Effect of radioisotope sentinel node mapping in patients with cT1 N0 M0 lung cancer

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Background: Application of the sentinel node concept to lung cancer is still controversial. Patients with peripheral small lung cancers would gain the most benefit from this concept, if it were valid. We sought to determine whether it is possible to choose between limited lymph node sampling and systematic lymphadenectomy from the distribution of sentinel lymph nodes in patients with node-negative disease on the basis of imaging.

Methods: Sixty-five consecutive patients with cT1 N0 M0 non–small cell lung cancer were enrolled. A radioisotope tracer (4 mCi of technetium-99m tin colloid, 2.0 mL) was injected in the vicinity of the tumor before surgical intervention with computed tomographic guidance. The radioactivity of each resected lymph node was measured separately with a hand-held gamma probe after complete tumor resection. Sentinel nodes were identified, and the accuracy of sentinel node mapping was examined. Whether the location of the sentinel node depended on the site of the primary tumor was also examined.

Results: Of the 65 patients, 3 were excluded because of the final pathologic results. Successful radionuclide migration occurred in 39 (62.9%) of the 62 patients. There was 1 (2.6%) false-negative result among 39 patients with a sentinel node, and therefore the sensitivity was 90%, and the specificity was 100%. The most common sentinel lymph nodes were at level 12 (46.7%), followed by level 11 (18.3%), the mediastinum (16.7%), and level 10 (11.7%).

Conclusion: The sentinel node concept is valid in patients with cT1 N0 M0 lung cancer. The lobar lymph nodes were identified as sentinel nodes more frequently than other lymph nodes. We need to make further efforts to increase the sentinel node identification rate. However, we believe that if sentinel nodes are identified, sentinel node mapping can allow the accurate intraoperative diagnosis of pathologic N0 status in patients with cT1 N0 M0 lung cancer.

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GTS

The sentinel node (SN) has been defined as being the "first lymph node that receives afferent lymphatic drainage from a primary tumor,"[1] and therefore this node should be the first site of lymphatic involvement if metastases have occurred. The histology of the SN is assumed to reflect the histology of the reminder of the nodal basin. Thus validation of the SN technique might allow accurate intraoperative identification of nodal involvement at the first lymphatic drainage site and potentially segregate patients who might require complete nodal dissection to remove further disease from those in whom more focused resection can be done as a result of negative SNs. The presence of larger tumors and grossly enlarged lymph nodes might cause lymphatic obstruction or alter the lymphatic channels, but sampling the SN in patients who have small tumors without adenopathy (cT1 N0

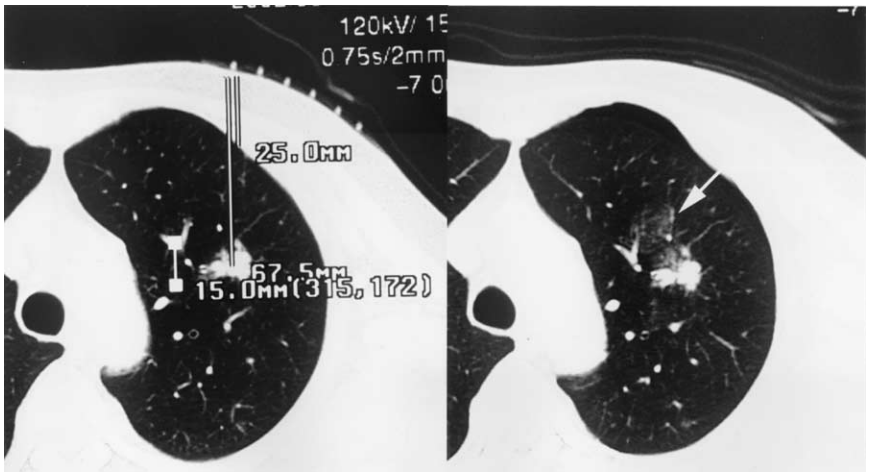

Figure 1. The scanner projected 6 parallel grids onto the skin as landmarks to determine the site for needle insertion. The distance from the skin to the pleura or to the tumor was measured *(left)*. After achievement of local anesthesia, technetium 99m tin colloid was injected in the vicinity of the lesion with a 22-gauge needle. Subsequently, the location of the injected technetium *(arrow)* and the lesion were confirmed by means of CT *(right)*. Injected radioisotope was confirmed as an area of ground-glass attenuation near the tumor.

M0) could permit regional lymph node staging and avoid the need for lymphadenectomy. Another benefit of SN detection is that this technique might allow better understanding of common drainage patterns from different tumor locations. On the basis of a detailed analysis of SNs in patients with cT1 N0 M0 lung cancer at various locations, reevaluation of the lymphatic vessels might be possible.

The 2 purposes of this study were to (1) assess the ability of the SN technique to predict N0 disease in patients with small tumors and (2) to evaluate the pathway of lymphatic drainage.

Materials and Methods

Eligibility

This study was approved by the National Sanyo Hospital Investigational Review Board for studies dealing with human subjects. Sixty-five consecutive patients with clinical T1 N0 M0 non–small cell lung cancer were enrolled after providing written informed consent. Patients were excluded if enlarged mediastinal lymph nodes were more than 1.0 cm in short-axis diameter on computed tomography (CT) or if the primary tumor was larger than 3 cm in size. Preoperative cervical mediastinoscopy was not performed in any patient. Only patients able to tolerate anatomic resection of their tumors and complete mediastinal node dissection were included in the study.

Administration of Radioactive Colloid

In Japan the use of radioisotopes is strictly limited to designated areas, and therefore the tracer could only be injected in a special room. A radioisotope tracer was injected on the day before surgical intervention, according to the following procedure. First, in the CT room the site for injection was marked on the skin, and the length of the needle required to reach the peritumoral region was determined (Figure 1, *left*). Then the patient was taken to the radioisotope room, and a 22-gauge needle (15 cm long) was introduced at the point marked on the skin and advanced to the peritumoral region on the basis of the depth measured. Then 4 mCi of technetium tin colloid (in a volume of 2.0 mL) was injected as a bolus. Finally, the patient was taken back to the CT room to confirm the proper location of the injected radioisotope in the vicinity of the tumor (Figure 1, *right*). The injected radioisotope was confirmed as an area of ground-glass attenuation near the tumor.

Operative Technique

Standard lobectomy or segmentectomy combined with systematic lymph node dissection was performed to achieve anatomic resection of the tumor.

Measurement of Radioactivity

The radioactivity of each dissected lymph node was measured away from the operating field and separate from the tumor specimen with a hand-held gamma probe (Navigator GPS; Auto Suture Japan, Tokyo, Japan). The background radioactivity was measured at the superior vena cava on the right side or at the descending thoracic aorta on the left side. The level of radioactivity was recorded for a 10-second period at each site.

Definition of an SN

Migration of the technetium tin colloid was considered successful if a specific lymph node station registered more than 5 times the background value of counts per second. If a lymph node station was found to have the highest number of counts per second or more than 50% of the highest number on ex vivo measurements and the level was greater than 5 times the intrathoracic background, then that station was classified as the SN. The lymph node nomenclature used was similar to that of the lymph node map for lung cancer, which was reported previously.[2]

TABLE 1. Characteristics of patients with and without SNs

	SN present	SN absent	*P* value
No. of patients	39	23	
Age (y)	63 ± 12	68 ± 9	.03
Male/female	21/18	11/12	.65
Tumor size (mm)	24 ± 14	23 ± 14	.42
Lung function tests			
VC (L)	2.89 ± 0.88	3.04 ± 0.77	.47
% VC	103.0 ± 19.3	104.1 ± 12.3	.78
FEV1.0 (L)	2.28 ± 0.79	2.22 ± 0.73	.76
FEV1.0%	81.2 ± 8.1	74.5 ± 11.0	.02
Primary location			
RUL	13	5	.39
RML	4	1	
RLL	7	4	
LSD	8	6	
LLD	5	2	
LLL	2	5	
Histology			
Ad	28	19	.22
Sq	10	3	
Adsq.	0	1	
pN status			
pN0	29	22	.09
pN1	5	1	
pN2	5	0	
Procedure			
Lobectomy	33	17	.35
Segmentectomy	5	6	

VC, Vital capacity; *%VC,* percent VC relative to the predicted value; *FEV1.0,* forced expiratory volume in 1 second, FEV1.0%; FEV1.0/forced vital capacity; *RUL,* right upper lobe; *RML,* right middle lobe; *RLL,* right lower lobe; *LSD,* left superior division; *LLD,* left lingular division; *LLL,* left lower lobe; *Ad,* adenocarcinoma; *Sq,* squamous cell carcinoma; *Adsq,* adenosquamous cell carcinoma.

Pathologic Evaluation

After identification of the SN, the nodes were examined according to a standard protocol. After formalin fixation and embedding in paraffin, 2 or 3 sections were cut and stained with hematoxylin and eosin. All resected nodes were examined by using conventional techniques, with one or 2 sections stained with hematoxylin and eosin being studied for each node. The nodes were not examined by means of immunohistochemistry with cytokeratin.

Statistical Analysis

Results are presented as the mean ± SD, and analysis of significance was done with the unpaired *t* test.

Results

No significant complications of SN mapping were observed, and preoperative radioisotope injection did not create a need for tube drainage, except for slight intrapulmonary bleeding and a very small pneumothorax in 1 and 7 patients, respectively. Of the 65 patients, 3 were excluded from the study because the final pathologic diagnosis was not primary lung cancer (2 had metastatic lung cancer, and 1 had small cell carcinoma).

Successful radionuclide migration occurred in 39 (62.9%) of the 62 patients with primary lung cancer. The time between radioisotope injection and detection of SNs was 1203 ± 150 minutes (range, 990-1490 minutes). Histopathologic examination detected metastatic disease in 10 (25.6%) of the 39 SNs that were examined. Nodal metastatic disease was only present in 1 of the 23 patients in whom the radionuclide did not migrate (this patient had N1 nodal metastases).

The characteristics of the 39 patients with identifiable SNs and the features of the 23 patients without identifiable SNs are shown in Table 1. The mean age was 63 ± 12 years for the patients with identifiable SNs, which was significantly less than the age of 68 ± 9 years for the patients without SNs ($P = .03$). Forced expiratory volume in 1 second/forced vital capacity (FEV1.0%) was 74.5% ± 11.0% in the patients without SNs, which was significantly lower than the FEV1.0% of 81.2% ± 8.1% in patients with SNs ($P = .02$).

The sensitivity of the SN technique was 90% (9/10), and the specificity was 100%. A false-negative SN finding occurred in 1 of 39 patients. This patient had a 28-mm tumor in the left upper lobe. The SN was classified as being at level 5, but histologic examination revealed that the only positive nodes were located at level 12. An error in 1 of 39 patients resulted in a false-negative rate of 2.6%.

Of the 60 SNs identified in the 39 patients who had detectable SNs (1.5 SNs per patient), 28 (46.7%) nodes were found at level 12, 10 (16.7%) nodes were located in the mediastinum, 11 (18.3%) nodes were found at level 11, 7 (11.7%) nodes were found at level 10, and only 4 (6.7%) nodes were found at level 13. The lobar lymph nodes were identified as SNs more frequently than the other lymph nodes. Among the 10 patients with mediastinal sentinel lymph nodes, 7 had SNs in both the mediastinal and hilar regions. The remaining 3 patients had SNs only among the mediastinal nodes (level 5 in 2 patients with primary tumors located in the left upper lobe and level 4 in one patient with a primary tumor located in the right upper lobe).

The most common site of the SN in patients with primary tumors located in the right upper lobe was at level 12u (61.0%, Figure 2). Two (33.3%) of six patients with primary tumors in the right middle lobe each had SNs at levels 11s, 11i, and 12. The most common SNs in patients with primary tumors of the right lower lobe were found at level 12l (54%). Six (50%) of the 12 patients with primary tumors in the left superior division and SNs had their sentinel lymph nodes at level 12u, whereas 4 (33%) had these nodes at level 5. Four (40%) of the 10 patients with a primary tumor at the left lingular division and SNs had their nodes in level 11. One each of the 3 patients with primary tumors in the left lower lobe and SNs had the sentinel lymph node at levels 12l, 10, and 4.

Discussion

During the last decades of the 20th century, Japanese surgeons have shown interest in evaluating the survival benefit of systematic lymphadenectomy in patients with lung cancer, and they have emphasized the excellent palliative effect, low operative mortality, and acceptable survival among patients treated in this way.[3,4] However, Izbicki and colleagues[5] performed a randomized trial in which radical systematic lymphadenectomy was compared with limited lymph node dissection of interlobar, peribronchial, and hilar nodes (representing levels 10, 11, and 12) for clinical N0 or N1 lung cancer. According to their data, radical systematic mediastinal lymphadenectomy did not influence either disease-free survival or overall survival in patients with pN0 disease, and limited dissection caused less morbidity than radical systematic dissection. It is difficult to identify patients who are potentially curable by means of limited node dissection, even with CT scanning, magnetic resonance imaging, and positron emission tomographic scanning.

Identification of the SN, which is the first draining node from a primary lesion, has been used to individualize lymph node dissection for melanoma,[1] but application of this concept to lung cancer is still controversial. The safety and efficacy of the SN technique has already been documented in patients with lung cancer.[6-10] Liptay and coworkers[7] performed intraoperative radionuclide SN mapping in patients with lung cancer and established the feasibility of this technique, providing the basis for the evolving field of SN mapping in lung tumors. Recently, Schmidt and associates[8] used technetium-99m sulfur colloid and achieved an identification rate for sentinel lymph nodes of more than 80%. Nomori and colleagues[9] used technetium-99m tin colloid to identify SNs in patients with lung cancer undergoing curative resection plus mediastinal lymph node dissection, and their identification rate was 87%. These reports have several similarities: (1) the identification rate of sentinel lymph nodes was more then 80% by using radioisotopes; (2) mediastinal sentinel lymph nodes were found in 20% to 35% of patients; and (3) false-negative results were observed in less than 5% of patients. The group of patients that has the most potential to benefit from application of the SN concept is the group with small tumors and clinically negative lymph nodes because the incidence of nodal metastatic disease in these patients has been reported to range between 15% and 20%.[11] We investigated the validity of this concept for cT1 N0 M0 lung cancer by using a radioactive tracer to detect the SN, and we found that it was possible to make an accurate intraoperative diagnosis and provide minimally invasive surgical treatment tailored to the individual patient. In patients with node-negative disease, on the basis of imaging studies, the choice between limited lymph node dissection and systematic lymphadenectomy could be determined by the distribution of SNs.

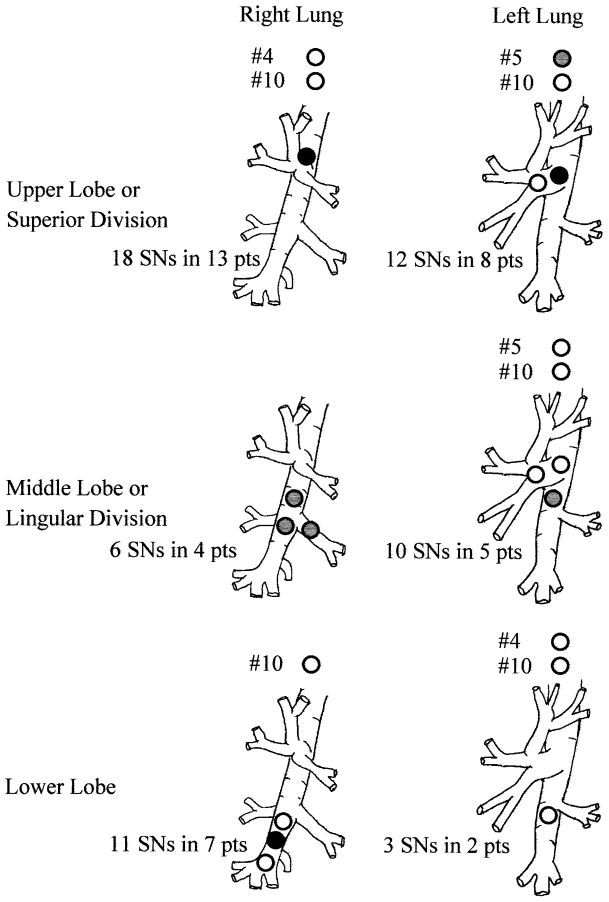

Figure 2. Locations of sentinel lymph nodes in relation to the primary tumor. *Filled circles* indicate a high incidence (≥50%) of SNs, *shaded circles* indicate a moderate incidence (≥30%), and *open circles* indicate a low incidence (<30%).

Liptay and associates[7] have noted a lower success rate of the SN technique in patients with large necrotic tumors, as well as in those with hilar and mediastinal adenopathy. Larger necrotic tumors might be associated with changes to the lymphatic and vascular supply, whereas established adenopathy might cause efferent lymphatic obstruction. Likewise, grossly enlarged lymph nodes that are clinically positive should be routinely removed for accurate staging and to ensure complete resection. We noted that the FEV1.0% of patients without SNs was significantly lower than that of patients with SNs. Nomori and colleagues[9] also reported that patients with chronic obstructive pulmonary disease were less likely to have identifiable SNs. One possible explanation would be a decrease of lymphatic vessels along with the loss of alveoli and functional lung tissue that occurs as a result of emphysema.

Among the hilar lymph nodes, SNs were most frequently identified at level 12. The reason for the lower frequency of SNs at levels 11 and 10 can be explained by the fact that

these nodes are located further away from the primary tumor than level 12 nodes. However, although level 13 was nearer to the primary tumor than level 12, there were fewer SNs at this level than at the latter. This observation is similar to previous findings, which have demonstrated that lymph node metastases of lung cancer are more frequent at level 12 than at level 13.[12,13] It is possible that some of the lymph flow passes through lymphatic vessels beneath the visceral pleura and goes to level 12 nodes but not level 13 nodes. The lungs have an extensive network of lymphatic vessels in the loose connective tissue beneath the visceral pleura, as well as in the connective tissue of the interlobular septa and in the peribronchial vascular sheaths.[14] Collections of lymphatic cells might be seen along the course of these lymphatic channels and within the bronchi, but actual intrapulmonary lymph nodes are infrequent in contrast to the common detection of bronchopulmonary nodes. The extensive subpleural networks are primarily drained by channels in the interlobular septa to the hilar region, but direct connections to the mediastinum have also been recorded. Mediastinal lymph node stations contained the sentinel lymph nodes in 10 (25.6%) of 39 patients, and 3 (7.7%) patients had SNs only in the mediastinal nodes (level 5 in 2 patients with primary tumors located in the left upper lobe and level 4 in one patient with a primary tumor located in the right upper lobe). Our study showed that the lymphatic route to each mediastinal lymph node station was specific for each lobe (ie, lymph flowed from the right upper lobe to level 4 and from the left superior division to level 5). This finding is supported by previous reports, which have shown a similar prevalence of mediastinal lymph node metastases from each lobe.[11,12,15,16] Riquet and colleagues[17] reported the existence of direct lymphatic channels running from the subpleural plexus of the lobar segments to various mediastinal lymph nodes without passing through the bronchopulmonary nodes. These direct channels were observed in 36.3% and 38.6% of the right and left upper lobes, respectively, being more frequent than in 22.3% and 21.1% of the right and left lower lobes, respectively. This skip metastasis pattern of drainage occurs more frequently in upper lobe tumors and adenocarcinomas.[17,18] In our study SNs were found in the mediastinum of 22% and 33% of patients with tumors in the right upper lobe and left superior division, respectively. The intraoperative identification of SNs might allow more accurate characterization of these unique patterns of tumor lymphatic drainage. Although the SN technique might not be useful to separate patients requiring full mediastinal node dissection from those needing sampling or no dissection, the information gained from detailing the actual nodal drainage of each tumor will continue to blur the lines between N1 and N2 disease, leading to reconsideration of the mechanism of nodal metastasis.

In Japan the use of radioisotopes is strictly limited to designated areas, and therefore intraoperative injection is impractical. The benefits of preoperative tumor injection on the night before surgical intervention include better logistic coordination with the nuclear medicine section and better radiation safety. These advantages are balanced by the patient requiring a separate procedure and the small (but real) risk of pneumothorax, bleeding, and tumor seeding along the needle track.[19] However, a comparison of previous reports suggests that the use of sulfur colloid or tin colloid and preoperative injection or intraoperative injection do not make a significant difference to SN mapping.[6,7,9] The technique that will ultimately be used is still unclear because currently available data show that both methods achieve reasonable SN detection rates. In our study successful radionuclide migration occurred in 39 (62.9%) of 62 patients with primary lung cancer, which was a lower identification rate than previous reports of more than 80%. The reason for this difference in the identification rates is not clear. We need to make further efforts to increase the identification rate of SNs. In this study we injected 4 mCi of radioisotope on the day before surgical intervention, which was twice the radioisotope dose for intraoperative injection. Nomori and colleagues[9] reported that 8 mCi of radioisotope could achieve a satisfactory identification rate of more than 85% for SNs using the same technique as ours (ie, reference CT scans and injection on the day before the operation). Therefore an increase in the dosage of radioisotope injected could probably increase the identification rate.

Okada and coworkers[11] reported that segmentectomy with mediastinal lymph node dissection for lung cancer less than 2 cm in size and clinical N0 stage achieved a 5-year survival similar to that seen after lobectomy. However, their procedure required intraoperative pathologic diagnosis of all the dissected lymph nodes, including the mediastinal nodes, whereas our procedure could reduce the number of lymph nodes examined during the operation. Identification of the SN could be useful as an indication for segmentectomy. If all the dissected hilar or mediastinal SNs reveal no metastasis, segmentectomy could be adequate for curative resection, especially in patients with small lung cancers.

In conclusion, intraoperative SN mapping by means of preoperative injection of technetium-99–labeled colloid is highly accurate in patients with cT1 N0 M0 lung cancer, and thoracic surgeons might eventually become more confident in withholding or proceeding to more radical nodal dissection on the basis of intraoperative SN data. Although we have to make a continuous effort to increase the SN identification rate, sentinel lymph node biopsy in patients with cT1 N0 M0 lung cancer could reduce the need for systemic mediastinal lymph node dissection.

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