Precise Anatomical Sublobar Resection Using a 3D Medical Image Analyzer and Fluorescence-Guided Surgery With Transbronchial Instillation of Indocyanine Green

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We developed a novel approach combined with 3D image analyzer and infrared thoracoscopy for pulmonary sublobar resection. The purpose of this study was to investigate the feasibility of this procedure. From October 2014 to April 2018, 65 cases were enrolled, and 58 cases were evaluated. For each case, several virtual sublobar resections were created by 3D image analyzer preoperatively. The surgical margin was measured in each simulated sublobar resection and the most appropriate procedure was selected. Surgical resection with matching virtual sublobar resection was performed using infrared thoracoscopy with transbronchial indocyanine green (ICG) instillation. We evaluated the border clarity of ICG fluorescence to investigate success of ICG injection and compared pre- and postoperative CTs to determine whether the correct area could be removed according to the simulation. We also compared short-term surgical outcomes between the ICG cases and historical segmentectomy cases by propensity score matching. The success rate of transbronchial ICG injections was 89.2% (58/65). These 58 patients were eligible for evaluation of our procedure. Sublobar resection included subsegmental resection (5), simple segmentectomy (15), complex segmentectomy (16), and extended segmentectomy (22). The shortest distances to the surgical margin by simulation and by actual measurement were 21.5 ± 11.2 mm and 23.5 ± 8.3, respectively ($P = 0.190$). Fifty-four of 58 cases underwent sublobar resection matched with the simulation (93.1% concordance rate). Operative results and short-term outcomes were similar between the 2 groups by propensity score matching. ICG-guided sublobar resection by transbronchial ICG instillation is feasible and applicable to any type of sublobar resection.

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Keywords: Synapse 3D, Sublobar resection, Indocyanine green, Fluorescence imaging, Lung neoplasms

Virtual segmentectomy and intraoperative fluorescence image of ICG-guided segmentectomy.

Central Message

The combination of preoperative simulation by 3D image analyzer and transbronchial ICG-guided sublobar resection is applicable to precise anatomical sublobar resection.

Perspective Statement

In standard segmentectomy, vascular and bronchial transections are followed by division of intersegmental planes. Transbronchial instillation of ICG improves initial identification of the resection area, making a complicated sublobar resection possible. Preoperative simulation by 3D image analyzer is ideal for deciding the most appropriate sublobar resection to obtain sufficient surgical margins.

Abbreviations: ICG, indocyanine green; VATS, video-assisted thoracoscopic surgery; CT, computed tomography; 3D, three dimensional; AB, autologous blood

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This study was registered in the Japan University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) on August 11, 2014. Registration no. R000017236.

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INTRODUCTION

Pulmonary sublobar resection is one option for complete resection of early stage lung cancers[1] and metastatic lung tumors. The standard approach to anatomical lung segmentectomy is vascular and bronchial transections followed by division of the intersegmental planes. However, this method has several limitations. The identification of segmental bronchi and their associated vessels can be difficult sometimes, and intraoperative inflation of the lung is an obstacle to thoracoscopic visualization. Although the confirmation of an appropriate tumor resection margin is crucial for reducing the risk of local recurrence,[2] there is no universally accepted method of intraoperative measurement except pathology.

We previously developed a novel approach for performing segmentectomy using infrared thoracoscopy with transbronchial instillation of indocyanine green (ICG).[3] We have now improved this method and combined it with virtual sublobar resection by 3D medical image analyzer, which allows us to establish a precise anatomical sublobar resection with sufficient surgical margins.

METHODS: SURGICAL TECHNIQUE

Creation of Virtual Segmentectomy

Before surgery, high-resolution CT, three-dimensional (3D) pulmonary angiography, and virtual bronchoscopy were performed to confirm tumor location and associated vessels and bronchi. Several simulated sublobar resections were performed in order to determine the appropriate tumor resection margin. In detail, subjects underwent multislice enhanced CT, using 320-slice scanners (Aquilion ONE/ViSION Edition; Toshiba Medical Systems, Tokyo, Japan) (Fig. 1) to create pulmonary angiography and virtual bronchoscopy, to simulate anatomical sublobar resection, and to measure lung volume by Volume Analyzer Synapse 3D VINCENT (Fujifilm co., Tokyo, Japan) for planning sublobar resection before operation (Fig. 2). The shortest distance from the tumor to the resection margin was measured by VINCENT and the most appropriate area of sublobar resection was selected based on the following criteria: resection margin approximately 2 cm from the tumor or greater than the tumor diameter. Nomenclature of lung segments was based on the report by Jafek and Carter[4] and *Nomina Anatomica*.[5]

Transbronchial ICG Injection

After induction of general anesthesia, a single-lumen endotracheal tube or laryngeal mask was introduced for transbronchial ICG instillation. ICG, 25 mg/10 mL, was diluted in 70 mL of saline and 20 mL of autologous blood (AB) for a 10-fold-diluted ICG solution because adsorption of ICG to human serum albumin can increase its fluorescence intensity.[6]

With the patient in a supine position, a thin-bronchoscope (BF-P260F, Olympus Medical Co., Tokyo, Japan) was inserted into the targeted bronchus. A bronchial catheter with balloon (Olympus disposable balloon catheter B5-2C/2LA, Olympus Medical Co., Tokyo, Japan) was inserted and the balloon was inflated at the orifice of the bronchus. Ten milliliter of the 10-fold saline-AB-diluted ICG was instilled into each target subsegmental bronchus, and 300−400 mL of air was then directed into the bronchus to distribute ICG to the peripheral regions (Video 1). During this maneuver, the bronchoscope was fitted over the balloon to prohibit ICG leakage and to visualize the tip of the catheter over the balloon. After ICG instillation, a double-lumen Broncho-cath tube was introduced, and 5 cm H_2O of positive end-expiratory pressure ventilation was maintained until the start of the operation. From the ICG instillation to the start of operation took approximately 20−30 minutes.

Anatomical Sublobar Resection

The surgery was done by 1 thoracic surgeon (Y.S.). At the beginning of the surgery, a near-infrared thoracoscope (PINPOINT, Stryker, MI) was used to visualize the intersegmental

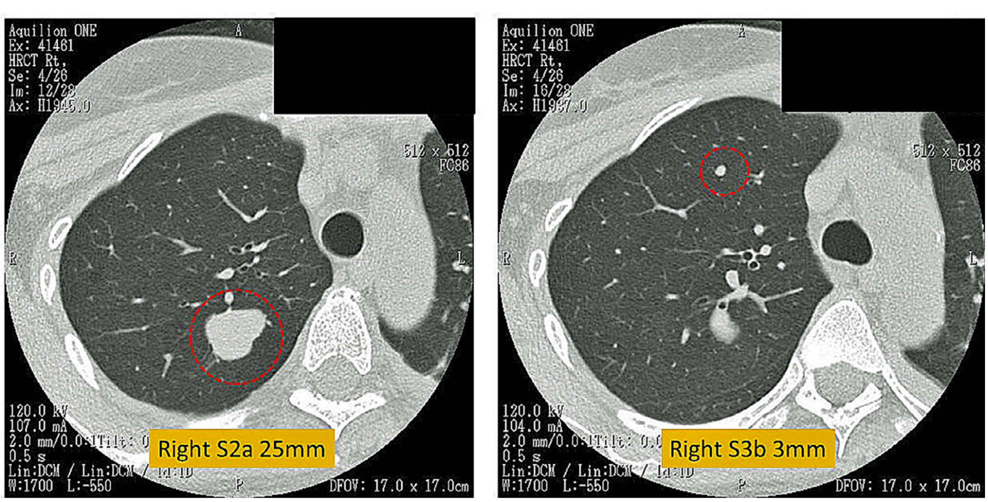


Figure 1. Right metastatic lung tumor from renal leiomyosarcoma in a 42-year-old female. She had already undergone left S10b+c subsegmentectomy. There are 2 nodules in the right upper lobe at S2a and S3b.

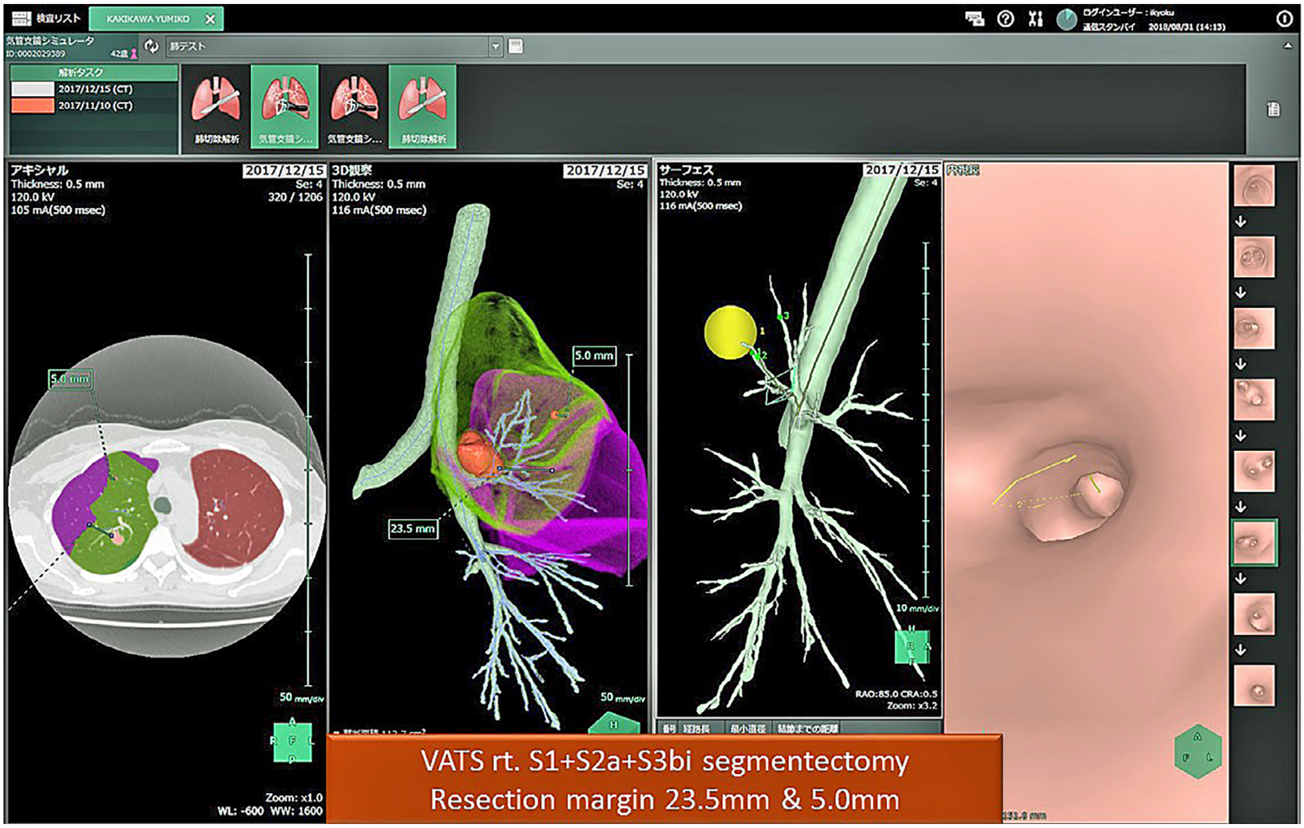


Figure 2. Virtual segmentectomy and bronchoscopy of patient in Figure 1. After creating several virtual segmentectomies, the most appropriate resection area was selected based on the surgical margin. Right S1 (segment) + S2a (subsegment) + S3bi (subsubsegment) resection were selected.

lines and planes. The visceral pleura was marked using electric cautery along the border of ICG fluorescence (Fig. 3). Simultaneous vascular and bronchial division and segmental division can be performed based on the initial identification of segmental planes. Finally, the intersegmental planes were divided by electric cautery and/or endostaplers to complete the sublobar resection. After complete resection, the infrared thoracoscope could identify no residual tissues that should be

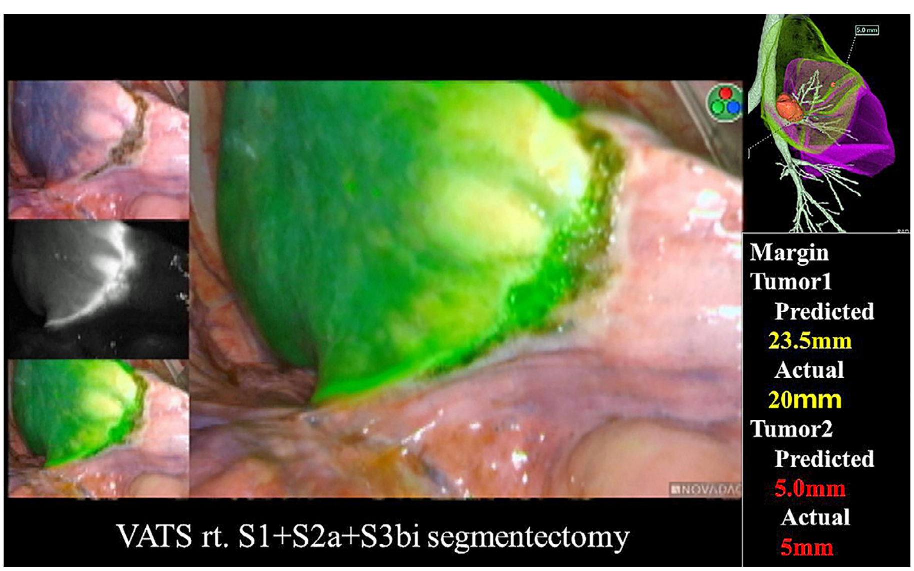


Figure 3. ICG fluorescence of the patient in Figure 1 is clearly visualized at the initial time of operation. The real image was completely matched with a virtual image.

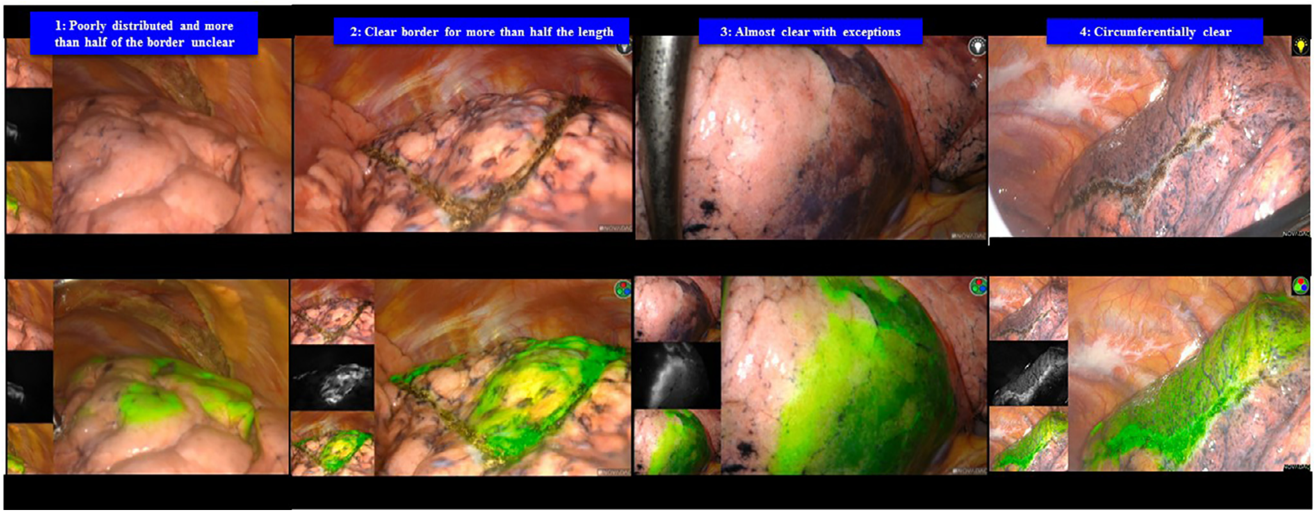


Figure 4. Clarity of the ICG fluorescence border 0–30 minutes from the beginning of operation: 1 = poorly distributed and more than half of the border unclear; 2 = more than half of the border is clear; 3 = almost clear with exceptions; and 4 = circumferentially clear.

resected. Sufficient distance from the tumor to the resection margin was measured on the resected specimen (Video 2). The types of segmentectomy included the following: subsegmental resection; simple segmentectomy, defined as a simple plane cut with the pulmonary division, that is, S6, basal, left lingual, and left upper division segmentectomy; complex segmentectomy, defined as multiple planes of the pulmonary division; and extended segmentectomy, defined as segmentectomy with adjacent subsegmental resection.

PATIENTS AND METHODS

The study protocol was approved by the Research Ethics Board of Tokyo Women's Medical University, Japan. This study was a single-center, phase II, feasibility test. Written informed consent was obtained from all patients. Inclusion criteria were the following: early stage lung cancer, defined as a maximum diameter of tumor consolidation of 2 cm or shorter in the peripheral region without any evidence of nodal and distant metastasis (c-stage IA1 or IA2) (active limited resection); metastatic lung tumor amenable to sublobar resection; benign diseases such as suspected benign tumor in the intermediate portion; and a lung cancer patient at high risk due to exacerbated cardiopulmonary function or poor general condition who was not a candidate for lobectomy (c-stage IA1 to IA3) (passive limited resection). Exclusion criteria were a history of iodine allergy and patient refusal.

From October 2014 to April 2018, 67 cases were approached to obtain an informed consent, and 65 cases accepted and were enrolled. Two cases were converted from sublobar resection to lobectomy because of hilar lymph node metastasis confirmed by on-site pathology. Furthermore, 5 cases had poor identification of ICG and an obscure border that made it necessary to switch to standard segmentectomy. Finally, 58 cases were evaluated.

To evaluate the initial ICG distribution, we classified the border clarity of ICG fluorescence into 4 grades at 0–30 minutes from the beginning of operation: 1 = poorly distributed and more than half of the border unclear; 2 = clear border for more than half the length; 3 = almost clear with exceptions; 4 = circumferentially clear (Fig. 4). When grade 2–4 was identified, we could draw an intersegmental line and determine a successful procedure of transbronchial ICG instillation. When the fluorescence image was grade 1, we converted the operative procedure from fluorescence-guided surgery to a standard segmentectomy.

In order to confirm whether ICG fluorescence-guided surgery could remove the correct area that was matched with the simulation, we created virtual bronchoscopy from the chest CT. We analyzed the structure of residual segments 6 months after the operation and compared the results with the preoperative simulation (Fig. 5). We carefully compared the structure of the bronchial tree to define the removal area. We evaluated the segmental area (53 cases, excluding 5 subsegmental resections) and the subsegmental area 27 cases in 5 subsegmental resections and 22 extended segmentectomies). The subsubsegmental area was impossible for evaluation because of surgical artifact on CT (difficult to display the subsubsegmental bronchus postoperatively).

Furthermore, to evaluate the efficacy of the ICG method (ICG group), we compared surgical outcomes between the ICG group and a Control group of 59 patients who underwent traditional thoracoscopic segmentectomy between September 2008 and July 2014. Since VINCENT was introduced in July 2014, it was not used in all control patients. In the traditional segmentectomy, the target segment was confirmed by using temporary aeration into the associated bronchus. We compared the patients' clinical data and short-term surgical outcomes between the 2 groups retrospectively. However, since

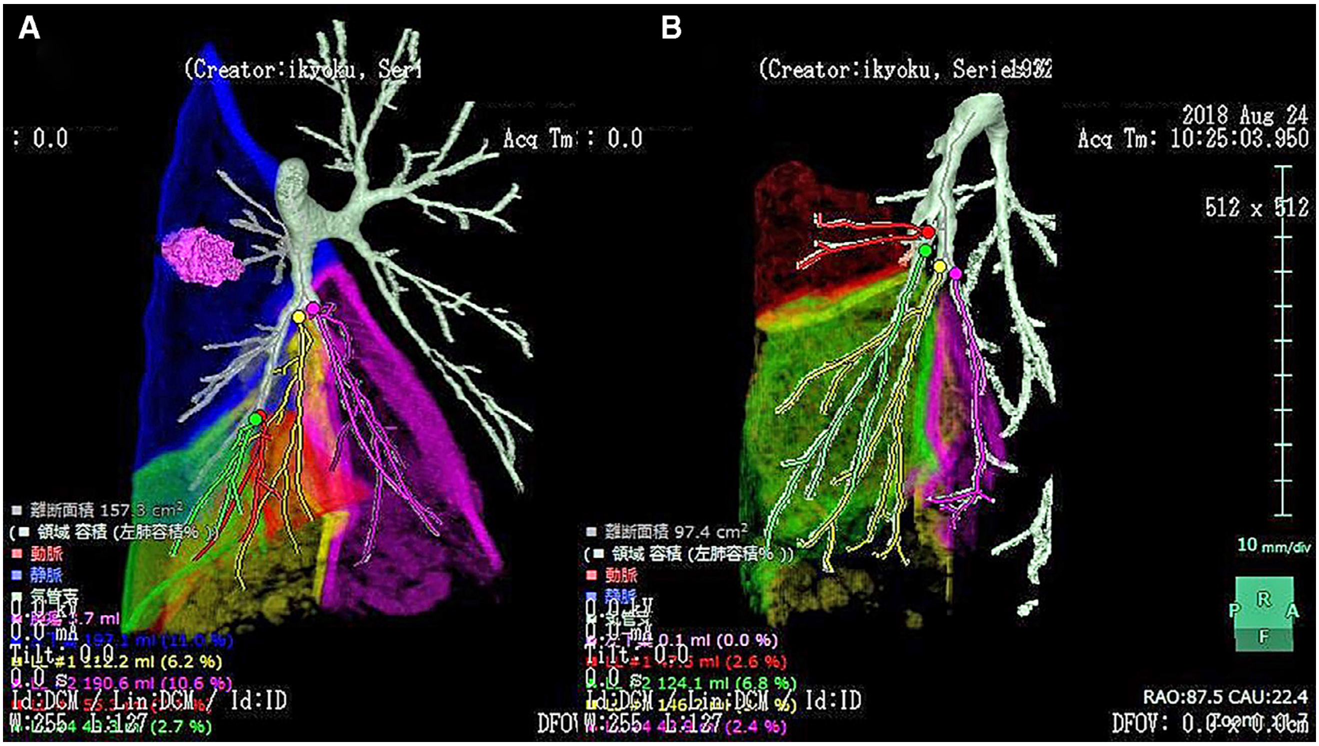


Figure 5. Comparison between pre- and postoperative bronchial and segmental structures. (A) Preoperative image with virtual S6 + S10a + S10* segmentectomy (blue area) (pink: S8, yellow: S9, red S10b, green: S10c); (B) Postoperative image (pink; S8, green: S9, red: S10b+c). Color version of figure is available online at http://www.semthorcardiovascsurg.com.

the follow-up duration in the ICG group was significantly shorter than that in the Control group (823 ± 365 days vs 1820 ± 905 days in control, $P < 0.0001$), long-term outcomes (recurrence rate) were not compared.

STATISTICAL ANALYSES

Data were analyzed using SPSS Statistics 20 (IBM Japan; Tokyo, Japan). Results were expressed as mean ± SD. To compare the differences between the ICG and Control groups, the Mann-Whitney *U* test was utilized to analyze for continuous variables and the Chi-square test was used to analyze for categorical variables. To reduce potential selection bias, we included results from propensity score-matched analyses and generated 2 groups (ICG and Control) with comparable characteristics. The propensity score was the probability of our ICG method, estimated using a logistic regression model that included age, gender, type of disease, and type of sublobar resection, for comparison between 2 groups. All reported *P* values were 2-sided, and *P* values less than 0.05 were considered to indicate a statistically significant difference.

RESULTS

The average number of virtual segmentectomies performed in 65 enrolled patients was 4.6 ± 1.6. In terms of clarity of the fluorescence border, 5 of 65 cases were grade 1; they did not undergo fluorescence-guided surgery and were switched to the standard segmentectomy. Fifty-five of 65 cases (84. 6%) had well-visualized ICG fluorescence (grade 3 or 4) to define a border easily. In 5 patients with grade 2, we could speculate on the correct line by connecting the fluorescence areas and could continue fluorescence-guided surgery. Two cases (1 in grade 3 and 1 in grade 4) were converted to lobectomy due to hilar nodal metastasis confirmed by on-site pathology. Finally, 58 cases (89.2%) completed ICG fluorescence-guided surgery (Table 1). There was no adverse event on ICG instillation.

The following procedures were performed: subsegmental resection in 5 patients, simple segmentectomy in 15 patients, complex segmentectomy in 16 patients, and extended segmentectomy in 22 patients (Fig. 6; Supplementary Table). The shortest distances from the tumor to the resection margin by simulation and actual measurement in the ICG group of 58 patients were 21.5 ± 11.2 mm and 23.5 ± 8.3 mm, respectively ($P = 0.190$; Table 1).

We compared the preoperative virtual segmentectomy and postoperative segmental structure. Segmental resection could be done according to the simulation in all cases. However, the adjacent subsegmental area that should have been preserved was not confirmed in 3 cases, and a part of the subsegmental area that should have been removed was identified in 1 case. This was because subsegmental bronchus was not transected at the orifice and the central portion of the subsegment was remained. But it did not affect the surgical margin. The concordance rate was 93.1% (54/58; Table 1).

Table 1. The Evaluation of Transbronchial ICG Instillation in the ICG Fluorescence-Guided Surgery

Average number of virtual segmentectomies 4.6 ± 1.6 (enrolled 65 cases)			
Clarity of fluorescence border (enrolled 65 cases)*			
Grade 1	5		
Grade 2	5		
Grade 3	26		
Grade 4	29		
Surgical margin (*n* = 58)	*P* = 0.190		
Virtual (mm)	21.5 ± 11.2		
Actual (mm)	23.5 ± 8.3		
Concordance between preop virtual segmentectomy and postop segmental structure†			
	Segment (53 cases)	Subsegment (27 cases)	All cases (58 cases)
Well matched	53	23	54
Unmatched	0	4	4

*ICG fluorescence-guided surgery was done in 58 patients with grade 2–4, excluding 2 cases (1 in grade 3 and 1 in grade 4), which were converted to lobectomy due to nodal metastasis.
†Segmental resection was evaluated in 53 patients with simple, complex, and extended segmentectomy; subsegmental resection was evaluated in 27 patients with subsegmental resection and extended segmentectomy.

Before propensity score matching, complicated sublobar resections, such as subsegmental resection and extended segmentectomy, were more frequently performed in the ICG group ($P < 0.0001$), and operating time was significantly longer in the ICG group. By propensity score matching, operating time, blood loss, length of hospital stays, and postoperative complications were similar between the 2 groups (Table 2).

DISCUSSION

This feasibility study demonstrated that although surgical outcomes were not superior compared to the standard segmentectomy, complicated sublobar resections can be done by using this technique. The success rate of transbronchial ICG injection was 89.2%, and the concordance rate between the preoperative simulation and the postoperative evaluation was 93.1%. The

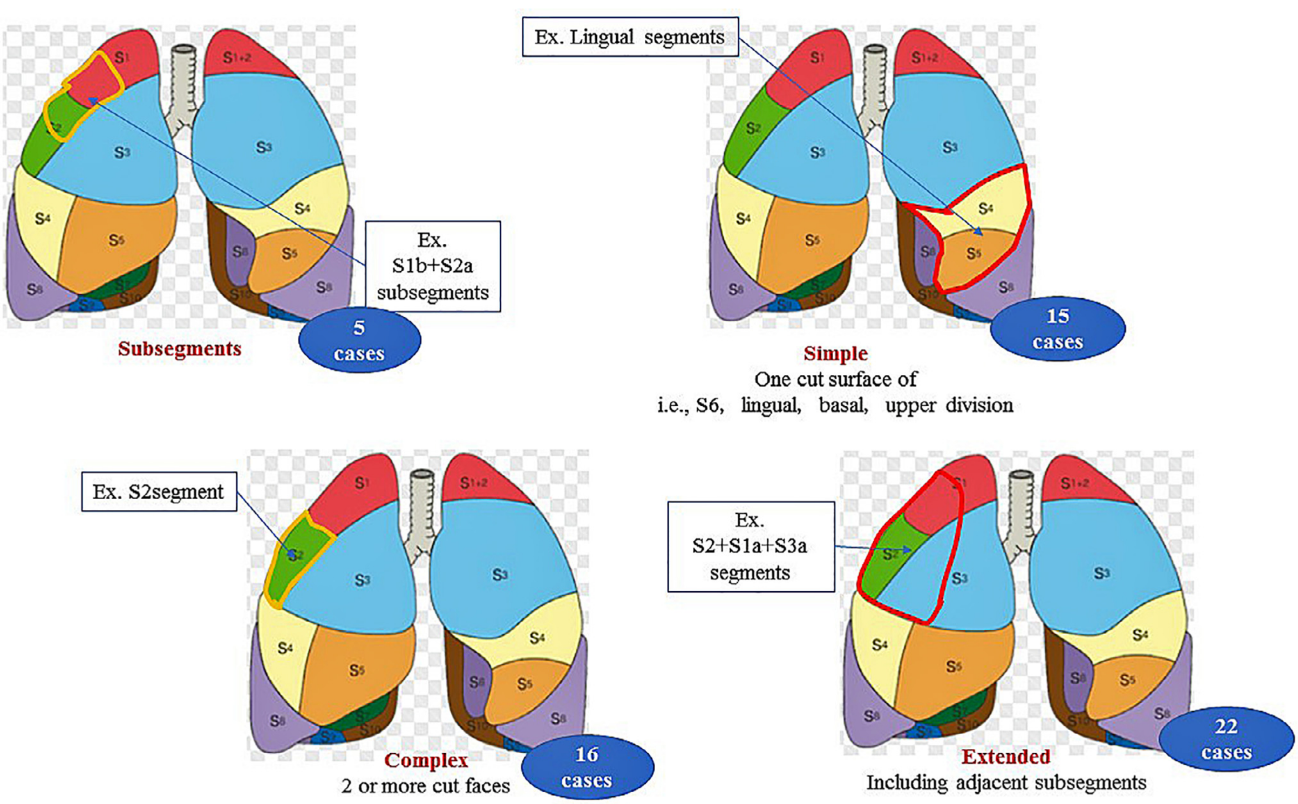


Figure 6. Fifty-eight cases of ICG sublobar resection were performed, including 5 cases of subsegmental resection, 15 cases of simple segmentectomy, 16 cases of complex segmentectomy, and 22 cases of extended segmentectomy.

Table 2. Comparison Between ICG and Control Groups Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	ICG	Control	*P* Value	ICG	Control	*P* Value
Number	58	59		31	31	
Age	68.7 ± 10.9	72.4 ± 7.6	0.036	70.3 ± 9.4	71.7 ± 8.5	0.545
Gender (M/F)	32/26	35/24	0.650	16/15	14/17	0.611
Disease			0.116			0.755
Lung cancer	39	47		25	24	
Metastatic tumor	16	12		6	7	
Benign disease	3	0		0	0	
Type of sublobar resection			<0.0001			0.995
Subsegment	5	1		1	1	
Simple	15	34		14	15	
Complex	16	23		15	14	
Extended	22	1		1	1	
Op. time (min)	212.4 ± 53.0	188.6 ± 48.4	0.013	203.2 ± 53.2	186.2 ± 39.8	0.162
Blood loss (mL)	108.9 ± 86.0	82.0 ± 95.7	0.113	95.7 ± 85.2	74.5 ± 68.0	0.282
Length of hospital stay (d)	8.4 ± 5.7	10.8 ± 12.2	0.175	8.0 ± 3.8	11.8 ± 15.7	0.191
Postop complications	4	10	0.094	2	5	0.229
Prolonged air leak	3	5	0.479	1	3	0.301
Pneumonia	1	3	0.317	0	2	0.151
Atrial fibrillation	1	2	0.569	1	1	1.000
Acute lung injury	1	2	0.569	1	1	1.000

Data are expressed as mean ± SD.

results of concordance rate of perioperative CT analyses supported the accuracy of transbronchial ICG injection.

The use of ICG and an infrared thoracoscope to identify lung resection borders has been reported by several authors.[7,8] These studies primarily used intravenous injection of ICG, which limits fluorescence visualization to only a few minutes. The advantages of our method are (1) it is applicable to any type of sublobar resection, (2) it allows for the initial determination of the resection area during the operation, (3) it leads to transection of only those vessels and bronchi required for removal of the lung, and (5) fluorescence persists during operation and the removal area can be checked at any time. On the other hand, the limitations of this method are (1) the necessity of near-infrared thoracoscopy and a 3D medical image analyzer, (2) knowledge of precise bronchial anatomy, (3) advanced bronchoscopy skills, and (4) initial nonuniform distribution of ICG and distribution of ICG into adjacent areas with the passage of time.

Transbronchial ICG instillation can maintain ICG fluorescence for several hours, allowing for persistent visualization of the boundary line. The most critical and important part is transbronchial instillation of ICG. When the transbronchial instillation is successful, the ICG boundary line is continuously visible, making complicated sublobar resection much easier. Furthermore, when we hesitate to decide whether small vessels and bronchi should be transected, we can only treat those that connect to the removal area. This is a significant advantage in complicated sublobar resection. However, if ICG is instilled into the wrong bronchus, surgery may be difficult and confusing because rechallenge is impossible. To reduce this problem, we applied precise virtual bronchoscopy to identify bronchi into which we should inject ICG and a bronchial balloon catheter to prohibit ICG leakage. Five cases of grade 1 in clarity of the border were relatively initial cases of this study and our procedure could be stabilized. We expect that ICG instillation mixed with diluted contrast media can confirm the ICG injection area by using cone-beam CT intraoperatively. This may be a future challenge.

Volume Analyzer Synapse 3D VINCENT is a highly advanced technology for visualizing 3D organ structures.[9] It allows us to perform a simulation before the operation and minimize excision volume. However, it can be difficult to precisely match the operation with the simulation. Transbronchial ICG-sublobar resection is an ideal procedure to bridge this gap.

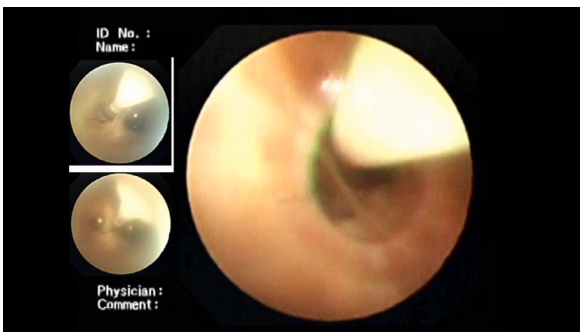
Sawabata reviewed locoregional recurrence after intentional pulmonary segmentectomy for NSCLC.[10] He suggested that a sufficient margin distance is crucial to reducing locoregional recurrence. Schuchert et al. reported that anatomic segmentectomies for stage I NSCLC resulted in a higher rate of recurrence when margin/tumor ratios were less than 1.[11] This suggests that a 2 cm or greater surgical margin is necessary for early stage lung cancer. Since the follow-up duration was not enough, we cannot comment on the efficacy of long-term outcomes.

The limitations of this study are the following: (1) this was a single-center noncomparative study; (2) failed cases were excluded, and only successful cases were analyzed; (3) there was no comparison of long-term outcomes; and (4) there was no evaluation of the contribution of transbronchial ICG instillation and virtual segmentectomy separately. We need a multicenter comparative study with standard sublobar resection for further evaluation and long-term outcomes.

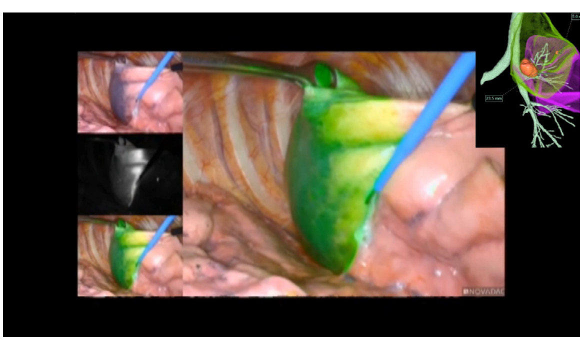
In conclusion, the combination of virtual sublobar resection and ICG-guided sublobar resection using transbronchial ICG injection may be applicable to any type of sublobar resection. This kind of technique is an advancement over current techniques because of the additional improvements such as the injection technique and intraoperative confirmation of the ICG injection area.

SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:



Video 1. Transbronchial ICG instillation. Tenfold-diluted ICG is instilled into each associated bronchus.



Video 2. Operative procedure of VATS S1+S2a+S3bi sublobar resection after transbronchial ICG instillation. ICG fluorescence is well visualized and a complicated operation can be done.

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