Video-assisted thoracoscopic indocyanine green fluorescence imaging system shows sentinel lymph nodes in non–small-cell lung cancer

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Objective: The primary objective was to assess the feasibility and accuracy of intraoperative sentinel lymph node mapping by using a video-assisted thoracoscopic indocyanine green fluorescence imaging system in patients with clinical stage I non–small-cell lung cancer.

Methods: Thirty-one patients who underwent operation between January 2009 and September 2009 were investigated for sentinel node biopsy. Indocyanine green fluorescence imaging was applied by an infrared light charge-coupled device, and sentinel nodes were identified intraoperatively and dissected. Histologic examination by hematoxylin-eosin staining was used to evaluate metastases.

Results: Sentinel lymph nodes were identified by segmentectomy in 11 of 14 patients (78.5%) and by lobectomy in 14 of 17 patients (82.4%). The total identification rate was 80.7% (25/31 patients), the false-negative rate was 0% (0/24 patients), and the overall accuracy rate was 80.7% (25/31 patients).

Conclusion: Video-assisted thoracoscopic indocyanine green fluorescence image-guided surgery is feasible for sentinel node biopsy and may be a powerful tool to eliminate unnecessary lymph node dissection in patients with lung cancer. (J Thorac Cardiovasc Surg 2011;141:141-4)

Sentinel node navigation surgery has been the standard treatment for malignant melanoma[1] and breast cancer[2] surgery. The sentinel lymph node is defined as the first lymph node within the lymphatic basin from the tumor. However, the application of sentinel node navigation surgery in non–small-cell lung cancer (NSCLC) is not popular because of the difficulty of sentinel node identification and the low incidence of complications after systemic lymph node dissection.[3] As previously reported, sentinel lymph node biopsy using isosulfan blue dye failed because of a lower detection rate caused by anthracotic black lymph nodes.[4] Liptay and colleagues[5] reported radiolabeled tracer methods that used technetium 99mTc sulfur colloid. Their results were satisfactory and showed an 82% identification rate and a 95% accuracy rate. The technique of radiolabeled tracer injection during the operation, in vivo and ex vivo mapping as described previously,[6] was reported in the results of the Cancer and Leukemia Group B 140203 phase II trial.[7] However, the complexity of radiolabeled tracer injection may lead to low use of this technique.[3]

Because the dye including indocyanine green (ICG) is not visible in anthracotic lymph nodes, ICG was not used for sentinel node biopsy of lung cancer. However, because ICG is known to absorb infrared rays in vivo binding with serum protein, the ICG fluorescence imaging system was developed and applied to gastric,[8] breast,[9] and skin[10] surgery, but not lung surgery. This report shows the new technique of sentinel node navigation surgery by video-assisted thoracoscopic ICG fluorescence imaging in NSCLC.

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MATERIALS AND METHODS

Eligibility

Patients aged more than 20 years with clinically diagnosed stage I lung cancers were considered for enrollment in this study. Patients with prior radiotherapy or chemotherapy of lung cancer were excluded. This feasibility study was started in January 2009. The study was approved by the institutional review board of Oita University, and all patients completed informed consent forms. The samples were histologically diagnosed for primary lung cancer by hematoxylin & eosin staining.

Objective

The primary objective of this study was to assess the feasibility and accuracy of intraoperative sentinel lymph node mapping in patients with clinical stage I NSCLC at Oita University. The sentinel node accuracy rate was based on the number of patients with sentinel nodes positive for metastatic disease and on the number of patients with sentinel nodes negative for nonmetastatic disease and no metastases in any other hilar or mediastinal lymph nodes.

Technique

After initial thoracoscopic exploration, ICG fluorescence imaging was applied by an infrared light charge-coupled device (CCD) (Olympus, Tokyo, Japan) equipped to filter out light with 800 nm wavelength. Light through an exciting filter (690–790 nm) leads to image formation, and it was converted to a digital image under monitor view. Two milliliters

Abbreviations and Acronyms
CCD = charge-coupled device
ICG = indocyanine green
NSCLC = non–small-cell lung cancer

(5 mg/mL) of ICG were injected around the tumor using 25-gauge needles, and sentinel nodes were detected 10 minutes after injection. During the time allowed for migration of the ICG through the lymphatics, care was taken to avoid leakage or intrathoracic spreading because these effects make the true sentinel nodes invisible. Therefore, we immediately closed the injection site by using an EndoClip (Covidien, Mansfield, Mass) or Endoloop (Medcompare, South San Francisco, Calif) after injection. Sentinel node sampling was followed by lobar or segmental resection of the lung. Green fluorescent nodes were dissected as sentinel nodes (Figure 1). All systemic lymph node dissection, which includes a full hilar and mediastinal node dissection, was followed by lung cancer resection for feasibility. In the case of segments in the upper lobe, intersegmental, interlobar, hilar, and upper mediastinal nodes were dissected. In the lower lobe, subcarinal and lower mediastinal node dissection was added to the lymphadenectomy described above.

Pathologic Examination

After sentinel node dissection, sentinel nodes were examined by standard histology with hematoxylin-eosin by conventional methods. One-half of the sentinel nodes were fixed in formalin and embedded in paraffin for histologic examination.

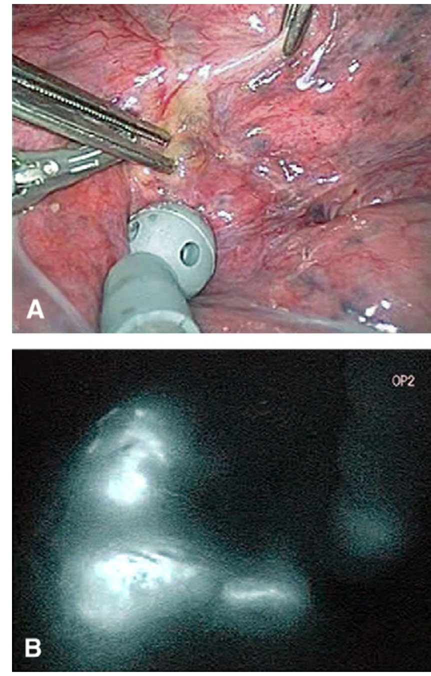

FIGURE 1. Video-assisted thoracoscopic ICG fluorescence imaging system shows the sentinel nodes at the interlobar nodes (11i) in the primary lung adenocarcinoma of the right lower lobe. A, Thoracoscope with normal light does not show the green dye staining because of anthracosis. B, Fluorescence imaging system visualizes the lymph nodes.

RESULTS

Thirty-one patients who underwent operation at Oita University Hospital (Oita, Japan) between January 2009 and September 2009 were eligible for this study. The characteristics of the patients are shown in Table 1. Intraoperative ICG fluorescence imaging was applied by an infrared light CCD system. The sentinel nodes were detected 10 minutes after injection of 2 mL (5 mg/mL) of ICG around the tumor. Sentinel node sampling was followed by lobar (17 cases) or segmental (14 cases) resection of the lung. Green fluorescent nodes were dissected as sentinel nodes (Figure 1) and examined by hematoxylin-eosin staining. All systemic lymph node dissection was followed by lung cancer resection for feasibility. Sentinel lymph nodes were identified by segmentectomy in 11 of 14 patients (78.5%) and by lobectomy in 14 of 17 patients (82.4%) (Table 2). The total identification rate was 80.7% (25/31). The causes of failure are shown in Table 2. The average number of sentinel nodes was 1.4 by segmentectomy and 1.3 by lobectomy. The only case in the left upper lobe showed sentinel node positivity by conventional methods (Table 2). One case of pathologic N2 disease was confirmed by positive sentinel nodes (number 10) and mediastinal nodes (number 5). The other cases showed no metastases in the sentinel nodes, and all dissected nodes were staged as N0 by examination of pathologic specimens. The false-negative rate was 0% (0/24 patients), and the overall accuracy rate was 80.7% (25/31 patients). Of the 31 patients, 24 had pathologically identified negative sentinel lymph nodes.

DISCUSSION

Sentinel node biopsy is the standard technique in surgery for melanoma[1] and breast cancer.[2] The sentinel node is the

TABLE 1. Patient characteristics

Characteristics	
Age y	
Median (range)	63 (54–83)
Gender	
Male (%)	18 (58)
Female (%)	13 (42)
Histologic type	
Ad (%)	13 (42)
Sq (%)	2 (7)
BAC (%)	15 (48)
Others (%)	1 (3)
p-Stage	
IA (%)	27 (87)
IB (%)	3 (10)
IIIA (%)	1 (3)
Operation	
Segmentectomy (%)	14 (45)
Lobectomy (%)	17 (55)

BAC, Bronchioloalveolar carcinoma; *Sq*, squamous cell carcinoma; *Ad*, adenocarcinoma.

TABLE 2. Patient data

No.	Age y	Gender	Histology	Location	Operation	pT	pN	SLN	Metastasis	Cause of failure
1	75	F	BAC	LtS^{1+2}	seg	1	0	10, 11	negative	
2	63	F	BAC	LtS^{6}	seg	1	0	11, 13	negative	
3	71	M	BAC	LtS^{1+2}	seg	1	0	ND		adhesion
4	70	F	BAC	RtS^{3}	seg	1	0	ND		adhesion
5	62	F	BAC	LtS^{3}	seg	1	0	10, 11	negative	
6	59	M	Ad, BAC	RtS^{6}	seg	2	0	12	negative	
7	60	M	Ad	LtS^{10}	seg	1	0	10	negative	
8	56	M	BAC	RtS^{1}	seg	1	0	13	negative	
9	71	M	Ad	LtS^{1+2}	seg	1	0	10, 12	negative	
10	71	M	BAC	LtS^{1+2}	seg	1	0	ND		leakage
11	54	F	BAC	RtS^{3}	seg	1	0	10	negative	
12	79	F	La	LtS^{8}	seg	1	0	12	negative	
13	65	M	BAC	LtS^{3}	seg	1	0	10	negative	
14	73	F	Ad	LtS^{1+2}	seg	1	0	10	negative	
15	62	F	BAC	RtS^{4}	lob	1	0	10, 11s	negative	
16	80	M	Sq	RtS^{2}	lob	1	0	11	negative	
17	64	M	Sq	LtS^{1+2}	lob	1	0	4, 11	negative	
18	57	F	BAC	LtS^{3}	lob	2	2	10	positive	
19	63	M	Ad	RtS^{6}	lob	2	0	11i	negative	
20	74	F	BAC	RtS^{3}	lob	1	0	3	negative	
21	83	F	Ad	RtS^{3}	lob	2	0	4, 10	negative	
22	63	M	Ad	LtS^{9}	lob	1	0	ND		incomplete fissure
23	61	F	BAC	RtS^{9}	lob	1	0	11s	negative	
24	60	M	Ad	RtS^{1}	lob	1	0	ND		leakage
25	62	M	Ad	LtS^{6}	lob	1	0	10	negative	
26	55	F	BAC	RtS^{1}	lob	1	0	11s	negative	
27	61	M	BAC	RtS^{4}	lob	1	0	11i	negative	
28	70	M	Ad	RtS^{8}	lob	1	0	10, 11i	negative	
29	73	M	Ad	RtS^{2}	lob	1	0	10	negative	
30	63	M	Ad	RtS^{2}	lob	1	0	ND		leakage
31	70	F	Ad	RtS^{2}	lob	1	0	11s	negative	

SLN, Sentinel lymph node; *BAC,* bronchioloalveolar carcinoma, *Ad,* adenocarcinoma, *Sq,* squamous cell carcinoma; *La,* large cell carcinoma, *seg,* segmentectomy; *lob,* lobectomy; *ND,* not detected; *LtS,* left; *RtS,* right.

first lymph node drained from the lymphatic basin and represents the state of the remaining regional nodes. Sentinel node biopsy avoids unnecessary dissection of non-metastatic nodes and limits morbidity. Another benefit is the possibility of more focused pathologic or molecular evaluation (eg, serial sections, immunohistochemistry, reverse transcriptase-polymerase chain reaction) for staging. The latter may be a primary benefit in lung cancer surgery.

This study focused on the development of a new technique of sentinel lymph node navigation surgery in patients with NSCLC. ICG fluorescence image-guided surgery has been performed in patients with gastric,[8] breast,[9] and skin[10] cancers. ICG is widely used in a variety of examinations, such as hepatic function tests,[11] and applied to sentinel node detection.[12] However, because ICG is not visible in anthracotic lymph nodes, the ICG dye-guided system was not applied to lung surgery. On the other hand, although the ICG fluorescence imaging system can improve this disadvantage, there have been no reports on ICG fluorescence image-guided surgery for lung cancer or the use of video-assisted thoracoscopic surgery with this imaging system. The thoracoscopic ICG imaging system in this study was useful for video-assisted thoracoscopic surgery with sentinel node navigation surgery for lung cancer; 80.7% of our identification rate was similar to that obtained by radioactive tracer injection. The Cancer and Leukemia Group B 140203 trial[7] showed an unexpected low identification rate of 51.2% for several reasons, such as technical failure, aerosolization of radioactivity, and shine-through effect. Our technique improved the outcome despite these limitations, especially in hilar-located tumors, because there was no shine-through effect and feasible results were obtained. Another benefit of this technique is less radioactivity for both patient and surgeon. The sentinel nodes of 3 patients were not identified by segmentectomy or lobectomy because the ICG leaked from the injection site and eliminated specific visualization from the background; the injection sites were closed with an EndoClip or Endoloop. Although the previous report about dye-guided methods in breast cancer showed a learning curve,[13] the failure of identification in our results revealed the possibility of a learning curve because these failures were found at the beginning of this study. The other reasons for missing sentinel nodes were the adhesion of pleura (2 patients) and incomplete fissure of lobes (1 patient). The deeply located sentinel nodes from the lung parenchyma or mediastinal fat tissue were invisible. A study including a large population sample may help explain these failures.

Systemic radical lymph node dissection after lobectomy or segmentectomy and pathologic examination proved these sentinel nodes to be accurate sentinel nodes (negative sentinel nodes with no positive nodes or positive sentinel nodes with mediastinal positive nodes). The fact that 24 of 31 patients had pathologically identified negative sentinel lymph nodes may reflect the patient population. Many patients had bronchioloalveolar carcinoma (48%), which is known to show less frequent nodal metastasis. If the positive sentinel node was found by frozen-section analysis or real-time reverse transcriptase-polymerase chain reaction using CK-19 (data not shown) in segmentectomy during the operation, the algorithm of the operation method was conversion from segmentectomy to lobectomy, similar to that described in a previous report.[14] However, we found no positive sentinel nodes in segmentectomy, and conversion was unnecessary. A larger number of patients in a further study may lead to more accurate results.

CONCLUSIONS

Our study demonstrated that video-assisted thoracoscopic ICG fluorescence image-guided surgery may be a powerful tool to accurately detect the first basin of lymph drainage and to eliminate unnecessary lymph node dissection in patients with lung cancer.

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