


ORIGINAL ARTICLE

Application of indocyanine green fluorescence for precision sublobar resection

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Keywords

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Abstract

Background: Increasing identification of small pulmonary nodules promotes sublobar resection, but localization and surgical margins of non-palpable pulmonary nodules through sublobar resection are challenging. Our aim was explicate the feasibility of applying indocyanine green (ICG) fluorescence to localized nodules, and to carry out surgical resection.

Methods: A total of 46 patients with subpleural pulmonary nodules <3 cm were enrolled, including 35 for wedge resection and 11 for segmentectomy. For wedge resection, patients underwent computed tomography-guided percutaneous injection of ICG preoperatively. Wedge resection was carried out after confirmation of the fluorescence using fluoroscopy. For segmentectomy, ICG was injected through the peripheral vein during surgery and resection of the segmental plain was carried out. Detailed measurements were taken and information was collected for the whole procedure.

Results: A total of 33 out of 35 patients underwent successful wedge resection using ICG fluorescence. Segmentectomy was successfully carried out for all 11 patients who underwent the procedure. For two patients, the nodules failed to be localized with unclear fluorescence, and one patient with an undetected nodule was altered to perform lobectomy. For wedge resection, the mean tumor size and depth from the pleural surface were 7.8 ± 0.5 mm and 10.5 ± 1.6 mm, respectively. The median time taken for preoperative computed tomography-guided percutaneous injection was 28 min (range 18–40 min), and 25 min (range 16–30 min) for wedge resection. For segmentectomy, the ICG fluorescence occurred 14 s after injecting ICG through the peripheral vein, and the median duration was 15 min. All surgical margins were negative based on pathological evaluation.

Conclusions: The implementation of ICG fluorescence could provide surgeons carrying out precision sublobar resection with a time-saving surgical technique with less unnecessary intraoperative damage.

Introduction

Lung cancer is the leading cause of cancer death worldwide.¹ With the extensive use of thoracic computed-tomography (CT), an increasing number of small pulmonary nodules can be found preoperatively. Most

small pulmonary nodules are referred to as very early-stage lung cancer and are eligible for surgical resection.^{2,3} The five-year survival rate for those pathological confirmed atypical adenomatous hyperplasia, adenocarcinoma *in situ*, and minimally invasive adenocarcinoma is almost

100%, and even 75–90% for stage IA (<3 cm in longest diameter) through complete surgical resection.⁴ Given that rapid progress of minimally invasive surgery, early detection of suspected pulmonary nodules might lead to a fast-track surgery with less pain, fast recovery, and better quality of life.^{5,6} For small subsolid nodules, increasing evidence suggests that sublobar resection, including wedge resection and segmentectomy, is biologically adequate to remove the tumor completely and shows comparable survival with lobectomy.^{7–9} Traditional localization methods for wedge resection primarily included hook wire and computed tomography (CT)-guided percutaneous methylene.^{10–12} For segmentectomy, traditional methods to ensure the segmental plain were the inflation-deflation method and jet ventilation through a bronchoscope.¹³ However, for wedge resection, the current technique for localizing subpleural pulmonary nodules without appearance on visceral pleura limits its advantage, especially when the lesion appears to be <10 mm, deep to the pleural surface, or pure ground glass opacity.^{14,15} Previous reports showed great performance of CT-guided hook wire. Xu *et al.*¹⁶ reported a hook wire localization success rate of 97.6%, which is almost the same as what Miyoshi¹⁷ and Dendo¹⁸ achieved. However, the limitations are significant, including diffusion of dyeing, dislodgment, pneumothorax, and pulmonary hemorrhage.^{10,19} Similarly, traditional methods to detect the segmental plain are clinically applicable, but suffer from several limitations, including unnecessary pulmonary parenchyma damage due to repeatedly inflation and unclear segmental plain. A previous animal study has demonstrated a novel near-infrared (NIR) thoracoscopic lung nodule localization by using fluorescent indocyanine green (ICG),²⁰ and its efficacy has been verified by a phase I study.²¹ The application of ICG in sublobar resection shows a promising future and should be further verified in clinical practice.

In this study, we explored whether the application of ICG fluorescence may be clinically feasible, safe, and provide high efficacy in carrying out precision sublobar resection.

Methods

Study design and patients

We consecutively enrolled 46 patients with small pulmonary nodules (≤3 cm) of whom 35 were scheduled for wedge resection and 11 were scheduled for segmentectomy. An overview of the enrolled patients through wedge resection is presented through a visualized heat map (Fig 1). Patients with peripheral nodules <3 cm accidentally found on CT-scan were evaluated and scheduled for either segmentectomy or wedge resection. For wedge resection, CT-guided ICG injection was carried out followed by video-assisted thoracoscopic surgery wedge resection. For segmentectomy, 4–5 mL of ICG was injected through the peripheral vein and fluoroscope was applied to detect the segmental plain, which was then dissected by a stapler. During segmentectomy, we also re-confirmed if the vessels to be dissected belonged to targeted segments by ligating the vessel. No suspicious metastasis of lymph nodes was found preoperatively. In the case of missing metastasis lymph nodes, we carried out lymph nodes sampling for some patients who presented with a higher consolidation/tumor (C/T) ratio. All enrolled patients gave informed consent.

Materials

In this research we applied indocyanine green (ICG). It is a water-soluble anionic, amphiphilic NIR fluorophore with an excitation wavelength of 790 nm. Before wedge resection, a dose of 0.1–0.2mL of ICG at a concentration of 2.5 mg/mL was injected into the lung parenchyma through CT-guided percutaneous injection. The selection of the dose for ICG was determined by our preliminary experiment of several cases, and we found 0.1–0.2mL would be adequate to show the position with the minimal dose. We used NIR thoracoscopy to capture the ICG fluorescence. This is a Food and Drug Administration and Health Canada-approved rigid thoracoscopy, which has a 10-mm

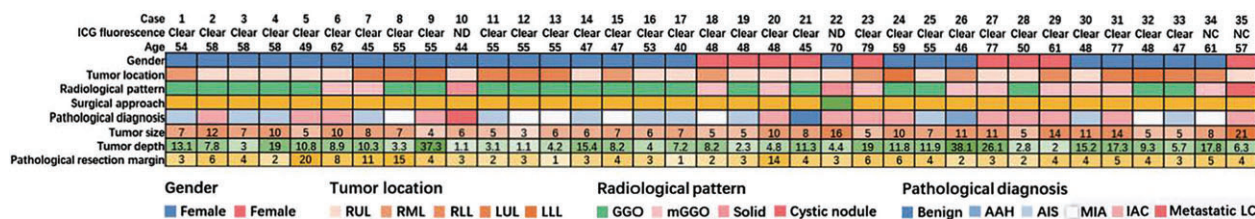


Figure 1 Overview for patients' characteristics and study outcome with visualized heat map. AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; IAC, invasive adenocarcinoma; GGO, ground-glass opacity; LLL, left lower lobe; LUL, left upper lobe; Metastatic IC, metastatic lung tumor from colon cancer; mGGO, mixed ground-glass opacity; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

diameter and a 30-cm length in a straight, rigid scope. The optical system has a 0 degree or 30 degree view angle, and a 70 degree field of view, transmitting both visible light and 808 ± 5 nm NIR laser. The laser power is classified as class 3R at the tip of the scope, as per the International Electro-Technical Commission IEC60825-1. Pulse duration is 17 ms in the maximum setting at 20 pulses/s.

Procedure

Patients scheduled for nodules localization and wedge resection were first sent to a room called the “CT-guided room” at Guangdong General Hospital, Guangzhou, China, which was equipped with a 64-slice spiral CT. A 20-G needle was injected to localize the lesion nearby after local anesthesia and radiological localization. Then, a dose of 0.1–0.2 mL of ICG was delivered through a needle core. After confirmation of a satisfactory injection of ICG from a CT scan, patients were sent directly to the operating room for general anesthesia and preparation of surgical resection. During video-assisted thoracoscopic surgery wedge resection, the NIR thoracoscope was used to localize the subpleural nodules (Fig 2). The surgical margin was determined by the extent of ICG, and surgical staplers were then used to remove the lung parenchyma containing the entire ICG fluorescence site. We also used a NIR thoracoscope to further confirm if the fluorescence still existed in the resected specimen (Fig 3). Then the resected specimen was cut along the maximum section of nodules to evaluate whether the surgical margin was adequate. If we considered the surgical margin to be inadequate, additional resection was carried out, and all specimens were sent for pathological evaluation. All pathological evaluations were reviewed by specialized pathologists.

Results

Between January 2018 and April 2018, 46 consecutive patients were enrolled, of whom 35 were scheduled for nodules localization plus wedge resection, and 11 were scheduled for segmentectomy. The patient characteristics and surgical information for wedge resection are summarized in Table 1. Detailed information of lesions and surgery for both wedge resection and segmentectomy are presented in Fig 1 and Table 2, respectively.

For wedge resection, nine male and 26 female patients were enrolled, with a mean age of 54.7 years (range 40–79 years). Radiological patterns included 21 pure ground glass nodules, 11 part-solid nodules, two solid nodules, and one cystic nodule. The median tumor size based on CT scan was 7 mm (range 3–20 mm). The median depth of nodules from the surface was 8.2 mm for 35 patients through wedge resection. The median time

taken for preoperative CT-guided percutaneous injection was 28 min (range 18–40 min), and 25 min (range 16–30 min) for wedge resection. According to intraoperative findings for wedge resection, ICG was successfully injected in all patients. No suspected lymph node metastasis was captured before surgery. During wedge resection, three out of 35 patients (11.4%) failed to localize the nodules, with two unclear fluorescence and one undetected nodule. In this patient, the nodule was 6 mm in size and 1.1 mm of tumor depth, and lesion was not detected from the resected specimen. Therefore, we carried out a lobectomy in the case of missing the lesion only by additional resection. The other two cases failed to localize with unclear fluorescence, probably caused by insufficient ICG injection and ICG leakage to the thoracic cavity. After carrying out wedge resection, we used a fluoroscope to confirm the ICG fluorescence in the resected specimen. All patients who underwent fluorescence localization showed no ICG-related adverse effects. Patients were discharged from the hospital without apparent complications. The median length of stay was 2.4 days (range 2–4 days). The pathological diagnosis of the 35 patients included 33 adenocarcinomas (94.2%), one benign disease (2.9%), and one metastatic lung cancer from colon cancer (2.9%). Among 33 adenocarcinomas, one was atypical adenomatous hyperplasia, 12 were adenocarcinoma *in situ*, seven were minimally invasive adenocarcinoma, four were lepidic predominant adenocarcinoma, and nine were acinar predominant adenocarcinoma.

For segmentectomy, five male and six female patients were enrolled, with a mean age of 53.5 years (range 40–77 years). Radiological patterns included six pure ground glass nodules, four part-solid nodules, and one solid nodule. The median tumor size based on CT scan was 8 mm (range 4–22 mm). The median depth of nodules from the surface was 10.5 mm (range 4.1–58) for 35 patients through wedge resection. The median time taken for fluorescence after injection of ICG was 14 s (range 10–18 s). All targeted segments were detected visually through a fluoroscope (Fig 4). Re-confirmation of the vessel to be dissected showed a significant role in differentiating uncertain segmental vessels by using ICG (Fig 4). Nine out of 10 resected specimens were pathologically diagnosed as adenocarcinoma, and one was benign disease.

Discussion

The number of subsolid pulmonary nodules increases as the number of CT examinations carried out during screening increases. Subpleural pulmonary nodules might be non-palpable, especially for lesions with a lower solid component. The surgical approach is the standard of care for such patients. Sublobar resection is considered as an

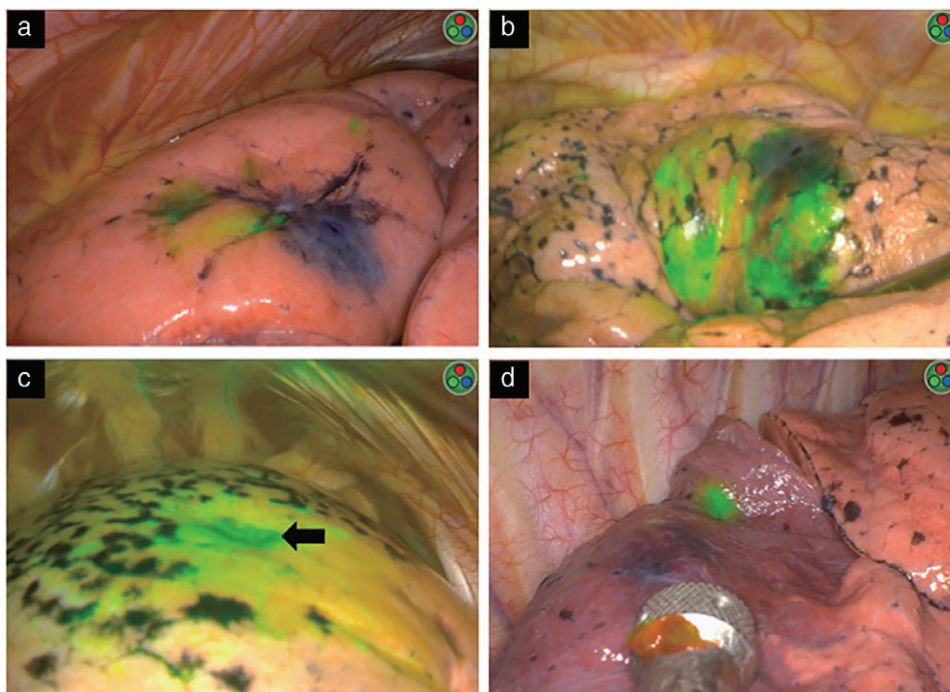


Figure 2 (a–d) Intraoperative fluorescence using near-infrared thoracoscope. Fluorescence merge image. (c) Slight diffusion of fluorescence, but (b) high concentration of indocyanine green was captured in the middle.

optimal and optional choice for these small pulmonary nodules.^{7–9} The traditional localization technique, including hook wire and CT-guided percutaneous methylene, might

help to localize the pulmonary nodules. Several studies had revealed extraordinary results from applying a CT-guided hook wire to localize pulmonary nodules.^{9–11} However,

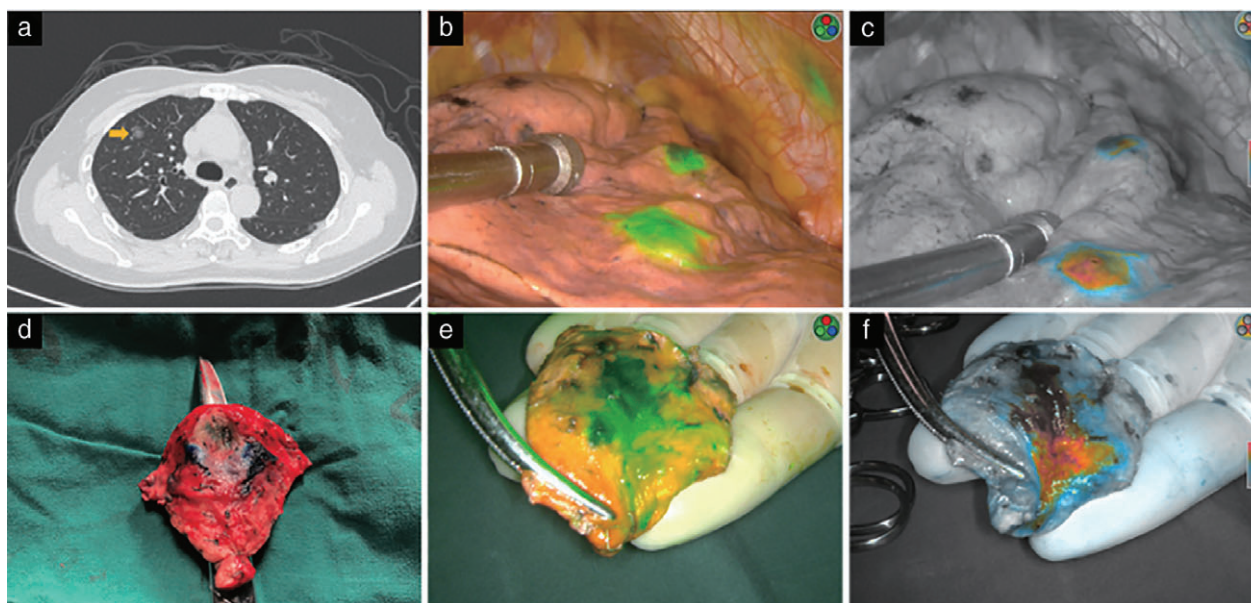


Figure 3 Consecutive view before, during, and after the entire procedure. (a) Preoperative computed tomography scan showed pure ground-glass nodule (yellow arrow) located in the right upper lobe with 6 mm in the longest diameters. (b) Intraoperative findings under near-infrared thoracoscope. (c) This pattern showed the concentration of indocyanine green with red color indicating high concentration, and grey color indicating low concentration. (d) Gross appearance of the resected specimen. (e) Confirmation of fluorescence in resected specimen under near-infrared thoracoscope. (f) Malignant nodule was found within the site with the highest concentration of indocyanine green.

Table 1 Patients' characteristics and detailed tumor parameters for both segmentectomy and wedge resection

Patient characteristics and tumor parameters	n (%)	
	Wedge resection n = 35	Segmentectomy n = 11
Gender		
Male	9 (25.8%)	5 (45.5%)
Female	26 (74.2%)	6 (54.5%)
Median age, years (range)	55 (40–79)	53.5 (40–77)
Median nodule size, mm (range)	7 (3–20)	8 (4–22)
Median depth of nodule from surface, mm (range)	8.2 (1.1–38.1)	10.5 (4.1–58)
Nodule location		
Left upper lobe	7 (20%)	1 (9.1%)
Left lower lobe	3 (8.6%)	3 (27.3%)
Right upper lobe	18 (51.4%)	6 (54.5%)
Right middle lobe	5 (14.3%)	0 (0%)
Right lower lobe	2 (5.7%)	1 (9.1%)
Radiological pattern		
Pure ground glass nodule	21 (60%)	6 (54.5%)
Part-solid nodule	11 (31.4%)	4 (36.4%)
Solid nodule	2 (5.7%)	1 (9.1%)
Cystic nodule	1 (2.9%)	0 (0%)
Median distance from surgical margin to tumor, mm (range)	4 (1–20)	4 (3–26)
Pathological diagnosis		
Adenocarcinoma	33 (94.2%)	10 (90.9%)
Atypical adenomatous hyperplasia	1	0
Adenocarcinoma in situ	12	1
Minimally invasive adenocarcinoma	7	3
Lepidic predominant adenocarcinoma	4	3
Acinar predominant adenocarcinoma	9	3
Metastatic lung cancer	1 (2.9%)	0 (0%)
Benign disease	1 (2.9%)	1 (9.1%)

limitations and complications can sometimes occur, including dislodgment, pain, and pulmonary hemorrhage.^{12,13} For segmentectomy, the time taken for deflation and unclear segmental plain might also confound the use of traditional methods.

In these preliminary attempts to localize pulmonary nodules, we first report the feasibility and safety of applying ICG fluorescence in both localizing subpleural small nodules and the detection of segmental plain with the largest Chinese-based population. By using CT-guided percutaneous ICG injection and fluorescence, 94.3% of the small pulmonary nodules and all segmental plains were successfully captured. No adverse effects were seen during the procedures. Compared with traditional techniques, diffusion of dyeing and dislodgment could be avoided with the application of CT-guided ICG injection to the greatest

extent. Currently, bronchoscopy is considered as a promising method for nodules localization. A relevant prospective trial assessing the efficacy of electromagnetic navigation bronchoscopy in peripheral pulmonary nodules was recently published.²² It seemed that bronchoscopy might be efficient for localizing small pulmonary nodules. The ENB-specific time of the procedure in that study was 25 min, which showed no superiority to conventional methods. In addition, it required well-trained physicians to carry out the procedure and depended heavily on equipment. Also, with our single-center experience in using bronchoscopy for pulmonary nodules, it seemed that there were some difficulties in localizing nodules located in upper lobes and the peripheral site with bronchoscopy. Additionally, more visualized regions will save time and assist the surgeons to determine the precise surgical margin for resection. For wedge resection, the whole procedure takes <1 h, and all patients are discharged from hospital within 2–3 days. The the applicable implementation of localizing small pulmonary nodules and detecting segmental plain with ICG fluorescence by fluoroscopy and comparable localization accuracy to previously reported localization with microcoil placement and other techniques was shown.^{16–18}

Another interesting finding from the present study was that among these consecutive enrolled patients, female patients seemed more likely to develop subsolid pulmonary nodules confirmed to be malignant diseases than male patients (69.6% vs. 30.4%), which, in a way, is consistent with the current published finding.²³ Whether gender should be taken into consideration for constituting screening and surveillance strategy warrants further verification.

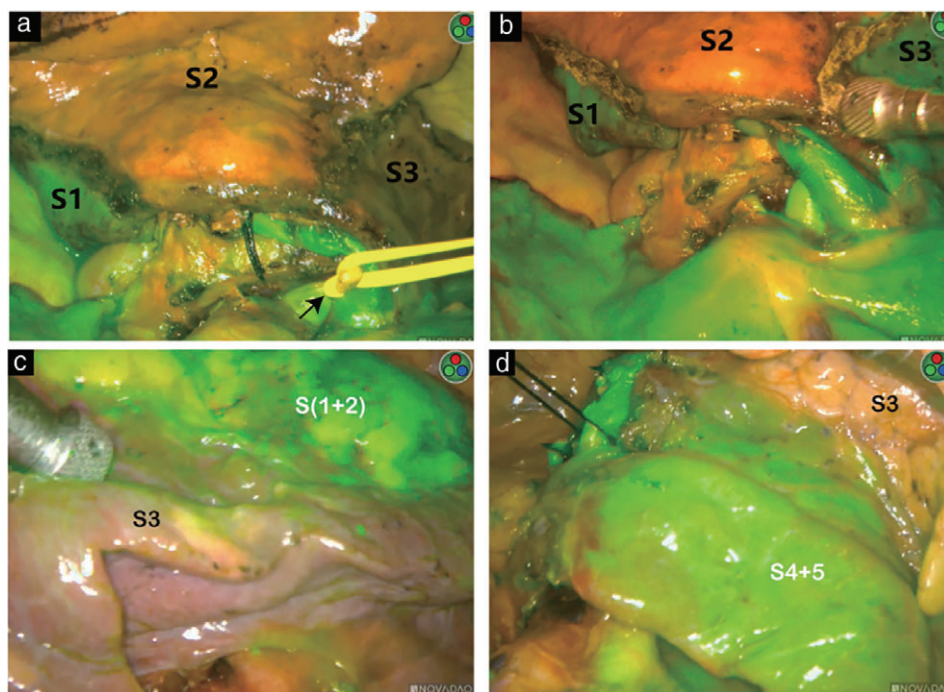
Despite the superiority with the application of ICG fluorescence, limitations should also be noted. Fluoroscopy is necessary for tracing ICG fluorescence, which is not under extensive use in other hospitals. Furthermore, leakage or insufficient ICG injection will significantly influence the surgeons' ability to locate the nodules with an unclear injection site. The optimal ICG dose reported in previous studies for percutaneous localizations is much lower compared with our study. Although it seems to be against the purpose of pin-point marking, the use of ICG is based on the manufacturer's instructions. Also, when using ICG in clinical practice, we barely found to be unsatisfactory in ICG fluorescence. Just two cases showed wide-range diffusion, it but hardly affected the surgery due to the brightest NIR fluorescence in the injected site. Collectively, it is optional to follow the manufacturer's instructions for using ICG in thoracic surgery. In addition, the optimal contrast dose of NIR through the vein can vary depending on the histology of the tumor.²⁴ A previous study has reported that it is difficult to capture the ICG fluorescence with air volume retention.¹⁴ However, we did not find any relevant

Table 2 Detailed information of lesion and surgery for segmentectomy

Case	Age	Gender	Tumor location	CT findings	Tumor size	Depth from surface	Pathological resection margin	Pathologic diagnosis	ICG fluorescence
1	50	M	LUL	Solid	4	4.1	16	AIS	Clear
2	53	M	LLL	GGO	4	55	11	MIA	Clear
3	38	F	RUL	mGGO	5	25	18	LPA	Clear
4	60	F	LUL	mGGO	8	20.6	18	LPA	Clear
5	41	M	RML	mGGO	9	23.4	26	LPA	Clear
6	57	F	RUL	GGO	11	58	15	APA	Clear
7	40	M	RML	GGO	12	13.5	7	Benign	Clear
8	53	F	RUL	GGO	15	38.1	3	MIA	Clear
9	55	M	LLL	GGO	16	11.3	4	APA	Clear
10	55	F	LUL	GGO	18	9.8	5	MIA	Clear
11	77	F	RUL	mGGO	22	16.5	3	APA	Clear

AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; APA, acinar predominant adenocarcinoma; CT, computed tomography; F, female; RUL, right upper lobe; GGO, ground-glass opacity; IAC, invasive adenocarcinoma; ICG, indocyanine green; LLL, left lower lobe; LPA, lepidic predominant adenocarcinoma; LUL, left upper lobe; M, male; Metastatic IC, metastatic lung tumor from colon cancer; mGGO, mixed ground-glass opacity; MIA, minimally invasive adenocarcinoma; RLL, right lower lobe; RML, right middle lobe.

Figure 4 Verification of targeted vessels and segmental plain by injecting indocyanine green through the peripheral vein. (a) To ensure whether the artery (black arrow) belongs to S3, we used colored ribbon to ligate the artery before injecting indocyanine green. Both S2 and S3 received no dye. (b) When we loosened the ribbon, S3 received dye immediately, confirming the uncertain artery should be preserved. (c,d) Both segmental plains were clearly marked by indocyanine green fluorescence.



cases in this study. Besides, CT-guided localization may inevitably cause too much radiation exposure to humans with extra CT scan.⁸ Currently, a pilot study reported a novel localization technique by using 3-D prints to model the surface of the chest wall.²⁵ With the guidance of the model, percutaneous injection was carried out without extra CT exposure, and patients were under anesthetic during implementation of percutaneous injection without feelings of pain and discomfort. We believe the combination of 3-D printing and ICG fluorescence will develop a more harmless, painless, and time-saving systemic technique to help localize pulmonary nodules.

In summary, application of ICG to localize subpleural nodules or detect segmental plain has shown promising clinical value. A combination of novel techniques to carry out precision surgery warrants further investigation to optimize both minimally invasive surgery and enhanced recovery after surgery.

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Disclosure

No authors report any conflict of interest.

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