—**Original**—

Sentinel Lymph Node Detection, Location, and Number on SPECT/CT Can Help Predict Pathological Axillary Lymph Node Metastasis in Women with Breast Cancer

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Background: Use of radiocolloids for sentinel lymph node (SLN) detection in breast cancer (BC) offers the advantage of utilizing single-photon emission computed tomography/computed tomography (SPECT/CT). This study explored whether SPECT/CT findings can predict pathological axillary lymph node (ALN) metastasis.

Methods: A consecutive series of patients with invasive BC (clinical stage, T1-3, N0, and M0) who underwent SLN biopsy (SLNB) using SPECT/CT between January 2011 and December 2016 were included. SLN detection, location, and number on SPECT/CT, number of excised SLNs, and clinical and pathological characteristics were analyzed in relation to pathological ALN metastasis.

Results: Data from 408 patients (412 cases) with BC were analyzed. Patient age ranged from 28 to 93 years (mean: 59). SPECT/CT identified one to four SLNs (mean: 1.3) in 407 cases (98.8%) and no SLNs in 5 cases (1.2%). Of the 407 cases with at least one identified SLN, SLNs were solely in level I of the axilla in 394 cases (96.8%), both in and outside level I in 12 (2.9%), and solely outside of level I in 1 (0.2%). The number of ALNs removed via SLNB ranged from one to eight (mean: 2.0). SPECT/CT findings, including absence of SLN detection ($P<0.001$), SLN locations outside of axillary level I ($P<0.001$), and an increased number of SLNs ($P=0.034$), as well as removal of ≥3 SLNs ($P=0.028$), were significantly correlated with pathological ALN metastasis.

Conclusions: SLNB with SPECT/CT yields useful information on pathological ALN metastasis in BC patients. (J Nippon Med Sch 2025; 92: 170–180)

Key words: breast cancer, sentinel lymph node biopsy, SPECT/CT, axillary lymph node metastasis

Introduction

The sentinel lymph node (SLN) is the first node reached by lymphatic drainage and where metastasis occurs[1]. In women with clinically node-negative breast cancer (BC), SLN biopsy (SLNB) is a safe and reliable procedure to diagnose axillary lymph node (ALN) metastasis[2]. ALN dissection (ALND) can be safely avoided in patients without SLN metastases[3,4]. In addition, the results of a previous randomized controlled trial indicate that ALND is unnecessary even for patients with positive SLNs if the pathological size of the metastasis is 2 mm or smaller, if one to two nodes are positive with breast-conserving surgery followed by whole-breast irradiation, or if patients undergo radiation therapy for regional nodes[5–7]. SLNB is currently a gold-standard method in patients with clinically node-negative BC.

SLNs can be detected by using blue dyes or radiocolloids. Use of radioactive tracers is superior to using blue

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dyes because trapped radiocolloids in SLNs can be detected without skin incision. Lymphoscintigraphy is a common imaging modality to identify SLNs that contain radioactive tracers[8–10], and the additional use of hybrid single-photon emission computed tomography (SPECT)/computed tomography (CT) imaging can provide further valuable information on SLNs, including their anatomical location, size, shape, and probability pathological ALN metastasis, all of which facilitate an accurate SLNB[11–14]. Although SLN SPECT/CT yields valuable information, the rate of SLN detection with an intraoperative gamma probe and/or blue dye is reported to be high[15], which limits the use of SPECT/CT to a small number of hospitals.

ALNs are classified on the basis of their anatomical location[16]. Level I is the bottom level, below the lateral border of the pectoralis minor muscle. Level II lies underneath the pectoralis minor muscle, and level III is between the medial border of the pectoralis minor muscle and the tendon of the subclavius. In most BC patients, lymphatic drainage primarily goes to the axilla and enters the level I axillary lymph nodes, and almost all SLNs are in level I[13,14]. However, a few studies that used lymphoscintigraphy and/or SPECT/CT showed that some patients had potential drainage to SLNs outside level I of the axilla, such as level II or III of the axilla, internal mammary, supraclavicular, or intramammary regions[11,17–19]. Preoperative identification of these drainage sites could help surgical planning.

SLN SPECT/CT has been performed for almost all BC patients treated with SLNB in our hospital; however, the real-world data have not yet been analyzed. Several studies reported that SLN detection, location, and number on SPECT/CT correlated with the presence of pathological metastasis in ALNs[13,18,20,21]. However, the patient groups and methods of these studies varied, as follows: stage 0 and III cases were included[18,21], the tumor periphery was included as the injection site for the radioactive tracer[13,18], and cases where SLNs were detected only in axillary level I were targeted[20]. The present study retrospectively analyzed real-world SLN SPECT/CT data from our hospital and focused on whether information from SLN SPECT/CT, such as the detection, location, and number of SLNs, could predict pathological ALN metastasis. Our real-world data are from patients that received tracer injections under the areola in all instances, and all cases were classified as stage I or II. Therefore, as compared with previous reports, our data better reflect practical clinical settings. Additionally, this study analyzed whether clinical and pathological characteristics correlated with the presence of pathological ALN metastasis.

Materials and Methods

Patients

This study was approved by the Ethics Committee of Nippon Medical School Hospital (approval number: B-2022-572)[22]. Informed consent was not obtained from any patient, as approval was assumed to have been obtained by posting this study on the hospital website, unless a patient objected.

The inclusion criteria for this study were as follows: A consecutive series of women with biopsy-confirmed invasive BC (clinical stage T1-3, N0, and M0 [I-IIB]) and SLNB performed between January 2011 and December 2016, with SLN SPECT/CT imaging performed the day before or the day of SLNB. SLNB was performed for all patients with clinical node-negative BC, except noninvasive carcinoma. SPECT/CT was routinely performed for all patients who underwent SLNB. The exclusion criteria were treatment with neoadjuvant chemotherapy or neoadjuvant endocrine therapy or previous ipsilateral axillary surgery.

At our hospital, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is currently used for initial assessment of most BC patients. Consequently, an increased number of patients are excluded from initial surgery with SLNB because of a diagnosis of metastasis-positive axillary lymph nodes (ALNs). Instead, a larger proportion of patients undergoes neoadjuvant therapy. Conversely, ALND is more frequently omitted even when pathological SLN metastasis is present. This study analyzed data from patients treated before these changes in practice.

SLN Scintigraphy with SPECT/CT

All patients underwent SLN scintigraphy with SPECT/CT. Approximately 37-74 MBq of Tc-99 m-phytate (Techne Phytate Kit, Fujifilm, Japan) in a total volume of 1 mL was injected into a subareolar site with a 26-gauge needle 1 day before surgery or on the day of surgery. With the patient in supine position, anterior, left anterior oblique, and right anterior oblique planar images of the chest were acquired with a dual-head gamma camera (BrightView; Philips Japan, Tokyo, Japan) at 3 hours after the injection. SPECT/CT images were acquired immediately after the planar acquisitions by using a SPECT/CT hybrid system equipped with a dual-head gamma camera, Symbia T2 (Siemens Healthcare Japan, Tokyo, Japan).

A low-energy, high-resolution collimator was used. The image resolution was 128 × 128 pixels, pixel size was 4.8 mm, and the energy window was set to a 140 keV photopeak with a 20% symmetrical energy window. A total of 30 projection images were acquired over an orbit of 360° in 6° increments at a rate of 15 seconds per projection. The SPECT images were reconstructed using an iterative image reconstruction algorithm, Flash 3D, with six subsets and eight iterations. A non-contrast-enhanced CT scan (tube voltage: 110 keV; tube current time product: 10-40 mA; detector configuration: 2 × 4 mm; matrix: 256 × 256 pixels; reconstruction thickness: 5 mm) was also performed for the SPECT/CT image acquisition.

Data on the detection, location, and number of SLNs on SPECT/CT were retrieved via electronic records. The location of SLNs was classified as level I, II, or III of the axilla and other specified interpectoral (Rotter's nodes), supraclavicular, internal mammary, intramammary, and other areas.

SLNB and Surgery

A handheld gamma probe (Gamma Finder II) was used to identify radioactive lymph nodes in the axilla after induction of anesthesia and before the start of surgery. Just before beginning surgery, a blue dye (Indigocarmine Injection, Daiichi Sankyo, Japan) of a 1-mL volume was subdermally injected into the areola, followed by a gentle massage of the injection site for approximately 1 minute.

All hot radioactive nodes detected with the gamma probe and blue nodes were removed. A hot node was defined as a node with a radioactivity value of 10% or more, as compared with the hottest node with the highest radioactivity. Non-blue, non-hot nodes suspected of metastasis are those that are enlarged on palpation and removed. Furthermore, non-blue, non-hot nodes located close to SLNs are sometimes removed unintentionally. These non-blue, non-hot nodes were also classified as SLNs.

In instances where SLNs are not identifiable on SPECT/CT, ALND is not routinely planned. Instead, SLNs are identified using a blue dye or intraoperative gamma probe. Should these methods also fail to identify SLNs, enlarged ALNs detected through palpation are excised.

All removed SLNs were examined ex vivo with the gamma probe to count the radioactivity and classified as blue hot nodes, hot-only nodes, blue-only nodes, and non-blue, non-hot nodes. All removed SLNs were immediately sent to the pathology department for intraoperative histological examination. In this study period, level I and II ALND was routinely performed in patients with metastases in SLNs, irrespective of the size of metastatic foci or the number of metastatic nodes.

Pathological Examination

All removed SLNs were intraoperatively examined for metastases, using frozen sections comprising divided SLNs of approximately 2-mm thickness along a short axis stained with hematoxylin and eosin. SLNs were fixed with 20% buffered formalin over 24 hours and subsequently embedded in paraffin. The paraffin-embedded sections of these SLNs were again examined for metastases using hematoxylin and eosin staining.

The removed tissues were fixed with 20% buffered formalin over 24 hours and subsequently cut and divided into blocks embedded in paraffin. Estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki67 levels were evaluated using immunohistochemical staining. ER and PgR expressions were classified as positive (≥10%) or negative (<10%). HER2 was scored as 0, 1+, 2+, or 3+ and classified as positive for scores of 3+ and 2+ with an HER2/CEP17 ratio of ≥2.0 via in situ hybridization. The Ki67 labeling index was classified as 0-15%, 16-30%, or 31% or higher.

Clinical and Pathological Characteristics

The factors analyzed for correlation with ALN metastasis were patient age at surgery, pathological tumor size (maximum diameter of invasive lesion), histologic type, nuclear grade, ER, PgR, HER2, Ki67, numbers and areas of SLNs detected on SPECT/CT, numbers of ALNs removed during SLNB, numbers of SLNs diagnosed as metastases, numbers of ALNs, and numbers of metastatic ALNs removed via ALND. Invasive tumor sizes were categorized as pT1 (≤20 mm), pT2 (21-50 mm), and pT3 (≥51 mm). ALN metastasis was categorized as no metastasis (pN0), micrometastasis (pN1mi), 1 to 3 metastatic nodes (pN1a), and four or more metastatic nodes (pN2-3).

Statistical Analysis

Pearson's chi-square test was used to analyze correlations of these factors with pathological ALN metastases. P values of less than 0.05 were considered statistically significant. The statistical analyses were performed using BellCurve for Excel (SSRI. Inc. Japan).

Results

Data from 408 patients (412 cases) with BC, including four patients with bilateral BC, were included in the analysis. The numbers and locations of SLNs identified by SPECT/CT and patient and tumor characteristics are shown in **Table 1**. Patient age ranged from 28 to 93 years (median: 59 years). Pathological tumor size ranged from 3 to 140 mm (mean: 21 mm).

SPECT/CT detected at least one SLN in 407 cases, an SLN detection rate of 98.8%. The mean number of detected SLNs was 1.3, ranging from one to four. Specifically, one SLN was detected in 305 (74.0%) cases, two SLNs in 79 (19.2%) cases, and three to four SLNs in 23 (5.6%) cases (**Table 1**).

Among the 407 cases, SLNs were solely in level I of the axilla in 394 cases (96.8%), both in and outside level I in 12 (2.9%), and solely outside level I in 1 (0.2%). Among the 13 cases with at least one SLN detected outside of level I, SLNs were detected in levels I and II in seven cases (53.8%); levels I and III in one case (7.7%); levels I, II, and III in one case (7.7%); level I and Rotter's area in two cases (15.4%); level I and the internal mammary area in one case (7.7%); and Rotter's area only in one case (7.7%). Among the 13 cases with SLNs identified outside of axillary level I, three cases are presented herein with SLN scintigraphy and SPECT/CT images (**Fig. 1〜3**).

The mean number of harvested SLNs via SLNB was 2.0 (range, 1-8) nodes (**Table 1**). In five cases without an SLN detected on SPECT/CT, a blue-only node was intraoperatively identified in two cases, a hot-only node was intraoperatively identified using a gamma probe in one case, and at least one suspiciously large non-blue, non-hot node (suggesting metastasis) was intraoperatively identified using palpation in two cases. In all 13 cases in which at least one SLN was detected by SPECT/CT outside of axillary level I, at least one SLN was harvested and pathologically examined intraoperatively.

Five cases with no detected SLNs were reviewed. The ages of the patients ranged from 61 to 76 years, and the median age was 69, which was older than the median age of 59 for the entire sample. The tumor size was pT2 in four cases and pT3 in one case, indicating that the tumors were larger than the mean tumor size for the entire sample. The number of excised ALNs was one in one patient and two in four patients.

The ALNs were pathologically negative for metastasis in 326 cases (79.1%) and positive for metastasis in 86 cases (20.9%) (**Table 1**). Of the five cases with no SLNs detected by SPECT/CT, four (80.0%) were pathologically positive for ALN metastasis. In these cases with positive ALN metastasis, two ALNs were excised in each case and both ALNs were pathologically positive for metastasis. The incidence of pathological ALN metastasis (80.0%) was significantly higher than for cases with detected SLNs ($P<0.001$). The clinical and pathological characteristics of the five patients are described below.

Regarding the area of SLNs detected by SPECT/CT, of the 13 cases with at least one SLN identified outside axillary level I, 10 (76.9%) were positive for metastasis of at least one SLN in axillary level I, which was significantly higher than the incidence for patients with SLNs detected only in axillary level I (18.3%; $P<0.001$). The clinical and pathological characteristics of the 13 cases with SLNs detected outside axillary level I are as follows. The age of the patients ranged from 37 to 94 years, with a median age of 56, which is close to the median age of 59 for the entire sample. The tumor size was pT1 and pT2 both in six cases and pT3 in one case, indicating slightly larger tumors as compared with the entire sample. The number of SLNs detected by SPECT/CT ranged from one to four, with a mean of 2.3, which was slightly higher than the mean of 1.3 for the entire sample. The number of excised SLNs ranged from one to six, with a mean number of 2.9, which is higher than the mean of 2.0 for the entire sample. In 10 cases of pathological SLN metastasis, the numbers of positive SLNs ranged from one to four.

Regarding the number of SLNs detected on SPECT/CT, which ranged from one to four, the number of detected SLNs significantly positively correlated with the incidence (from 17.7% to 66.7%) of pathological ALN metastasis ($P=0.034$) (**Table 1**).

There was no statistically significant correlation between the number of removed SLNs and the presence of pathological ALN metastasis (**Table 1**); however, when the number of removed SLNs was classified as ≤2 SLNs and ≥3 SLNs, the latter was significantly associated with a pathological ALN metastasis (P-value, 0.028).

Among the clinical and pathological characteristics analyzed, greater invasive tumor size (from pT1 to pT3) was significantly associated with an increase in incidence from 15.7% to 33.3% for pathological ALN metastases ($P=0.011$) (**Table 1**). Conversely, patient age, histological type, nuclear grade, ER, HER2, PgR, and Ki67 were not correlated with incidence of pathological ALN metastasis. In addition, no clinical or pathological characteristic was significantly correlated with SLN detection or location (**Table 2**).

Table 1 SLN detection, location, and number using SPECT/CT, and clinical and pathological characteristics correlated with SLN metastasis

	Total	%	Pathological ALN metastasis				P-value	Size and number of pathological ALN metastasis					
			Negative	%	Positive	%		Micromets	%	1-3	%	4 or more	%
Total	412	100	326	79.1	86	20.9		9	2.2	69	16.7	8	1.9
SLN location													
None	5	1.2	1	20.0	4	80.0		0	0.0	1	20.0	3	60.0
Level I only	394	95.6	322	81.7	72	18.3		9	2.3	62	15.7	1	0.3
Outside of Level I	13	3.2	3	23.1	10	76.9	<0.001	0	0.0	6	46.2	4	30.8
No. of SLNs detected by SPECT/CT													
0	5	1.2	1	20.0	4	80.0		0	0.0	1	20.0	3	60.0
1	305	74.0	251	82.3	54	17.7		5	1.6	49	16.1	0	0.0
2	79	19.2	60	75.9	19	24.1		3	3.8	12	15.2	4	5.1
3	20	4.9	13	65.0	7	35.0		1	5.0	6	30.0	0	0.0
4	3	0.7	1	33.3	2	66.7	0.034	0	0.0	1	33.3	1	33.3
No. of SLNs and non-SLNs excised													
1	176	42.7	143	81.3	33	18.8		1	0.6	31	17.6	1	0.6
2	126	30.6	104	82.5	22	17.5		1	0.8	17	13.5	4	3.2
3	69	16.7	49	71.0	20	29.0		5	7.2	15	21.7	0	0.0
4	27	6.6	20	74.1	7	25.9		1	3.7	3	11.1	3	11.1
5-	14	3.4	10	71.4	4	28.6	0.46	1	7.1	3	21.4	0	0.0
Age													
≤55	182	44.2	142	78.0	40	22.0		4	2.2	34	18.7	2	1.1
≥56	230	55.8	184	80.0	46	20.0	0.62	5	2.2	35	15.2	6	2.6
pT													
1	229	55.6	193	84.3	36	15.7		3	1.3	32	14.0	1	0.4
2	153	37.1	113	73.9	40	26.1		5	3.3	31	20.3	4	2.6
3	30	7.3	20	66.7	10	33.3	0.011	1	3.3	6	20.0	3	10.0
Histological type													
IDC NST	351	85.2	275	78.3	76	21.7		8	2.3	61	17.4	7	2.0
Mucinous	22	5.3	22	100.0	0	0.0		0	0.0	0	0.0	0	0.0
Apocrine	8	1.9	7	87.5	1	12.5		1	12.5	0	0.0	0	0.0
IMPC	9	2.2	5	55.6	4	44.4		0	0.0	3	33.3	1	11.1
ILC	22	5.3	17	77.3	5	22.7	0.17	0	0.0	5	22.7	0	0.0
Nuclear grade													
1	214	51.9	177	82.7	37	17.3		5	2.3	29	13.6	3	1.4
2	141	34.2	105	74.5	36	25.5		2	1.4	29	20.6	5	3.5
3	57	13.8	44	77.2	13	22.8	0.16	2	3.5	11	19.3	0	0.0
Estrogen receptor													
Negative	68	16.5	57	83.8	11	16.2		3	4.4	6	8.8	2	2.9
Positive	344	83.5	269	78.2	75	21.8	0.30	6	1.7	63	18.3	6	1.7
Progesterone receptor													
Negative	116	28.2	95	81.9	21	18.1		4	3.4	15	12.9	2	1.7
Positive	296	71.8	231	78.0	65	22.0	0.75	5	1.7	54	18.2	6	2.0
HER2													
Negative	369	89.6	294	79.7	75	20.3		9	2.4	60	16.3	6	1.6
Positive	43	10.4	32	74.4	11	25.6	0.64	0	0.0	9	20.9	2	4.7
Ki67 Labeling index (%) *													
≤15	265	64.3	213	80.4	52	19.6		5	1.9	43	16.2	4	1.5
16-30	87	21.1	67	77.0	20	23.0		2	2.3	15	17.2	3	3.4
≥31	55	13.3	41	74.5	14	25.5	0.56	2	3.6	11	20.0	1	1.8

*Data from three cases are missing.

HER2, human epidermal growth factor receptor 2; IDC NST, invasive ductal carcinoma of no special type; ILC, invasive lobular carcinoma; IMPC, invasive micropapillary carcinoma; micromets, micrometastasis; No., number; SLN, sentinel lymph node; SPECT/CT, single-photon emission computed tomography/computed tomography.

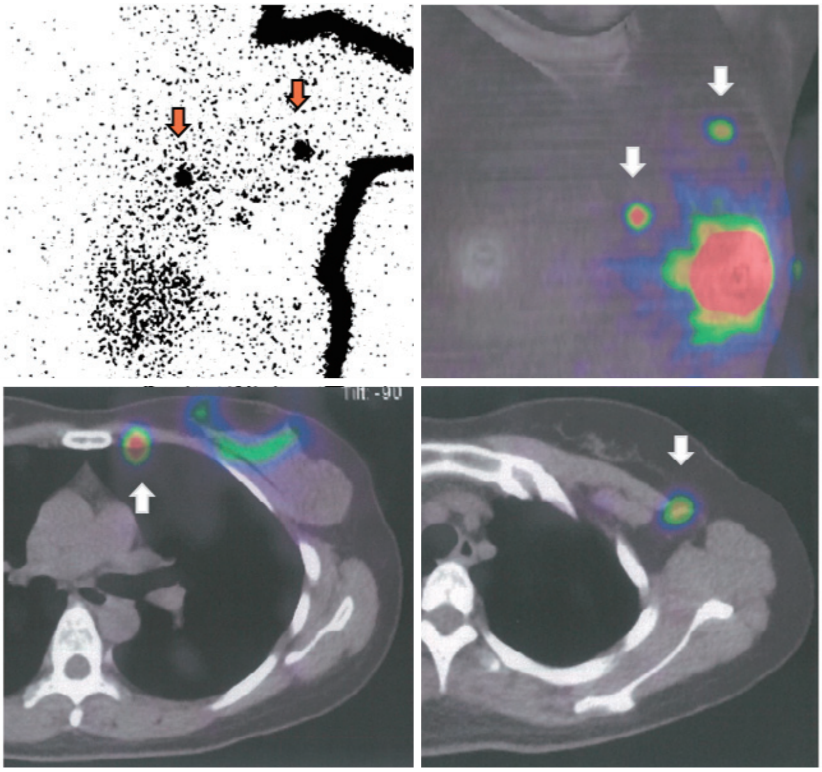
A  B
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Fig. 1 A 37-year-old woman with clinical stage IIA (T2 N0 M0) left-sided BC. One SLN was detected in axillary level I and another in the internal mammary area. Both SLNs were excised, and no pathological metastasis was identified.
Lymphoscintigraphy (planar image) (A) and SPECT/CT (MIP image) (B) show two SLNs, one in the axilla and the other outside the axilla. SPECT/CT (horizontal image) shows one SLN in the internal mammary area (C) and another in the axillary level I (D).
MIP, maximum intensity projection; SLN, sentinel lymph node; SPECT/CT, single-photon emission computed tomography/computed tomography.

Discussion

The SLN detection rate in the present study was approximately 99%, which was similar to previously reported rates for SPECT/CT[13,14]. Of the 407 cases in which SLNs were identified, 406 (99.8%) had at least one SLN detected in axillary level I. Of these 406 cases, other SLNs were identified outside of axillary level I in 12 cases (3.0%). The gist of SLN theory is that there are special lymph nodes to which tumor lymphatic flows first. The present results support this SLN theory, as almost all SLNs were in axillary level I. These results slightly differed from previous findings[13,18,20,21] in that SLN theory applied to most cases, perhaps because our study targeted early-stage cases and the tracer was injected subcutaneously under the areola in all instances. These methods for SLNB reflect practical clinical settings.

Controversy exists as to whether tracers should be injected in subdermal overlying skin, the areola, or the peritumoral or intratumoral area during SLNB[23]. Intratumoral tracer administration resulted in lower SLN detection rates, which required a second radiotracer injection[24]. SLN detection rates, however, did not significantly differ between superficial and deep injections of radioactive tracers[23]. Deep injections of radioactive tracers more frequently detect extra-axillary SLNs[23]; however, this may not significantly affect clinical management because these SLNs are not usually removed[25]. The tracer was subdermally injected in the areola in all the present patients, and the rate of SLNs detected outside axillary level I was low; an internal mammary SLN was detected in only one patient (**Fig. 1**).

An important theory of SLNs is that metastases form first in the SLN during cancer progression; however, false-negative cases with no metastases in the SLN and positive metastases in non-SLNs have been reported in previous trials in which ALND was performed after SLNB. Meta-analysis of these studies showed that the false-negative rate of SLNB was 7.3%[2]. However, the

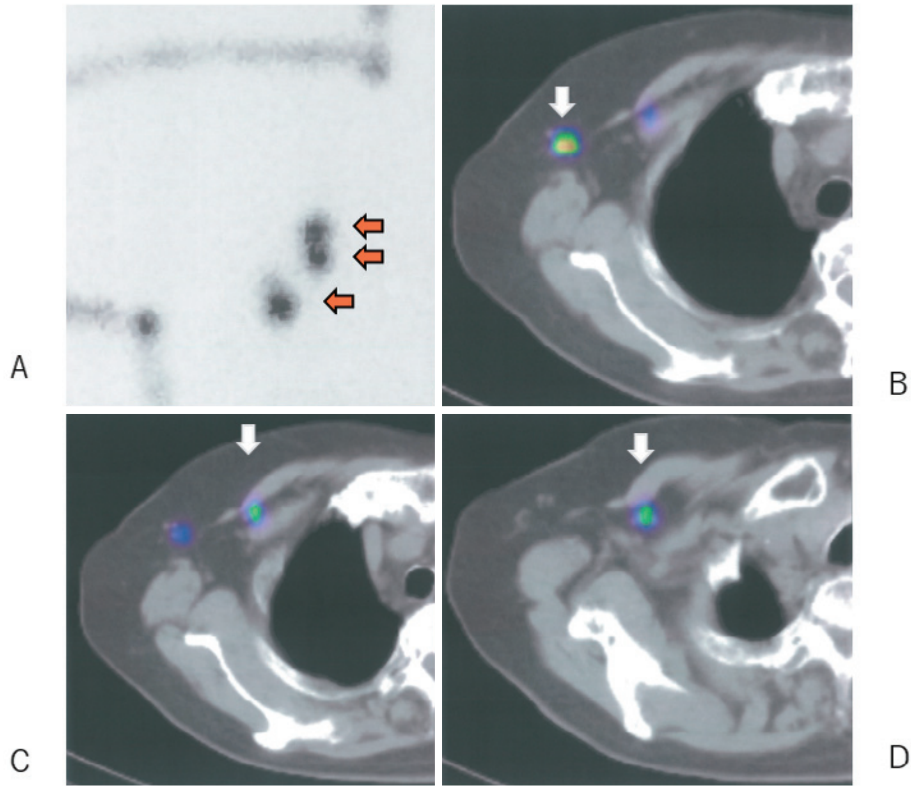

Fig. 2 An 83-year-old woman with clinical stage IIA (T2 N0 M0) right-sided BC. One SLN was detected in axillary level I and two SLNs were detected in Rotter's area. All three SLNs were excised, and no pathological metastasis was identified intraoperatively in frozen sections; however, one SLN was later diagnosed with metastasis in permanent sections.
Lymphoscintigraphy (planar image) (A) shows three SLNs. SPECT/CT (horizontal image) shows one SLN in axillary level I (B) and two SLNs in Rotter's area (C, D).
SLN, sentinel lymph node; SPECT/CT, single-photon emission computed tomography/computed tomography.

ALND range does not include Rotter's area, axillary level III, or the internal mammary area; thus, the false-negative rate of SLNB was calculated mostly within the axillary level I region[2–4]. Consequently, the frequency of skip metastases to regions outside axillary level I was not clarified in previous studies.

Pathological ALN metastasis was found in 4 of 5 cases in which no SLN was detected and in 10 of 13 cases in which SLNs were detected outside of axillary level I, which indicates a significantly higher frequency of positive metastases in ALNs than in cases with SLNs identified only in axillary level I. In cases for which SLN theory does not apply, there is the option of performing ALND at the beginning. However, there are cases in which ALN metastases are negative without detection of SLN, in which case ALND is overtreatment. To prevent such overtreatment, the following protocol has been developed. First, use dye to identify SLNs intraoperatively; second, use a gamma probe to search for areas with even slightly elevated radioactivity; and third, use palpation to identify ALNs suspected of harboring metastases.

The absence of SLN detection by SPECT/CT indicates a condition where the SLN concept is inapplicable, resulting in a significantly higher frequency of metastasis to ALNs. Similar studies have reported that the number of ALNs positive for metastasis is significantly higher in cases where SLNs are not detected by lymphoscintigraphy or SPECT/CT, as compared to cases with detected SLNs[8,21,26]. Although prognostic analysis was not performed in this study, our results strongly suggest that there are significantly more positive cases of axillary lymph node metastasis in the case group where the SLN theory is not applied than in the case group where it is applied, thus leading to a lower survival rate.

Metastases were detected in ALNs in axillary level I in all patients for whom the SLN concept was likely inap-

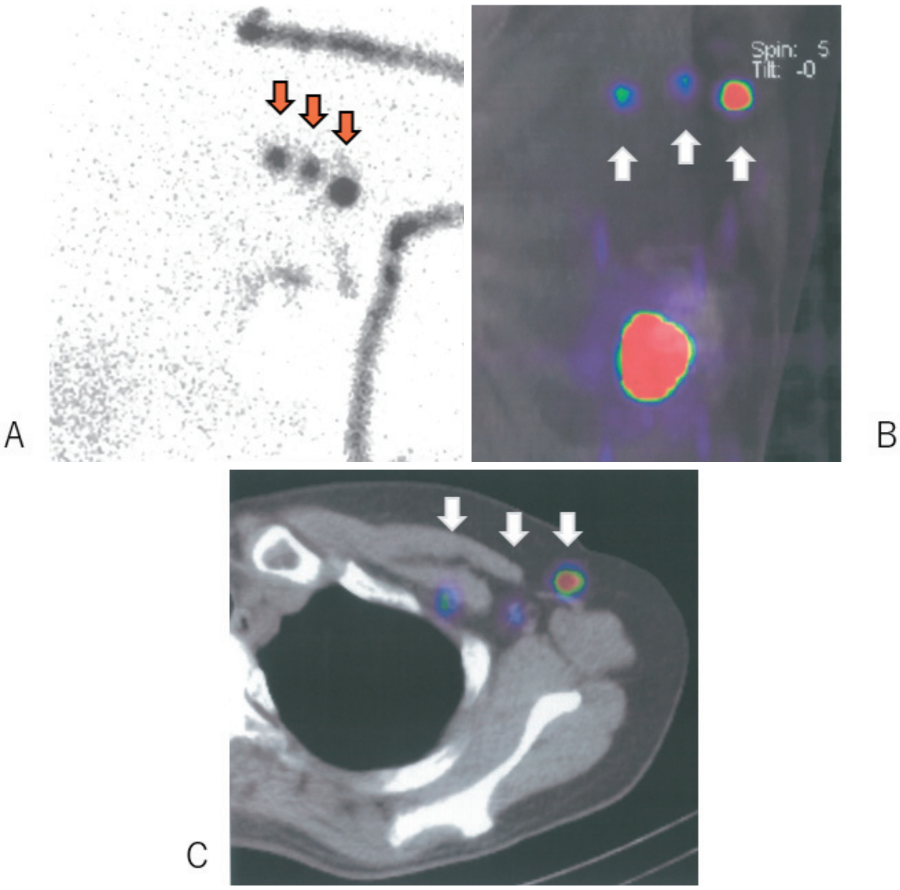

Fig. 3 A 46-year-old woman with clinical stage I (T1c N0 M0) left-sided BC. Two SLNs were detected in axillary level I and one in axillary level II. Six SLNs, including non-blue, non-hot nodes, were excised from axillary levels I and II, and two SLNs were intraoperatively diagnosed with metastasis.
Lymphoscintigraphy (planar image) (A) and SPECT/CT (MIP image) (B) show three SLNs. SPECT/CT (horizontal image) (C) shows two SLNs in the axillary level I and one SLN in the axillary level II.
MIP, maximum intensity projection; SLN, sentinel lymph node; SPECT/CT, single-photon emission computed tomography/computed tomography.

plicable. These results indicate that tumor lymphatic flows enter the SLNs located in axillary level I in the early stages. Then, the first metastases form in the SLNs, and there are very few false-negative cases in which a metastasis skips axillary level I lymph nodes and spreads to other areas. The present study showed that the incidence of ALN metastasis increased as the number of SLNs detected increased. Furthermore, as compared with cases of SLNs detected only in axillary level I, the incidence of ALN metastasis was higher for patients with SLNs detected outside axillary level I and much higher for patients with no detected SLNs. Similar results were reported in previous studies[8,10,18,20,21,26]. These results indicate that most SLNs are present only in axillary level I in the early stages; when metastases begin to form in these SLNs, lymphatic flows change and increase to non-SLNs in axillary level I. Those flows increase to other non-SLNs outside axillary level I and lymphatic flows are ultimately totally blocked in some cases.

In this study, an increased number of SLNs removed by SLNB significantly correlated with a higher incidence of pathological ALN metastasis when comparing groups with one or two SLNs versus three or more SLNs. When the SLN concept begins to fail because metastases form in SLNs, the number of detected and subsequently excised SLNs increases. Consequently, the number of excised SLNs correlates with the rate of pathological ALN metastasis, consistent with the findings of a previous study[20].

SLNB has been the standard of care for patients with early BC and clinically node-negative disease and has spared many patients from the adverse effects of ALND,

Table 2 Clinical and pathological characteristics correlated with SLN detection and location on SPECT/CT

	Total	%	Location of sentinel lymph node						P-value
			Level I only	%	Outside Level I	%	None	%	
Total	412	100.0	394	95.6	13	3.2	5	1.2	
Age									
≤55	182	44.2	176	96.7	6	3.3	0	0.0	
≥56	230	55.8	218	94.8	7	3.0	5	2.2	0.30
pT									
1	229	55.6	223	97.4	6	2.6	0	0.0	
2	153	37.1	143	93.5	6	3.9	4	2.6	
3	30	7.3	28	93.3	1	3.3	1	3.3	0.46
Histological type									
IDC NST	351	85.2	338	96.3	9	2.6	4	1.1	
Mucinous	22	5.3	20	90.9	2	9.1	0	0.0	
Apocrine	8	1.9	8	100.0	0	0.0	0	0.0	
IMPC	9	2.2	7	77.8	2	22.2	0	0.0	
ILC	22	5.3	21	95.5	0	0.0	1	4.5	0.56
Nuclear grade									
1	214	51.9	206	96.3	7	3.3	1	0.5	
2	141	34.2	134	95.0	4	2.8	3	2.1	
3	57	13.8	54	94.7	2	3.5	1	1.8	0.93
Estrogen receptor									
Negative	68	16.5	64	94.1	2	2.9	2	2.9	
Positive	344	83.5	330	95.9	11	3.2	3	0.9	0.36
Progesterone receptor									
Negative	116	28.2	110	94.8	4	3.4	2	1.7	
Positive	296	71.8	284	95.9	9	3.0	3	1.0	0.99
HER2									
Negative	369	89.6	354	95.9	12	3.3	3	0.8	
Positive	43	10.4	40	93.0	1	2.3	2	4.7	0.090
Ki67 Labeling index (%)*									
≤15	265	64.3	255	96.2	8	3.0	2	0.8	
16-30	87	21.1	83	95.4	2	2.3	2	2.3	
≥31	55	13.3	51	92.7	3	5.5	1	1.8	0.95

*Data from three cases are missing.
HER2, human epidermal growth factor receptor 2; IDC NST, invasive ductal carcinoma of no special type; ILC, invasive lobular carcinoma; IMPC, invasive micropapillary carcinoma; SLN, sentinel lymph node; SPECT/CT, single-photon emission computed tomography/computed tomography.

such as postoperative lymphedema, pain, and numbness[2–7,27]. It is now possible to select patients with positive SLN metastasis for whom ALND can be omitted and for whom radiotherapy can substitute for ALND[5–7,27]. Cases for which SLNB is unnecessary will likely be identified in the future[28].

In most cases of early BC, SLNs can be detected with an intraoperative gamma probe alone. The advantage of SPECT/CT is that it can detect SLNs located outside the axilla, which are unlikely to be detected by intraoperative gamma probing alone. This study indicates that SLNs are in axillary level I in almost all cases of clinically node-negative early BC. Therefore, it is unclear if SPECT/CT should be recommended for all these patients. Additionally, implementation of SPECT/CT necessitates access to specialized equipment and the involvement of highly trained personnel, resulting in substantial costs. These factors are considered significant disadvantages of SPECT/CT, limiting its use to a small number of facilities in Japan. In cases of previous ipsilateral axillary surgery, however, it has been reported that SLNs are more frequently detected outside axillary level I[29,30]. Therefore, the use of SPECT/CT is recommended in these cases. This study excluded patients with a history of axillary surgery and showed that no clinical and pathological characteristics correlated with the detection or location of SLNs, which indicates that it is difficult to select patients suitable for SPECT/CT.

This study had limitations. First, the present patients were from an earlier treatment period. FDG-PET/CT is currently performed for almost all cases before starting treatment, enabling accurate diagnosis of initial ALN metastasis. In such ALN metastasis-positive cases, neoadjuvant treatment is often administered, and the present inclusion criteria excluded them from the analysis. Consequently, the anticipated outcomes might differ from the results of this study if this study included recently treated patients. Second, this study did not investigate treatment and survival after surgery; thus, the impact of SLN SPECT/CT assessment on treatment and survival is unknown. Third, this study did not examine incidental findings from SPECT/CT because SPECT/CT was reported to have the advantage of being able to identify such incidental findings[31]. However, FDG-PET/CT performed before treatment can now identify most of these incidental findings.

In conclusion, SPECT/CT-guided SLNB yields useful information on pathological ALN metastasis. The absence of detected SLNs, the presence of SLNs outside axillary level I, a higher number of detected SLNs, and a higher number of excised SLNs are potential risk factors for pathological ALN metastases due to the failure of lymphatic drainage systems of the breast.

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