Original Article

Feasibility and safety of computed tomography-guided intrapulmonary injection of indocyanine green for localization of peripheral pulmonary ground-glass nodules

Lei Wang[1#], Sai'e Shen[2#], Tiantian Qu[3], Tienan Feng[3], Xuequn Huang[3], Runmin Chi[4], Fengqing Hu[1], Haibo Xiao[1]

[1]Department of Cardiothoracic Surgery, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Department of Anesthesiology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Clinical Research Institute, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [4]Department of Radiology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Contributions: (I) Conception and design: L Wang, S Shen; (II) Administrative support: F Hu, H Xiao; (III) Provision of study materials or patients: L Wang, H Xiao; (IV) Collection and assembly of data: R Chi, T Qu, X Huang; (V) Data analysis and interpretation: T Feng, F Hu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Fengqing Hu, MD, PhD; Haibo Xiao, MD, PhD. Department of Cardiothoracic Surgery, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China. Email: hufengqing@xinhuamed.com.cn; xiaohaibo@xinhuamed.com.cn.

Background: The early surgical intervention for pulmonary ground-glass nodules (GGNs) has become increasingly important, but accurate identification of these nodules during thoracoscopic surgery poses challenges due to the need for sublobar resections and reliance on visual and tactile perception alone. The prognosis of the procedure is closely tied to the use of precise positioning technology. Thus, it is crucial to develop an accurate positioning technology that can improve patient prognosis.

Methods: Clinical data from the cardiothoracic department of a tertiary hospital in Shanghai were collected and analyzed between January 2020 and December 2021. The patients were categorized into 2 groups: an indocyanine green (ICG) group and a hook-wire group. Outcome measures including success rate, complications, procedure time, localization-related pain, and interval time were assessed. Adverse events and reactions were reported and compared between the 2 groups.

Results: A total of 62 patients (17 males and 45 females, aged 50.5±13.2 years) were in the ICG group, while 66 patients (23 males and 43 females, aged 48.4±12.9 years) were localized in the hook-wire group. The success rate was comparable between the 2 groups. However, the ICG group showed significant advantages over the hook-wire group in terms of procedure time (22.6±4.4 *vs.* 24.1±4.9 min; P=0.012), localization-related pain (P<0.001), and interval time [median and interquartile range (IQR): 3 (0.7, 104.9) *vs.* 1.2 (0.5, 3.3) h; P<0.001]. In the ICG group, there were 11 cases of pneumothorax, 4 cases of hemothorax, and 2 cases of ICG diffusion. In the hook-wire group, there were 24 cases of pneumothorax, 25 cases of hemothorax, and 2 cases of dislodgement. The ICG group had fewer complications, including pneumothorax (P=0.018) and hemothorax (P=0.007), compared to the hook-wire group.

Conclusions: Computed tomography (CT)-guided intrapulmonary injection of ICG for preoperative localization of peripheral pulmonary GGNs is a practical and safe technique. It offers advantages in terms of reduced procedure time, localization-related pain, and interval time compared to the hook-wire method. Moreover, the ICG technique results in fewer complications, making it a valuable preoperative localization technique worthy of popularization.

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

Keywords: Indocyanine green (ICG); preoperative localization; pulmonary ground glass nodules (pulmonary GGNs); thoracoscopic surgery

Submitted Jan 30, 2023. Accepted for publication Sep 04, 2023. Published online Sep 22, 2023.
doi: 10.21037/qims-23-117
View this article at: https://dx.doi.org/10.21037/qims-23-117

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide. However, advancements in comprehensive treatment, particularly surgery, have significantly improved the 5-year survival rates for non-small cell lung cancer (1,2). Notably, the frequency of early detection of ground-glass nodules (GGNs) in the lungs has increased with the aid of imaging technologies such as computed tomography (CT), leading to a nearly 100% 5-year survival rate for patients with early-stage lung cancer characterized by GGNs (3,4). As a result, early surgical intervention for pulmonary GGNs has gained significant importance (5). However, many of these nodules require sublobar resections, posing challenges for their accurate identification during thoracoscopic surgery with visual and tactile perception alone. Precise localization of pulmonary GGNs has become a critical issue in thoracoscopic surgery (6,7).

To address this challenge, this study used CT-guided percutaneous lung puncture with indocyanine green (ICG) injection for localization, yielding promising results in terms of both localization accuracy and treatment outcomes.

Methods

Data collection

Clinical data from patients who underwent thoracic surgery at the department of cardiothoracic surgery in a tertiary hospital in Shanghai between January 2020 and December 2021 were collected and analyzed. The study included patients who met the following inclusion criteria: (I) diagnosed with pulmonary GGNs based on chest CT before surgery and suspected early-stage lung cancer, (II) solitary nodules with a diameter ≤20 mm, located within the outer one-third of the lung field and considered suitable for sublobar resection, and (III) patients who provided informed consent and signed both the informed consent form for the study and the informed consent form for clinical surgery and CT-guided lung puncture. Meanwhile, the following exclusion criteria were applied: (I) patients with clear contraindications to surgery or those who were unable to tolerate surgical treatment; (II) patients with apparent contraindications to lung puncture or at high risk of complications from the procedure; (III) patients with evident emphysema, bullae, or pleural effusion; and (IV) lesions located in close proximity to the pleura, exhibiting pleural traction signs, and palpable under direct vision during the operation.

Prior to the procedure, preoperative patient education sessions were conducted to provide information about the different localization methods. Patients were given the opportunity to make an informed decision regarding their preferred localization method.

Initially, a total of 132 patients met the inclusion criteria for the study. However, 3 patients decided to withdraw their consent, and 1 patient in the ICG group did not undergo localization. As a result, the remaining patients were divided into 2 groups: the ICG group, consisting of 62 cases (including 17 males and 45 females, with an average age of 50.50±13.21 years), and the hook wire group, consisting of 66 cases (including 23 males and 43 females, with an average age of 48.42±12.92 years).

Localization procedure for ICG injection

The following steps were followed for the localization procedure with ICG (*Figure 1A-1D*):

- ❖ Step 1: the anatomical location of the pulmonary nodules was analyzed based on the chest CT images. If feasible, 3-dimensional image reconstruction was performed to assess the relative relationship between the nodules and surrounding blood vessels, organs, or tissues.
- ❖ Step 2: after the initial analysis, the target area for localization was selected. The optimal needle entry point, entry angle, depth, and entry plane were determined based on the nodule's location. This helped establish the appropriate procedure position.
- ❖ Step 3: standard disinfection and draping procedures

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

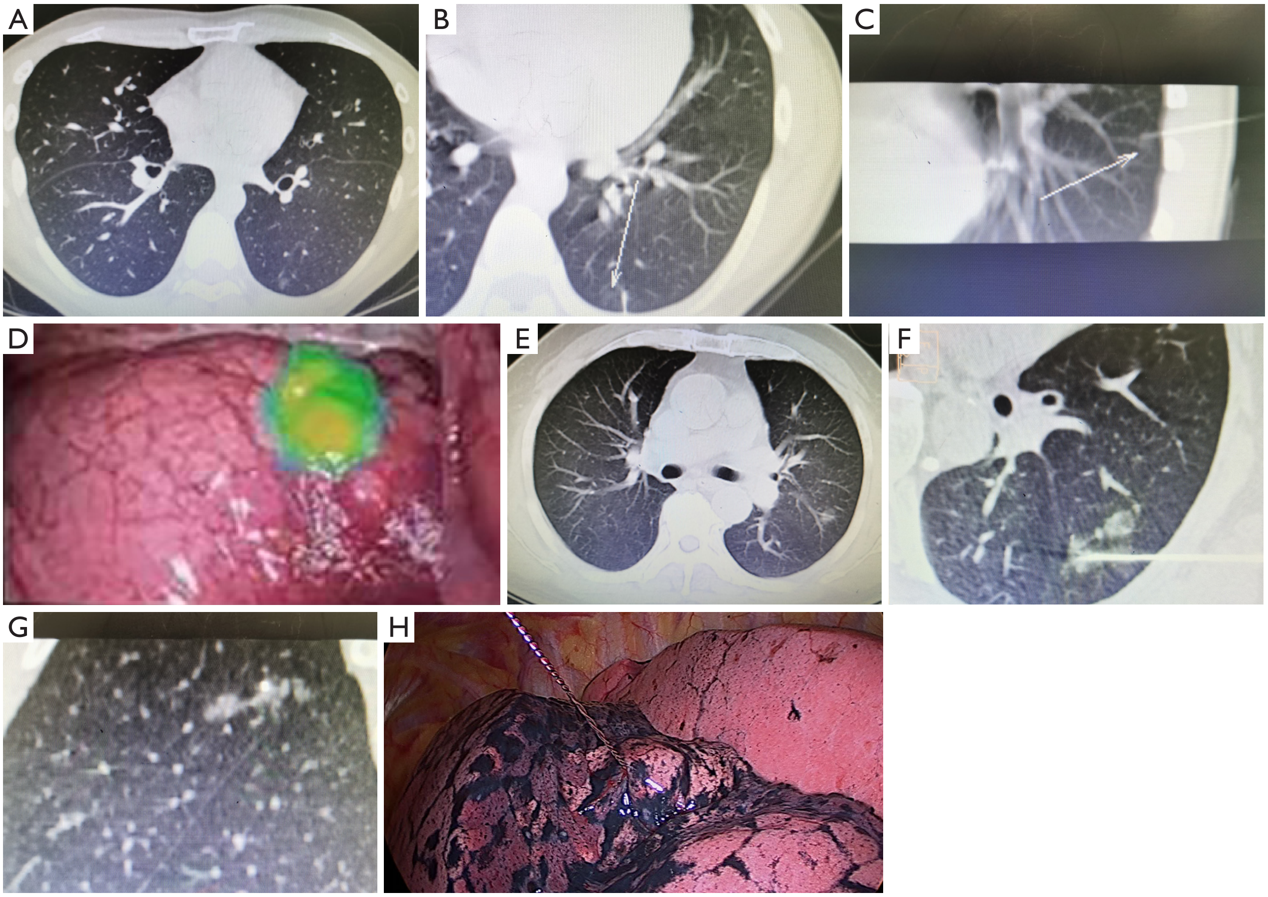

Figure 1 CT-guided ICG localization for peripheral pulmonary ground glass nodules. CT showed a left lower pulmonary nodule (A), which was located with percutaneous lung puncture ICG (B,C), and fluoroscopic thoracoscopy showed a localized pulmonary nodule (D). CT showed a left upper pulmonary nodule (E), which was located with the percutaneous lung nodule (F,G), and thoracoscopy showed localization of the pulmonary nodules (H). White arrows: location of the lesion. CT, computed tomography; ICG, indocyanine green.

were carried out. Local infiltration anesthesia with 2% lidocaine was administered along the puncture point to ensure patient comfort.

- ❖ Step 4: with a 5-mL syringe needle, a trial puncture was performed along the preestablished route, with care taken not to puncture the pleura. A CT scan was conducted to verify the accuracy of the puncture route.
- ❖ Step 5: once the correct puncture route was confirmed, a disposable intravenous indwelling needle with its needle core was inserted along the determined route toward the lesion. If the CT scan revealed an incorrect trial route, adjustments were made based on the CT image. Subsequently, ICG was injected into the lung through the puncture needle.
- ❖ Step 6: ICG was dissolved in 10 mL of water for injection. From this solution, 1 mL was extracted and diluted to 10 mL with normal saline. Then, 1 mL of the diluted solution was drawn into a 1-mL syringe and slowly injected into the vicinity of the lesion.
- ❖ Step 7: after the localization procedure was completed, a CT scan was performed again to assess any potential complications, such as pneumothorax or hemorrhage. This step ensured the accuracy of the localization and guided subsequent surgical treatment.

The patient was then transferred back to the ward for further management and surgical intervention.

The following steps were followed for the localization procedure with a hook wire (*Figure 1E-1H*):

- ❖ Step 1: similar to the ICG group, the anatomical location of the pulmonary nodules was analyzed based on chest CT images. Three-dimensional image

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

reconstruction was performed, if feasible, to assess the relative relationship between the nodules and surrounding structures.

- ❖ Step 2: the target area for localization was selected, and the appropriate needle entry point, entry angle, depth, and entry plane were determined based on the nodule's location.
- ❖ Step 3: similar to the ICG group, a trial puncture was performed along the preestablished route. A CT scan was conducted to verify the accuracy of the puncture route.
- ❖ Step 4: once the correct puncture route was confirmed, a hook wire was inserted using a hook wire positioning system trocar. If the CT scan indicated an incorrect trial route, adjustments were made based on the CT image. The try-on route was modified, and another CT scan was performed to confirm the correct route.
- ❖ Step 5: the hook wire was released when the positioning pin was observed to be within 10 mm of the pulmonary nodule. A subsequent CT scan was performed to evaluate the presence of any pneumothorax or bleeding following the positioning.
- ❖ Step 6: after the positioning was completed, the tail wire of the positioning needle close to the skin was cut off. The skin at the positioning site was covered with an applicator for protection.

The patient was then returned to the ward for further surgical treatment.

Main positioning materials and instruments

In the ICG group, the CT-guided puncture needle used was the Merit Advance AD18T71W (Merit Medical, South Jordan, UT, USA), an 18 G coreless puncture needle. The positioning fluorescent agent used was Rado brand ICG (Dandong Yichuang Pharmaceutical Co., Ltd., Dandong, China), with a dosage of 25 mg × 1. For intraoperative fluorescence thoracoscopy, the OPTO-CAM2100 fluorescence camera system was used (Guangdong OptoMedic Technologies Inc., Foshan, China). The CT-guided lung puncture kit used was the LW0107 breast puncture positioning needle (Bard Peripheral Vascular, Inc., Tempe, AZ, USA).

Outcome indicators

The outcome indicators of the study were localization success rate, positioning operation time, time interval between positioning and operation, activities after positioning, localization-related complications, and pain after positioning, among other recorded parameters.

In the ICG group, the success of localization was confirmed via a CT scan after the procedure to verify that the ICG was injected into the vicinity of the pulmonary nodule. Thoracoscopy was then used for thoracic exploration. A fluorescence pattern that was not diffuse indicated successful localization. In the hook-wire group, positioning success was confirmed via a CT scan showing that the hook-wire was placed near the pulmonary nodule within the lung. During thoracic exploration through thoracoscopic surgery, the positioning was considered successful if the hook-wire remained in place without decoupling.

The positioning operation time was considered to be the duration required to complete the positioning steps 1 to 4.

The time interval between positioning and operation was defined as the duration between the completion of positioning and the start of the surgical operation. It included the time spent returning the patient to the ward after positioning and the wait before the operation began.

Activities after positioning were categorized into 2 groups based on the ability to move independently. One group consisted of patients who were able to move freely, while the other group consisted of patients who were unable to move independently.

Localization-related complications encompassed various issues such as pneumothorax, pleural hemorrhage, intrapulmonary hemorrhage (characterized by a sudden appearance of a new high-density shadow around the puncture site in the lung on CT, with or without progressive enlargement), chest tightness, etc.

Pain after positioning was evaluated using the visual analogue scale, in which a score of 0 denoted no pain, scores ranging from 1 to 3 denoted mild pain, scores from 4 to 6 denoted moderate pain, and scores from 7 to 10 denoted severe pain.

Other recorded parameters included the surgical method, operation time, postoperative hospital stay, and postoperative paraffin pathology, which were directly recorded for both the ICG group and the hook-wire group.

Statistical analysis

Statistical analysis was conducted using SPSS 18.0 software (IBM Corp., Armonk, NY, USA). Continuous variables

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

Table 1 Comparison of basic data between the 2 groups of patients

Clinical information	ICG group (n=62)	Hook-wire group (n=66)	P value
Age (years)	50.5±13.2	48.4±12.9	0.371
Gender			0.365
Male	17 (27.4)	23 (34.8)	
Female	45 (72.6)	43 (65.2)	
Smoking history			0.794
Current/ever smoker	12 (19.4)	14 (21.2)	
Never smoker	50 (80.6)	52 (78.8)	
Nodule size (mm)	9.2±3.0	9.1±2.7	0.868
Nodule type			0.659
Pure ground-glass nodules	39 (62.9)	39 (59.1)	
Partially solid ground-glass nodules	23 (37.1)	27 (40.9)	
Nodule location			0.561
Right upper lung	17 (27.4)	21 (31.8)	
Right middle lung	4 (6.5)	4 (6.1)	
Right lower lung	15 (24.2)	13 (19.7)	
Left upper lung	16 (25.8)	21 (31.8)	
Left lower lung	10 (16.1)	7 (10.6)	
Procedure position			0.885
Supine position	17 (27.4)	38 (57.6)	
Prone position	27 (43.6)	12 (18.2)	
Lateral position	18 (29.0)	16 (24.2)	
Shortest distance from nodule to lung surface (mm)	10.1±7.8	11.8±6.0	0.167

Numeric data are presented as mean ± standard deviation and countable data as number (frequency). ICG, indocyanine green.

with a normal distribution are presented as mean ± standard deviation, and between-group comparisons were assessed using the *t*-test. For nonnormally distributed variables, median values and 95% confidential interval are provided, and between-group comparisons were evaluated using the rank-sum test. Categorical data are described as frequencies and percentages, and group comparisons were performed using the chi-squared test. A P value less than 0.05 was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and has been reviewed by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (No. XHEC-D-2022-083). Informed consent was obtained from all the patients.

Results

Preoperative basic data of the 2 groups of patients

There were no significant differences between the 2 patient groups in terms of gender (P=0.365), age (P=0.371), smoking history (P=0.794), nodule size (P=0.868), nodule type (P=0.659), nodule location (P=0.561), or the body position during puncture (*Table 1*).

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

Comparison of the outcomes of the 2 groups of patients

Both groups of patients achieved successful positioning, with positioning success rates of 96.8% in the ICG group and 97.0% in the hook-wire group. The difference between the 2 groups was not statistically significant.

The positioning operation time of the ICG group was 22.6±4.4 min, while that of the hook-wire group was 24.1±4.9 min, with the former being significantly shorter than the latter (P=0.012). In the ICG group, 60 patients were able to get out of bed and move freely, while 2 patients required closed chest drainage at the bedside due to moderate to massive pneumothorax after positioning and remained in bed. In contrast, all patients in the hook-wire group had to return to the ward and maintain a lying position without being able to rise from bed. The ICG group showed significantly better outcomes in this regard (P<0.001). The time interval between positioning and operation was [median and interquartile range (IQR)]: 3 (0.7, 104.9) h in the ICG group and 1.2 (0.5, 3.3) h in the hook-wire group. Patients in the ICG group had the flexibility to undergo surgery on the same day, every other day, or every other week, whereas those in the hook-wire group needed to undergo surgery as soon as possible after positioning. The optional surgery time was significantly longer in the hook-wire group (P<0.001).

In the ICG group, there were 11 cases of pneumothorax after localization, of which 10 had a small amount of pneumothorax and did not require treatment and 1 had pneumothorax improve after thoracic closed drainage, which did not affect the subsequent operation. There were 4 cases of thoracic hemorrhage, all of which included a small amount of thoracic hemorrhage that was found during surgical thoracoscopy and did not require special treatment. In 2 patients, the preoperative CT localization operation was successful, but after fluorescence mode was activated during thoracoscopic, we found that the ICG was diffused and the localization had failed. After we switched to the normal white light mode, deep staining on the surface of the needle into the lung was visible, so wedge-shaped resection was performed according to the deep staining, and a sample was sent to pathology; the operation was successfully completed. In the hook-wire group, there were 24 cases of pneumothorax without special treatment and 15 cases of thoracic hemorrhage. Among the 15 cases, 2 involved of moderate or greater thoracic hemorrhage, with active intercostal arterial bleeding during the operation, which was resumed after electrocoagulation to stop the bleeding. The preoperative CT positioning in 2 patients was successful, but thoracoscopy revealed that the positioning hook fell off and did not remain in the chest cavity. The positioning hooks of these two 2 were found and removed in the subcutaneous tissue at the skin puncture site, and CT was performed during the operation. The anatomical location of the suggested pulmonary nodule was performed. Compared to the hook-wire group, the ICG group had a significantly lower frequency of pneumothorax (P=0.018) and pleural oozing (P=0.007).

Pain assessment following positioning was also a significant aspect of this study. In the ICG group, 60 patients reported no significant pain or only mild pain, while 2 patients experienced moderate to severe pain. In the hook-wire group, 56 patients reported no significant pain or only mild pain, while 10 patients experienced moderate to severe pain. Regarding pain after positioning, the ICG group exhibited significantly superior outcomes than did the hook-wire group based on the Visual Analogue Scales (VAS) score (P=0.031; *Table 2*).

Comparison of surgical conditions between the 2 groups

Both groups initially underwent wedge resection for the treatment of pulmonary nodules. The operation time for wedge resection in the ICG group was 30.5±8.4 min while that of the hook-wire group was 33.5±7.1 min. The operation time for wedge resection in the ICG group was significantly shorter than that in the hook-wire group (P=0.029). The postoperative hospital stay in the ICG group was 4.8±1.6 days, which did not represent a significant difference compared to the 4.6±1.2 days in the hook-wire group (P=0.287).

Regarding postoperative pathology, there was 1 benign nodule, 4 cases of atypical adenomatous hyperplasia (AAH), 15 cases of adenocarcinoma in situ (AIS), 32 cases of minimally invasive adenocarcinoma (MIA), and 10 cases of adenocarcinoma (AD) in the ICG group; in comparison, there was1 benign nodule, 4 cases of AAH, 16 cases of AIS, 36 cases of MIA, and 9 cases of AD in the hook-wire group (*Table 3*).

Discussion

In recent years, the advancement of high-resolution CT and other imaging technologies has led to the increased detection of early-stage lung cancers presenting as GGNs in the lungs (8,9). The progression of these lesions is often characterized by nodule enlargement or increased

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

Table 2 Comparison of the positioning of patients in the 2 groups

Clinical item	ICG group (n=62)	Hook-wire group (n=66)	P value
Success rates	60 (96.8)	64 (97.0)	0.975
Duration of location procedure (min)	22.6±4.4	24.1±4.9	0.012
Time interval between positioning and surgery (h)	3 (0.7, 104.9)	1.2 (0.5, 3.3)	<0.001
Getting out of bed after positioning			<0.001
Getting out of bed	60 (96.8)	0 (0.0)	
Inability to get out of bed	2 (3.2)	66 (100.0)	
Positioning-related complications			0.595
Pneumothorax	11 (17.7)	24 (36.4)	0.018
Bleeding in the chest cavity	4 (6.5)	15 (22.7)	0.007
Positioning hook displacement/ICG diffusion	2 (3.2)	2 (3.0)	0.975
Pain level after positioning			0.031
Mild or no pain	60 (96.8)	56 (84.8)	
Moderate or severe pain	2 (3.2)	10 (15.2)	

Numeric data are presented as the median (IQR) for nonnormally distributed data or mean ± standard for normally distributed data, with countable data expressed as number (frequency). ICG, indocyanine green; IQR, interquartile range.

Table 3 Comparison of intraoperative and postoperative condition of the 2 groups

Observation indicator	ICG group (n=62)	Hook-wire group (n=66)	P value
Wedge resection operation time (min)	30.5±8.4	33.5±7.1	0.029
Postoperative hospital stay (days)	4.8±1.6	4.6±1.2	0.287
Postoperative pathology			0.926
Inflammatory	1 (1.6)	1 (1.5)	
AAH	4 (6.5)	4 (6.1)	
AIS	15 (24.2)	16 (24.2)	
MIA	32 (51.6)	36 (54.7)	
AD	10 (16.1)	9 (13.6)	

Numeric data are presented as mean ± standard deviation and countable data as number (frequency). ICG, indocyanine green; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma; AD, adenocarcinoma.

solid components, and timely follow-up and early surgical intervention are crucial for effective treatment (10,11). Due to their small size, low density, and challenging accessibility during surgery, thoracoscopic minimally invasive surgery following preoperative localization has emerged as an optimal surgical approach. However, there remains a considerable debate regarding the safest and most efficient methods for preoperative localization given the unique characteristics of pulmonary GGNs (12,13).

Park *et al.* reported that lipiodol had a high success rate in localizing pulmonary nodules and caused less bleeding. However, the use of intraoperative fluoroscopic imaging with a C-arm machine increased the complexity of the operation and exposed patients to radiation. This implies that the procedure may be more challenging and entail a degree of risk due to the need for specialized equipment and radiation exposure (14). Wen *et al.* indicated that microcoils had a positive effect in locating small pulmonary

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

nodules. However, the soft texture of the microcoil and reliance on the operator's palpation sometimes leads to prolonged operation times and increased radiation exposure. This suggests that procedures using microcoils may be more time-consuming and carry a higher risk of radiation exposure due to the difficulty in accurately locating nodules (15). Hu *et al.* found that 3-dimensional navigation puncture-free positioning could avoid the drawbacks associated with puncture. This method was used for localizing GGNs in the central area of lung segments or subsegments, close to blood vessels. However, the process was relatively complex, requiring high intraoperative navigation and operational skills. This suggests that procedures using 3-dimensional navigation are more intricate and demand skilled operators (16). Hook-wire is another commonly used preoperative positioning method that offers convenience and accurate positioning (17). However, it has the drawback of leaving the positioning wire in the body, which runs through the skin surface to the lung tissue (18). Patients who undergo hook-wire localization need to maintain their position at the time of positioning, avoid movement and coughing, and minimize wire movement. Prompt surgical intervention is advised after positioning. This method may cause discomfort for patients due to the presence of the positioning wire and potential complications such as accidental injury to blood vessels during positioning and interference with blood vessel coagulation, leading to continuous bleeding in the thoracic cavity. Additionally, there is a risk of decoupling at the beginning of the operation, especially if the nodule is located close to the pleura, potentially due to inadequate anchoring of the hook wire. Previous studies have reported a success rate of approximately 98% for hook-wire localization, but occasional cases of decoupling occurred during the operation, resulting in an overall success rate of around 94% (excluding decoupling cases) (14,19).

In recent years, there has been growing interest in fluorescence-guided surgery (FGS) as a potential method for visualizing and localizing tumors in real-time across various types of cancer (20). One commonly studied agent for FGS is ICG, which has been extensively researched in the context of pulmonary and thoracic malignancies, mesothelioma, high-grade gliomas, meningiomas, and brain metastases (21-25). In the detection of lung cancer, 3 main techniques for administering ICG have been identified: percutaneous CT-guided injection, intrabronchial injection, and intravenous injection (26). When locating undetectable pulmonary nodules, fiberoptic bronchoscopy or electromagnetic navigation bronchoscopy is often used, with ICG being injected through intrabronchial access. Wang *et al.* introduced a method that involves injecting ICG under the guidance of electromagnetic navigation bronchoscopy for localizing pulmonary nodules (27). Alternatively, for real-time assessment of surgical margins, ICG is commonly administered intravenously. Yotsukura *et al.* demonstrated that ICG marking may provide a more precise demarcation of the intersegmental plane compared to air injection (28).

Currently, virtual-assisted lung mapping (VAL-MAP) has emerged as a valuable method for localizing pulmonary nodules (29). This bronchoscopic dye-marking technique offers advantages, such as reduced complications, compared to other methods. However, VAL-MAP does have certain limitations including difficulties in identifying the dye during resection and on CT images. To address these limitations, Tokuno *et al.* have improved the VAL-MAP technique by incorporating CT contrast and ICG dye. Their study demonstrated that surgeons were able to easily identify 100% of ICG-VAL-MAP markings on CT scans. The addition of ICG significantly improved the visibility of the markings compared to VAL-MAP alone. However, it is important to note that ICG-VAL-MAP requires the availability of bronchoscopic dye marking and the installation of a near-infrared (NIR) scope at the medical institution where the procedure is performed (29). As an alternative, CT-guided percutaneous intrapulmonary injection of ICG has been proposed for localizing peripheral pulmonary GGNs. This method may offer advantages in terms of cost-effectiveness and convenience compared to ICG-VAL-MAP. However, further research and clinical evaluation are necessary to validate the efficacy and safety of CT-guided percutaneous injection of ICG for this purpose.

To address the limitations of hook-wire positioning, this study used preoperative puncture positioning with ICG. The positioning principles and operation steps of ICG positioning are similar to those of hook-wire positioning, and the overall success rate of the 2 methods in this study were not significantly different. However, ICG positioning offers several of the following advantages.

ICG positioning is straightforward, provides more chances for accurate localization, and has a relatively low cost. In this study, the ICG positioning time was significantly shorter compared to hook-wire positioning likely due to the absence of hook release and wire truncation required in hook-wire positioning. ICG localization can be performed on the day of surgery or a few days prior and is

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

well-tolerated by patients. The fluorescence of ICG does not decay or diffuse during intraoperative localization. Additionally, the price of ICG is lower than that of the hook-wire positioning puncture kit.

Additionally, ICG positioning allows for a flexible surgical plan. ICG appears as a dark blue dye under visible light, providing an alternative plan for fluorescence diffusion during surgery. By examining the deeply stained area on the lung surface under white light mode, clinicians can clarify the approximate localization. Hook-wire positioning may occasionally result in significant positioning errors. To ensure proper incision placement and prevent residual positioning hooks in the body, an expanded resection range might be necessary. In contrast, ICG localization eliminates concerns of foreign body residue. The relative position of the nodule can be determined based on the deeply stained area on the lung surface, allowing for flexibility in selecting the surgical plan.

In the ICG group, the time interval between positioning and surgery was significantly longer than that of hook-wire positioning. This is likely because patients experience minimal discomfort after ICG positioning, and there are no adverse consequences associated with the movement of positioning foreign bodies. Therefore, the timing of surgery can be adjusted flexibly. Unlike hook-wire positioning, ICG positioning allows for intraday or immediate surgery. One study has reported that ICG positioning before surgery results in nodules exhibiting fluorescence the following day. However, this study mainly focused on solid nodules, and the imaging effect of GGNs was not clear (30).

In our study, it was found that 21.1% (27/128) of patients underwent surgery on the day after or later following ICG positioning, and some patients even underwent surgery 1 week after positioning due to special circumstances. Interestingly, the fluorescence of ICG remained effective without diffusion during this time period. This demonstrates the durability and stability of ICG localization. From the patient's perspective, ICG positioning resulted in mild pain and a comfortable feeling, without significantly affecting their normal activities. After ICG positioning, the patients felt more comfortable and were able to resume their daily activities. In contrast, the hook-wire group required patients to keep their position as unchanged as possible after positioning, leading to discomfort and limited mobility. The majority (96.8%) of patients in the ICG group were able to move freely after positioning. Furthermore, it was observed that hook-wire-located nodules were generally deeper and farther from the pleura as compared to ICG-located nodules. This finding is important as it suggests that for superficial GGNs, hook-wire localization carries an increased risk of decoupling. In contrast, even if ICG-located nodules appeared diffuse in fluorescence mode, they could still be observed on the lung surface in white light mode, allowing for salvage surgery in the hyperstained areas (18,19).

Thus far, few studies have been published comparing dye localization with other techniques. One study by Ding *et al.* suggested that ICG localization had a lower complication rate compared to hook-wire localization (31). However, it is worth noting that our study found a significant difference in the time interval between positioning and surgery, which might have influenced the outcomes. Moreover, we found that ICG markings remained visible on CT scans even on the next day or week after positioning, attesting to the long-lasting effectiveness of ICG localization (Figure S1). Tokuno *et al.* made advancements in the visualization of VAL-MAP by incorporating ICG. They reported that this technique of combining ICG with VAL-MAP (ICG-VAL-MAP) could be beneficial to the resection of nonpalpable small lung lesions (29). It is important to note that in our research, ICG marking was performed without the use of a bronchoscope, which differs from the bronchoscopic dye-marking technique used in ICG-VAL-MAP. The different approaches may have implications for the applicability and technique of ICG marking. In contrast to our study, that by Yotsukura *et al.* found that ICG imaging could effectively visualize surgical margins and could be widely applicable in pulmonary segmentectomy. This suggests that ICG marking may have a significant role to play in both wedge resection and segmentectomy of the lung (28). Overall, while there are some discrepancies among the studies, the use of ICG marking shows promise in improving the visualization and localization of pulmonary nodules, offering potential benefits for various surgical procedures.

Previous studies have reported that CT-guided lung puncture carries an overall complication rate ranging from 9% to 54%, with an average of 20%. Common complications include pneumothorax, thoracic hemorrhage, and intrapulmonary hemorrhage, with serious complications requiring surgical treatment occurring in fewer than 5% of cases (30,32). A notable finding in our study was that the incidence of pneumothorax was significantly lower in the ICG group than in the hook-wire group.

In CT-guided lung puncture, thoracic hemorrhage often results from intercostal blood vessel injury caused by the puncture needle. However, in the case of ICG positioning,

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

there are no residual foreign bodies after the procedure, and even if intercostal blood vessels are damaged, only minor bleeding is typically observed. On the other hand, when using a hook-wire for positioning, the wire remains in the body, affecting the coagulation process of any intercostal vascular injury and potentially leading to continuous thoracic hemorrhage over time (14,30). In our study, we failed to locate the nodules in 2 patients in the ICG group due to fluorescence diffusion during the operation. However, as a result of the distinctive blue dye nature of ICG, deep staining of the pulmonary pleura could still be identified in the normal white light mode of fluoroscopy-assisted thoracoscopy during the surgery. Consequently, the same surgical outcomes were achieved. In contrast, after hook-wire positioning and decoupling, identifying the needle insertion point in the pleural layer becomes challenging and often results in excessive or inadequate resection. Moreover, the detached positioning hooks can be frequently concealed in subcutaneous tissue, requiring additional time and effort to locate them.

Air embolism is a rare but potentially serious complication that can occur during percutaneous CT-guided lung biopsy. The exact mechanism of air embolism in this context is not yet fully understood, but it is believed to involve the formation of a fistula between an air-filled space and a pulmonary vein when the biopsy needle penetrates through the lung parenchyma. Several risk factors for fistula formation have been identified in previous studies, including the length of the needle path through the ventilated lung, the depth of needle penetration into the nodule, and the number of biopsy samples obtained (33,34). A recent study found a higher radiological incidence of air embolism of 3.92%, which was unexpectedly higher than that reported in previous research; however, it should be mentioned that many of the detected cases were asymptomatic, and only 0.98% of patients experienced symptoms related to air embolization (35). In our study, no cases of air embolism were detected in either the ICG group or the hook-wire group.

Although the ICG group demonstrated significant advantages over the hook-wire group in terms of operation time, positioning, and operation time interval, patient mobility, and pain level, there was no significant difference between the 2 groups in terms of the impact on subsequent thoracoscopic surgery. The postoperative hospital stay did not show a significant difference between the groups except for the significantly shorter wedge resection time in the ICG group. The longer operation time observed in the hook-wire group during hand wedge resection may be attributed to factors such as the need for wire length adjustment during the procedure (trimming the protruding part of the wire from the lung surface) and the requirement for precise incision margin planning (ensuring complete nodule removal while avoiding wire retention in the body).

Recently, a group of Chinese scholars collaborated on the release of the *Expert Consensus on Preoperative Assisted Localization Technology for Small Pulmonary Nodules* (2019 Edition) (36). This consensus document provides a comprehensive overview of current clinical methods for preoperative localization, analyzing the advantages and disadvantages of each technique. It emphasizes the importance of selecting the appropriate localization method based on the specific conditions of the medical institution.

Based on clinical practice and experience with ICG positioning, the following key points have been identified: (I) the concentration of ICG has been fine-tuned through continuous exploration. Currently, the following steps are recommended: to dissolve ICG in 10 mL of water for injection, draw 1 mL of the solution, dilute it to 10 mL with normal saline, and then draw 1 mL from the diluted solution using a 1-mL syringe. The injection should be performed slowly in the vicinity of the lesion. This method has shown obvious and nondiffusing effects, with a long retention time. (II) The areas in which ICG positioning is appropriate have been defined. ICG positioning is particularly suitable for superficial pulmonary GGNs. However, for nodules located deep within the lung parenchyma, if they are not affected by the scapula, ribs, or large blood vessels, the hook-wire method may be a more feasible option.

A previous study demonstrated that after entering the human body, ICG binds to proteins and can maintain fluorescence locally for an extended period. It has a penetration capacity of up to 10 mm of tissue (37).

Although our study demonstrated the advantages of CT-guided percutaneous injection of ICG for localization of peripheral pulmonary GGNs, there are still some limitations to consider. The assistance of fluoroscopic thoracoscopy is required for ICG localization, and there is a possibility of ICG diffusion, which may limit the penetration of fluorescence and affect the localization of deep-seated nodules within the lung parenchyma. These limitations should be further explored, summarized, and resolved to enhance the effectiveness of ICG localization.

In conclusion, our findings suggest that CT-guided percutaneous injection of ICG for the localization of peripheral pulmonary GGNs is a safe, effective, time-saving,

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

and convenient technique. It provides benefits such as facilitating the selection of surgical timing and surgical plan and is well-tolerated by patients. Overall, this preoperative localization technique shows promise and warrants further promotion in clinical practice.

Acknowledgments

The authors would like to thank all the staff members for their assistance in carrying out the study.
Funding: This work was supported by grants from the National Natural Science Foundation of China (No. 82173382 to H Xiao).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-117/coif). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and has been reviewed by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (No. XHEC-D-2022-083). Informed consent obtained from all the patients.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, Mariotto AB, Lowy DR, Feuer EJ. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med 2020;383:640-9.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
3. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, Kauczor HU, Maldonado SG, Miller AB, Kaaks R, Delorme S. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. Int J Cancer 2020;146:1503-13.
4. Meza R, Jeon J, Toumazis I, Ten Haaf K, Cao P, Bastani M, Han SS, Blom EF, Jonas DE, Feuer EJ, Plevritis SK, de Koning HJ, Kong CY. Evaluation of the Benefits and Harms of Lung Cancer Screening With Low-Dose Computed Tomography: Modeling Study for the US Preventive Services Task Force. JAMA 2021;325:988-97.
5. Suzuki K, Watanabe SI, Wakabayashi M, Saji H, Aokage K, Moriya Y, Yoshino I, Tsuboi M, Nakamura S, Nakamura K, Mitsudomi T, Asamura H; . A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer. J Thorac Cardiovasc Surg 2022;163:289-301.e2.
6. Huang CS, Chien HC, Chen CK, Yeh YC, Hsu PK, Chen HS, Hsieh CC, Hsu HS, Huang BS, Shih CC. Significance of preoperative biopsy in radiological solid-dominant clinical stage I non-small-cell lung cancer. Interact Cardiovasc Thorac Surg 2021;32:537-45.
7. Migliore M, Fornito M, Palazzolo M, Criscione A, Gangemi M, Borrata F, Vigneri P, Nardini M, Dunning J. Ground glass opacities management in the lung cancer screening era. Ann Transl Med 2018;6:90.
8. Liu J, Yang X, Li Y, Xu H, He C, Qing H, Ren J, Zhou P. Development and validation of qualitative and quantitative models to predict invasiveness of lung adenocarcinomas manifesting as pure ground-glass nodules based on low-dose computed tomography during lung cancer screening. Quant Imaging Med Surg 2022;12:2917-31.
9. Hattori A, Suzuki K, Takamochi K, Wakabayashi M, Aokage K, Saji H, Watanabe SI; . Prognostic impact of a ground-glass opacity component in clinical stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg 2021;161:1469-80.
10. Mazzone PJ, Lam L. Evaluating the Patient With a Pulmonary Nodule: A Review. JAMA 2022;327:264-73.
11. Succony L, Rassl DM, Barker AP, McCaughan FM, Rintoul RC. Adenocarcinoma spectrum lesions of the lung: Detection, pathology and treatment strategies. Cancer Treat Rev 2021;99:102237.

12. Liu J, Wang X, Wang Y, Sun M, Liang C, Kang L. Comparison of CT-guided localization using hook wire or coil before thoracoscopic surgery for ground glass nodules. Br J Radiol 2020;93:20190956.
13. Li C, Liu B, Jia H, Dong Z, Meng H. Computed tomography-guided hook wire localization facilitates video-assisted thoracoscopic surgery of pulmonary ground-glass nodules. Thorac Cancer 2018;9:1145-50.
14. Park CH, Lee SM, Lee JW, Hwang SH, Kwon W, Han K, Hur J; . Hook-wire localization versus lipiodol localization for patients with pulmonary lesions having ground-glass opacity. J Thorac Cardiovasc Surg 2020;159:1571-9.e2.
15. Wen H, Sun H, Ma Q, Xiao F, Zhang Z, Liang C. Pulmonary nodules localization via microcoil and anchor with scaled suture guided by CT in thoracoscopic surgery: A retrospective cohort study. Chinese Journal of Clinical Thoracic and Cardiovascular Surgery 2022;29:50-5.
16. Hu S, Wang Q, Wei H, Pan X, He Z, Xu J, Zhu Y, Wu W, Chen L. Puncture positioning versus free-of-puncture positioning under three-dimensional navigation in the anatomical segmentectomy for pulmonary nodules: A retrospective cohort study. Chinese Journal of Clinical Thoracic and Cardiovascular Surgery 2021;28:1202-6.
17. Zhao G, Yu X, Chen W, Geng G, Li N, Liu H, Yin P, Sun L, Jiang J. Computed tomography-guided preoperative semi-rigid hook-wire localization of small pulmonary nodules: 74 cases report. J Cardiothorac Surg 2019;14:149.
18. Zuo T, Shi S, Wang L, Shi Z, Dai C, Li C, Zhao X, Ni Z, Fei K, Chen C. Supplement CT-Guided Microcoil Placement for Localising Ground-glass Opacity (GGO) Lesions at "Blind Areas" of the Conventional Hook-Wire Technique. Heart Lung Circ 2017;26:696-701.
19. Xu X, Yao Y, Shen Y, Zhang P, Zhou J. Clinical Analysis of Percutaneous Computed Tomography-Guided Hook Wire Localization of 168 Small Pulmonary Nodules. Ann Thorac Surg 2015;100:1861-7.
20. De Ravin E, Venkatesh S, Harmsen S, Delikatny EJ, Husson MA, Lee JYK, Newman JG, Rajasekaran K. Indocyanine green fluorescence-guided surgery in head and neck cancer: A systematic review. Am J Otolaryngol 2022;43:103570.
21. Cho SS, Salinas R, De Ravin E, Teng CW, Li C, Abdullah KG, Buch L, Hussain J, Ahmed F, Dorsey J, Mohan S, Brem S, Singhal S, Lee JYK. Near-Infrared Imaging with Second-Window Indocyanine Green in Newly Diagnosed High-Grade Gliomas Predicts Gadolinium Enhancement on Postoperative Magnetic Resonance Imaging. Mol Imaging Biol 2020;22:1427-37.
22. Newton AD, Predina JD, Nie S, Low PS, Singhal S. Intraoperative fluorescence imaging in thoracic surgery. J Surg Oncol 2018;118:344-55.
23. Newton AD, Predina JD, Corbett CJ, Frenzel-Sulyok LG, Xia L, Petersson EJ, Tsourkas A, Nie S, Delikatny EJ, Singhal S. Optimization of Second Window Indocyanine Green for Intraoperative Near-Infrared Imaging of Thoracic Malignancy. J Am Coll Surg 2019;228:188-97.
24. Teng CW, Cho SS, Singh Y, De Ravin E, Somers K, Buch L, Brem S, Singhal S, Delikatny EJ, Lee JYK. Second window ICG predicts gross-total resection and progression-free survival during brain metastasis surgery. J Neurosurg 2021;135:1026-35.
25. Teng CW, Huang V, Arguelles GR, Zhou C, Cho SS, Harmsen S, Lee JYK. Applications of indocyanine green in brain tumor surgery: review of clinical evidence and emerging technologies. Neurosurg Focus 2021;50:E4.
26. Gkikas A, Lampridis S, Patrini D, Kestenholz PB, Scarci M, Minervini F. How effective is indocyanine green (ICG) in localization of malignant pulmonary nodules? A systematic review and meta-analysis. Front Surg 2022;9:967897.
27. Wang G, Lin Y, Zheng L, Liang Y, Zhao L, Wen Y, Zhang R, Huang Z, Yang L, Zhao D, Lachkar S, Baste JM, Shinagawa N, Ng CSH, Sato M, Kim MP, Zhang L. A new method for accurately localizing and resecting pulmonary nodules. J Thorac Dis 2020;12:4973-84.
28. Yotsukura M, Okubo Y, Yoshida Y, Nakagawa K, Watanabe SI. Indocyanine green imaging for pulmonary segmentectomy. JTCVS Tech 2021;6:151-8.
29. Tokuno J, Chen-Yoshikawa TF, Nakajima D, Aoyama A, Motoyama H, Sato M, Date H. Improved visualization of virtual-assisted lung mapping by indocyanine green. JTCVS Tech 2021;10:542-9.
30. Kleedehn M, Kim DH, Lee FT, Lubner MG, Robbins JB, Ziemlewicz TJ, Hinshaw JL. Preoperative Pulmonary Nodule Localization: A Comparison of Methylene Blue and Hookwire Techniques. AJR Am J Roentgenol 2016;207:1334-9.
31. Ding N, Wang K, Cao J, Hu G, Wang Z, Jin Z. Targeted Near-Infrared Fluorescence Imaging With Iodized Indocyanine Green in Preoperative Pulmonary Localization: Comparative Efficacy, Safety, Patient Perception With Hook-Wire Localization. Front Oncol 2021;11:707425.
32. Boskovic T, Stanic J, Pena-Karan S, Zarogoulidis P, Drevelegas K, Katsikogiannis N, Machairiotis N, Mpakas A, Tsakiridis K, Kesisis G, Tsiouda T, Kougioumtzi

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

I, Arikas S, Zarogoulidis K. Pneumothorax after transthoracic needle biopsy of lung lesions under CT guidance. J Thorac Dis 2014;6 Suppl 1:S99-107.
33. Jang H, Rho JY, Suh YJ, Jeong YJ. Asymptomatic systemic air embolism after CT-guided percutaneous transthoracic needle biopsy. Clin Imaging 2019;53:49-57.
34. Monnin-Bares V, Chassagnon G, Vernhet-Kovacsik H, Zarqane H, Vanoverschelde J, Picot MC, Bommart S. Systemic air embolism depicted on systematic whole thoracic CT acquisition after percutaneous lung biopsy: Incidence and risk factors. Eur J Radiol 2019;117:26-32.
35. Maehara Y, Miura H, Hirota T, Asai S, Okamoto T, Ohara Y, Yamada K. Frequency and Risk Factors for Air Embolism in Computed Tomography Fluoroscopy-Guided Biopsy of Lung Tumor With the Use of Noncoaxial Automatic Needle. J Comput Assist Tomogr 2023;47:71-7.
36. Gu C, Liu B, Wang Q, Jiang J, Li X, Zhang L, et al. Expert consensus on preoperative localization of small pulmonary lesions (2019). Chinese Journal of Clinical Thoracic and Cardiovascular Surgery 2019;26:109-13.
37. Alander JT, Kaartinen I, Laakso A, Pätilä T, Spillmann T, Tuchin VV, Venermo M, Välisuo P. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging 2012;2012:940585.

Cite this article as: Wang L, Shen S, Qu T, Feng T, Huang X, Chi R, Hu F, Xiao H. Feasibility and safety of computed tomography-guided intrapulmonary injection of indocyanine green for localization of peripheral pulmonary ground-glass nodules. Quant Imaging Med Surg 2023;13(10):7052-7064. doi: 10.21037/qims-23-117

© Quantitative Imaging in Medicine and Surgery. All rights reserved.

Supplementary

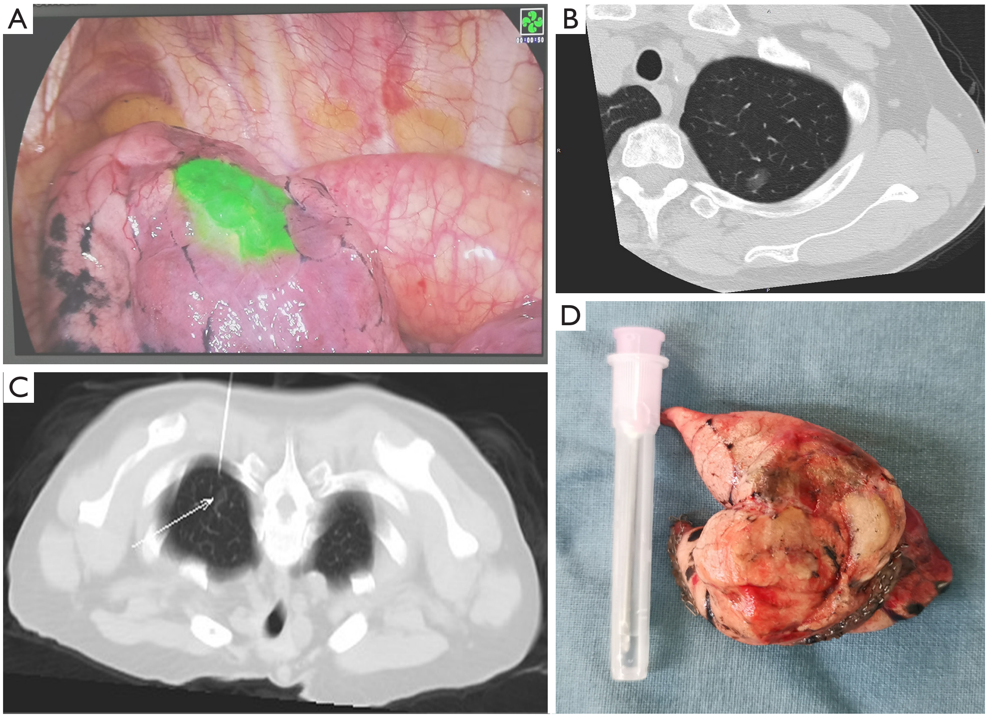

Figure S1 Case of a 65-year-old female. Intraoperative images of a 65-year-old female with a left upper lung nodule who was operated upon on day 8 after fluoroscopic localization (A). Preoperative CT of the 65-year-old female (B). Use of CT in positioning of the 65-year-old female (C). Postoperative specimens of the 65-year-old female (D). White arrow: location of the lesion. CT, computed tomography.

© Quantitative Imaging in Medicine and Surgery. All rights reserved.
https://dx.doi.org/10.21037/qims-23-117