Review Article

Advantages and rational application of indocyanine green fluorescence in pulmonary nodule surgery: a narrative review

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Background and Objective: The early detection and early treatment of high-risk pulmonary nodules directly affect the long-term survival rate of patients. However, conventional nodule localization methods, such as hook-wire, technetium-99m, and methylene blue are associated with issues such as a high-frequency of complications, low patient tolerance, serious side effects, and inability to identify pigmented lungs. For patients who require segmentectomy, there is often a lack of effective path planning, resulting in insufficient resection margins or excessive loss of lung function. Therefore, effective and rational nodule localization and surgical approaches are crucial. This narrative review aimed to evaluate the advantages of indocyanine green (ICG) fluorescence in pulmonary nodule surgery and clarify its application in various types of patients.

Methods: We searched the PubMed and Web of Science databases from January 2010 to January 2024 using the terms "localization of pulmonary nodules", "localization of pulmonary nodules AND indocyanine green", "localization of pulmonary nodules AND complication", "localization of pulmonary nodules AND surgical planning", and "localization of pulmonary nodules AND underlying lung disease". Information used to write this narrative review was from clinical phenomena, statistical data, and authors' conclusions.

Key Content and Findings: The commonly used localization methods of pulmonary nodule such as computed tomography (CT)-guided percutaneous placement of hook-wire are accompanied with serious complications: including hemopneumothorax and ache. Meanwhile, routine dye commonly fails to localize the nodules in patients with anthracosis. ICG with the enhanced permeability and retention (EPR) effect can be used effectively for preoperative and intraoperative localization of pulmonary nodules and its nature of allowing the observance of the condition of pulmonary blood vessels has gradually become a hotspot of research in this field.

Conclusions: For nodules with a depth of less than 1 cm, no penetration depth problem is encountered when ICG fluorescence is used. Percutaneous puncture can effectively identify the location of nodules at low cost. Compared with other localization methods, it can effectively avoid problems such as pain, radiation exposure, marker displacement, and the existence of anthrax lesions in the lungs. For patients on whom it is difficult to locate nodules due to tissue results, virtual bronchoscopy or electromagnetic navigation bronchoscopy can effectively identify nodules and reduce complications such as pneumothorax. For patients whose operation is postponed due to fever, sudden cardiovascular and cerebrovascular diseases, there is no risk of nodule localization material detachment by using ICG. ICG can also be used in patients with pulmonary physiological or pathological diseases. Meanwhile, in patients with deep pulmonary nodules, ICG fluorescence can help plan the surgical path, ensure the margin of resection, reduce lung function damage, and prevent bronchial fistula. Therefore, the rational use of ICG fluorescence technology can effectively locate nodules, assist surgeons in planning surgical methods, potentially reducing complications and ultimately improving patient prognosis.

Keywords: Localization of pulmonary nodules; narrative review; indocyanine green (ICG); complication; surgical planning

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Introduction

Lung cancer is one of the most lethal malignancies in the world. According to Global Cancer Statistics 2020, there will be 2,200,000 new cases and 1,790,000 lung cancer-related deaths in China by 2030 (1), and it is also being estimated to be the most lethal cancer in America by that time (2). In general, the diagnosis of lung cancer begins with the detection of lung nodules, with a related study suggesting that nodule size is associated with malignancy (3). Research indicates that a malignant diagnosis occurs in 24% of nodules between 6 and 10 mm in diameter, 33% of nodules between 11 and 20 mm, and up to 80% for nodules exceeding 20 mm (4). The 5-year survival rate of lung cancer is not optimistic, at only about 16% (5), but if it can be diagnosed early, the survival rate can be increased to 54% (6,7).

Consequently, an increasing number of patients prefer surgical treatment when subcentimeter pulmonary nodules are diagnosed. Fortunately, as diagnostic technology improves, especially through techniques such as feature engineering with deep learning in thoracic computed tomography (CT) images, the sensitivity of preoperative diagnosis of pulmonary nodules (nodule diameter not exceeding 30 mm) can reach as high as 100% (8). Video-assisted thoracoscopic surgery (VATS) is recommended for pulmonary nodules ≤30 mm in diameter (9). However, some nodules are invisible or unpalpable during VATS; meanwhile, VATS has a nearly 63% miss rate for 5 mm < nodules ≤10 mm depth in from pulmonary surface (10). Therefore, it is crucial to recognize pulmonary nodules, retain sufficient margins, and avoid pulmonary function damage caused by excessive resection during VATS.

At present, the commonly used preoperative pulmonary nodule localization methods include CT-guided percutaneous placement of hook-wire (11), dye such as methylene blue (MB) (12), and fiducials and microcoils (13,14), among others. However, complications such as hemopneumothorax, ache, wire dislodgement, and migration are commonly observed (15); moreover, locations near to or beneath the scapula, sternum, or great vessels are challenging. Therefore, some centers have adopted bronchoscopic localization, but the frequently used patent blue V (PBV) or MB dye typically fails to locate the nodules in patients with anthracosis or other pulmonary diseases that involve textural and/or color changes with the visceral pleura (16). Intraoperative localization of pulmonary nodules is relatively rare, with most related reports indicating the use of intraoperative ultrasound (IU). Compared with the palpation method, IU can significantly reduce the diagnostic time (17) and avoid the risk of tumor metastasis (18,19), while also not causing blood pressure changes, bleeding, or other complications. However, IU typically fails to recognize pulmonary ground-glass nodules, especially pure ground-glass nodules and cannot be used in patients with complete pneumothorax (20).

Indocyanine green (ICG) is a relatively nontoxic, amphiphilic dye and is usually used for predicting liver reserve function (21). Through the enhanced permeability and retention (EPR) effect (22), ICG remains in tumor tissue for a longer time and with a peak wavelength of nearly 830 nm under near-infrared (NIR) light (23,24). Clinical endoscopic systems can be perfectly and easily equipped with such excitation probes, which cause ICG to reveal tumor location quickly with the appropriate instrument. In addition, compared with nonfluorescent PBV or MB, ICG has a more ideal penetration depth (25) and is now being widely used in tumor sentinel lymph node biopsy (26,27), revascularization (28), hepatic segment division (29), and tumor intraoperative localization (29). Newton *et al.* reported successfully identifying pulmonary nodules intraoperatively through the second window feature of ICG (30). Overall, ICG can be used effectively for the

Table 1 Summary of the search strategy

Items	Specification
Date of search	April 30th, 2024
Databases and other sources searched	PubMed, Web of Science
Search terms used	"localization of pulmonary nodules", "localization of pulmonary nodules AND indocyanine green", "localization of pulmonary nodules AND complication", "localization of pulmonary nodules AND surgical planning", "localization of pulmonary nodules AND underlying lung disease"
Timeframe	January 2010 to January 2024
Inclusion criteria	Controlled trials, retrospective studies, reviews, meta-analyses, and case reports and series.
Selection process	Three authors (B.D., A.Y., and Y.Z.) screened all the articles

preoperative and intraoperative localization of pulmonary nodules, observing the condition of pulmonary blood vessels, informing surgical plans, and reducing surgical complications.

We conducted a narrative review with the aim of providing a broad overview of the evidence for the advantages of ICG fluorescence in displaying pulmonary nodules through various pathways rather than simply introducing fluorescence techniques in a systematic review. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1502/rc).

Methods

To conduct this narrative review, we searched the PubMed and Web of Science databases from January 2010 to January 2024 using the search terms "localization of pulmonary nodules", "localization of pulmonary nodules AND indocyanine green", "localization of pulmonary nodules AND complication", "localization of pulmonary nodules AND surgical planning", and "localization of pulmonary nodules AND underlying lung disease". We included retrospective studies, review articles, meta-analyses, case reports and series, and controlled trials written in English. Three authors (B.D., A.Y., and Y.Z.) retrieved relevant articles and extracted relevant data conclusions. For details, please refer to *Table 1*.

Discussion

Localization of pulmonary nodules with ICG

Advantages of ICG in preoperative CT-guided pulmonary nodule localization

As the most commonly used dye applied for clinical procedures (31), ICG has been widely accepted by surgery centers due its low toxicity, good visual effect, and nonobstruction of the surgical field of view (32) and there are few reports of adverse reactions of ICG, mainly hypersensitivity reactions (33). ICG has been used for the preoperative CT-guided localization of lung nodules, demonstrating satisfactory results (34-36). There are several commonly used CT-guided positioning materials, each with unique advantages and disadvantages as compared with ICG. These are discussed below and summarized in *Table 2*. CT-guided hook-wire placement is the earliest and the most common method for pulmonary nodule localization (11). In a meta-analysis by Park *et al.*, the success rate of hook-wire localization was around 98% (38). However, complications are also common, with pneumothorax being reported to occur in nearly 7.5–49% of these procedures (39) and parenchymal hematoma in 5.9–21%, with the risk of being increased with greater lesion depth (40). The dislodgement rate of hook-wire placement is about 2.4–7.5% (41,46), and the hook-wire can cause fear and severe pain for patients waiting for surgery. In contrast, CT-guided ICG fluorescence

Table 2 Comparison of ICG and other methods in pulmonary nodule localization

ICG *vs.* other methods	Advantages	Disadvantages
ICG *vs.* hook-wire (37-42)	(I) Less discomfort or pain	(I) Requires fluorescence equipment
	(II) No marker dislodgement or migration	(II) Not suitable for patients with delayed surgery
	(III) No risk of air embolism	(III) Limited information on lesion depth
ICG *vs.* fiducials or microcoils (34,43)	(I) No risk of gas embolism	(I) Requires fluorescence equipment
	(II) No additional radiation exposure	(II) Not suitable for patients with delayed surgery
		(III) Limited information on lesion depth
ICG *vs.* PBV or MB (12,16)	(I) Better penetration depth	None
	(II) Suitable for circumstances of lung damage, anthracosis, and pulmonary hemorrhage	
	(III) Better for pathological diagnosis	
ICG *vs.* barium (44)	(I) No additional radiation exposure	(I) Requires fluorescence equipment
	(II) Better for pathological diagnosis	(II) Not suitable for patients with delayed surgery
		(III) Limited information on lesion depth
ICG *vs.* lipiodol (45)	(I) No additional radiation exposure	(I) Requires fluorescence equipment
	(II) No risk of embolism risk	(II) Not suitable for patients with delayed surgery
		(III) Limited information on lesion depth
ICG *vs.* technetium-99m (46)	(I) No additional radiation exposure	(I) Requires fluorescence equipment
	(II) No need for gamma probe	(II) Limited information on lesion depth

ICG, indocyanine green; PBV, patent blue V; MB, methylene blue.

localization does not have the problem of marker shedding or migration. In a clinical study by Ding *et al.* (37), the successful targeting rate in the ICG study group was 100% (85/85), and the overall complication rate in this group was lower than that in the hook-wire group (35.4% *vs.* 37.0%; P=0.038) as was the respiratory pain score (2.85±1.05 *vs.* 3.70±1.25; P<0.001). The hook-wire method also has the disadvantage of being unable to confirm margins in real time (42). Compared with hook-wire, microcoil is found to be associated with less discomfort, a lower migration rate, and fewer preoperative-related complications while also being more conducive to delayed surgery (43). However, this technology needs to be guided under fluoroscopy, causing additional radiation exposure for both medical staff and patients (47), and large microcoils can increase the risk of gas embolism (48). In contrast, ICG involves almost no radiation exposure problem, as it only needs to inject ICG into the nodule or adjacent area, and under the action of intraoperative fluorescence endoscopy, the fluorescent nodule can be directly observed without gas embolism. Zhong *et al.* reported the first clinical trial of the CT-guided NIR fluorescence marking of lung lesions in China. No complications occurred in 30 patients in whom ICG was administered. Compared with microcoils, ICG can effectively determine the location of nodules without requiring fluoroscopy (34). PBV and MB are commonly used location dyes. Tseng *et al.* performed CT-guided PBV staining on 217 pulmonary nodules of 100 patients, with a success rate of 99%. Only one patient had obvious pneumothorax (1%), another patient had an allergic reaction (1%), and there were other mild complications which did not require treatment (49). Tsai *et al.* performed PBV staining of deep pulmonary nodules (median depth of 31.6 mm) in 27 patients and reported a 100% success rate with no complications that required treatment (50); however, PVB may be defective in recognizing a deeply located pulmonary lesions (>10 mm) (25). Lin *et al.* performed CT-guided MB staining in 337 patients with single nodules and 51 patients with multiple nodules, with a mean nodule depth of 6.1±5.4 and 5.6±5.9 mm, respectively, and achieved a success rate of 98.8%, with only one patient experiencing significant pneumothorax (51). However, lung damage, anthracosis, and pulmonary hemorrhage can make localization with PBV and MB difficult (16), while ICG can still achieve satisfactory results in these circumstances (52) and is also superior to other dyes in pathological diagnosis (53,54). Moreover, Anayama *et al.* found that the maximum detection depth of ICG can reach 24 mm from the inflated lung surface (55). Other potential useful materials are rarely used in clinical setting due to certain drawbacks; for instance, barium is associated with radiation exposure and interference with pathological judgment (44), lipiodol with embolism risk (45), and technetium-99m with radiation exposure and a cumbersome operation (46). Unlike technetium-99m, ICG does not require hybridization surgery nor transfer to the radiology department one day before surgery, avoiding harms to the operator and patient caused by radioactive substances.

Disadvantages of ICG in CT-guided pulmonary nodule localization

Although CT-guided ICG has many advantages, but there are also several shortcomings. (I) Due to the anatomical structure, as with other CT-guided positioning materials, the positions next to the great vessels, pericardium, and lower sternum cannot be located. (II) Since the ICG spreads to the surrounding lung tissue after localization, surgery is required within 3 hours to avoid diagnostic failure, so it is not suitable for patients with delayed surgery (56). (III) The NIR fluorescence signal has a limited depth and cannot be used to detect tumors deeper in the pleural surface. (IV) ICG has the disadvantage of not being able to distinguish inflammatory tissues and the lack of perfect stability in fluorescence, which is a challenge faced by ICG for pulmonary nodule localization. (V) ICG overflow and subsequent diffusion of dye in the chest cavity would result in CT guided ICG localization failure. (VI) ICG may be injected by force or in an incorrect position which would mislead surgeons during surgery. (VII) When multiple nodules are targeted, it will significantly increase the positioning time like bronchoscopy (57). (VIII) Finally, CT-guided percutaneous localization of multiple lung lesions is not possible (58).

Remedial measures*: *bronchoscopic placement of ICG

In recent years, virtual bronchoscopy (VB) and electromagnetic navigation bronchoscopy (ENB) have become increasingly popular methods for localizing pulmonary nodules. The technique of injecting ICG using bronchoscopy allows for marking of multiple small pulmonary nodules without causing pneumothorax. VB reconstructs the three-dimension (3D) shape of the bronchial tree through high-resolution CT and computer software and performs navigation and real-time bronchoscopy in 3D space (59). Virtual-assisted lung mapping (VAL-MAP) is a technique in which VB is used to inject ICG into multiple lesions. Kuwata *et al.* confirmed that with this technique, the operation time can be significantly reduced (60). Moreover, Anayama *et al.* performed CT-guided ICG injection labeling on 15 patients and VB-guided ICG injection labeling on 22 patients (localization of multiple pulmonary nodules was performed on six patients, and localization failed on one patient). The success rate of CT-guided ICG was 100% (15/15) while that of VB-guided ICG was 95.5% (21/22). However, in the CT group, 20% of patients developed a small pneumothorax, resulting in unsuccessful subsequent localization (61). In their other clinical study, VB demonstrated a 100% recognition success rate in patients with multiple nodules with no complications (62). Tokuno *et al.* performed VAL-MAP for ICG on 142 pulmonary nodules from 63 patients followed by a repeat CT scan, and the legibility of each marker was divided into three grades: easy, faint, and not identifiable. All the 142 nodules in the ICG-VAL-MAP group were easily identified, the localization success rate was 99.3% in intraoperative observation (141/142), and no related complications such as pneumothorax were observed. Furthermore, for patients with emphysema and interstitial pneumonia, ICG has advantages over other dyes in patients with anthracosis, emphysema, or interstitial pneumonia (63). In the clinical study of Yanagiya *et al.*, the localization success rate of VAL-MAP with ICG was close to 93%. It is worth noting that for patients who smoke, ICG can still successfully fluoresce the nodules, compensating for the limitations of other dyes (64).

EBN involves using patient's CT data to establish a lung "Global Positioning System (GPS) navigation" path. The navigation probe within the range of the electromagnetic field is accurately positioned in the lung bronchial tree in real time, and finally the probe is guided to the exact position of the lung lesion, thus establishing a diagnosis and treatment channel directly to the lesion (65). Compared to conventional bronchoscopy, ENB can access fourth-order bronchioles, making it more precise and applicable (66). The clinical application of ENB navigation was first reported in 2006, when Schwarz *et al.* demonstrated the safety and feasibility of the technique, with no surgery-related adverse reactions occurring, but a diagnostic rate of only 69% being achieved (67). In a recent single-center study, Jeong *et al.* performed EBN staining on 18 pulmonary nodules from 7 patients, and the success rate reached 94.4% (17/18), with no obvious surgical complications (58). Nonintubated uniportal VATS causes less surgical trauma and postoperative stress response but has higher requirements for safe and accurate localization of pulmonary nodules. Before performing nonintubated uniportal VATS, Wang *et al.* conducted ENB-guided ICG on 243 patients: the average navigation time was only 10.56±7.24 min, the localization success rate was 98.80% (248/251), there were no serious complications, and the average hospital stay was only 1.80±0.83 days, representing a significant reduction in the length of hospital stay (68). Zhang *et al.* performed ENB-guided ICG on 173 patients, and the localization success rate was 98.3% (178/181). They further found that the identification accuracy was positively correlated with bronchial signs (P<0.001) and reported that the nodules located in the anterior segment of the left upper lobe and the upper lingual segment were more difficult to locate (69). Yang *et al.* performed CT-guided ICG localization on 35 patients and EBN-guided ICG localization on 12 patients, achieving a success rate of 94.3 (33/35) and 100% (12/12), respectively and only one patient in the EBN group developed pneumothorax (70). Therefore, bronchoscope injection of ICG can be used as an improved method of percutaneous puncture injection, which can locate multiple pulmonary nodules while causing fewer complications and avoiding difficult or dangerous puncture sites; however, this approach requires experienced operating physicians and a hybrid operating room, which is expensive, and can only be applied on certain patients and under certain medical conditions.

Intraoperative localization of pulmonary nodules by ICG

Intraoperative fluorescence only requires intravenous injection of ICG and does not require CT guidance or bronchoscopy, making it easier for surgeons to operate. Newton *et al.* proposed the concept of the second window of ICG, injecting a high dose of ICG (generally 5 mg/kg) intravenously 24 hours or more before surgery and then using the EPR effect of tumor tissue to locate pulmonary nodules during surgery or tumor (71). Meanwhile, the second window compensates for the lack of preoperative ICG positioning and can be used for patients with delayed surgery. Singhal's team used this technology to perform intraoperative fluorescence on 18 patients, reporting a success rate of 88.9% (16/18). In addition, intraoperative fluorescence also revealed five subcentimeter pulmonary nodules that were overlooked by CT scans (72). In terms of metastatic pulmonary nodules, a second window can also provide good results. Kawakita *et al.* performed intraoperative fluorescence on 11 metastatic pulmonary nodules from 6 patients. Intravenous injection of 0.5 mg/kg of ICG 1–3 days before surgery yielded a localization success rate of 90.9% (10/11); failure occurred with only one patient because of the inability to implement NIR irradiation due to the application of minimal incision thoracotomy (73). Predina *et al.* conducted a clinical study of 30 patients with pulmonary nodules suggestive of metastatic sarcoma, with 10 patients undergoing thoracotomy and 20 patients undergoing VATS. In the thoracotomy group, ICG successfully fluoresced 14 metastatic nodules (14/16), with three cases of occult metastatic nodules being found via fluorescence. In the VATS group, ICG successfully localized 33 nodules (33/37) and found an additional 24 lesions, of which 21 were confirmed to be metastatic nodules. All unsuccessful identifications of lesions occurred because the nodules were too deep (74). However, in addition to the penetration depth problem, the second window technology cannot distinguish between the tumor tissue and inflammatory tissue well, and this can easily mislead the surgeon's during the operation. Watershed analysis is a software used to target nodules located in the segmental arteries or subsegmental arteries. According to the preoperative 3D-CT reconstruction imaging, after the target pulmonary artery occlusion is simulated, the negative staining area of ICG is intravenously injected to determine the lung segment where the nodule is located, evaluate the resection margin, guide the surgical plan, and ultimately complete the operation. Chu *et al.* conducted a clinical study in which this technique was used on 26 patients: 25 patients had successful localization, and one patient failed due to unclear staining boundaries (75). Regardless of a delay in surgery, this method does not cause obvious pain, pneumothorax, nor other puncture complications, and the positioning effect is not affected by lung inflation. However, only a few clinical studies have examined this method, and more research is needed.

ICG fluorescence for the planning pulmonary nodule resection

Preoperative surgical planning

Pulmonary nodule resection is often performed with wedge resection and segmentectomy depending on the location and size of the nodule. For ground glass pulmonary nodules, preoperative localization is often suggested to perform on patients without 3D reconstruction of CT scan to ensure surgical accuracy and preserve sufficient margins. Pulmonary anatomical segmentectomy can obtain adequate surgical margins, but anatomical variation of pulmonary vessels is common (76), which increases the risk of VATS and may require conversion to thoracotomy. Moreover, for this procedure, it is necessary to correctly identify the intersegmental plane and rationally segment the lung parenchyma to avoid atelectasis or insufficient residual lung function. Methods for identifying lung identification segmental planes include ICG segmental bronchial perfusion and the use of the segmental pulmonary arteries (77). Segmental bronchial perfusion is based on the preoperative CT-simulated nodule anatomy results, while ICG depends on the corresponding bronchus during the operation in accurately identifying the site and scope of resection. Sekine *et al.* used this method on 28 patients with wedge resection, which ensured sufficient tumor margins. The results confirmed that all targets were within the target range and sufficient margins were preserved (78). Sekine *et al.* also performed bronchial targeted perfusion on 10 patients, and successfully identified the target segment plane and the intersegmental plane of the lung parenchyma, thereby effectively preserving the residual lung tissue. Compared with patients with traditional thoracoscopic resection, those treated via bronchial targeted perfusion experienced a shortened length of hospital stay without increased surgical risk (79).

Targeted pulmonary artery technology is used to ligate the pulmonary artery in the target area, inject ICG intravenously, and determine the segmental plane in combination with the adjacent pulmonary veins. Its advantage is that it does not require lung inflation (80). Yotsukura *et al.* conducted a study on 209 patients who underwent segmentectomy, and on 184 (88.0%) patients, segmental planes were successfully identified by targeting the pulmonary vessels and administering ICG (81). Mun *et al.* used the targeting of the pulmonary artery combined with ICG technology on 20 patients undergoing thoracoscopic surgery and successfully marked the segment plane without obvious surgical complications. However, there are some limitations associated with this technique: (I) patients may have insufficient blood supply due to conditions such as anthracosis, resulting in unclear fluorescence contours; and (II) fluorescence is confined to the lung surface and cannot be observed on the plane being dissected (82).

Other functions of ICG

ICG can detect hemodynamics, so it can also be used in pulmonary nodule resection to avoid surgical complications. When anatomic lung resection is performed on high-risk patients, tissue flaps should be placed over the bronchial stump to prevent bronchopleural fistulas, such as pedicled intercostal muscle flaps, which require adequate blood flow to the flap, thus promoting sufficient blood supply and nutrition to the bronchial stump, and facilitating its healing. Kawamoto *et al.* used flaps to reinforce the stump on 27 high-risk patients prone to bronchopleural fistula and assessed the flap blood supply via ICG fluorescence. They confirmed that ICG fluorescence can be used to prevent flap ischemia and surgical complications (83).

Conclusions

ICG can locate pulmonary nodules, aid in planning the operation via fluorescence, and reduce surgical complications while requiring almost no radiation exposure or complex operations that are often associated with other techniques. Pulmonary nodules can be located either preoperatively or intraoperatively depending on the depth of the nodule, operating room conditions, and financial circumstances of the patients.

Obviously, for nodules with a depth of less than 1 cm, the percutaneous localization effect of ICG is highly effective, as there is no penetration depth issue with ICG fluorescence. There is also no risk of displacement or detachment of the marker, which can cause severe pain or fear in patients. Moreover, compared with other dyes, ICG can effectively distinguish patients with physiological or pathological lung diseases such as anthracosis and interstitial pneumonia, and in contrast to IU, there are no concerns for conditions such as pneumothorax (20). There is, however, the issue of rapid dye diffusion in ICG. Although some research centers have combined lipiodol to effectively solve this problem, the safety of this technique needs to be further verified (84). For patients with difficult percutaneous puncture locations, VB- or ENB-guided ICG localization is a good option. Although

Table 3 The method of ICG application under different conditions

Method	Indications	Disadvantages or contraindications
CT-guided	(I) Superficial pulmonary nodules	(I) Dangerous or difficult-to-manage puncture site
	(II) Immediate surgery	(II) Multiple pulmonary nodules
	(III) Solitary pulmonary nodule	(III) Delayed surgery
		(IV) Patients with poor pain tolerance
		(V) Deep lung nodules
		(VI) Lack of hybrid operation room
VB or ENB	(I) Superficial pulmonary nodules	(I) Deep lung nodules
	(II) Immediate surgery	(II) Delayed surgery
	(III) Solitary or pulmonary multiple nodule	(III) Lack of hybrid operation room
	(IV) Dangerous or difficult-to-manage puncture site	(IV) High cost to patients
	(V) Patients with poor pain tolerance	
Segmental bronchial perfusion	(I) Lung segment plane recognition	(I) Lung nodules cannot be localized
	(II) Immediate or delayed surgery	(II) Highly reliant on operator's bronchoscopic technique
		(III) Potential risk of allergic or inflammatory reaction to the lung
Intravenous injection	(I) Superficial or deep pulmonary nodules	For nodule location:
	(II) Solitary or pulmonary multiple nodule	(I) Deep lung nodules
	(III) Lung segment plane recognition	(II) Inability to distinguish inflammatory tissue
		(III) Immediate surgery
		For segmental plane recognition:
		(I) Patients with insufficient blood supply to the lung surface
		(II) Cannot be observed on the plane being dissected

ICG, indocyanine green; CT, computed tomography; VB, virtual bronchoscopy; ENB, electromagnetic navigation bronchoscopy.

this operation relies on a hybrid operating room and is expensive, this method can further reduce pneumothorax and bleeding complications. For patients with delayed surgery, intraoperative localization of ICG is a viable option, as it is simple and only requires intravenous injection of ICG 1–3 days before surgery to locate pulmonary nodules well. Combined with preoperative CT, pulmonary nodules can be effectively identified, but a means to distinguishing inflammatory tissue needs to be further investigated. For deep pulmonary nodules, only segmental resection can be performed to ensure the success of the operation. ICG fluorescence can effectively identify the segmental plane, inform the surgical scope, and ensure the resection margin while preserving normal lung tissue as much as possible to reduce impairment of lung function. In addition, in patients with high bronchial fistulas, ICG can assess the blood flow of the covering and prevent surgical failure.

Therefore, ICG can be used for surgical operations on various types of pulmonary nodules. According to the location of the nodule, the patient's physical condition, pain tolerance ability, and economic conditions, there are different ICG-related approaches and surgical methods (*Table 3*) that can be selected to ensure the success the operation and minimize complications.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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