Use of technetium-99m tin colloid for sentinel lymph node identification in non-small cell lung cancer

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Received for publication Nov 7, 2001; revisions requested Feb 5, 2002; revisions received Feb 28, 2002; accepted for publication March 6, 2002.

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J Thorac Cardiovasc Surg 2002;124:486-92

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0022-5223/2002 \$35.00+0 12/1/124496

doi:10.1067/mtc.2002.124496

Background: To test the reliability of sentinel lymph node identification in non-small cell lung cancer, sentinel nodes were localized with a radioactive colloid in patients undergoing surgery.

Methods: Forty-six patients with non-small cell lung cancer undergoing curative resection with mediastinal lymph node dissection were examined. The day before surgery, technetium-99m (^{99m}Tc) tin colloid was injected into the peritumoral region. At operation, the radioactivity of the lymph nodes was counted with a handheld gamma counter before (in vivo) and after (ex vivo) dissection. Lymph nodes with an ex vivo radioactive count more than 10 times the background value were identified as sentinel nodes. The correlation between the in vivo and ex vivo results was examined.

Results: Lymphoscintigraphy revealed that it took longer than 6 hours for sufficient ^{99m}Tc tin colloid to reach the sentinel nodes. Sentinel nodes could be identified in 40 patients (87%). Patients whose sentinel nodes could not be identified had a significantly lower ratio of forced expiratory volume in 1 second to forced vital capacity than did those with identifiable sentinel nodes ($P = .03$). No false-negative sentinel nodes were detected in 14 patients with N1 or N2 disease (0%). In the hilar lymph node stations, the lobar lymph nodes were most frequently identified as sentinel nodes (as often as 85% of the time). Fourteen patients (35%) had sentinel nodes in the mediastinum, the distribution of which depended on the lobe. In vivo and ex vivo counting showed 88% concurrence for the identification of sentinel nodes in mediastinal lymph node stations.

Conclusion: The identification of sentinel nodes with ^{99m}Tc tin colloid is a reliable method of establishing the first site of nodal metastasis in non-small cell lung cancer. Sentinel nodes could be hardly identified in patients with a low ratio of forced expiratory volume in 1 second to forced vital capacity because of such conditions as chronic obstructive pulmonary disease. In vivo identification of sentinel nodes in the mediastinum could be useful approach to guide mediastinal lymph node sampling or dissection.

Systemic node dissection is a useful procedure for complete local control of non-small cell lung cancer (NSCLC), with subsequent improvement in survival as well as nodal staging.¹⁻³ To minimize the damage caused by systemic node dissection, several authors have examined the characteristics of lymphatic drainage, as well as the prevalence of lymph node metastasis, with respect to the location of the primary tumor.⁴⁻⁷ In small lung cancers, which have a relatively low frequency of mediastinal lymph node metastasis, systemic mediastinal lymph node dissection

Figure 1. By computed tomographic examination, site of injection of radioactive tracer is marked on skin and angle and depth of needle to reach peritumoral region are determined. At *right bottom*, angle and depth are recorded.

could be reduced by an intraoperative pathologic diagnosis of sentinel lymph nodes (the first lymph node within the lymphatic basin reached by lymph draining from the primary lesion).

Recently, identification of sentinel lymph nodes with a radioisotope tracer with or without isosulfan blue dye has been used during surgery for melanoma, breast cancer, and gastrointestinal cancers, with an accuracy greater than 80%.⁸⁻¹⁰ In lung cancer surgery, Little and colleagues¹¹ demonstrated the identification rate of sentinel lymph nodes in fewer than 50% of patients with isosulfan blue dye, because intrathoracic lymph nodes were usually black, which made the blue dye method inaccurate. Recently Liptay and associates¹² used a technetium Tc 99m sulfur colloid and reported that the identification rate for sentinel lymph nodes was 82% and the accuracy was 95%. In this study, sentinel lymph nodes were identified with technetium Tc 99m tin colloid in patients with NSCLC undergoing curative resection with mediastinal lymph node dissection. The accuracy and usefulness of this method for effective lymph node dissection and sampling were determined.

Material and Methods

Eligibility

The study was approved by the ethical committee of Saiseikai Central Hospital in July 2000. Informed consent was obtained from all patients after discussion of the risks and benefits with the operating surgeons. Eligible patients had lung cancers less than 5 cm in size and were candidates for lobectomy or more resection with mediastinal lymph node dissection.

Administration of Radioactive Colloid

Under Japanese law, the radioisotope could only be injected in a radioisotope room. A radioisotope tracer was therefore injected

according to the following procedure: (1) in the computed tomography room, the site for radioisotope injection was marked on the skin and the angle and depth of the needle required to reach the peritumoral region was determined (Figure 1); (2) the day before surgery, in the radioisotope room, a 23-gauge needle was introduced from the marked point on the skin to the peritumoral region according to the angle and depth measured; (3) 6 to 8 mCi of technetium tin colloid suspended in a volume of 1 to 1.5 mL was injected with a single shot; and (4) lymphoscintigraphy was performed 5 minutes after the injection and the next morning just before surgery.

Time Course after Radioisotope Injection

For the first 10 patients, the time course was monitored by lymphoscintigraphy to determine the optimal timing for radioisotope injection before surgery. Lymphoscintigraphy was performed 5 minutes and 1, 6, 9, and 24 hours after the injection.

Counting of Radioactivity

The radioactivity in the lymph nodes was counted before (in vivo) and after (ex vivo) dissection with a handheld gamma probe (Navigator; Auto Suture Japan, Tokyo, Japan). The radioactivity count was recorded for a 20-second period. If there was incomplete fissure between the lobes, the in vivo radioactivity of the hilar lymph node stations was counted after dividing the fissure and exposing the lymph nodes.

Criteria for Sentinel Nodes

The lymph node nomenclature used was similar to the lymph node map for lung cancer reported previously (Table 1).¹³ For in vivo counting, sentinel lymph nodes were identified as any node for which the count was 10 times the intrathoracic background value. For ex vivo counting, sentinel lymph nodes were defined as any node for which the count was 10 times the radioactivity of the resected lung tissue with the lowest count or the resected subder-

TABLE 1. Lymph node nomenclature

N2 node		N1 node	
Station	Name	Station	Name
Superior mediastinal		Hilar	
1	Highest mediastinal	10	Hilar
2	Paratracheal	11	Interlobar
3	Pretracheal	12	Lobar
4	Tracheobronchial	Intrapulmonary	
Aortic		13	Segmental
5	Botallo	14	Subsegmental
6	Para-aortic		
Inferior mediastinal			
7	Subcarinal		
8	Paraesophageal		
9	Pulmonary ligament		

mal tissue. Finally, sentinel lymph nodes identified by ex vivo counting were determined to be the true sentinel lymph nodes, because in vivo counting could include radioactivity from the primary tumor.

Pathologic Examinations

The dissected lymph nodes were examined histologically by using formalin-fixed and paraffin-embedded sections with hematoxylin and eosin staining. Sentinel lymph nodes without metastasis were further examined by using three-step sections and immunohistochemical methods with a monoclonal anti-human cytokeratin antibody (DAKO Corporation, Carpinteria, Calif).

Correlation Between in Vivo and ex Vivo Counting

To clarify the accuracy of in vivo sentinel lymph node identification, the correlations for both hilar and mediastinal lymph node stations between in vivo and ex vivo results were examined.

Statistical Analysis

The Fisher exact test for nominal variables was used to compare successful sentinel lymph node identification according to the patient's age, sex, ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC), tumor location, and pathologic N stage. The other data were analyzed for significance with the 2-tailed Student *t* test.

Results

From August 2000 to October 2001, a total of 52 patients were enrolled consecutively into this study. There were no complications associated with radioisotope injection necessitating tube drainage, such as bleeding or pneumothorax. Of the 52 patient, 6 were excluded from the study because of the following reasons: (1) major pulmonary resection could not be conducted because of the advanced tumor stage (*n* = 5) and (2) the tumor was identified as small cell carcinoma (*n* = 1). Of the remaining 46 patients, sentinel lymph nodes could be identified in 40 (87%). The charac-

TABLE 2. Patient characteristics

	Sentinel lymph nodes	
	Identified	Not identified
Age (y)		
Mean ± SD	62 ± 11	65 ± 9
Range	38–82	56–78
Sex (No.)		
Male	36	6
Female	4	0
FEV ₁ /FVC ratio (%)		
Mean ± SD	74.5 ± 9.9	65.3 ± 9.2
Range	51–90	55–76
Tumor location (No.)		
Right upper lobe	12	2
Right middle lobe	4	1
Right lower lobe	8	1
Left upper lobe	10	1
Left lower lobe	6	1
Histologic type (No.)		
Adenocarcinoma	27	4
Squamous cell carcinoma	12	2
Adenosquamous carcinoma	1	0
Operative procedure (No.)		
Lobectomy	38	6
Pneumonectomy	2	0
pTNM (No.)		
N0		
T1 N0 M0	16	3
T2 N0 M0	8	1
T4 N0 M0	2	0
N1		
T1 N1 M0	4	0
T2 N1 M0	1	1
N2		
T1 N2 M0	2	0
T2 N2 M0	5	0
T3 N2 M0	1	0
T4 N2 M0	1	1
Total (No.)	40	6

teristics of the 40 patients with identifiable sentinel lymph nodes and of the 6 patients with no identifiable sentinel lymph nodes are shown in Table 2. The mean value of FEV₁/FVC was 65.3% ± 9.2% among the patients with unidentifiable sentinel lymph nodes, which was significantly lower than the 74.5% ± 9.9% value among the patients with identifiable sentinel lymph nodes (*P* = .03). There were no significant differences between the two groups in factors other than FEV₁/FVC ratio.

Figure 2 shows the time course after radioisotope injection determined by lymphoscintigraphy. Five minutes after the injection, some of the radioisotope had leaked into the tracheobronchus. One hour after the injection, the radioisotope in the tracheobronchus had washed out, but it had not

Figure 2. Time course examined by lymphoscintigraphy shows lymph node clearly demonstrated 6 hours after injection of radioactive technetium tin colloid.

been taken up by the lymph nodes. More than 6 hours after the injection, sufficient radioisotope had been taken up by the lymph nodes, and its detection did not change until 24 hours after the injection.

The mean number of sentinel lymph nodes identified was 2.0 ± 0.7 (range 1-4) stations per patient. Table 3 shows the sentinel lymph nodes identified in the hilar lymph node stations. The hilar lymph node (No. 10) was identified as a sentinel lymph node in 7 patients (18%), the interlobar node (No. 11) was identified in 12 (30%), the lobar node (No. 12) was identified in 34 (85%), and the segmental node (No. 13) was identified in 13 (33%). The lobar lymph nodes were identified as sentinel lymph nodes significantly more frequently than were the other lymph node stations ($P = 1.6 \sim 1.9 \times 10^{-9}$).

In the mediastinal lymph node stations, the sentinel lymph nodes were identified in 14 (35%) of the 40 patients. Thirteen of the 14 patients had sentinel lymph nodes in both the mediastinal and hilar lymph node stations. The remaining patient had sentinel lymph nodes only in the Botallo lymph node, with primary tumor located in the left upper lobe. The distribution of mediastinal sentinel lymph nodes is shown in Table 4. Five (42%) of 12 patients with primary tumors in the right upper lobe had sentinel lymph nodes at the pretracheal (No. 3) or tracheobronchial (No. 4) lymph nodes. Two (25%) of 8 patients with primary tumors in the right lower lobe had sentinel lymph nodes in both the tracheobronchial (No. 4) and subcarinal (No. 7) lymph nodes. Five (50%) of 10 patients with primary tumors in the left upper lobe had sentinel lymph nodes at the Botallo (No. 5) lymph node. Two of six (33%) patients with primary tumors in the left lower lobe had sentinel lymph nodes in the subcarinal (No. 7) lymph nodes.

TABLE 3. Sentinel lymph node mapping in the hilar lymph node stations

Station		Sentinel nodes	
		No.	%
10	Hilar	7/40	18
11	Interlobar	12/40	30
12	Lobar	34/40	85
13	Segmental	13/40	33

TABLE 4. Tumor locations at which sentinel nodes were identified in the mediastinal lymph node stations

Tumor location	Station of mediastinal sentinel node	No.	%
Right upper lobe	Pretracheal or tracheobronchial	5/12	42
Right lower lobe	Tracheobronchial and subcarinal	2/8	25
Left upper lobe	Botallo	5/10	50
Left lower lobe	subcarinal	2/6	33

The false-negative rate for sentinel lymph node identification was assessed by the presence of metastatic lymph nodes not identified as sentinel lymph nodes with the labeled sentinel lymph nodes histologically appearing uninvolved. As a result, no false-negative sentinel lymph nodes were detected in any of the 14 patients with N1 or N2 disease (0%).

Step sections and immunohistochemical examination revealed micrometastasis in 1 of the 63 sentinel lymph nodes (2%), without metastasis in the routine hematoxylin and eosin-stained sections. This result did not change the tumor stage in that patient.

Whereas the relationship between in vivo and ex vivo results for the hilar lymph node stations showed concurrence in 20 patients (50%) for the hilar lymph nodal stations, 35 patients (88%) showed concurrence for the mediastinal lymph node stations; this difference was statistically significant ($P = .0003$). Of the 5 patients who did not show a correlation in the mediastinal lymph node stations, 1 appeared to have an additional sentinel lymph node on ex vivo counting, whereas the sentinel lymph nodes identified by in vivo counting in the other 4 were judged not to be sentinel lymph nodes by ex vivo counting.

Discussion

The procedure described in this study identified sentinel lymph nodes in 40 of 46 patients (87%) with NSCLC, a rate that is comparable to those described in previous reports for other organs.⁸⁻¹⁰ Sentinel lymph nodes were difficult to identify in patients with a low FEV₁/FVC ratio, such as those with chronic obstructive pulmonary disease. In breast cancer, it has been reported that the sentinel lymph node identification rate is significantly lower in older than in younger patients, probably because breast tissue becomes progressively replaced by fat and its lymphatic vessel density decreases in older patients.⁸ We consider that lung tissue in patients with chronic obstructive pulmonary disease could also have a lower density of lymphatic vessels or low lymphatic flow than normal lung tissue, resulting in the lower sentinel lymph node identification rate.

Liptay and associates¹² identified sentinel lymph nodes in lung cancer after intraoperative injection of ^{99m}Tc sulfur colloid with a particle size of approximately 40 nm diameter. The particles of ^{99m}Tc tin colloid, on the other hand, are much larger than those of a ^{99m}Tc sulfur colloid, about 1000 nm in diameter, and should therefore take longer to reach the sentinel lymph nodes than the ^{99m}Tc sulfur colloid. As shown in Figure 2, it took several hours for sufficient ^{99m}Tc tin colloid to reach the sentinel lymph nodes. Although the optimum particle size for the radioisotope tracer for sentinel lymph node identification in lung cancer patients has not been clarified, we believe that ^{99m}Tc tin colloid would be more suitable than ^{99m}Tc sulfur colloid for the following reasons. First, ^{99m}Tc sulfur colloid can reach the sentinel lymph nodes rapidly, because of its small particle size, but could pass through the true sentinel lymph nodes and flow further up the chain of nodes, resulting in false-negative results. Actually, it has been reported that the hottest node with ^{99m}Tc sulfur colloid is not always the sentinel lymph node in patients with melanoma.¹⁴ On the other hand, a ^{99m}Tc tin colloid, because of its large particle size, could be lodged within the sentinel lymph nodes for a longer period than a ^{99m}Tc sulfur colloid, which could make the false negative rate lower. Second, unlike in other organs, radioisotope injected into the lung frequently leaks into the tracheobronchus, as shown in Figure 2. This could make in

vivo counting unreliable immediately after the injection. A ^{99m}Tc sulfur colloid procedure, because of its intraoperative injection, could result in the radioisotope tracer leaking into the tracheobronchus and make the radioactivity of lymph nodes around the tracheobronchus higher than the true value. On the other hand, because ^{99m}Tc tin colloid has to be injected a few hours before surgery, the material leaked into the tracheobronchus has been already washed out at surgery, resulting in more reliable in vivo counting. Finally, intraoperative injection of ^{99m}Tc sulfur colloid might not reveal the natural lymphatic flow because of the thoracotomy itself and intraoperative manipulation of lung. However, a comparison of our results with those of Liptay and associates¹² with ^{99m}Tc sulfur colloid revealed similar results: (1) the identification rate for sentinel lymph nodes was 82% by the method of Liptay and associates,¹² compared with 87% by our method; (2) mediastinal sentinel lymph nodes were found in 22% of patients by Liptay and associates¹² and in 35% in this study; and (3) false-negative results were observed in 5% of patients by Liptay and associates¹² and in none of our patients.

In the hilar lymph node stations, sentinel lymph nodes were identified most frequently in the lobar lymph node (No. 12). The reason for the lower frequency of sentinel lymph nodes in the interlobar (No. 11) and hilar (No. 10) lymph nodes can be explained by the fact that these nodes are located further away from the primary tumor than are the lobar (No. 12) nodes. However, although the segmental (No. 13) lymph nodes were located nearer to the primary tumor than the lobar (No. 12) nodes, the former were identified as sentinel lymph nodes less frequently than the latter. This observation is similar to those in previous reports, which demonstrated that lymph node metastases of lung cancer were more frequent in the lobar (No. 12) lymph nodes than in the segmental (No. 13) nodes.^{4,15} We consider that this might be due to the following reasons: (1) some of the lymphatic flow passes through lymphatic vessels of the visceral pleura and goes to the lobar lymph nodes but not through the segmental nodes and (2) some of the lymphatic flow within the lung tissue goes directly to the lobar lymph nodes without passing through the segmental nodes.

Skip metastasis to the mediastinal lymph nodes has been reported to occur in 20% to 40% of patients with NSCLC,^{4-6,15} which could be because some lymphatic flow from the lung goes directly to the mediastinum through the pleura and not to the hilar lymph node stations.¹⁶ Our study showed that sentinel lymph nodes were identified in 35% of mediastinal lymph nodes, and that the lymphatic route to each mediastinal lymph node station was lobe specific; the lymphatic flow from the right upper lobe proceeds to the pretracheal or tracheobronchial lymph nodes, the left upper lobe to the Botallo node, and the lower lobe to the subcarinal node. This result is supported by previous

reports, which showed a similar distribution of prevalence of mediastinal lymph node metastases from each lobe.^{4-6,15}

One of the potential benefits of sentinel lymph node identification is that pathologists can focus on fewer lymph nodes when identifying micrometastases by immunohistochemical assay or polymerase chain reaction. Izbicki and coworkers¹⁷ used immunohistochemical methods and reported that 27% of patients with N0 and 45% with N1 staged from frozen tissue sections had micrometastases in the mediastinal lymph node stations, resulting in upstaging. However, both step sections and immunohistochemical assay for sentinel lymph nodes in this study showed micrometastases in only 1 of the 40 patients (3%). This could be because we examined formalin-fixed and paraffin-embedded tissue sections but not frozen sections alone.

There have been few reports comparing sentinel lymph node identification by in vivo and ex vivo counting, including other organ tumors. Although ex vivo counting is more accurate than in vivo counting, it is not practical for sentinel lymph node navigation surgery because it is only available after dissection. To be of practical use for sentinel lymph node navigation surgery, the in vivo counting data have to be accurate. We therefore examined the correlation between in vivo and ex vivo counting for both hilar and mediastinal lymph node stations. Our results indicated that whereas the hilar lymph node stations showed concurrence between the in vivo and ex vivo results in only 50% of patients, the mediastinal nodes showed concurrence in 88%. This could be because the mediastinal lymph node stations were less affected by “shine through” from the hot primary. Of the 4 patients with inconsistency between in vivo and ex vivo results for the mediastinal lymph node stations, only 1 showed an additional sentinel lymph node by ex vivo counting. That is to say, the rate of overlooking sentinel lymph nodes by in vivo counting of mediastinal lymph node stations was only 3% (1 of 40 patients). We therefore believe that sentinel lymph node identification by in vivo counting of mediastinal lymph node stations could be a useful approach to guide mediastinal lymph node sampling or dissection. We also recommend ^{99m}Tc tin colloid rather than ^{99m}Tc sulfur colloid for sentinel lymph node identification in lung cancer surgery, because in vivo counting by the former procedure could be less affected by the radioisotope leaked into tracheobronchus, as discussed previously.

How can sentinel lymph node biopsy change surgical procedures for NSCLC? First, it should be stated that sentinel lymph node identification is not practical for lung wedge resection, because the radioactivity of hilar lymph node stations cannot be determined by the wedge resection procedure. To evaluate the hilar lymph nodal stations, segmentectomy or greater resection is necessary. Second, we consider that sentinel lymph node biopsy could reduce systemic mediastinal lymph node dissection. For example,

if all the dissected hilar lymph node stations and the mediastinal sentinel lymph nodes identified by in vivo counting showed no metastasis after lobectomy, mediastinal lymph node dissection would not be necessary. Third, sentinel lymph node identification could be useful as an indication for segmentectomy; after segmentectomy, if all the dissected hilar lymph node stations and mediastinal sentinel lymph nodes identified by in vivo counting revealed no metastasis, segmentectomy could be enough for curative resection, especially for small lung cancers. Okada and coworkers¹⁸ reported that segmentectomy with mediastinal lymph node dissection for lung cancers less than 2 cm in size with clinical N0 stage carried a 5-year survival similar to that seen with lobectomy. Whereas their procedure required intraoperative pathologic diagnosis for all the dissected lymph nodes, including the mediastinal nodes, our procedure could reduce the number of lymph nodes examined during surgery.

Although sentinel lymph node biopsy was developed for breast cancer and melanoma, recent articles have demonstrated that this procedure has no advantage relative to elective lymph node dissection or sampling in patients with these diseases.^{19,20} We therefore consider that further examination, including multicenter trials, is necessary to determine the role of sentinel lymph node identification in NSCLC.

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