Sentinel node identification in clinical stage Ia non-small cell lung cancer by a combined single photon emission computed tomography/computed tomography system

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Drs Nomori, Mori, and Ikeda (left to right). The bronze statue is Dr. Shibasaburo Kitasato.

Objective: A gamma probe can identify sentinel nodes before nodal dissection in the mediastinum but not in the hilum, owing to high radioactivity from primary tumors. We evaluated the utility of fused single photon emission computed tomography/computed tomography (SPECT/CT) images for the identification of sentinel nodes in the hilum for patients with clinical stage Ia non-small cell lung cancer.

Methods: Technetium-99m tin colloid was injected into the peritumoral region approximately 18 hours before surgery in 63 patients with clinical stage Ia non-small cell lung cancer. On the morning of the operation, approximately 16 hours after administration of tin colloid, sentinel nodes were identified by fused SPECT/CT; this was followed by intraoperative sentinel node identification in the dissected lymph nodes by gamma probe. Because the gamma probe is a standard method for sentinel node identification, the sensitivity of fused SPECT/CT images was examined on the basis of the data of the gamma probe.

Results: Fused SPECT/CT images could identify sentinel nodes at segmental and lobar lymph nodes with a sensitivity of 0.87 and 0.74, both of which were significantly higher than 0.40 in the mediastinum ($P < .001$ and $P = .012$, respectively). In 5 patients with pathologic N1 or N2 disease, both SPECT/CT and the gamma probe could identify sentinel nodes with metastases.

Conclusions: SPECT/CT could identify sentinel nodes of the hilum especially in segmental and lobar lymph nodes but not in the mediastinum. Because the gamma probe can identify sentinel nodes before nodal dissection in the mediastinum but not in the hilum, a combination of SPECT/CT and the gamma probe can be used to identify sentinel nodes before nodal dissection in both the hilum and the mediastinum, which will enable sentinel node navigation surgery in non-small cell lung cancer.

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Sentinel lymph node (SN) sampling with a gamma probe has allowed surgeons to be more selective in performing a formal lymph node dissection in melanoma, breast cancer, and gastrointestinal cancers.¹⁻³ However, the gamma probe method in lung cancer surgery cannot identify SNs before lymph node dissection in the hilum owing to high radioactivity from primary tumors.^{4,5} Therefore, previously reported SN identifications with the gamma probe method in lung cancer surgery have been based on radioactivity measured in the dissected lymph nodes,⁵⁻¹⁰ which cannot be used to guide lymph node dissection or sampling. This difficulty with the gamma probe method makes it difficult for SN navigation surgery to be of practical use in non-small cell lung cancer (NSCLC).

Planar scintigram with a radioactive colloid has also been used to identify SNs, especially in melanoma of the head and neck.¹¹⁻¹³ However, in lung cancer surgery, localization of nodal stations by planar scintigram is difficult because SNs cannot

Abbreviations and Acronyms

CT	= computed tomography
NSCLC	= non-small cell lung cancer
SN	= sentinel lymph node
SPECT	= single photon emission computed tomography
^{99m} Tc	= technetium-99m

readily be discriminated owing to the lack of tomography images. In 2002, we installed a combined single photon emission computed tomography/computed tomography (SPECT/CT) system that is composed of a gantry-free gamma camera and an 8-row multidetector CT. So that we can avoid positional differences between the SPECT and CT studies, imaging is performed on the same platform, which makes fusion of SPECT and high-performance CT images possible. Because the SPECT/CT system has enabled us to identify SNs on the basis of the fusion images, without the adverse effect of overlapping radioactivity from the primary site, it allows preoperative SN localization in relation to nearby anatomic structures, which enables an intraoperative SN biopsy to be easy and accurate. We¹⁴ previously identified SNs in 35 patients with melanoma by the SPECT/CT system; the identification rate was 100%.¹⁴ The present study evaluated the usefulness of fused SPECT/CT images, compared with the gamma probe, for SN identification in lung cancer surgery.

Patients and Methods**Patient Eligibility**

This study of SN identification in patients with clinical stage Ia NSCLC was approved by the ethical committee of the Graduate School of Medical Sciences, Kumamoto University, in March 2005. Clinical staging was performed by body CT, brain magnetic resonance imaging, and positron emission tomography. Informed consent was obtained from all patients after a discussion with the surgeons regarding the risks and benefits. Eligible patients had clinical stage Ia peripheral type NSCLC and were candidates for lobectomy or segmentectomy with mediastinal lymph node dissection. The patients without preoperative histologic diagnosis of tumors were excluded. The lobectomy with mediastinal lymph node dissection was performed via thoracoscopy, as described before.¹⁵ Segmentectomy with hilar and mediastinal lymph node dissection was performed via open thoracotomy, as described before.¹⁶ All of the lymph nodes at the hilum were dissected during segmentectomy with taping of the vessels and bronchus.

Lymph Node Nomenclature

The lymph node nomenclature used was based on the original lymph node map for lung cancer.¹⁷

Administration of Radioactive Colloid

Administration of the radioactive colloid was based on the method reported previously.^{4,5} In the SPECT/CT room, approximately 18

hours before the operation, 6 to 8 mCi of technetium-99m (^{99m}Tc) tin colloid suspended in a volume of 1 to 1.5 mL was injected into the peritumoral region.

SPECT/CT System

On the morning of the operation, approximately 16 hours after administration of the ^{99m}Tc tin colloid, SNs were identified by the SPECT/CT system. This system was composed of a commercially available gantry-free SPECT with dual-head detectors (Skylight; ADAC Laboratories, Milpitas, Calif) and an 8 multidetector-row CT scanner (Light-Speed Ultra Instrument; General Electric, Milwaukee, Wis). The two instruments were juxtaposed so that the CT table bearing the patient could be moved directly into the SPECT scanner before CT scanning. As a result, each patient was identically positioned for SPECT and CT imaging.

SPECT data acquisition was performed with a vertex general-purpose parallel-hole (VXGP) collimator. A 360 SPECT scan was acquired and was followed by CT scanning. Reconstructive CT images were processed into Digital Imaging and Communications in Medicine (DICOM) data and then transferred to Pegasys (ADAC Laboratories, Milpitas, Calif), which is a workstation for SPECT processing. One lumen of a 3-way stopcock (inner diameter 4 mm, length 10 mm) containing an aqueous solution of ^{99m}Tc tin colloid and a contrast medium was used as an external fiducial marker. So that a precise record of both images could be obtained, external fiducial markers were fixed to the common platform for SPECT and CT imaging. The two scans were performed sequentially. Fusion of the SPECT images with the CT images was manually performed by aligning the external fiducial markers of the two images on the workstation, enabling localization of SN on CT images (Figure 1). An SN was visually identified on the SPECT/CT images by two experienced radiologists before surgery (S.S. and K.K.).

Gamma Probe Method

The radioactivity of the dissected lymph nodes was determined by a handheld gamma probe (Navigator; Auto Suture Japan, Tokyo, Japan), as reported previously.^{4,5} An SN was defined as any node for which the radioactivity count was 10 times that of the background level.

Pathologic Examination

SNs were examined by intraoperative frozen section analysis using 2- to 3-mm thick sections. The dissected lymph nodes were examined histologically by use of formalin-fixed and paraffin-embedded sections with hematoxylin and eosin staining.

Statistical Analysis

Because the use of a gamma probe to measure radioactivity of dissected lymph nodes is now a standard method for SN identification, the sensitivity of SPECT/CT was examined on the basis of data gathered with the gamma probe, which was calculated as true positive/true positive + false negative. All data were analyzed for statistical significance by the χ^2 test. All values in the text and tables are given as mean $\pm$ standard deviation.

Figure 1. Fused SPECT/CT images in lung cancer of the left upper lobe. A, Primary tumor. B, Radiolabeled lymph node (segmental nodal station) can be detected (arrow).

Results

From April 2005 to September 2006, 79 patients with clinical stage Ia peripheral NSCLC underwent surgery at the Department of Thoracic Surgery of Kumamoto University Hospital. Of these, 16 patients could not be enrolled in this study because of the following reasons: (1) Preoperative histologic diagnosis was not obtained in 5 patients; (2) SPECT/CT could not be used because of the other examinations in 10 patients; and (3) one patient refused to participate in the study. As a result, 63 consecutive patients were enrolled in this study. The gamma probe identified SNs in 49 (78%) of the 63 patients, whose pathologic N stages were N0 in 44, N1 in 2, and N2 in 3 (Table 1). SPECT/CT could identify SNs in 39 (62%) patients, whose pathologic N stages were N0 in 34, N1 in 2, and N2 in 3 (Table 2). The SN identification rate by SPECT/CT imaging was lower than that achieved by the gamma probe with marginal significance ($P = .052$). The mean number of SNs identified by the gamma probe in the 48 patients was 1.6 ± 0.8 (range: 1-4); the value obtained by SPECT/CT in the 38 patients was 1.5 ± 0.6 (range: 1-3). However, there was no significant difference between the two methods in this respect.

TABLE 1. Patient characteristics of SN identification by gamma probe

	Sentinel nodes by gamma probe	
	Identified	Not identified
Age (y)		
Mean $\pm$ SD	68 $\pm$ 7	74 $\pm$ 8*
Range	53-81	65-82
Sex (No.)		
Male	25	10
Female	24	4
Mean tumor size (mm)	19 $\pm$ 7	24 $\pm$ 8†
Tumor location (No.)		
Right upper lobe	13	3
Right middle lobe	2	1
Right lower lobe	8	3
Left upper lobe	17	5
Left lower lobe	9	2
Histologic type (No.)		
Adenocarcinoma	44	8
Squamous cell carcinoma	3	6
Adenosquamous carcinoma	1	0
Small cell carcinoma	1	0
Operative procedure (No.)		
Lobectomy	7	4
Segmentectomy	42	10
p-TNM (No.)		
T1 N0 M0	43	13
T2 N0 M0	1	1
T1 N1 M0	2	0
T1 N2 M0	3	0
Total	49	14

SN, Sentinel node. * $P = .01$; † $P = .024$.

Between the 49 patients with identifiable SNs and the 14 without by gamma probe, the mean age was younger and the mean tumor size was smaller in the former than in the latter, with significance ($P = .01$ and $.024$, respectively). However, there were no significant differences of other variables between patients with identifiable SNs and those without when both the gamma probe and SPECT/CT were used. Tumors in 2 patients were pathologically classified as T2: one tumor was involved over the pleura and the other one was larger than 3 cm in the permanent section. Although 2 patients needed tube drainage because of pneumothorax after the injection of the isotope, there were no other complications.

Table 3 shows the correlation between SPECT/CT imaging and the gamma probe method for SN identification at each nodal station of the hilum and mediastinum in the 49 patients whose SNs were identified by gamma probe. In the lymph node stations at the hilum, the gamma probe and SPECT/CT corresponded with each other in 46 (94%) patients at nodal station No. 10, 46 (94%) at No. 11, 42 (86%)

at No. 12, and 39 (80%) at No. 13. In the mediastinum of the right lung, the gamma probe and SPECT/CT corresponded with each other in 21 (91%) patients at nodal station No. 3, in 22 (96%) at No. 4, and in 22 (91%) at No. 7. In the mediastinum of the left lung, the gamma probe and SPECT/CT corresponded with each other in 26 (100%) patients at nodal station No. 4, in 22 (85%) at No. 5, and in 22 (85%) at No. 7. SNs were not identified at the other mediastinal nodal stations, that is, Nos. 1, 2, 8, and 9, using both methods.

The sensitivity of SPECT/CT based on Table 3 was 0.82 at nodal station No. 13, 0.74 at No. 12, 0.63 at No. 11, 0.40 at No. 10, and 0.31 at the mediastinal nodal stations (Figure 2). The sensitivity of SPECT/CT decreased numerically from nodal station No. 13 to No. 10 and was the lowest in the mediastinal lymph nodes. The sensitivity of SPECT/CT in the mediastinal lymph nodes was significantly lower than those at nodal station No. 13 and No. 12 ($P < .001$ and $P = .012$, respectively). The specificity of SPECT/CT based on Table 3 was 0.76 at No. 13, 0.93 at No. 12, 1.0 at No. 11, 1.0 at No. 10, and 0.99 at the mediastinum.

TABLE 2. Patient characteristics of SN identification by SPECT/CT

	SNs by SPECT/CT	
	Identified	Not identified
Age (y)		
Mean $\pm$ SD	68 $\pm$ 6	69 $\pm$ 7
Range	54-81	53-82
Sex (No.)		
Male	20	15
Female	19	9
Mean tumor size (mm)	19 $\pm$ 7	20 $\pm$ 7
Tumor location (No.)		
Right upper lobe	11	5
Right middle lobe	0	3
Right lower lobe	7	4
Left upper lobe	15	7
Left lower lobe	6	5
Histologic type (No.)		
Adenocarcinoma	34	18
Squamous cell carcinoma	4	5
Adenosquamous carcinoma	0	1
Small cell carcinoma	1	0
Operative procedure (No.)		
Lobectomy	5	6
Segmentectomy	34	18
pTNM (No.)		
T1 N0 M0	33	23
T2 N0 M0	1	1
T1 N1 M0	2	0
T1 N2 M0	3	0
Total	39	24

SN, Sentinel node; SPECT/CT, single photon emission computed tomography.

TABLE 3. Correlation between SPECT/CT and gamma probe for SN identification

Station	Patient number with SN identified by				Total
	Gamma probe (+)		Gamma probe (−)		
	SPECT (+)	SPECT (−)	SPECT (+)	SPECT (−)	
	True	False	False	True	
	positive	negative	positive	negative	
Hilum					
10	2	3	0	44	49
11	5	3	0	41	49
12	14	5	2	28	49
13	23	5	5	16	49
Mediastinum					
Right					
3	1	2	0	20	23
4	1	1	0	21	23
7	0	1	0	22	23
Left					
4	1	0	0	25	26
5	2	3	1	20	26
7	0	4	0	22	26

SN, Sentinel node; SPECT/CT, single photon emission computed tomography. +, Sentinel node is identified; −, sentinel node is not identified.

Pathologic examination showed lymph node metastases in 5 patients, that is, N1 in 2 patients and N2 in 3 (Table 4). Frozen section of the SNs identified by both SPECT/CT and the gamma probe could show metastases in all 5 patients.

Discussion

The present study demonstrated that SPECT/CT was inferior to the gamma probe method for SN identification in the mediastinal lymph nodes. This discrepancy could be caused by the following: (1) the ability to measure radioactivity with SPECT/CT images is inferior to that of direct mea-

Figure 2. Sensitivity of SPECT/CT at each lymph node station.

TABLE 4. SNs identified by SPECT/CT and gamma probe in patients with N1 or N2 disease

No.	Age/sex	Tumor location	Histology	Metastatic node	SN		pTNM
					SPECT/CT	Gamma probe	
1	60/M	RLL	Ad	No. 13	No. 13	No. 13	T1 N1 M0
2	72/M	RLL	Ad	No. 11	No. 11	No. 11	T1 N1 M0
3	80/M	LUL	Ad	No. 5	No. 5	No. 5	T1 N2 M0
4	59/M	LUL	Ad	Nos. 5, 12, 13	Nos. 12, 13	Nos. 5, 12	T1 N2 M0
5	54/F	LLL	Ad	Nos. 7, 11, 12	Nos. 12, 13	No. 12	T1 N2 M0

SPECT/CT, Single photon emission computed tomography/computed tomography; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; Ad, adenocarcinoma.

surement by a gamma probe and (2) the radioactivity of mediastinal SNs is usually lower than that of hilar SNs, because the former is further away from the primary tumor. Therefore, we conclude that SPECT/CT cannot easily identify SNs in the mediastinum. However, SPECT/CT could identify SNs at nodal station No. 12 and No. 13 with a sensitivity of 0.82 and 0.74, respectively. This may be because SNs at nodal station No. 12 and No. 13 are close to the primary tumor, which makes their radioactivity high enough for detection by SPECT/CT. In fact, in 5 patients with N1 or N2 disease, SPECT/CT imaged metastatic SNs in the hilum before the operation.

We⁴ previously evaluated SN identification by using a gamma probe in 104 patients with clinical stage I NSCLC and concluded that although the gamma probe could identify SNs in the mediastinum before lymph node dissection (in vivo SN identification), it could not in the hilum owing to high radioactivity from primary tumors. Because the present study showed the usefulness of SPECT/CT for the in vivo SN identification in the hilum, we believe that the combination of SPECT/CT and the gamma probe could be useful for in vivo SN identification in both the hilum and the mediastinum.

Recently, it has been reported that segmentectomy could be an alternative to lobectomy for pathologic T1 N0 M0 NSCLC.^{16,18,19} So that the final indication of segmentectomy can be determined, intraoperative frozen sections must be examined for all of the hilar and lobe-specific mediastinal lymph nodes to confirm the intraoperative N stage to be N0.^{18,19} We consider that the application of SPECT/CT could be used for determining the final indication of segmentectomy as follows: (1) SNs identified in the hilum by SPECT/CT and those identified in the mediastinum by gamma probe are submitted for frozen sections; (2) when frozen sections of SNs show metastases, segmentectomy is converted to lobectomy. Even after segmentectomy, in vivo SN identification by gamma probe is usually difficult for the hilum owing to high radioactivity in the remaining segments. Therefore, if SPECT/CT is not used, all lymph nodes in the hilum have to be dissected during segmentectomy for SN identification by gamma probe, which is hard as well as

time-consuming. On the other hand, for lobectomy, SN identification by SPECT/CT would not be necessary because lymph nodes at the hilum are routinely removed during lobectomy and can be examined for SN identification by gamma probe.

The sensitivities of SN identification at nodal station No. 10 and No. 11 by SPECT/CT were still low. Because station No. 10 is close to the mediastinum, the gamma probe can identify SNs at this station after resection of the primary tumor, as there will no longer be any interference of radioactivity from the primary tumor. Nodal station No. 11 is usually easy to excise even during segmentectomy, enabling SN identification by gamma probe.

Several tracers have been used for SN identification, such as ^{99m}Tc tin colloid, ^{99m}Tc sulfur colloid, and ^{99m}Tc phytate. Of these, ^{99m}Tc tin colloid has the largest particles, that is, about 1000 nm in diameter. The reason that we have used ^{99m}Tc tin colloid is as follows. Because the particles of tin colloid are large, they take longer to reach SNs than the other tracers with small particles. In lung cancer surgery, unlike operations for cancer in other organs, radioisotope injected frequently leaks into the tracheobronchus, which makes in vivo SN identification unreliable immediately after the injection. Because ^{99m}Tc tin colloid has to be injected a few hours before the operation to reach SNs, the material that leaked into the tracheobronchus is already washed out at surgery, resulting in more reliable in vivo SN identification than the other tracers with small particles.⁴ We⁴ previously confirmed that the radioactivity of ^{99m}Tc tin colloid in SNs was stable from 9 to 24 hours after the injection. On the other hand, ^{99m}Tc sulfur colloid can reach SNs rapidly because of their small particles, approximately 40 nm in diameter, but could pass through the true SNs and flow further up the chain of nodes, resulting in false negative results. Therefore, ^{99m}Tc sulfur colloid has to be injected immediately before surgery, which would make the in vivo SN identification difficult because of material leaking into the tracheobronchus. In fact, the previous reports using ^{99m}Tc sulfur colloid identified SNs in the dissected lymph nodes but not with in vivo identification.^{6,7}

In conclusion, SPECT/CT can be used to identify SNs in the hilum before surgery, especially at nodal station No. 12 and No. 13, but not in the mediastinum. Because the gamma probe method can identify SN before lymph node dissection in the mediastinum but not in the hilum, a combination of SPECT/CT and the gamma probe could be used to identify SNs before lymph node dissection in both the hilum and the mediastinum. This will enable SN navigation surgery in patients with clinical stage Ia NSCLC, especially for segmentectomy.

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