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Internal Mammary Sentinel Lymph Node Biopsy With Modified Injection Technique

High Visualization Rate and Accurate Staging

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Abstract: Although the 2009 American Joint Committee on Cancer incorporated the internal mammary sentinel lymph node biopsy (IM-SLNB) concept, there has been little change in surgical practice patterns because of the low visualization rate of internal mammary sentinel lymph nodes (IMSLN) with the traditional radiotracer injection technique. In this study, various injection techniques were evaluated in term of the IMSLN visualization rate, and the impact of IM-SLNB on the diagnostic and prognostic value were analyzed.

Clinically, axillary lymph nodes (ALN) negative patients (n = 407) were divided into group A (traditional peritumoral intraparenchymal injection) and group B (modified periareolar intraparenchymal injection). Group B was then separated into group B1 (low volume) and group B2 (high volume) according to the injection volume. Clinically, ALN-positive patients (n = 63) were managed as group B2. Internal mammary sentinel lymph node biopsy was performed for patients with IMSLN visualized.

The IMSLN visualization rate was significantly higher in group B than that in group A (71.1% versus 15.5%, $P < 0.001$), whereas the axillary sentinel lymph nodes were reliably identified in both groups (98.9% versus 98.3%, $P = 0.712$). With high injection volume, group B2 was found to have higher IMSLN visualization rate than group B1 (75.1% versus 45.8%, $P < 0.001$). The IMSLN metastasis rate was only 8.1% (12/149) in clinically ALN-negative patients with successful IM-SLNB, and adjuvant treatment was altered in a small proportion. The IMSLN visualization rate was 69.8% (44/63) in clinically ALN-positive patients with the IMSLN metastasis rate up to 20.5% (9/44), and individual radiotherapy strategy could be guided with the IM-SLNB results.

The modified injection technique (periareolar intraparenchymal, high volume, and ultrasound guidance) significantly improved the IMSLN visualization rate, making the routine IM-SLNB possible in daily practice. Internal mammary sentinel lymph node biopsy could provide individual minimally invasive staging, prognosis, and decision making of the internal mammary radiotherapy, especially for clinically ALN-positive patients.

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Abbreviations: ACR = American College of Radiology, ALN = axillary lymph nodes, BMI = body mass index, IMLN = internal mammary lymph nodes, IMSLN = internal mammary sentinel lymph nodes, IM-SLNB = internal mammary sentinel lymph node biopsy, LIQ = lower inner quadrant, LOQ = lower outer quadrant, SLN = sentinel lymph nodes, SLNB = sentinel lymph node biopsy, UIQ = upper inner quadrant, UOQ = upper outer quadrant.

INTRODUCTION

As the first-echelon nodal drainage sites of breast cancer, the status of axillary lymph nodes (ALN) and internal mammary lymph nodes (IMLN) is valuable both for regional staging and treatment choice. The status of ALN could be routinely evaluated with sentinel lymph node biopsy (SLNB) and/or surgical dissection. Accurate regional staging, however, could not be achieved by depending on the status of the ALN alone, which might lead to understage and under/overtreatment. Interest in metastasis to IMLN culminated with the extended radical mastectomy,¹ but this radical surgical procedure was abandoned because of its extra complications, longer operation time, and no survival benefit.² With the widespread application of effective systemic therapy in the era of molecular subtyping today, it is worth rethinking about whether or not this conclusion in the 1950s still fits into today's clinical practice.

Recently, a meta-analysis, including the MA.20 (n = 1832), the EORTC 22922/10925 (n = 4004), and the French trial (n = 1334) shows that additional regional radiotherapy to the IMLN and medial supraclavicular lymph nodes significantly improves the disease-free survival, distant metastasis free survival, and overall survival in stage I to III breast cancer.³ The inclusion criteria (high-risk patients/no histopathologic confirmation of IMLN) in these studies, however, meant that they could not identify patients who would really benefit from adjuvant radiotherapy, and individual IMLN radiotherapy could not be performed. The internal mammary sentinel lymph node biopsy (IM-SLNB) is a less invasive method for evaluating IMLN than surgical dissection, and this might refine regional staging and allow individual IMLN radiotherapy. Although the 2009 American Joint Committee on Cancer staging incorporated the IM-SLNB concept, there, however, has been little change in surgical practice patterns of IM-SLNB because of the low visualization rate of internal mammary sentinel lymph nodes (IMSLN) with the traditional injection technique.⁴⁻⁶

Several studies have discovered that superficial injection (intradermal, subdermal, periareolar, and subareolar) of radiotracer was hard to identify IMSLN, whereas intraparenchymal injection (peritumoral, intratumoral, or subtumoral) was more reliable.^{4,7-10} These results suggest that the dermal and subdermal lymphatic flow is rarely directed to the internal

mammary region, whereas some intraparenchymal lymphatic flow is directed to the internal mammary region. Unfortunately, with the traditional intraparenchymal injection technique, the internal mammary hotspots were only seen in a small proportion of patients (average 13%, range 0%–37%), which has restricted the clinical studies and daily practice of IM-SLNB to date.^{4–6,11}

In the current study, various injection techniques were evaluated in term of the IMSLNB visualization rate in clinically ALN-negative patients, and the impact of IM-SLNB on staging, prognosis, and prediction of systemic and regional radiotherapy were analyzed both in clinically ALN-negative (NCT01642511) and ALN-positive patients (NCT01668914).

METHODS

From January 2012 to March 2015, 470 patients (clinically ALN-negative 407 and positive 63) from Shandong Cancer Hospital with biopsy-proven invasive breast cancer were enrolled in this study. The median age was 47 years (range, 24–80 years). The exclusion criteria included pregnancy, metastatic breast cancer, and neoadjuvant chemotherapy. The study was approved by the ethics committee and each patient provided informed consent.

Radiotracer Injection and Grouping

Sulfur colloid was labeled with ^{99m}Tc after filtering through a Millipore filter with a pore size of 220 nm. In each patient, ^{99m}Tc-labeled sulfur colloid (^{99m}Tc-SC) was injected into the parenchyma under the ultrasound guidance 3 to 18 hours before surgery.

Clinically Axillary Lymph Nodes-Negative (n = 407)

From January 2012 to November 2014, the patients with clinically negative ALN (clinically abnormal ALN and negative

fine needle aspiration cytology were also included) were classified into 2 groups according to exploratory stage and radiotracer injection technique:

Traditional Technique: Group A (Peritumoral Intraparenchymal Injection)

The first 58 patients were enrolled in this group between January 2012 and April 2012, the median age of patients was 45.5 years (range, 26–70 years). Each patient received an intraparenchymal injection of ^{99m}Tc-SC (18.5–44.4 MBq/0.4–1.0 mL) at 1 to 2 points surrounding the primary tumor.

Modified Technique: Group B (Periareolar Intraparenchymal Injection)

A total of 349 patients were included in this group from May 2012 to November 2014. The median age of patients was 48 years (range, 24–80 years). Two syringes of 9.25 to 18.5 MBq ^{99m}Tc-SC in 0.2 to 0.7 mL volume were injected intraparenchymally at the 6 and 12 o'clock positions 0.5 to 1.0 cm from areola (about 2.0–4.0 cm from the nipple) (Fig. 1).

Group B was then separated into 2 groups according to the radiotracer injection volume: group B1, low volume (<0.5 mL/point, n = 48); group B2, high volume (≥0.5 mL/point, n = 301).

Clinically Axillary Lymph Nodes -Positive (n = 63)

From February 2014 to March 2015, 63 patients with clinically positive ALN (confirmed with positive ALN by fine needle aspiration cytology) were managed as group B2.

Preoperative Lymphoscintigraphy

All patients underwent a preoperative lymphoscintigraphy with a digital gamma camera computer system (Toshiba GCA

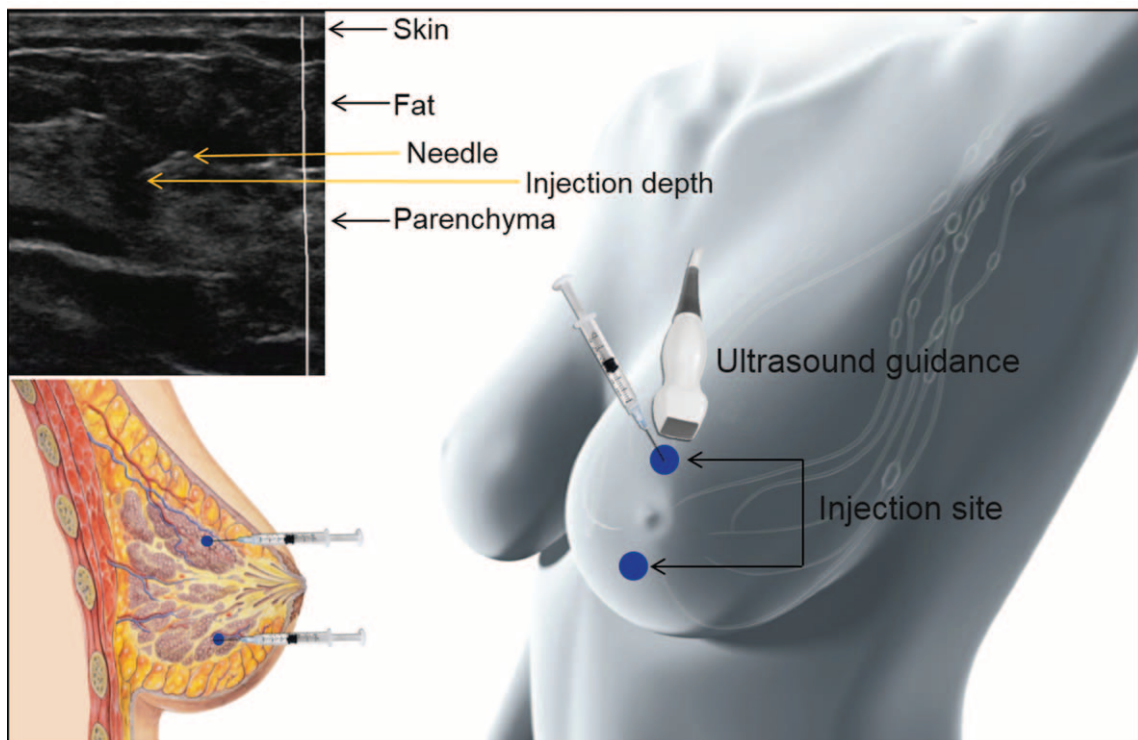


FIGURE 1. Schematic model of the modified injection techniques.

901AHG). Matrix size was 256×256 or 512×512 , and the magnification factor was 1. Anterior and oblique anterior images were performed with the patients in the prone position and the injection was administered 30 minutes before surgery. The focal accumulations of radioactivity (hotspots) outside the injection sites were identified as sentinel lymph nodes (SLN).

INTERNAL MAMMARY SENTINEL LYMPH NODE BIOPSY

Internal mammary sentinel lymph node biopsy was performed in all patients with IMSLN visualized on preoperative lymphoscintigraphy and/or detected by the intraoperative gamma probe; all hotspots in the internal mammary basin were harvested. The IM-SLNB was usually performed using the mastectomy incision. In breast-conserving therapy, IM-SLNB was performed through the same incision when the tumors were located in the medial position, and a small additional horizontal incision (2.5–3.0 cm) over the hotspot interspace was made for IM-SLNB in patients with lateral tumors. Intraoperative identification of the IMSLN was based on gamma probe detection (Neoprobe, Neo2000 gamma detection system, Johnson and Johnson). Postoperative chest x-ray was performed in case of accidental pleural lesion.

Sample Size

Results of previous studies showed that approximately 13% (from 0% to 37%) of IMSLN were identified after traditional peritumoral injection.^{4–11} To be able to detect an improvement of IMSLN visualization rate at least 50% in the modified injection group, at the 5% significance level, minimum 31 patients per group were required to reach a power of 90% (2-sided test).¹²

Statistical Analysis

The data were analyzed with the SPSS 17.0 software package. χ^2 test or Fisher exact test was performed to compare the visualization rates among the groups, and the *t* test or Mann–Whitney test was used to compare the differences in means between the groups. A *P* value <0.05 was considered significant.

RESULTS

Visualization Rate of Internal Mammary Sentinel Lymph Nodes

The visualization rate of IMSLN was analyzed in clinically ALN-negative patients, and the clinicopathologic characteristics of these 407 enrolled patients are presented in Table 1. The visualization rate of IMSLN by preoperative lymphoscintigraphy was significantly higher in group B (63.6%, 222/349) than that in group A (13.8%, 8/58, $P < 0.001$), and the visualization rate of axillary sentinel lymph nodes (ASLN) was similar in both groups (87.4% versus 77.6%, $P = 0.149$) (Table 2).

The visualization rate of SLN was improved by the intraoperative gamma probe: group A (axilla: 77.6% \rightarrow 98.3%, 57/58, $P = 0.001$; internal mammary: 13.8% \rightarrow 15.5%, 9/58, $P = 0.794$) and group B (axilla: 87.4% \rightarrow 98.9%, 345/349, $P < 0.001$; internal mammary: 63.6% \rightarrow 71.1%, 248/349, $P = 0.036$) (Figure 2). The IMSLN visualization rate by the intraoperative gamma probe was significantly higher in group B compared with group A (71.1% versus 15.5%, $P < 0.001$), and ASLN were reliably identified in both groups (98.9% versus 98.3%, $P = 0.712$).

In the group of patients receiving periareolar intraparenchymal injection (group B, $n = 349$), only radiotracer volume ($P = 0.002$) were significantly correlated with the IMSLN visualization rate. Patients age, body mass index (BMI), mammographic density, tumor size, tumor location, tumor type, radiotracer intensity, and time interval (between injection and SLNB) did not affect the frequency of IMSLN visualization (all $P > 0.05$; Table 3).

The radiotracer injection volume were analyzed in group B, and the IMSLN visualization rate for patients with 0.2, 0.3, 0.4, 0.5, 0.6, and 0.7 mL/point injection volume was 38.5%, 42.9%, 52.4%, 71.9%, 78.7%, and 85.7%, respectively (Figure 3). The internal mammary hotspots were more frequently seen in patients with high volume of radiotracer (group B2: ≥ 0.5 mL/point) compared those with low volume (group B1: < 0.5 mL/point) (75.1% versus 45.8%, $P < 0.001$).

In clinically ALN-positive group (managed as group B2), there were 44 of 63 patients who showed internal mammary hotspots. Except for the ALN status, clinically ALN-positive group and group B2 were well-balanced with regard to patient's age, BMI, mammographic density, tumor size, tumor location, tumor type, radiotracer intensity, radiotracer volume, and time interval between injection and SLNB (all $P > 0.05$, data not shown), and the IMSLN visualization rate was similar in both groups (69.8% versus 75.1%, $P = 0.388$).

INTERNAL MAMMARY SENTINEL LYMPH NODE BIOPSY

In the patients with internal mammary drainage (257 for clinically ALN-negative and 44 for clinically ALN-positive patients, respectively), IM-SLNB was performed in 65.4% patients (197/301), with the success rate was 98.0% (193/197) and the median number of IMSLN was 1 (total 315; range 1–5). The IMSLN were concentrated in the second and third intercostal space (Figure 4). A small pleural lesion was noted intraoperatively in 5.1% (10/197) and no pneumothorax was seen postoperatively on chest x-rays. Intraoperative bleeding from the internal mammary artery occurred in 9.1% patients (18/197), and was successfully resolved. In addition, no side effect associated with the radiotracer injection was observed in this study.

Change in Staging and Treatment

Clinically Axillary Lymph Nodes-Negative

In this group, IMSLN were positive in 8.1% patients (12/149) who underwent successful IM-SLNB. Of these 12 patients, 7 had positive ALN and 5 had positive IMSLN only. In the patients who underwent successful IM-SLNB, lymph node staging was changed in 8.1% patients, and IMLN radiotherapy was guided by these results; however, systemic treatment was changed in only 3.4% of patients.

Clinically Axillary Lymph Nodes-Positive

The IMSLN was positive in 20.5% patients (9/44) who underwent successful IM-SLNB. Based on unfavorable primary tumor characteristics and/or ALN metastasis, chemotherapy was indicated in all these 9 patients, and the IM-SLNB did not affect the adjuvant systemic therapy. The IMLN radiotherapy, however, could be individually performed in positive IMSLN patients, and could be avoided in negative IMSLN patients. The individual radiotherapy strategy could be arrived in all these 44 patients with the guidance of IM-SLNB.

TABLE 1. Descriptive Characteristics of Eligible Patients

Characteristic	Group A (Traditional Technique)		Group B (Modified Technique)		P
	No.	%	No.	%	
No. of patients	58	349			
Age, y					0.102
Median	45.5	48			
Range	26–70	24–80			
≤50	43	74.1	220	63.0	
>50	15	25.9	129	37.0	
BMI					0.227
Median	23.2	24.0			
Range	17.9–31.2	16.7–36.5			
Mammographic density*					0.904
ACR 1	1	1.7	19	5.4	
ACR 2	33	56.9	173	49.6	
ACR 3	22	37.9	148	42.4	
ACR 4	2	3.4	9	2.6	
Tumor size					0.876
T1	31	53.4	191	54.7	
T2	26	44.8	151	43.3	
T3	1	1.7	7	2.0	
Tumor location					0.700
UOQ	25	43.1	181	51.9	
LOQ	12	20.7	35	10.0	
UIQ	14	24.1	80	22.9	
LIQ	5	8.6	18	5.2	
Central	2	3.4	35	10.0	
Tumor type					0.352
Ductal	49	84.5	310	88.8	
Lobular	3	5.2	12	3.4	
Mixed	2	3.4	8	2.3	
Other	4	6.9	19	5.4	
Radiotracer intensity, MBq	36.667	33.855	0.099		
Radiotracer volume, mL/point	0.478	0.515	0.222		
Time intervals between injection and SLNB					0.823
3–5 hours	27	46.6	168	48.1	
16–18 hours	31	53.4	181	51.9	

ACR = American College of Radiology, BMI = body mass index, LIQ = lower inner quadrant, LOQ = lower outer quadrant, UIQ = upper inner quadrant, UOQ = upper outer quadrant.

*Mammographic density was assessed by 2 radiologists of the University Hospital Ulm applying the classification of the ACR including 4 categories: ACR 1 = almost entirely fat, glandular tissue <25%, ACR 2 = scattered fibroglandular densities (ca. 25–50% of breast), ACR 3 = heterogeneously breast dense (ca. 51–75% of breast), and ACR 4 = extremely dense (>75% of breast).

DISCUSSION

In addition to the ALN, the IMLN drainage is also an important lymphatic channel of the breast. The National Comprehensive Cancer Network Clinical Practice Guidelines recommend to strongly consider radiotherapy to IMLN for patients with positive ALN or tumor >5 cm (category 2B), noting “radiotherapy should be given to the IMLN that are clinically or pathologically positive; otherwise the treatment to the IMLN is at the discretion of the treating radiation oncologist” on this topic.¹³ A minimally invasive method, however, is still lacked to evaluate the status of IMLN, and individual IMLN radiotherapy could not be performed.

The IM-SLNB is a less invasive method for assessing IMLN than surgical dissection, and may affect decision making for regional and systemic therapy.⁴ Unfortunately, the internal mammary hotspots are only visualized in a small proportion of patients (average 13%, range 0%–37%) with the traditional injection technique, which has restricted the clinical studies and daily practice of IM-SLNB to date.^{4–6,11} In the initial stage of this study, the IMSLN visualization rate was 15.5% in patients with traditional peritumoral injection, and this result was in accordance with the previous studies (Table 4).^{7–10,14,15}

Current evidence has shown that the ASLN receive the lymphatic drainage from not only the primary tumor area, but

TABLE 2. Sentinel Lymph Nodes Visualization by Preoperative Lymphoscintigraphy

Characteristic	Group A (Traditional Technique)		Group B (Modified Technique)	
	No.	%	No.	%
No. of patients	58	349		
Location of SLN	46	79.3	325	93.1
Total axilla	45	77.6	297	87.4
Total internal mammary	8	13.8	222	63.6
Axilla only	38	65.5	103	29.5
Internal mammary only	1	1.7	28	8.0
Axilla + internal mammary	7	12.1	194	55.6
No location	12	20.7	24	6.9

SLN = sentinel lymph nodes.

also the entire breast organ.^{16,17} Tanis et al¹⁸ described that the breast parenchyma has extensive lymphatic network and has rich anastomoses with the superficial cutaneous lymph plexus of the developing skin. It is considered that radiotracer, wherever injected, could flow to the same ASLN. Based on the above new concept of ASLN, we hypothesized that the IMSLN receive lymphatic drainage from not only the primary tumor area, but also the entire breast organ (in other words, the radiotracer could flow to the same IMSLN wherever injected). Based on this hypothesis of the internal mammary lymphatic drainage pattern, we injected radiotracer intraparenchymally into 2 sites of the breast to achieve a relatively high visualization rate of IMSLN. The injection sites were chosen at the 6 and 12 o'clock positions 0.5 to 1.0 cm from areola (about 2.0–4.0 cm from the nipple), because the parenchyma was relatively rich as compared with the tumor site, and the shine-through phenomenon could be avoided as compared with 3 and 9 o'clock positions.¹⁹ Meanwhile, the IMSLN detected by our modified technique (6 and

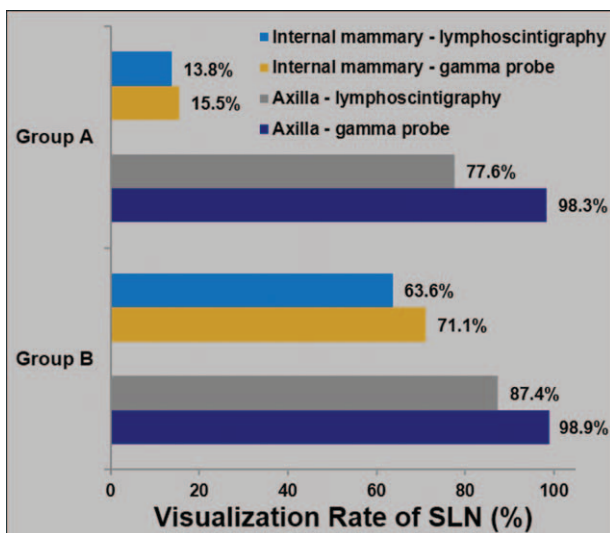


FIGURE 2. Sentinel lymph nodes visualization rate according to different group by preoperative lymphoscintigraphy and/or intraoperative gamma probe.

TABLE 3. Characteristic Correlation in Patients With Internal Mammary Sentinel Lymph Nodes Visualization

Characteristic	IMSLN Identification		P
	Yes	No	
No. of patients	248	101	
Age, years			0.057
Median	47	49	
Range	24–79	31–80	
BMI			0.488
Median	23.9	24.1	
Range	16.7–36.5	17.2–32.0	
Mammographic density			0.553
ACR 1	10	9	
ACR 2	126	47	
ACR 3	105	43	
ACR 4	7	2	
Tumor size			0.079
T1	132	59	
T2	111	40	
T3	5	2	
Tumor location			0.535
UOQ	131	50	
LOQ	26	9	
UIQ	54	26	
LIQ	12	6	
Central	25	10	
Tumor type			0.814
Ductal	221	89	
Lobular	8	4	
Mixed	5	3	
Other	14	5	
Radiotracer intensity, MBq	33.633	34.373	0.124
Radiotracer volume, mL/point	0.530	0.479	0.002
Time intervals between injection and SLNB			0.082
3–5 hours	112	56	
16–18 hours	136	45	

ACR = American College of Radiology, BMI = body mass index, IMSLN = internal mammary sentinel lymph nodes, LIQ = lower inner quadrant, LOQ = lower outer quadrant, SLNB = sentinel lymph node biopsy, UIQ = upper inner quadrant, UOQ = upper outer quadrant.

12 o'clock positions periareolar intraparenchymal injection) were concentrated in the second and third intercostal space, which were consistent with the traditional technique (peritumoral intraparenchymal injection),^{4–6} and also coincided with the sites of IMLN metastasis, which was reported in the previous studies of extended radical mastectomy.^{20,21} These results indirectly confirmed our hypothesis of the internal mammary lymphatic drainage pattern.

The visualization rate of IMSLN is partially associated with breast density,^{6,22} and local pressure at the injection site could be increased with a high volume of radiotracer, which contributed to IMSLN visualization. In current study, the

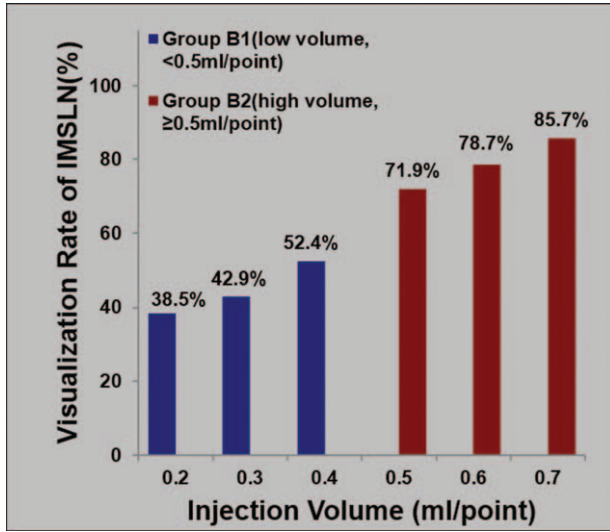


FIGURE 3. Internal mammary sentinel lymph nodes visualization rates according to different injection volume.

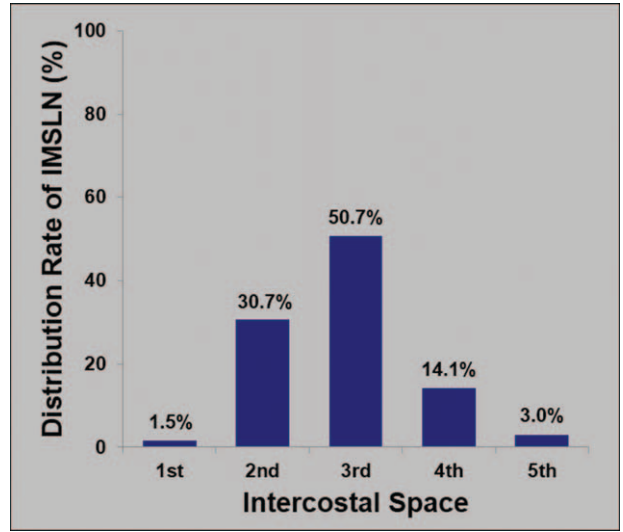


FIGURE 4. The distribution location of internal mammary sentinel lymph nodes.

internal mammary hotspots were commonly seen in patients who were injected with a higher volume of radiotracer. For this reason, we divided group B into 2 groups, according to the radiotracer injection volume, and found that the IMSLN visualization rate could be further improved with high injection volume.

Another technical issue, which could affect the IMSLN visualization rate is how to ensure the radiotracer is injected intraparenchymally. Intraparenchymal injection requires considerable experience, and it is often difficult to inject radiotracer into the parenchyma to the correct depth. Thus, the variation in IMSLN visualization rate between different studies could be partially attributed to the technical differences in radiotracer injection.⁷⁻¹⁰ In our study, the radiotracer was injected under ultrasound guidance, and the accuracy of injection depth was

guaranteed so that the radiotracer was drained to the internal mammary region.

Owing to such a high IMSLN visualization rate with our modified injection technique, more clinical benefit would be emerged. As IM-SLNB leads to more complete regional staging,²³ it provides guidance for tailored regional therapy, with maximal benefit and minimal invasion. Recently, several studies reported that radiotherapy to the IMLN and medial supraclavicular lymph nodes could improve breast cancer survival in high-risk IMLN metastasis patients (positive ALN and/or medial/central tumor location).^{24,25} These eligibility criteria, however, might induce over- and undertreatment, because high risk did not mean IMLN metastasis and low risk did not mean IMLN negative. Because IMLN radiotherapy increased cardiac and pulmonary side effects, the appropriate identification of

TABLE 4. Studies of Sentinel Lymph Nodes Visualization With Different Injection Site (No. (%))

Authors	Year	No. of Patients	Injection Site	Successful Visualization	
				Axilla	Internal Mammary
Shimazu ⁷	2003	41	Intraparenchymal (peritumoral)	20 (48.8)	1 (2.4)
		40	Intraparenchymal (subtumoral)	28 (70.0)	15 (37.5)
		70	Periareolar	59 (84.3)	3 (4.3)
		45	Intradermal	39 (86.7)	0
Park ⁸	2005	83	Intraparenchymal (peritumoral)	NA	14 (16.9)
		58	Intradermal	NA	0
Rodier ⁹	2007	216	Intraparenchymal (peritumoral)	158 (73.2)	29 (13.4)
		216	Periareolar	184 (85.2)	13 (6.0)
Garcia-Manero ¹⁰	2010	74	Intraparenchymal (intra-tumoral)	72 (97.3)	8 (10.8)
		59	Periareolar	59 (100)	0
Wang ¹⁴ (our center)	2007	636	Subdermal	625 (98.3)	25 (3.9)
Sun ¹⁵ (our center)	2010	290	Subdermal	286 (98.6)	4 (1.4)
This study	2015	58	Intraparenchymal (peritumoral)	57 (98.3)	9 (15.5)
		349	Intraparenchymal (periareolar)	345 (98.9)	248 (71.1)

SLN = sentinel lymph nodes.

patients who could benefit from adjuvant radiotherapy is essential, and should be based on IM-SLN metastasis rather than high-risk estimation only. Internal mammary lymph nodes radiotherapy should be tailored and balanced between the potential benefit and toxicity, and IM-SLNB guidance could achieve this goal.²⁶

Although several studies indicated that the presence of IMSLN metastasis rarely influenced adjuvant treatment strategy and did not affect overall survival,^{5,6,27} it should be interpreted with caution for the limitation of their study population. Studies of SLNB (both axilla and internal mammary) have been limited to the clinically ALN-negative patients, and it is adequate for the axillary staging. More attention, however, should be focused on the IM-SLNB in clinically ALN-positive patients, as IMLN metastasis is mostly found concomitantly with ALN metastasis.²¹ In our study, the IMSLN metastasis rate was only 8.1% in clinically ALN-negative patient, and adjuvant treatment was altered in a small proportion. The IMSLN metastasis rate was 20.5% in clinically ALN-positive patients, and individual radiotherapy strategy, however, could be guided with the IM-SLNB results. As a consequence, previous IM-SLNB studies failed to evaluate the status of IMLN who really were in need; we can see from the above results that there are a group of patients (clinically ALN-positive) who could really benefit from the IM-SLNB.

The basic problem in this study is the same as all the previous research: unlike in the axilla, a backup lymph node dissection have been performed, we could not verify the accuracy of IM-SLNB directly. Although the distribution of IMSLN detected by our modified technique exactly coincides with the sites of IMLN metastasis, which was reported in the previous studies of extended radical mastectomy,^{20,21} validation study (eg, involving IM-SLNB followed by complete IMLN dissection) should be required to confirm that the IMSLN could accurately reflect the nodal status of internal mammary basin before the clinical application of IM-SLNB.

In conclusion, the modified injection technique (periareolar intraparenchymal, high volume, and ultrasound guidance) significantly improved the IMSLN visualization rate, making the routine IM-SLNB possible in daily practice. Internal mammary sentinel lymph node biopsy could provide individual minimally invasive staging, prognosis, and decision making of the internal mammary radiotherapy for breast cancer patients, especially for clinically ALN-positive patients.

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