Recent fluorescence-based optical imaging for video-assisted thoracoscopic surgery segmentectomy

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Background: The importance of fluorescence-based optical imaging in various fields of surgery is increasing. This is a prospective cohort study aimed to investigate the feasibility and efficacy of indocyanine-green fluorescence (ICGF)-based navigation for near-infrared (NIR) thoracoscopic segmentectomy.

Methods: ICGF-based video-assisted thoracoscopic surgery (VATS) segmentectomy was performed in 149 patients. Each patient underwent preoperative evaluation by multidetector-row computed tomography (MDCT), which provided three-dimensional simulations of vascular structures, segmental bronchi, and lung tumor. During the procedure, low-dose ICG (0.25 mg/kg) was injected systemically after the target segmental pulmonary arteries and bronchus were divided. Under NIR-thoracoscopic guidance, an ICG fluorescent line was marked by electric scalpel, followed by division of lung parenchyma along the line by electric scalpel or endoscopic staples.

Results: An intersegmental line of ICGF was visible in 98% of patients, even with the use of low-dose ICG. Neither ICG-related adverse events nor procedure-related major complications occurred. The 5-year overall (OS) and recurrence-free survival (RFS) rates were 91.8% and 98%, respectively. Localized recurrence at the resected site did not occur in any patient.

Conclusions: ICGF-based navigation for NIR VATS segmentectomy for patients with lung cancer is feasible and effective.

Keywords: Video-assisted thoracoscopic surgery (VATS); indocyanine green (ICG); near-infrared thoracoscopy (NIR thoracoscopy); segmentectomy

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Introduction

Recently developed fluorescence-based optical imaging methods are being used for navigation in various fields of surgery (1,2). Indocyanine green (ICG) is used for evaluation of liver function, cardiac output, and so on (3). The emission of fluorescence by ICG can be detected even within deeply located structures because it is transmitted through tissue (4,5); therefore, ICG-based optical imaging can provide minimally invasive imaging of vessels and lymphatic ducts deep inside organs, and real-time imaging during surgery. ICG-based imaging has been recently used in the field of thoracic surgery for lung segmentectomy.

Since the 1960's, the standard procedure for resectable non-small cell lung cancer (NSCLC) has been lobectomy with systematic lymph node dissection and not segmentectomy (6). A current meta-analysis, however, elucidated that segmentectomy produced survival rates similar to those obtained by lobectomy for patients with stage I NSCLC (7). Moreover, segmentectomy preserves whole lung function better than lobectomy, because the lobe is not only preserved, but the function of the ipsilateral non-operated lobe(s) is improved (8). Although the importance of segmentectomy for stage I NSCLC has increased, segmentectomy remains a more difficult procedure than wedge resection or lobectomy. In addition, preoperative planning and decision making for segmentectomy vary among surgeons. Above all, the accurate intraoperative identification of the target intersegmental plane is essential to the procedure, especially with regard to video-assisted thoracoscopic surgery (VATS) segmentectomy. Several intraoperative methods for identifying the intersegmental plane have been reported (9-12).

In 2009, an experimental study conducted on pigs showed the feasibility of near-infrared (NIR) imaging and ICG fluorescence (ICGF) for identifying intersegmental planes (13). Subsequently, the usefulness of this approach for human patients was reported (14,15). This approach evaluates the blood supply to the lungs, allows arterial segmentation, and avoids the need for reinflating the lung. It has proved suitable for emphysematous lungs and the use of a VATS procedure instead of conventional bronchial segmentation.

In 2017, we reported our initial results from VATS segmentectomies under ICGF-based navigation (16), and the present study further reports the current patient outcomes from those procedures.

Methods

Patients

This study was approved by the Institutional Review Board of Clinical Research (No. 2010-1055) at the Cancer Institute Hospital, and written informed consent was obtained from each patient. From January 2013 to December 2017, 149 patients underwent VATS segmentectomy under ICGF-based navigation at our institute.

ICG/NIR thoracoscopy system

ICG is a hydrophilic tricarbocyanine dye with a molecular mass of 776 Da, which rapidly binds to plasma proteins in the body. Previous studies have reported that ICG was well tolerated, with no immediate or short-term complications related to its administration. When NIR light (805 nm) is absorbed by ICG in plasma, ICG emits fluorescence with a wavelength of 830 nm that is visible during NIR thoracoscopy. ICG administered after ligation of segmental arteries allows visualization of segmental boundaries during NIR thoracoscopy. We generally use a NIR thoracoscopy system (D-Light P system; Karl Storz Endoskope, Japan K.K., Tokyo, Japan) for segmentectomy under ICGF-based navigation. This scope was 10 mm in diameter with a 30-degree rigid scope. The imaging mode could be changed instantly between white light and ICGF by a foot-operated switch.

Surgical procedure

Every patient underwent multidetector-row computed tomography (MDCT) for preoperative planning. A software program (Volume Analyzer Synapse Vincent; Fujifilm Medical System, Tokyo, Japan) used MDCT data to create three-dimensional simulations of vascular structures, segmental bronchi, and tumor. The simulation workstation allowed us to create a virtual intersegmental plane after plotting the dominant segmental pulmonary artery and to measure the surgical margin extending from the tumor to the closest intersegmental plane, thus providing appropriate preoperative planning for each patient.

Although the definition of VATS in Japan varies, for this study it was defined as an operation performed entirely through 4 small incisions that measured 30, 15, 7, and 7 mm, without rib spreading, and that used video-monitor visualization only. After the dominant pulmonary arteries and segmental bronchus were divided, ICG (0.25 mg/kg) was injected into a peripheral vein. Under NIR visualization, the resulting line of ICGF was marked by electrocautery, and lung parenchyma was divided along the line by electrocautery or endoscopic staples. Generally, we tried to obtain a surgical margin larger than the size of the tumor (*Figures 1-4*).

Statistical analysis

Statistical analysis was performed by EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, EZR is a modified version of R commander, which was designed with additional statistical functions that are frequently used in biostatistics.

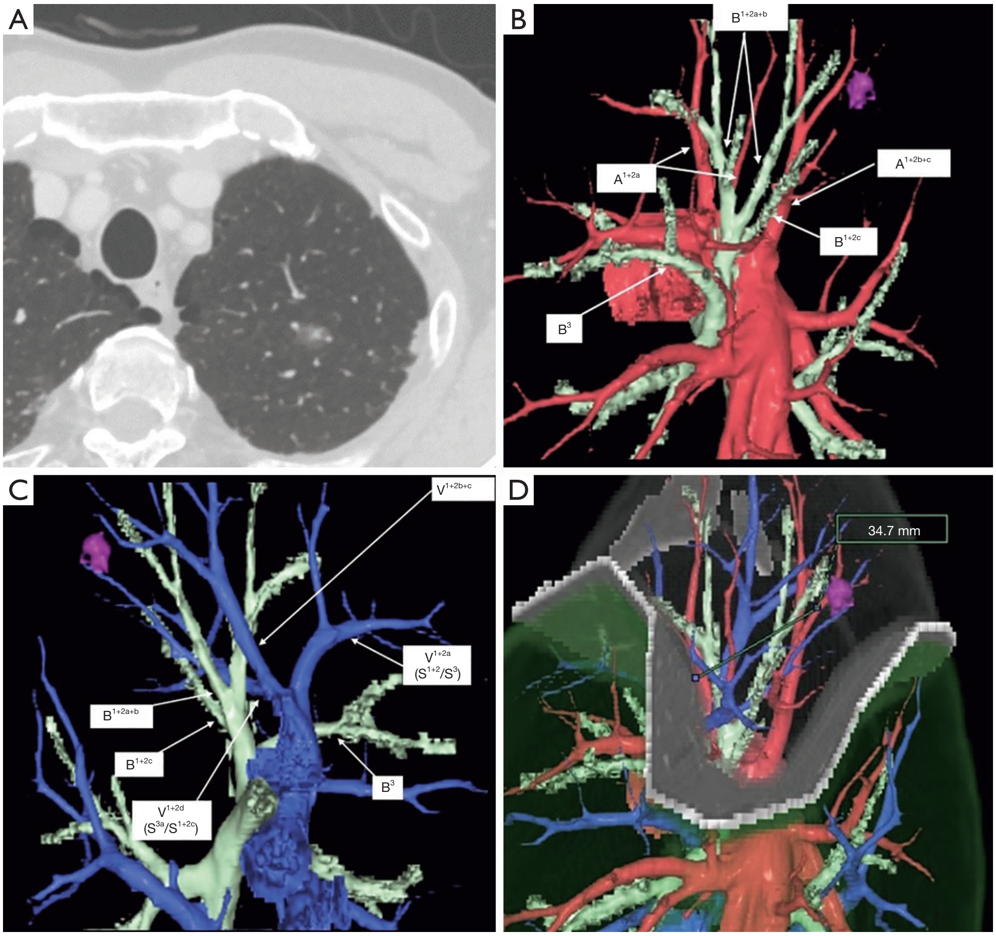

Figure 1 Preoperative evaluation. (A) Thin-slice computed tomography (CT) shows a partly solid ground-glass nodule (GGN) in the left S^{1+2} segments. (B) Three-dimensional (3D)-CT simulation shows tumor location, segmental arteries, and segmental bronchus. (C) 3D-CT shows intersegmental vein. (D) Virtual intersegmental plane is created based on the segmental artery.

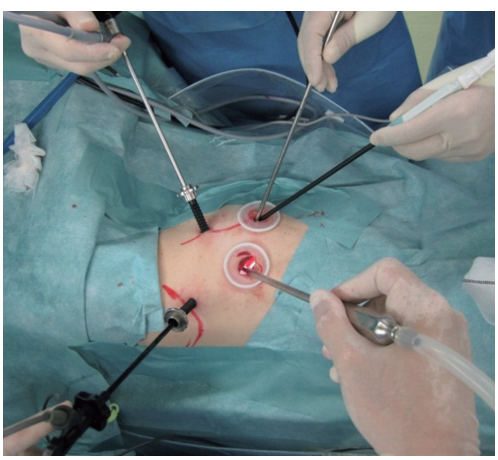

Figure 2 Port placement. Indocyanine green-fluorescence (ICGF)-based navigation for video-assisted thoracoscopic surgery (VATS) segmentectomy is performed via 4 incisions.

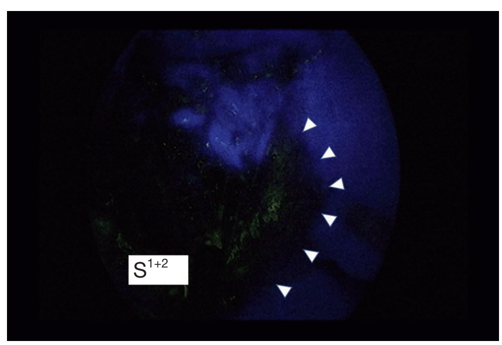

Figure 3 Intraoperative indocyanine green-fluorescence (ICGF) images. Left S^{1+2} appear dark, and residual segment appears bright. The border between these 2 regions is recognized as the intersegmental plane (arrowheads).

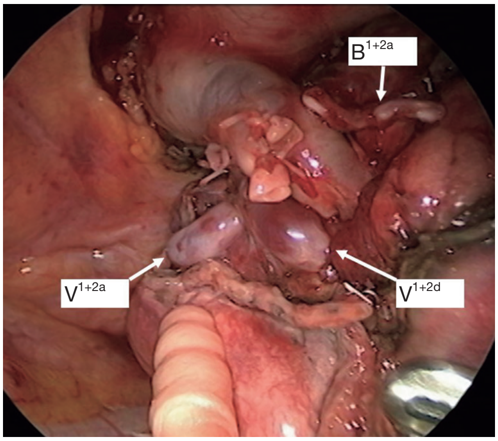

Figure 4 Final aspect after indocyanine green-fluorescence (ICGF)-based navigation for video-assisted thoracoscopic surgery (VATS) segmentectomy of left S^{1+2}.

Results

Patient characteristics and surgical outcomes

The baseline characteristics of patients are summarized in *Table 1*. The study patients comprised 75 men and 74 women (median age, 66 years; range, 30–87 years). There were 101 primary lung cancers, 40 metastatic lung tumors, and 8 benign diseases. Preoperatively, 81 patients (54%) had a documented history of smoking. The mean forced expiratory volume in 1 s (FEV_1) was 2.54 L (range, 1.26–4.87 L). The mean tumor size was 16 mm (range, 6–64 mm). The mean operative duration was 167 min (range, 80–319 min), and the mean volume of blood loss was 22 mL (range, 0–130 mL).

No ICG-related intraoperative or postoperative adverse events were observed. ICG-based identification of the target intersegmental plane was possible in 146 (98%) patients. The median duration of chest drainage was 1 day (range, 1–23 days), and the median postoperative hospital stay was 5 days, (range, 5–36 days). All patients were discharged without major complications; although 1 patient with primary lung cancer was readmitted and died of acute postoperative exacerbation of interstitial pneumonia.

The surgical margin was negative for malignancy in all patients; however, in 7 patients (4.7%), the width of the tumor margin was less than the size of the tumor. In a case of metastatic lung tumor case, 1 (0.7%) localized recurrence at the resected site occurred 12 months after the surgery. Radiotherapy was used to treat this patient.

Table 1 Baseline characteristics and surgical outcomes of patients

Variable	Value
Age, years, median [range]	66 [30–87]
Sex	
Male	75
Female	74
Disease	
Primary lung cancer	101
Metastatic lung tumor	40
Benign lesion	8
Smoking history	
Current and ever	81
Never	68
Smoking index, mean [range]	341 [0–2,240]
Pulmonary function, mean [range]	
FEV_1, L	2.54 [1.26–4.87]
Tumor size, mm, mean [range]	16 [6–64]
Operation time, min, mean [range]	167 [80–319]
Intraoperative blood loss, mL, mean [range]	22 [0–130]
Conversion to thoracotomy	0
ICGF	
Valid temporary	146
Invalid demarcation	3
Postoperative complications	
Prolonged air leakage	5
Arrhythmia	2
Others (pneumonia, IP/AE, chylothorax, empyema, subcutaneous hematoma, delirium)	6
Morbidity	13
Chest drainage, days, median [range]	1 [1–23]
Hospitalization, days, median [range]	5 [3–36]
30-day mortality	0
Surgical margin	
≥ tumor size	142
< tumor size	7
Local recurrence (resected site)	1

FEV_1, forced expiratory volume in 1 second; ICGF, indocyanine green fluorescence; IP/AE, acute postoperative exacerbation of interstitial pneumonia.

Table 2 Characteristics of patients with primary lung cancer

Variable	Value
Age, years, median [range]	69 [37–87]
Sex (male/female)	42/59
Pathological stage (UICC 7th)	
IA/IB/IIB/IIIA	97/2/1/1
Histologic type	
Ad (include AIS and MIA)	98
Sq	1
Ad-sq	1
SCLC	1
Resected segment	
Right side	34
Basal/S^2/S^6/S^8/S^{8a}/S^{9+10}	1/4/22/5/1/1
Left side	67
UD/UD + S^6/Ling/S^{1+2}/S^{1+2ab}/S^{1+2+6}/S^6/S^{8+9}	47/1/7/1/1/1/8/1
Fatal cases	1
Cause	IP/AE

UICC, Union for International Cancer Control; Ad, adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; Sq, squamous cell carcinoma; SCLC, small cell lung cancer; Basal, basal segment; UD, upper division tri-segment; Ling, lingular segment; IP/AE, acute postoperative exacerbation of interstitial pneumonia.

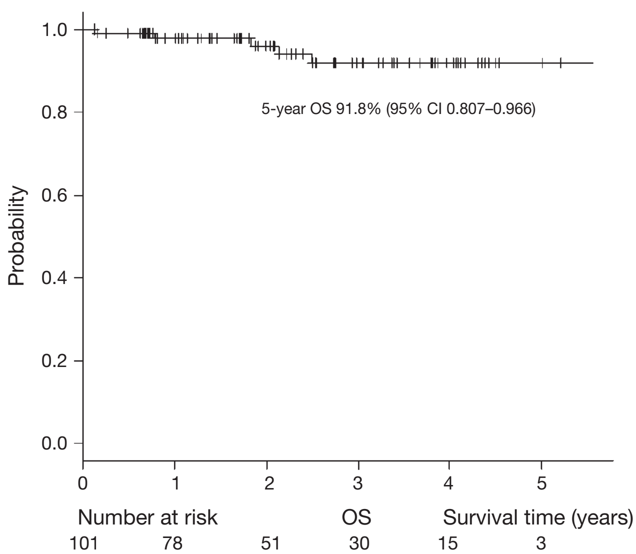

Figure 5 Overall survival (OS) analysis of patients with primary lung cancer by the Kaplan-Meier method.

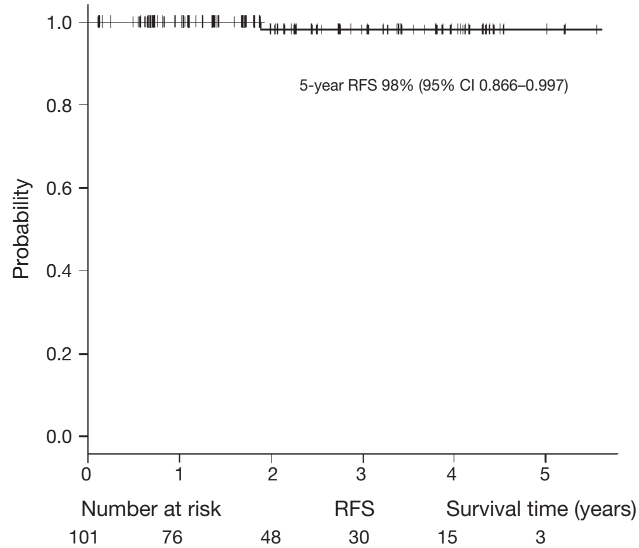

Figure 6 Recurrence-free survival (RFS) analysis of patients with primary lung cancer by the Kaplan-Meier method.

Therapeutic outcomes of patients with primary lung cancer

The characteristics of the patients with primary lung cancer are shown in *Table 2*. With a median follow-up time of 24 months, the 5-year overall survival (OS) rate and recurrence-free survival (RFS) rate were 91.8% and 98%, respectively (*Figures 5,6*). One patient died of distant metastases (bone and lung) due to primary lung cancer, and 6 patients died of other diseases without recurrence of cancer. None of primary lung cancer patients developed local recurrence at the resected site.

Discussion

This study investigated the feasibility and efficacy of the surgical procedures, strategies, and outcomes of VATS segmentectomy performed under ICGF-based navigation in our institute. To the best of our knowledge, our series is comprised of the largest number of patients. Previous studies on segmentectomy under ICGF-based navigation have shown efficacy for this guidance method. The intersegmental line could be identified and demarcated for 85–100% of patients (14,17), and no adverse events related to ICG administration were reported. In this study, we also identified the target intersegmental line for 98% of patients, despite the use of low-dose ICG; and did not observe related adverse events. In addition, an excellent therapeutic outcome for patients of primary lung cancer was shown in

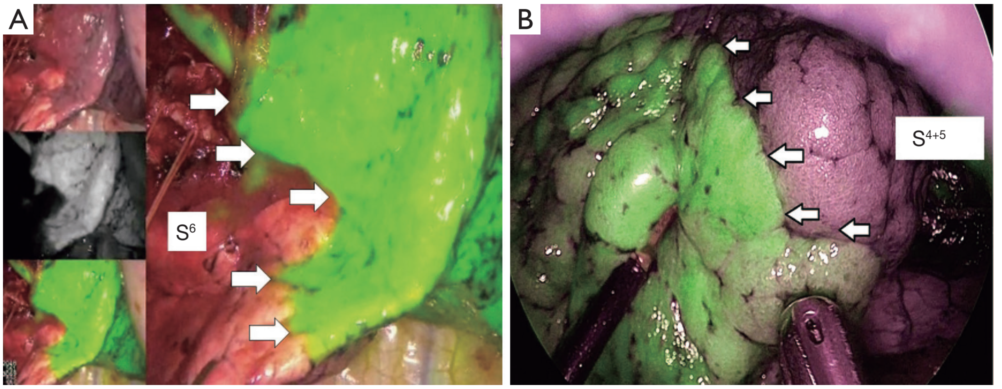

Figure 7 Near-infrared thoracoscopy. (A) Pinpoint; Novadaq, Kalamazoo, MI, USA. Intersegmental plane (arrows). (B) Visera Elite II; Olympus, Tokyo, Japan. Clear contrast is observed, with the background also apparent. Intersegmental plane (arrows).

this study. Although the follow-up period was short, the 5-year OS and RFS rates were excellent. Moreover, no local recurrence at the resected site was worthy of special mention. Our results indicate that VATS segmentectomy under ICGF navigation for our patient population was acceptable. However, as we previously reported, several limitations of this method should be acknowledged (16). First, ICG may rapidly be washed out, leading to the loss of staining. Second, in difficult settings such as severe anthracosis of the lung, visualization of an obvious contour can be problematic because of hypovascularity of peripheral lung. Third, ICGF can spread into target segments, resulting in reduced contrast. Fourth, although ICGF could be observed on the surface of the lung, it could not be seen in the ongoing dissection plane. Fifth, electrocautery to delineate the demarcation line must be performed carefully because the background is dark in the ICGF mode. And last, the NIR thoracoscopy system is expensive, and the equipment is not conventional. Some companies have now introduced NIR thoracoscopy systems that merge visible light images with the fluorescent images on the display monitor (*Figure 7*). Further technological developments may resolve some of the shortcomings.

Conclusions

In summary, ICGF-based navigation for NIR VATS segmentectomy for patients with lung cancer is feasible and effective. ICGF-based navigation can provide a clear surgical field by allowing maintenance of the deflated state of the lung and can achieve a high rate of accurate identification of the intersegmental line. The most important issue with segmentectomy, however, is how to obtain an adequate surgical margin. To tackle this issue, we should do more to identify patients appropriate for the procedure, and to select the most advantageous surgical procedure for those patients, to avoid local recurrence after segmentectomy. Selected patients who undergo segmentectomy should survive without recurrence using surgical treatment alone. Currently, two prospective randomized, multicenter phase III trials are being conducted by the Cancer and Leukemia Group B (CALGB 140503) (18) and the Japan Clinical Oncology Group (JCOG 0802) (19) to establish the effectiveness of intentional sublobar resections for small (2 cm) peripheral tumors. We look forward to the results of these studies, which should help to address this issue.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Review Board of Clinical Research (No. 2010-1055) at the Cancer Institute Hospital, and written informed consent was obtained from each patient.

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