A simple and effective technique for identification of intersegmental planes by infrared thoracoscopy after transbronchial injection of indocyanine green

Yasuo Sekine, MD, PhD,[a] Eitetsu Ko, MD, PhD,[a] Hideto Oishi, MD, PhD,[b] and Mitsuharu Miwa, MD[c]

Objective: Pulmonary segmentectomy has been recognized as an operative option for complete resection of early-stage lung cancer in patients with poor pulmonary function. However, identification of anatomic pulmonary segments is sometimes difficult in patients with emphysema. We developed an intraoperative method for identifying intersegmental planes of the lung with high-sensitivity infrared fluorescence imaging after transbronchial injection of indocyanine green.

Methods: The study included 10 patients with early-stage lung cancer who underwent thoracoscopic segmentectomy. Under general anesthesia, indocyanine green was injected into the bronchus of target pulmonary segments. The target segments of the lung were identified using the indocyanine green fluorescence endoscope (Hamamatsu Photonics, Hamamatsu, Japan). The intersegmental lines and planes were identified and allowed removal of the segments. To evaluate operative outcomes, we compared the indocyanine green injection group with a retrospective control group with 10 matched-pair patients who underwent traditional thoracoscopic segmentectomy.

Results: Accurate, real-time intraoperative detection of indocyanine green with an infrared thoracoscope was confirmed. Sparing of intersegments was safely performed using both staples and electric cautery. Furthermore, infrared thoracoscopy allowed visualization of any residual portion of resected segments after segmentectomy. There was no difference between the experimental indocyanine green and control groups in terms of operative time, duration of postoperative chest drainage, or postoperative complications. Length of stay was shorter in the indocyanine green group than in the control group ($P = .055$).

Conclusions: Transbronchial indocyanine green injection into the relevant bronchus with the use of an infrared thoracoscope allows identification of intersegmental lines and planes during thoracoscopic segmentectomy. (J Thorac Cardiovasc Surg 2012;143:1330-5)

Video clip is available online.

In patients with small, early-stage peripheral lung cancer in the setting of moderate to severe emphysema, limited surgical resection such as segmentectomy has become an accepted treatment option to preserve lung function and obtain a complete resection.[1,2] However, segmental planes may be diffusely obliterated in emphysematous lung, and it can be difficult to precisely identify an intersegmental line. Segmental lines can be identified intraoperatively with inflation/deflation of the target segment(s) by clamping and unclamping the relevant bronchus. However, during video-assisted thoracoscopic surgery, an inflated lung during such a maneuver may obstruct the exposure and limit visualization of the target segment. One alternative approach to segmental identification was suggested by Misaki and colleagues,[3] who reported a novel method for determining adjacent lung segments with infrared thoracoscopy in an animal model. After ligating the corresponding pulmonary artery of the target segment, indocyanine green (ICG) was administered intravenously during infrared thoracoscopy. Unfortunately, the duration of intravascular ICG visualization is short. Furthermore, because anatomic segmentectomy is ideally guided using bronchial segments, ICG staining via the associated bronchus is preferable. We developed a novel, simple, and effective technique for determining segmental planes with infrared thoracoscopy by immediate preoperative injection of ICG into the associated bronchus before segmentectomy.

MATERIALS AND METHODS

Patient Clinical Characteristics

We performed bronchial ICG-guided video-assisted thoracoscopic surgery segmentectomy using infrared thoracoscopy in 10 patients with stage IA peripheral lung cancer. The study protocol was approved by the

From the Departments of Thoracic Surgery[a] and Gastroenterological Surgery,[b] Tokyo Women's Medical University Yachiyo Medical Center, Chiba, Japan; and Hamamatsu Photonics KK,[c] Hamamatsu, Japan.

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Address for reprints: Yasuo Sekine, MD, PhD, Department of Thoracic Surgery, Tokyo Women's Medical University Yachiyo Medical Center, 477-96 Owada-Shinden, Yachiyo, Chiba, 276-8524, Japan (E-mail: ysekine@tymc.twmu.ac.jp).

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Abbreviation and Acronym
ICG = indocyanine green

Research Ethics Board of Tokyo Women's Medical University, Japan. Written informed consent was obtained from all patients. Seven male and 3 female patients participated in this study, with a mean age of 72.8 ± 6.5 years (range, 64–84 years) and mean tumor size of 17 ± 2.8 mm. Pathologic diagnoses were 6 adenocarcinomas, 3 squamous cell carcinomas, and 1 bronchioalveolar cell carcinoma. Nomenclature of lung segments was based on the *Nomina Anatomica*.[4] Segmentectomy regions included 1 right S3 segment (posterior segment of the upper lobe), 2 left lingual segments, 1 left S9 (lateral basal) and 1 S10 (posterior basal) segments, 1 right S6 segment (the superior segment of the lower lobe), 1 left superior division, 2 left S6 segments, 1 left S8 (anterior basal) segment, and 1 right basal segment (Table 1). All patients were preoperatively confirmed to have no drug allergy to ICG.

To evaluate the efficacy of this method, we established a control group of 10 matched-pair patients who underwent a traditional thoracoscopic segmentectomy for lung cancer between May 2009 and November 2010. In the traditional segmentectomy, the target segment was confirmed by using temporary aeration into the associated bronchus. We compared patient clinical data and surgical outcomes between the 2 groups retrospectively. The severity of emphysema on computed tomography was evaluated by the method reported by Goddard and colleagues[5]; from their classification, 4 patients (2 in the ICG group and 2 in the control group) were identified as having severe emphysema (Goddard score ≥ 15).

Data were analyzed using SPSS 15.0J (IBM Japan, Tokyo, Japan). To compare the differences between the ICG and control groups, the Mann–Whitney *U* test was used to analyze for continuous variables, and the Fisher exact or chi-square test was used to analyze for categoric variables.

Operative Technique

After induction of general anesthesia, a Univent endobronchial tube (Fuji Systems Co, Tokyo, Japan) was introduced for transbronchial ICG injection. In a supine position, 20 to 30 mL of 5-fold saline-diluted ICG was injected into each target segmental or subsegmental bronchus, and a total of 200 to 300 mL of air was then supplied into the bronchus to distribute ICG into peripheral regions. After ICG instillation, 5 cm H_2O of positive end-expiratory pressure ventilation was maintained until the start of the operation. The segments were removed by a stapler in 4 patients, electrical cautery in 4 patients, and a combination of both in 2 patients.

During the operation, a normal rigid thoracoscope (Olympus, Tokyo, Japan) and the ICG fluorescence endoscope (non-commercial prototype) (Hamamatsu Photonics, Hamamatsu, Japan) were used as appropriate to determine the intersegmental lines and planes. The ICG fluorescence endoscope uses a xenon light source, with an 800 nanometer low-pass filter set in the xenon light source to excite the ICG. The device uses a detector, which is a charge-coupled device camera, and a subsequently filtered light with a wavelength of less than 820 nm. The fluorescence signals are sent to a digital video processor for display on a television monitor. When ICG binds to human intra-alveolar plasma, ICG is detectable as fluorescence using the ICG fluorescence endoscope (Figure 1).[6] This system can efficiently switch between a normal light and an infrared ray. Therefore, we used the ICG fluorescence endoscope when necessary to identify intersegmental planes.

Thoracoscopic segmentectomy was done briefly as follows. An axillary 5-cm skin incision with 2 additional thoracic ports was made, and the appropriate pulmonary veins and arteries were divided with staplers or direct ligation. In the ICG group, after stapling and dividing the associated bronchus, the intersegmental planes were divided by stapling along the intersegmental lines or using electrical cautery under the guidance of infrared thoracoscopy. In the control group, before division of the associated bronchus, the lung was inflated, the associated bronchus was clamped, and the whole lung was deflated. The persistently inflated lung was recognized as the affected segmental region. The intersegmental planes were divided with staplers or electrical cautery in an identical manner to the ICG group.

TABLE 1. Patient characteristics in the indocyanine green and control groups

Group	ICG (10)	Control (10)	*P* value
Age, y	72.8 ± 6.5	77.0 ± 6.0	.139
Sex (M/F)	7/3	8/2	1.000
Tumor diameter	17.6 ± 3.7	19.9 ± 4.8	.360
Pathology			.208
Ad	6	4	
SCC	3	3	
BAC	1	2	
SCLC	0	1	
Pulmonary function			
FVC (L)	3.2 ± 0.7	2.6 ± 0.5	.121
FVC (%)	109 ± 22	91 ± 11	.007
FEV_1 (L)	2.3 ± 0.5	1.8 ± 0.4	.036
FEV_1 (%)	108 ± 23	97 ± 20	.248
FEV_1/FVC (%)	73 ± 9	69 ± 11	.436
Grade of emphysema on CT			
Goddard score	5.3 ± 6.0	5.7 ± 5.7	.818

ICG, Indocyanine green; *M,* male; *F,* female; *Ad,* adenocarcinoma; *SCC,* squamous cell carcinoma; *BAC,* bronchioalveolar cell carcinoma; *SCLC,* small cell lung cancer; *CT,* computed tomography; *FVC,* forced vital capacity; *FEV_1,* forced expiratory volume in 1 second.

RESULTS

There was no difference in patient clinical parameters between the ICG and control groups except in percentage of forced vital capacity and forced expiratory volume in 1 second (Table 1). There was no difference between the ICG and control groups in terms of operation time, blood loss, duration of postoperative drainage, or postoperative complications. Length of stay in the ICG group was relatively shorter than that in the control group ($P = .055$) (Table 2).

Throughout the operation, accurate and real-time detection of ICG with an infrared thoracoscope was possible in the ICG group. At the beginning of the operation, ICG was identifiable as dotted or heterogeneously stained regions by both normal and infrared thoracoscopes. ICG gradually distributed to the associated segments, and visualization with ICG became clearer than at the beginning of the operation. Although the presence of ICG usually could be identified as a green color under normal thoracoscopy, 5 patients did not have clear demarcation of segments under normal light, namely, a clear contrast between the green color of ICG staining and normal lung color. Visualization with the infrared thoracoscope was consistently clearer than with normal thoracoscopy.

In all cases, an infrared thoracoscope, but not normal thoracoscopy, allowed visualization of any residual portion of segments after segmentectomy. Lung parenchyma adjacent to resected segments was occasionally stained by

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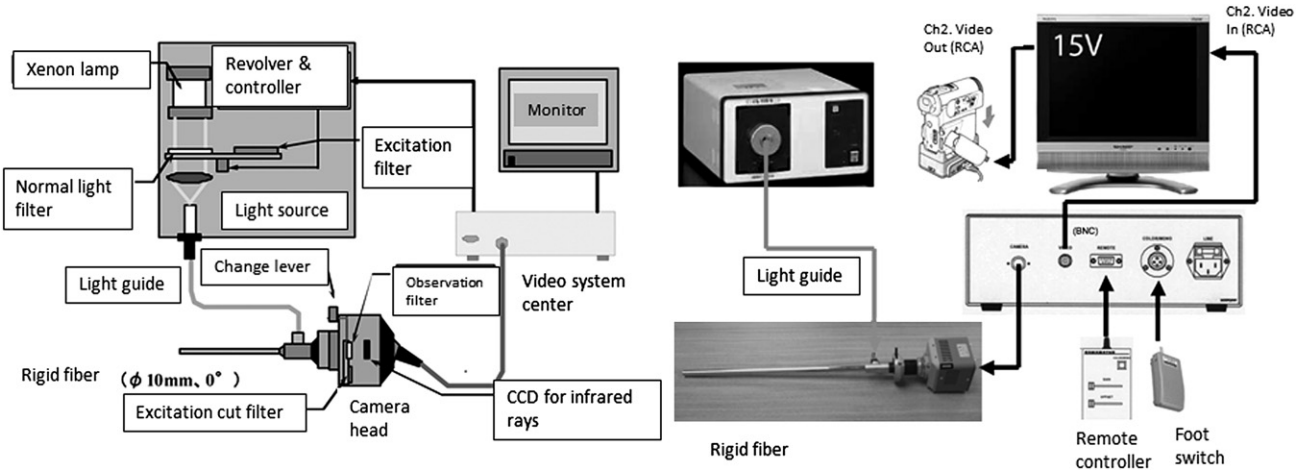

FIGURE 1. ICG fluorescence endoscope is equipped with a xenon light emitter and a charge-coupled device as an image detector with an optical high pass filter in front of the charge-coupled device so that the fluorescence signal can be detected efficiently. Without ICG, the object is dark. The fluorescence signal of ICG can be detected as bright white by using the ICG fluorescence endoscope. (The endoscope, lamp, and the video system are all manufactured by Hamamatsu Photonics, Hamamatsu, Japan.) *CCD,* Charge-coupled device.

TABLE 2. Summary of operative procedures

Group	ICG (10)	Control (10)	*P* value
Segmentectomy regions			.653
Right S2	0	1	
Right S3	1	0	
Right S6	1	0	
Right S8	0	2	
Right basal	1	1	
Left S1 + 2	0	1	
Left superior division	1	1	
Left lingual	2	1	
Left S5	0	1	
Left S6	2	1	
Lt S8	1	1	
Left S9, 10	1	0	
Division of segmental planes			.081
Staple	4	7	
Cautery	4	0	
Staple and cautery	2	3	
Additional sealing			.866
AS	6	5	
TC	5	4	
PGA	2	3	
FG	2	2	
None	1	0	
Operating time (min)	213 ± 40	205 ± 64	.650
Blood loss (g)	177 ± 158	157 ± 160	.597
Duration of drainage (d)	3.1 ± 1.7	3.5 ± 2.7	.935
Length of stay (d)	7.4 ± 2.7	9.9 ± 2.9	.055
Complications			1.000
None	9	9	
Prolonged air leakage	1	1	

Prolonged air leak means continuous air leak >7 days. *ICG,* Indocyanine green; *AS,* additional suturing; *TC,* TachoComb; *PGA,* polyglycolic acid felt; *FG,* fibrin glue.

ICG, but intersegmental lines were still constantly and clearly identified during the operation.

In 1 patient who underwent left basal segmentectomy, at the beginning of the operation, a thoracoscope was inserted and the green color of ICG could be identified in the target segment with a normal thoracoscope. However, the intersegmental line could not be clearly seen. In contrast, the whole basal segment was bright white and easily seen with infrared thoracoscopy (Figure 2, *A, B*). Left basal segmentectomy was then performed by electrical cautery under infrared thoracoscopic guidance (Figure 2, *C, D*). The adjacent residual left S6 segment was subsequently identified and had almost no ICG fluorescence (Figure 2, *E, F*).

In a patient who underwent left segmentectomy of S9 and S10, S9 was clearly demarcated next to S8, and stapled segmental division could be performed without inflation of the lung to identify the intersegmental line (Figure 3, *A, B*). A small portion of S8 was identified by ICG fluorescence (Figure 3, *C, D*).

DISCUSSION

ICG fluorescence-guided surgery may be performed with venous or lymphatic injection of ICG.[7,8] In general thoracic surgery, infrared fluorescence imaging has been used to detect bullous emphysema,[9] sentinel lymph nodes,[10] the thoracic duct,[11] tumor protease activity in lung cancer,[12] and pulmonary segments.[3] The only clinical applications of ICG in thoracic surgery have been for detection of bullous emphysema and sentinel lymph node mapping. In these studies, ICG was administered via vessels or adjacent to tumor tissue. One limitation of intravascular administration of ICG is that fluorescence imaging is provided for a short time. Gotoh and colleagues[9] reported that blue-white

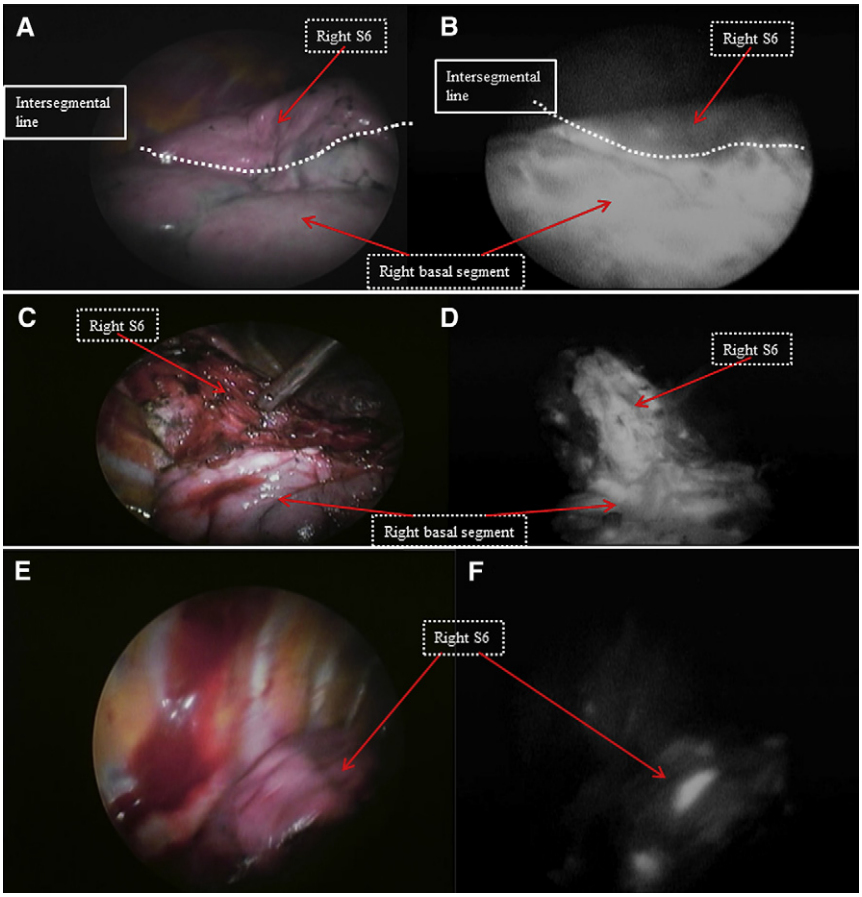

FIGURE 2. Determination of the intersegmental line by ICG fluorescence (A, B) is shown, sparing the segmental surface between S6 and basal segments with electric cautery (C, D) (right basal segmentectomy). E, F, Identification of a residual portion of right segment S6 after right basal segmentectomy. A, C, E, Image with a normal light. B, D, F, Image with an infrared light.

contrast by fluorescence lasted only 150 to 200 seconds. During traditional segmentectomy, we always confirm the target segment using temporary aeration into the associated bronchus, with dissection along intersegmental planes. Visualization of the whole intersegmental line requires a relatively long period of exposure. Our technique shows that ICG stays in the alveolar space until the segmentectomy is completed (up to several hours), and thus we do not require prolonged aeration to identify intersegmental planes. Sugimoto and colleagues[13] suggested that identification by dye injection though the bronchus or pulmonary artery could accurately delineate the intersegmental line. However, segmentectomy is performed on the basis of the bronchial anatomy, and transbronchial injection of ICG is ideal.

The merits of transbronchial administration of ICG are that bronchoscopy can be performed in a supine position, and identification of the bronchial anatomy and the ICG injection itself are straightforward. During the operation, bronchoscopy may be difficult because of the patient's lateral decubitus position. Intraoperative transbronchial injection into a divided target bronchus may be another option. However, with this maneuver, to deliver ICG to peripheral regions, a large volume of ICG or additional aeration may be needed because of the absence of endotracheal ventilation.

Variable staining by ICG may occur as the result of segmental anatomy. The 10 cases in this report are too few to identify which segment(s) are most amenable to ICG-based visualization with bronchial delivery. On the basis of our limited experience, it is likely that clearer staining is obtained in the lower lobes than in the upper lobes because transbronchial ICG injection is easier and distribution of ICG into peripheral regions seems to be more uniform in lower lobes than in the upper lobes. Distribution of ICG might be more difficult in emphysematous regions than in normal parenchyma. This may influence the variation in ICG visualization between the upper and lower lobes.

In our study, ICG injection did not shorten the operating time or decrease blood loss compared with the control group. Because this is an initial experience, the technique of transbronchial ICG injection and thoracoscopic visualization for ICG has not been definitively established. However, duration of chest drainage was similar to that in the control group, length of hospital stay was relatively shorter

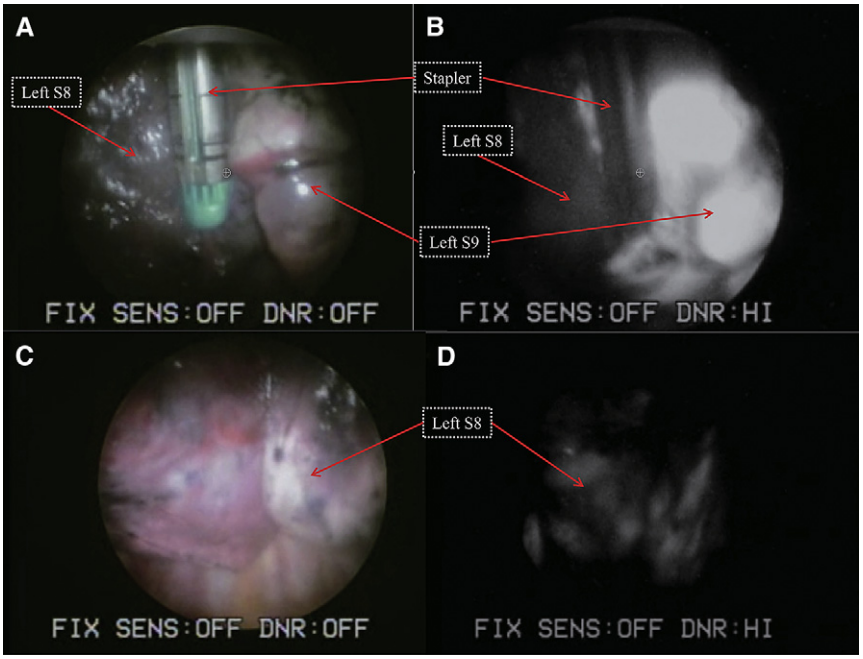

FIGURE 3. Stapling of the intersegmental line between left S8 and S9 as visualized by ICG fluorescence (left S9 and S10 segmentectomy) (A, B) and identification of residual lung after left S9 + 10 segmentectomy with an infrared thoracoscope (C, D). A, C, Image with a normal light. B, D, Image with an infrared light.

in the ICG group, and there were no severe postoperative complications. Therefore, we may reasonably conclude that our method is safe and feasible.

The risk of local injection of ICG is tissue toxicity. It has been reported that undiluted or high-concentration ICG can induce mucosal inflammation and ulcer and reticular epithelial injury.[14,15] However, with our technique ICG stays for only 2 hours and is ultimately removed with the resected specimen. Accordingly, there was no ICG toxicity in our series.

Another potential issue is the spread of ICG to adjacent regions during operation. ICG binds intra-alveolar proteins and stays in the alveolar space, and is finally absorbed into lung tissues. ICG gradually spreads beyond segmental borders. However, the border line could still be recognized because ICG did not spread easily or widely to adjacent regions. We confirmed with a preliminary experimental study in a pig model that transbronchial injection of 100- and 1000-fold diluted ICG, as well as undiluted ICG, could be identified with infrared thoracoscopy (data not shown). The reason that we used 5-fold dilution of ICG is that the green color can be identified with the naked eye, and this was helpful in the orientation of pulmonary segments under normal thoracoscopy. A greater than 10-fold dilution of ICG results in poor visualization by the naked eye, and undiluted ICG necessitates a large volume to fill the segments. Even though local concentration of ICG in the lung decreases with tissue infiltration and absorption time, the visualization provided by ICG persisted throughout the operation in our series.

CONCLUSIONS

Preoperative transbronchial ICG injection into the bronchus and visualization of the target segment with an infrared thoracoscope is a useful technique in the identification of intersegmental lines and planes during thoracoscopic segmentectomy.

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