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Intraoperative Nodal Palpation is a Mandatory Component of Sentinel Lymph Node Biopsy for Breast Cancer

Masakuni Noguchi*[a], Masafumi Inokuchi[a], Emi Morioka[a], Yusuke Haba[a], Akihiro Shioya[b], Sohsuke Yamada[b], Yasuo Iida[c]

[a]*Department of Breast and Endocrine Surgery, Breast Center, Kanazawa Medical University Hospital, Uchinada, Ishikawa, Japan*

[b]*Department of Clinical Pathology, Kanazawa Medical University Hospital, Uchinada, Ishikawa, Japan*

[c]*Department of Mathematics, General education, Kanazawa Medical University, Uchinada, Ishikawa, Japan*

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ABSTRACT

Background: In the era of Z-0011, it is mandatory to decrease not only the false negative rate (FNR) of sentinel lymph node (SLN) biopsy but also the risk of residual metastatic nodes after SLN biopsy.

Method: SLN biopsy with intraoperative nodal palpation (INP) was performed in patients with clinically node-negative (cN0) breast cancer. All identified blue and hot nodes were removed as blue/hot SLNs, and any suspicious palpable nodes were removed as palpable SLNs. Nodes that were incidentally removed with the neighboring blue/hot SLNs were classified as para-SLNs. Patients with positive SLNs on the frozen section underwent axillary lymph node dissection (ALND) except for patients who met the Z-0011 and AMAROS criteria for exemption.

Results: Palpable SLNs and para-SLNs were identified in 202 patients. Of 200 patients, excluding 2 patients only with palpable SLNs, 46 patients had involvements of blue/hot SLNs, and 14 had palpable and para-SLNs harboring additional metastasis. When false negative rate (FNR) was calculated based on blue/hot SLNs and palpable SLNs, the additional use of INP resulted in a FNR of 45.2%. Subsequently, ALND was performed in 43 patients with positive blue/hot or palpable SLNs. Residual nodal involvement was found in 28 (65%) of the 43 patients after removing blue/hot SLNs. However, after removing palpable SLNs, the rate of residual nodal metastases significantly decreased from 65% (28/43) to 36% (13/36) (P=0.0133).

Conclusion: INP decreased both the FNR of SLN biopsy and the risk of residual metastatic nodes after SLN biopsy.

INTRODUCTION

Sentinel lymph node (SLN) biopsy is a standard procedure for patients with clinically node-negative (cN0) breast cancer, playing a crucial role in determining the need for axillary lymph node dissection (ALND). ALND is unnecessary not only in patients with negative SLNs[1,2], but also in those with one or two positive SLNs undergoing breast-conserving surgery (BCS) with whole-breast radiation[3] or total mastectomy with axillary radiation[4]. Although residual disease may remain in the axilla after SLN biopsy in some cases[1-4], low-

***Address for correspondence:**
Masakuni Noguchi, MD, PhD,
Department of Breast and Endocrine Surgery, Kanazawa Medical University Hospital, Daigaku-1-1, Uchinada, Kahoku, Ishikawa, 920-0293, Japan.
Tel: +81762863511
E-mail:nogumasa@kanazawa-med.ac.jp

volume residual disease can be treated with radiotherapy and systemic therapy.[5]

Despite its benefits, it is important to acknowledge that SLN biopsy is not a perfect procedure for assessing the nodal status of the axilla. Although SLNs can be identified through dual mapping using blue dye and radioisotope, it has been suggested that the effacement of primary nodes by gross tumor may interfere with the uptake of blue dye and radioisotope by SLNs[6] (Figure 1).

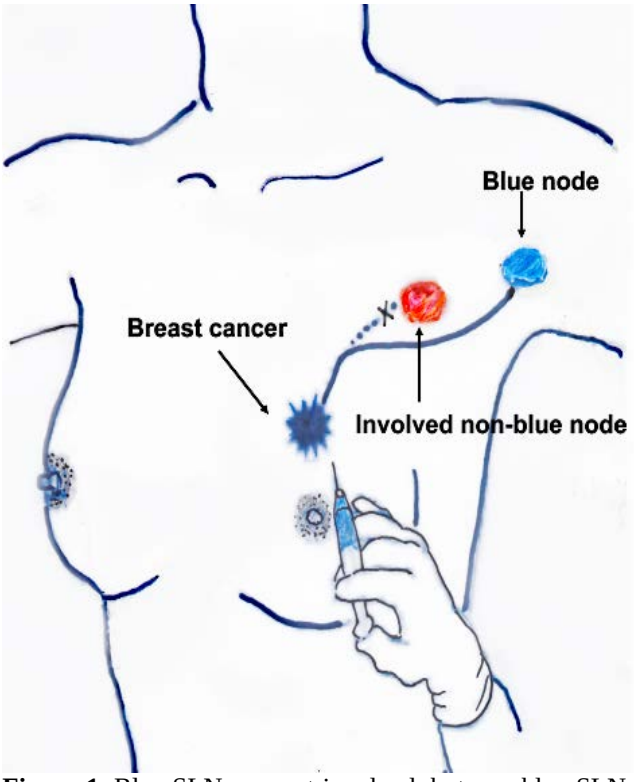

Figure 1. Blue SLN was not involved, but non-blue SLN was grossly involved.

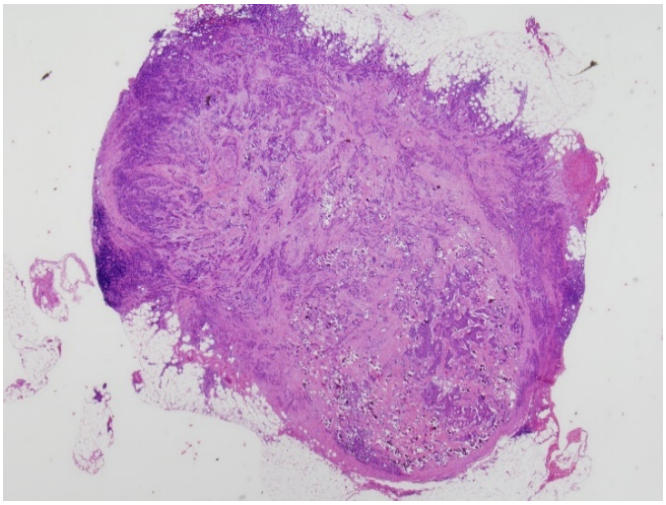

Figure 2 Histology of grossly involved SLN which was neither blue nor hot (H&E staining).

Consequently, in addition to removing blue and hot nodes, all suspicious palpable nodes in the axilla should be removed as SLNs.[7-12] This aligns with guidelines by the American Society of Clinical Oncology (ASCO), which recommend that suspicious palpable nodes, irrespective of their dye or radioisotope uptake should be removed as a part of SLN biopsy.[13] In SLN biopsy, intraoperative nodal palpation (INP) is important to decrease the false negative rate (FNR) of SLN biopsy and minimize the risk of residual metastatic nodes in the axilla after SLN biopsy. Moreover, it is a mandatory component of SLN biopsy even in the era of effective multimodality therapy.[14-16] However, the INP has not been widely investigated. The efficacy of INP mitigating these issues has been inconsistent across different studies[7-12,17,18], with variability occurring due to the subjective selection of sample nodes based solely on the surgeon's personal judgement and expertise. In this study, we evaluated whether INP could reduce both the false negative rate (FNR) of SLN biopsy and the risk of residual metastatic nodes after SLN biopsy. Moreover, we evaluated the relationship between intraoperative nodal status and histological involvement of non-blue/hot SLNs.

METHODS

Study design and participants

This is a cross-sectional study. Participants were selected using a convenience sampling method. Patients who underwent SLN biopsy together with INP were enrolled in the study, although 1132 consecutive patients with T1-2, cN0 breast cancer underwent SLN biopsy from April 2009 to March 2023 in the Kanazawa Medical University hospital. Preoperative diagnosis was established by core needle biopsy. Patients with ductal carcinoma in situ, those with bilateral breast cancer and those who underwent neoadjuvant chemotherapy (NAC) or a second SLN biopsy were excluded. Preoperatively, all patients underwent axillary sonography and magnetic resonance imaging (MRI). Suspicious axillary lymph nodes were examined by aspiration needle cytology, and patients with cytologically positive nodes were excluded from the study because they underwent ALND without SLN biopsy. All patients underwent SLN biopsy with INP, and those found to be SLN-positive subsequently underwent ALND. However, ALND was omitted in patients with less than 3 positive SLNs who met the Z-0011 and AMAROS criteria for exemption.[3-5] Before surgery, all patients provided written informed consent as required by the Clinical Investigation and Ethics Committees of our hospital. Patients' charts were retrospectively reviewed with approval from the institutional review board at Kanazawa Medical University Hospital.

Surgical procedures

Blue and hot SLNs were identified by dual mapping using blue dye and radioisotope. The dual mapping procedure has been described previously in detail.[19] All nodes identified as blue and hot were subsequently removed as blue/hot SLNs. INP was then performed to detect palpable SLNs that were neither blue nor hot. Any suspicious palpable nodes detected during INP were removed and classified as palpable SLNs. Additionally, nodes that were neither blue nor hot but that were incidentally removed in the process of excising blue/hot SLNs were classified as para-SLNs.[12] Subsequently, patients with positive SLNs underwent ALND except for patients who met the Z-0011 and AMAROS criteria for exemption. All patients underwent either breast-conserving surgery (BCS) or total mastectomy including skin- or nipple-sparing mastectomy, depending on the tumor characteristics and the patients' preferences.

Histopathological examination of SLNs and ALNs

During surgery, palpable SLNs, as well as blue/hot SLNs, were cut into 2mm-thick sections. Lymph nodes less than 5mm in a diameter were bisected. These sections were frozen, and histological hematoxylin and eosin (H&E)-stained slides were prepared for microscopic examination. Subsequently, all SLN samples were fixed in neutral buffered formaldehyde. Permanent sections were then cut and subjected to routine H&E staining. Postoperatively, dissected axillary lymph nodes (ALNs) and para-SLNs were bisected, and one section from each node was subjected to H&E staining. Nodes containing macrometastases or micrometastases were considered as positive nodes, whereas those containing no metastases or isolated tumor cells *(itc)* were considered as negative nodes.

Statistical analysis

Categorical variables were reported as frequency and percentage. Continuous variables were expressed as mean and standard deviation. A Chi-square test was used to check the association between intraoperative nodal status and histological involvement of non-blue/hot SLNs. Fisher's exact test was used to evaluate statistical differences in the FNR and the rate of residual nodal metastases after SLN biopsy. P values less than 0.05 were considered significant. All statistical analyses were performed using js-STAR XR+, release 1.4.0 j.

RESULTS

Palpable SLNs and para-SLNs were detected in 202 (17.8%) of the total 1132 patients. These 202 patients were enrolled in the study. Table 1 shows the characteristics of patients, tumors, and surgical procedures. The mean and standard deviation of age were 59.0±13.0 years.

Table 1. The characteristics of patients, tumors, and surgical procedures

Characteristics	N (%)
No. of patients	202
Age of patients (years) (mean ± SD)	59 ± 13
Menopausal status of patients (pre/post)	
Pre	56 (28%)
Post	146 (72%)
Tumor size (mm) (mean ± SD)	16 ± 10
Histological types of tumor	
IDC	177 (88%)
ILC	6 (3%)
IDC+ILC	1 (0%)
Special type of invasive carcinoma	18 (9%)
Molecular subtypes of tumor	
Luminal A type	149 (74%)
Luminal B type	37 (18%)
HER2 type	6 (3%)
Triple negative type	10 (5%)
Surgical procedures	
BCS	103 (51%)
Total mastectomy[#]	99 (49%)
SLN biopsy	159 (79%)
SLN biopsy followed by ALND	43 (21%)

ALND: axillary lymph node dissection; BCS: breast-conserving surgery; SLN: sentinel lymph node
IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma
#: total mastectomy included nipple- or skin-sparing mastectomy

A hundred forty-six (72%) patients were postmenopausal and 177 (88%) patients had invasive ductal carcinoma. When classifying the patients based on molecular subtypes, it was found that 149 (74%) were luminal A type, 37 (18%) were luminal B type, 6 (3%) were HER2 type and 10 (5%) were triple negative type. Of the enrolled patients, 159 of them underwent SLN biopsy alone, and 43 underwent SLN biopsy followed by ALND (Table 1).

Blue/hot SLNs were identified in 200 (99%) of the 202 patients with palpable SLNs. The remaining 2 patients had only palpable SLNs. The rate of SLN identification using dual mapping was 99% without INP and 100% with INP, indicating that the addition of INP did not significantly improve the rate of SLN identification (99% vs. 100%: p=0.4988). Regarding SLN distribution, the average number of blue/hot SLNs per one patient was 1.9±1.2 for the 202 patients. Among the 139 patients with palpable SLNs, the average number of palpable SLNs was 1.2±0.4. For the 56 patients with para-SLNs and the 7 patients with both palpable SLNs and para-SLNs, the average number of para-SLNs was 1.9±0.6.

The study evaluated the relationship between intraoperative nodal status and histological involvement of non-blue/hot SLNs. Among the 202 patients, 33 (16.3%) were found to have involved

palpable SLNs or para-SLNs. Specifically, involved palpable SLNs were identified in 30 (21.6%) of the 139 patients with palpable SLNs, whereas only 3 (5.4%) of 56 patients with para-SLNs had involved para-SLNs. The rate of involved palpable SLNs was significantly higher than the rate of involved para-SLNs (p=0.011). Although para-SLNs were involved in 3 (5.4%) of the 56 patients with para-SLNs, these 3 patients had also involved blue/hot SLNs. In the 7 patients with both palpable SLNs and para-SLNs, there was no involvement detected in the palpable SLNs and para-SLNs (Table 2).

Table 2. The relationship between intraoperative nodal status and histological involvement of non-blue/hot SLNs

Intraoperative nodal status of non-blue/hot SLNs	No. of cases	Histological involvement of non-blue/hot SLNs		
		Involved	Not involved	P-value *
Palpable SLNs	139	30 (21.6%)	109 (78.4%) ┐	p=0.011
Para SLNs	56	3 (5.4%) #	53 (94.6%) ┘	
Palpable and para SLNs	7	0 (0%)	7 (100%)	
Total	202	33 (16.3%)	169 (83.6%)	

#Three cases had not only involved para-SLNs but also involved blue/hot SLNs.
SLNs: sentinel lymph nodes
*Chi-square test

The study additionally evaluated the relationship between the histological involvement of blue/hot SLNs and palpable SLNs, including para-SLNs. Blue/hot SLNs were involved in 46 (23%) of the 200 patients excluding 2 patients only with palpable SLNs; however, in 14 patients with negative blue/hot SLNs, palpable SLNs were found to harbor additional metastases (Figure 2).

Consequently, involved SLNs were identified in 60 patients using a combination of blue/hot SLNs and palpable SLNs. Since patients without involved SLNs did not undergo ALND in this study, the FNR was not determined. When it was calculated based on blue/hot SLNs and palpable SLNs, however, the additional use of INP resulted in a FNR of 45.2%. Moreover, FPR was 17.1% (Table 3).

Table 3. Histological involvement in blue/hot SLNs and palpable SLNs including para-SLNs[&]

Histological involvement of blue/hot SLNs	No. of patients	Histological involvement of palpable SLNs*	
		Positive	Negative
Positive	46 (23%)	17 (37.0%) [a]	29 (63.0%) [b]
Negative	154 (77%)[#]	14 (9.1%) [c]	140 (90.9%) [d] [$]
Total	200 (100%)	31 (15.5%)	169 (84.5%)

&: excluding 2 patients only with palpable SLNs; *: including para-SLNs; #: including 7 patients with isolated tumor cells; SLNs: sentinel lymph nodes; $: The difference was statistically significant (P<0.001); The sensitivity [a/(a+c) x100] =54.8% (95%CI: 0.36. 0.73); the specificity [d/(b+d) x100] =82.8% (95%CI: 0.76. 0.88); the false negative rate [c/(a+c) x100] = 45.2% (95%CI: 0.27. 0.64); the false positive rate [b/(b+d) x100] =17.1% (95%CI: 0.12. 0.24).

Table 4. Residual nodal involvement after removing blue/hot SLNs and palpable SLNs

Types of involved SLNs (No. of cases)	Patients who underwent ALND	Residual nodal involvement (A)	Residual nodal involvement (B)	Residual nodal involvement (C)
No involvement of blue/hot and palpable SLNs (n=140)	0 (0%)	0%	0%	0
Involvement of blue/hot SLNs only (n=29)	14 (48%)	7% (1/14)	7% (1/14)	1
Involvement of palpable SLNs only (n=16)	13 (81%)	75% (12/13)	39% (5/13)	5
Involvement of blue/hot SLNs and palpable SLNs (n=17) ★	16 (94%)	100% (16/16)	75% (12/16)	7
Total (n=202)	43 (21%)	65% (28/43) [a]	42% (18/43) [b]	36% (13/36) [c]

ALND: axillary lymph node dissection; SLNs: sentinel lymph nodes; (A): after removing blue/hot SLNs; (B): after removing blue/hot SLNs and palpable SLNs; (C): when patients with 3 or more than 3 involved blue/hot SLNs and palpable SLNs were excluded; ★: Three patients with involved para-SLNs were included; a vs. b: P=0.05110.; a vs. c: p=0.0133.

ALND was performed in 43 of the 62 patients with involved SLN, but it was omitted in the remaining 19 patients as their patients were compatible with the Z-0011 and AMAROS criteria[3,4]. Subsequently, residual nodal involvement after SLN biopsy was evaluated in the 43 patients who underwent ALND. Residual nodal involvement was present in 28 (65%) of the 43 patients following the removal of blue/hot

SLNs, and in 18 (41.8%) of the 43 patients after removing blue/hot SLNs, palpable SLNs and para-SLNs. Although the use of INP led to a decrease in the rate of residual nodal metastases from 65% to 42%, the difference did not reach statistical significance (P=0.0511). However, the number of patients with 3 or more involved SLNs increased from 2 to 7 by including involved palpable SLNs. ALND is indicated in patients with 3 or more involved SLNs. When these 7 patients were excluded from the analysis, therefore, the rate of residual nodal metastases after SLN biopsy significantly decreased from 65% (28/43) to 36% (13/36) (P=0.0133) (Table 4).

DISCUSSION

SLN biopsy with dual mapping using blue dye and radioisotope is currently a standard procedure as it is associated with higher rates of SLN identification.[20,21] When surgeons use both blue dye and radioisotope, the success rate in identifying SLNs ranges from 87% to 98%, and the FNRs can range from 0% to 25%.[22] In early breast cancer, the American Society of Breast Surgeons recommends achieving an SLN identification rate of 85% with an FNR of 5% or lower.[13] Achieving a low FNR is important as false negative cases may compromise the efficacy of adjuvant radiotherapy and chemotherapy, leading to suboptimal results. Several reasons have been proposed to explain the occurrence of false negative cases, with the most prominent being a heavy tumor burden in the true SLN. This can cause dye and radioisotope to be diverted to a non-SLN due to blocked lymphatic flow[10] (Figure 1). Therefore, it is recommended that all suspicious palpable nodes should be removed in addition to any blue and hot SLNs.[7-13]

Although intraoperative suspicion of nodal metastatic involvement may be assessed by the node's consistency, size, and contour[7,23], in practice, this method is subjective and difficult to standardize. In fact, the sampling rate and involvement rate of suspicious palpable nodes have been inconsistent across previous studies.[7-9,12,17,18,24] In our previous study using the four nodes sampling based on the node's consistency, size, and contour, accuracy was 92%, sensitivity was 77% and specificity was 100%.[23] In our previous study involving axillary reverse mapping, on the other hand, the sampling rate of suspicious palpable nodes significantly decreased from 15% to 5% ($p<0.01$), while the rate of involved palpable SLNs significantly increased from 15% to 31% ($p<0.05$).[12]

As previously mentioned, it is important to maintain an FNR of 5% or lower in SLN biopsy. Previous studies have documented the results of different approaches to achieving this. Gui *et al.*[17] reported an FNR of 4.5% in the SLN biopsy group compared to 0% in the axillary sample group. However, Hoar and Stonelake found that the FNR decreased from 14.3% to 3.6% by performing nodal sampling in addition to the dual mapping.[18] In the present study, the FNR of INP was 45%, although determining the exact FNR was not possible as not all patients underwent ALND. On the other hand, removal of para-SLNs did not effectively reduce the FNR, as these patients had involvements in both para-SLNs and blue/hot SLNs. The observed FNR of 45% was comparatively higher than the rates reported in the other studies involving SLN biopsy.[1,20] Nevertheless, it is important to note that the present study included only 202 patients (18%) who underwent INP among 1132 cases who underwent SLN biopsy.

Recently, ALND can be avoided in selected patients with one or two positive SLNs undergoing BCS with breast radiation[3] or total mastectomy with axillary radiation.[4] Although residual disease may remain in the axilla after SLN biopsy in some cases[1-4], low-volume residual disease can be treated with radiotherapy and systemic therapy.[5] Nevertheless, in order to avoid axillary recurrence, it is important to decrease the risk of residual metastatic nodes after SLN biopsy. In the present study, the rate of residual nodal metastases decreased from 65% to 42%. This difference did not reach statistical significance (P=0.0511). However, given that Z-0011 and AMAROS guidelines indicate ALND if 3 or more SLNs are involved[3,4], patients that met this criterion were excluded from our analysis. Consequently, the rate of residual nodal metastases after SLN biopsy significantly decreased from 65% to 36% (P=0.0133), which is comparable to results from the Z-0011 and AMAROS trials.[3,4]

On the other hand, INP is effective not only in reducing FNR after neoadjuvant chemotherapy (NAC)[14,15] but also in decreasing residual tumor burden in the axilla.[16,25,26] The INP and the dual mapping using blue dye and radioisotope are complementary to each other. The risk of INP may miss small tumoral involvement. However, blue and radioisotope SLN biopsy can detect small tumoral involvement but miss large tumoral involvement that is radioresistant. Tailored axillary surgery (TAS) has been developed to reduce the tumor load to the point where adjuvant axillary radiation can control it. This approach consists of removing all palpable suspicious lymph nodes together with the SLNs, ideally performed with image-guided localization of the clipped node to achieve optimal results.[16,25,26] This procedure is performed on cN+ patients, either after NAC or in the upfront surgical setting. TAS aims to

turn cN+ patients into cN0 patients primarily through the selective removal of palpable suspicious nodes. Following TAS, axillary radiation is administered to treat any remaining nodal disease. Similarly, in targeted axillary dissection (TAD)[27], all nodes containing blue dye radioactivity, or those which were palpable were removed as SLNs after NAC. Nodal radiotherapy is effective in achieving local control in patients with low-volume remaining nodal disease as shown in the Z-0011 and AMAROS trials.[3,4] Thus, INP is a mandatory component of SLN biopsy even in the era of effective multimodality therapy.[14-16] A limitation of this study is the possibility that the removal of suspicious palpable SLNs was preferentially performed in patients with only a few blue/hot SLNs identified. All patients with involved SLNs did not always undergo ALND. ALND was omitted in the patients who were compatible with the Z-0011 and AMAROS criteria.[3,4] Moreover, lack of a specified study design, sampling strategy, and a predetermined sample size may make the findings susceptible to systematic and random error. Further studies are needed to confirm the efficacy of INP during SLN biopsy.

CONCLUSION

Dual mapping is a standard procedure in SLN biopsy as it is associated with higher rates of SLN identification. If a suspicious palpable lymph node is detected during INP, however, it should be considered as an SLN and removed for pathological evaluation, regardless of the presence or absence of radioisotope or dye. INP in the axilla is useful to decrease the FNR of SLN biopsy and the rate and volume of residual metastatic nodes after SLN biopsy. Thus, INP is a mandatory component of SLN biopsy even in the era of effective multimodality therapy.

ETHICAL CONSIDERATIONS

This study was approved by the Ethical Committee of Kanazawa Medical University Hospital (R 106).

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CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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