and ultrasonography: N1 metastasis to movable ipsilateral axillary lymph node(s); N2 metastasis in ipsilateral axillary lymph nodes fixed or matted node(s); and N3 metastasis in supraclavicular, infraclavicular, and/or internal mammary lymph nodes. For patients with lymph nodes with high UE scores and with no medulla structure, ultrasound-guided FNA was performed. Patients with no metastases were not included in the group; patients with lymph node metastases received NAC.

Patients chose treatment options voluntarily, after being made aware of advantages and disadvantages of each option. The appropriate treatment programs were developed based on the preoperative clinicopathological factors of patients and all patients received four to eight cycles of anthracycline/taxane-based neoadjuvant chemotherapy. Clinical response was assessed by axillary ultrasonography per two or three cycles according to the Response Evaluation Criteria in Solid Tumors. SLNB was performed during surgery by experienced surgeons.

All of the excised tissues, including the SLNs and axillary lymph nodes, were sent for pathological examination. The SLN was sliced into 2 mm along the axis. Hematoxylin and eosin staining was applied layer by layer or by continuous slice with or without immunohistochemical staining by microscopy by an experienced pathology physician. The response to chemotherapy is evaluated according to the Miller and Payne (MP) histological efficacy evaluation criteria.[13]

Operating methods of sentinel lymph node biopsy (SLNB)

Blue staining was performed 15 minutes prior to surgery using a subcutaneous single injection of 2 to 4 mL of 1% methylene blue (Jiangsu Jumpcan Pharmaceutical Co., Ltd, National Drug Approval No.: H32024827) or 0.5–1 mL of Carbon Nanoparticles Suspension Injection (Chongqing LUMMY Pharmaceutical Co., Ltd, National Drug Approval No.: H20073246) around the nipple, areola area or glandular tissue around the tumor.

The radionuclide method was also applied in this study. A single injection of 0.5~2 mL 99mTc-Sc-labeled sulfur colloid was subcutaneously applied in the surface of the primary tumor six to 18 hours after surgery. Two hours later, single-photon emission computed tomography (SPECT) radionuclide imaging and radiography positioning were applied for SLN imaging.

Lymph nodes were screened for blue staining in the lateral border of pectoralis major muscle, and verified by γ detector for SLN. The resected SLN was dyed blue and detector scanning of the surgical field determined whether there was still a "hot spot." The endpoint was defined as the point where the

Table 2 Tumor characteristics after neodjuvant chemotherapy

		Number ($n = 51$)	%
Neoadjuvant chemotherapy options	TE(C)	19	37.3%
	CEF	14	27.5%
	EC	7	13.7%
	T	11	21.6%
Pathologic tumor response	Grade 1 (no reduction in overall cellularity)	4	7.8%
	Grade 2 (up to 30% loss of tumor cells)	12	23.5%
	Grade 3 (30%-90% loss of tumor cells)	19	37.3%
	Grade 4 (90% loss of tumor cells)	5	9.8%
	Grade 5 (no identifiable malignant cells)	11	21.6%
Pathologic response in lymph node	N-A (no metastasis)	0	0
	N-B (no response to treatment metastases residues)	7	13.7%
	N-C (response to treatment, but still metastases residues)	31	60.8%
	N-D (disappeared after treatment)	13	24.5%
Pathological complete response (metastatic disappearance of primary tumor and lymph node)		11	21.6%

radiation dose was less than 10% of the original. The dyed and/or radionuclide traced lymph nodes, as well as their neighboring visible lymph nodes, were all defined as SLNs. SLNs were sent for a quick frozen pathology examination, and partial or full ALND was performed.

Statistical methods

SPSS 19.0 software was applied and evaluated as per University of Louisville SLNB technique criteria.[14] An χ^2 test was used to compare the sample rate and a Fisher exact test with $\alpha = 0.05$. Single factor analysis applied the fourfold table exact test (Fish exact test).

Results

Patient information and tumor response to neoadjuant chemotherapy

The mean age of the patients was 43.8 years. Twelve patients had skin involvement (T4 disease), 12 patients had multifocal disease (≥2), 26 patients had a family history of breast cancer in a first- or second-degree relative, and the mean tumor size was 3.17 cm. Table 1 shows the clinicopathologic characteristics of patients.

Clinical and pathologic responses to NAC are shown in Table 2. The mean tumor size of the patients was reduced from 3.17 to 2.24 cm. Eleven patients (21.6%) achieved complete pathological remission, and 13 patients (25.5%) achieved complete remission of axillary lymph nodes.

Details of surgical treatment and SLNB

All 51 patients underwent tentative lymphatic mapping and SLNB. Overall, there were 43 (84.3%) successful lymphatic mappings and eight (15.7%) unsuccessful lymphatic mappings. Those patients who had unsuccessful mapping continued to receive ALND. Details of surgical treatment and sentinel lymph node biopsy are shown in Table 3.

An average of 2.5 SLNs was detected in the successfully mapped patients, and 25 patients had ≥1 positive SLN. SLN was the only positive lymph node in nine of these patients. Twelve patients (27.9%) achieved complete remission of axillary lymph nodes, six patients had false negative findings, and the overall calculated false negative rate was 19.4%. Table 4 shows each index of SLNB and pathologic status of SLNs and axillary lymph nodes after surgery.

Table 3 Details of surgical treatment and sentinel lymph node biopsy

	No.	%
Type of surgery performed on primary tumor		
Segmental mastectomy	41	80.4%
Segmental mastectomy	10	19.6%
Method of lymphatic mapping		
Blue dye only	8	15.7%
Radioactive colloid only	7	13.7%
Both	36	70.6%
Location of radiocolloid injection		
Subareolar	17	33.3%
Peritumoral	34	66.7%
Operator		
Chief physician	29	56.7%
Associate Chief Physician	16	31.4%
Other	6	11.8%
SLN identified		
Yes	43	84.3%
No	8	15.7%
Median number of SLNs identified (range)	2.4 (1–7)	

SLN, sentinel lymph node.

Table 4 Pathologic status of sentinel lymph node and axillary lymph nodes after surgery

	Non-SLN status		
SLN status	(+)	(–)	Total
(+)	16	9	25
(–)	6	12	18
Total	22	21	43

Non-SLN, non-sentinel lymph node; SLN, sentinel lymph node. False-negative rate was 19.4% (6/31 * 100%). Sensitivity was 80.6% (25/31 * 100%). Positive prediction rate was 100%. Negative prediction rate was 66.7% (12/18 * 100%). The accuracy rate was 86.0% (37/ 43 * 100%).

SLNB results based on clinical factors

Table 5 summarizes the results of the correlations between the accuracy of SLNB (identification and false-negative rates) and clinicopathological factors. All of the clinicopathological factors shown in Table 5 were not significantly correlated with the identification and the false negative rate of SLNB for patients after NAC. However, lymphatic mapping, blue dye only, and radionuclide only methods, have tended to decrease the identification rate of SLNB ($P = 0.073$). The clinical nodal status prior to treatment tends to increase the false-negative rates of SLNB in patients after NAC ($P = 0.059$).

Table 5 Correlations between the accuracy of sentinel lymph node biopsy (identification and false-negative rates) and clinicopathological factors in breast cancer patients after neodjuvant chemotherapy

Clinicopathological factors	Identification rate (43/51)		False-negative rate (6/31)	
	n (%)	*P*	*n* (%)	*P*
Age				
≥50	22/27 (81.5%)	0.838	4/20 (20%)	1.000
<50	21/24 (87.5%)		2/11 (18.2%)	
Method of lymphatic mapping				
Blue dye only	5/8 (62.5%)	0.073	0/2	0.753
Radioactive colloid only	5/7 (71.4%)		1/4 (25%)	
Both	33/36 (82.1%)		5/25 (20%)	
Location of radiocolloid injection				
Subareolar	12/17 (70.6%)	0.134	2/8 (25%)	0.634
Peritumoral	31/34 (91.7%)		4/23 (17.4%)	
Operator				
Chief physician	26/29 (89.7%)	0.432	4/19 (21.1%)	0.836
Associate Chief Physician	12/16 (75.0%)		1/8 (12.5%)	
Other	5/6 (83.3%)		1/4 (25%)	
Tumor localization				
Upper outer	16/19 (84.2%)	0.992	3/13 (23.1%)	0.905
Central	10/12 (83.3%)		1/6 (16.7%)	
Other	17/20 (85.0%)		2/12 (16.7%)	
Histological type				
Invasive ductal carcinoma	32/39 (82.1%)	0.653	5/23 (21.7%)	0.744
Invasive lobular carcinoma	8/9 (88.9%)		1/6 (16.7%)	
Composite carcinoma	3/3 (100%)		0/2	
Tumor classification				
T1-2	29/32 (90.1%)	0.226	2/20 (10%)	0.151
T3-4	14/19 (73.7%)		4/11 (41.7%)	
Clinical nodal status before treatment				
N1	26/28 (92.9%)	0.143	1/18 (5.9%)	0.059
N2-3	17/23 (73.9%)		5/13 (35.8%)	
Pathologic tumor response				
Grade 1–2	12/16 (75%)	0.450	4/11 (36.4%)	0.175
Grade 3–4	21/24 (87.5%)		2/16 (12.5%)	
Grade 5	10/11 (90.9%)		0/4	
Pathologic response in lymph node				
N-B	5/7 (71.4%)	0.470	2/5 (40%)	0.241
N-C	26/31 (83.9%)		4/26 (15.4%)	
N-D	12/13 (92.3%)		—	

Discussion

In this study, we analyzed whether SLNB is feasible for patients after NAC with documented positive axillary lymph nodes. In our study, the identification rate of the patients receiving NAC was 84.3% (43 of 51). Newman *et al*.'s study of SLNB after NAC in pathologically documented axillary lymph node-positive patients found a high identification rate of 98%.[15] However, a similar study by Lee *et al*. indicated that the identification rate of SLN for patients with positive axillary lymph nodes receiving NAC was significantly lower than the patients who did not receive NAC (77.6% vs. 97% $P < 0.001$).[16] One of the largest trials investigating SLNB after NAC reported that 428 patients underwent SLNB with concomitant ALND after NAC, and the identification rate was 84.8%.[17] The meta-analysis of Kelly *et al*. regarding 24 studies involving a total of 1799 patients who received NAC, followed by SLNB and ALND, indicated an identification rate range between 63–100%, and an average identification rate of 91%.[8] The identification rate result of our study was not significantly different from the results of previously reported multicenter studies evaluating SLNB after NAC, however, all of the patients in our study were documented with positive axillary lymph nodes.

The clinicopathological factors shown in Table 5 were not significantly correlated with the identification rate of SLNB for patients after NAC. But the combined method of lymphatic mapping, compared with blue dye only and the radionuclide only methods, have presented a trend of an increase to the identification rate of SLNB (82.1% vs. 62.5% and 71.4%). Kim *et al*.'s meta-analysis involving 69 studies on SLNB reported that the identification rate of blue staining, radionuclide, and the United method were 83.1%, 89.2%, and 91.9%, respectively ($P = 0.007$).[18]

According to the results of this study, the false-negative rate of patients receiving NAC (19.4%) is higher than that reported in other studies.[8,9] The reason is unclear. A potential explanation could include the following points: first, as a result of the effect of chemotherapy, tumor emboli would occlude the lymphatic system, creating new drainage patterns; second, the effect of chemotherapy in patients with numerous positive nodes maybe uneven, that is, when SLNs are completely eradicated, but residual tumor cells persists in non-SLNs.[19] Thus, SLNB for axillary lymph node-positive breast cancer patients after NAC cannot accurately predict the status of axillary lymph nodes.

In our study, there were no clinicopathological factors influencing the false-negative rate after NAC. Clinical nodal status prior to treatment tends to increase the false-negative rate of SLNB ($P = 0.059$), although not significantly. In N1 patients, the false-negative rate was 5.9% (1/18), while it was as high as 38.9% (5/13) in N2-N3 patients; the identification rate was 92.9% and 73.9%, respectively. In Takahashi *et al*.'s study, the false-negative rate of patients who received NAC related with clinical nodal status before NAC, was 5.5% in N0 patients and 35.5% in N1 patients ($P = 0.001$) and the identification rate of their study between N0 and N1 patients is similar (87.8% vs. 87.3%).[20] Gimbergues *et al*. also found that in patients who received NAC related with clinical nodal status before NAC, the false-negative rate was 0% in N0 patients and 29.6% in N1-2 patients ($P = 0.003$) and the identification rate was 93.9% and 93.7% respectively; they concluded that for patients with clinically positive axillary nodes, SLNB after NAC should be contraindicated.[21] However, in Classe *et al*.'s study on SLNB after NAC, the false-negative rate between patients with or without positive axillary lymph nodes had no significant difference (9.4% vs. 15%, $P = 0.66$), while the identification rate between them was significantly different (94.6% vs. 81.5% $P = 0.008$).[22] Kinoshita *et al*. obtained similar results (97.6% vs. 88.6%).[23] However, the large sample study of Mamounas *et al*. did not indicate differences between the identification rate and false negative rate of SLNB after NAC.[17]

Previous studies have indicated that for patients with confirmed positive axillary lymph nodes prior to chemotherapy, SLNB cannot be used as an infallible indicator of axillary nodal status.[21,24] Our study demonstrated that SLNB is feasible for patients whose clinical axillary nodal status is N1, with an identification rate of 92.9% and a false-negative rate of 5.9%, and compared with results from conventional lymphatic mapping in early-stage disease, these rates are acceptable.[18,25] For patients whose clinical nodal status before NAC is N2-3, the false-negative rate is as high as 38.9%, and the identification rate is not very satisfying (73.9%), SLNB may not accurately predict the axillary node status.

Conclusion

In conclusion, the results of our study indicated that SLNB was feasible for patients whose clinical axillary lymph nodal status before NAC was N1. However, for patients with N2-3 status of clinical axillary lymph nodes, SLN cannot be used as an infallible indicator of non-SLN status.

Disclosure

No authors report any conflict of interest.

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