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Atomized inhalation of indocyanine green in thoracoscopic surgery for intralobar pulmonary sequestration: a multicenter study

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Abstract

Background Investigate the safety and efficacy of preoperative atomization inhalation of indocyanine green (ICG) solution in precise lesion resection of pediatric thoracoscopic intralobar pulmonary sequestration.

Methods A multicenter 1:1 matched case-control study was adopted, to compare the safety and efficacy of the ICG group (preoperative atomization inhalation of 0.5 mg/kg ICG solution) with traditional group (no preoperative atomization inhalation of ICG solution). The baseline, intraoperative, and postoperative recovery conditions of the two groups were observed. Outpatient follow-up visits were conducted 3 to 6 months after surgery, including lung CT scans and pulmonary ventilation function tests.

Results 134 patients were included in the study. The ICG group included 67 patients, and the traditional surgery group included 67 patients matched at a ratio of 1:1 according to age and lesion location. There were no reports of deaths or adverse reactions. The postoperative chest drainage tube indwelling time [(53.19 ± 8.15) hours vs. (73.25 ± 15.51) hours, $P < 0.001$] and postoperative hospital stay [(4.81 ± 1.84) days vs. (6.72 ± 1.31) days, $P < 0.001$] were shorter in the ICG group than in the traditional group. More importantly, the postoperative pulmonary function in the ICG group was better than that in the traditional group. No residual lesions were found in the postoperative CT examination of both groups.

Conclusions The innovative application of atomization inhalation of ICG provides the possibility for precise localization and lesion resection of pediatric thoracoscopic intralobar pulmonary sequestration. This maximizes the preservation of normal lung parenchyma, better improves postoperative pulmonary function, and shortens postoperative recovery time.

Keywords Indocyanine green, Atomization inhalation, Intralobar pulmonary sequestration, Pulmonary function

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Introduction

Pulmonary sequestration (PS) is the second most common congenital pulmonary disease [1]. PS refers to a condition where a portion of the lung tissue receives its blood supply from an abnormal systemic artery. There are three main types: intralobar, extralobar, and bronchopulmonary foregut malformation. Intralobar pulmonary sequestration (ILS) refers to masses of pulmonary parenchyma connected to adjacent normal lung tissue. Due to the long-term risk of infection [2] and tumor [3], current treatment strategies tend to favor early surgery. Thoracoscopic surgery has become the main method for treating ILS [4], with lobectomy or segmentectomy being the standard operation. However, due to the many drawbacks of lobectomy or segmentectomy, such as the loss of normal lung tissue during the resection of the lesion, there has been controversy over the treatment of ILS in recent years [5]. At the same time, lung-preserving surgeries such as wedge resection may increase the possibility of residual lesions [6]. Studies have shown that there is a natural ventilation obstruction between the diseased tissue and normal lung tissue in ILS, suggesting the possibility of delineating the boundaries between the two. Therefore, some pediatric thoracic surgeons have proposed non-anatomical precise resection of the lesion [7–9]. However, during surgery of lesion resection, the internal and external boundaries between the lesion and normal lung tissue cannot be confirmed with the naked eye, making it difficult for surgeons to accurately determine the resection range of the lesion. This limitation hinders the widespread application of this technique.

Indocyanine green (ICG) is a non-radiative fluorescent contrast agent that is widely used in clinical practice [10], and its safety has been repeatedly verified in clinical settings. In recent years, some studies have suggested that inhaling ICG is feasible and may help to visualize the edges of lung tumors during surgery [11, 12]. Therefore, we hypothesized that in ILS, due to the impaired ventilation function of the diseased lung tissue, the ICG administered by atomization inhalation cannot reach the diseased lung tissue, thereby distinguishing it from the normal lung tissue. With the assistance of fluorescence imaging technology, the lesion can be accurately located and removed during thoracoscopic surgery.

Methods

Study design

A multicenter 1:1 matched case-control study was adopted. Three tertiary teaching hospitals, including Tongji Hospital affiliated to Huazhong University of science and technology, the First affiliated Hospital of Zhengzhou University, and the First Affiliated Hospital of Guangxi medical University, participated in this study. Cases of ILS in patients younger than 14 years treated with ICG from January 2023 to December 2023 in the three hospitals were collected. Due to the use of traditional surgical methods without inhaling ICG from January 2022 to January 2023(mainly including lobectomy or segmentectomy), cases were matched at a ratio of 1:1 according to age and lesion location as a control group. Patients with other congenital pulmonary airway malformations were excluded. The patients' admission diagnosis, treatment history, surgical records, intraoperative videos and photos, postoperative recovery, and follow-up results were collected. The diagnosis of complications was based on the International Classification of Diseases, 10th edition (ICD-10). All patients were followed up for 3 to 6 months. The follow-up included pulmonary computed tomography (CT) scans and pulmonary ventilation function tests.

This study was approved by the Ethics Committee of Tongji Hospital (TJ-IRB20230125) and registered at ClinicalTrials.gov (NCT06302985). All patients received informed consent from their guardians before surgery.

Study intervention

ICG group: Inhale ICG solution 30 min before surgery, with a dose of 0.5 mg/kg, dissolved in 5 ml of saline. All patients were placed in the lateral position under general anesthesia and started to receive one-lung ventilation. A low flow rate (1 ~ 2 L/min) and low CO2 pressure (4 ~ 5 mm Hg) were maintained in the chest to establish artificial pneumothorax. The observation port was located at the 7th or 8th intercostal space along the midaxillary line, and the two operation ports were located at the 4th or 5th intercostal space along the anterior axillary line and the 8th or 9th intercostal space along the posterior axillary line. After entering the chest with a 30°, 10 mm fluorescence thoracoscope (Opto-Medic, China), the fluorescence endoscope was switched to the fluorescence display mode. (Fig. 1) Normal lung tissue stained with fluorescence and unstained lesion tissue could be clearly displayed on the screen. The outer boundary of the lesion was marked with an electric hook, and the mediastinal pleura and pulmonary pleura were opened along the outer boundary of the lesion. Then, the lung tissue was separated along the gap between the lesion and the lung tissue with an electrocautery hook and ultrasonic scalpel. Subsequently, the arteries and bronchi of the lesion site were freed. Smaller blood vessels could be directly resected with Ligasure or ultrasonic scalpel, while thicker blood vessels and bronchi should be resected with Hem-o-Lock until the lesion resection was completed.

Traditional group: Except for not inhaling ICG, the preoperative assessment and surgical preparation were the same as in the ICG group. Based on preoperative CT imaging data, a 30° 10 mm thoracoscope was used to

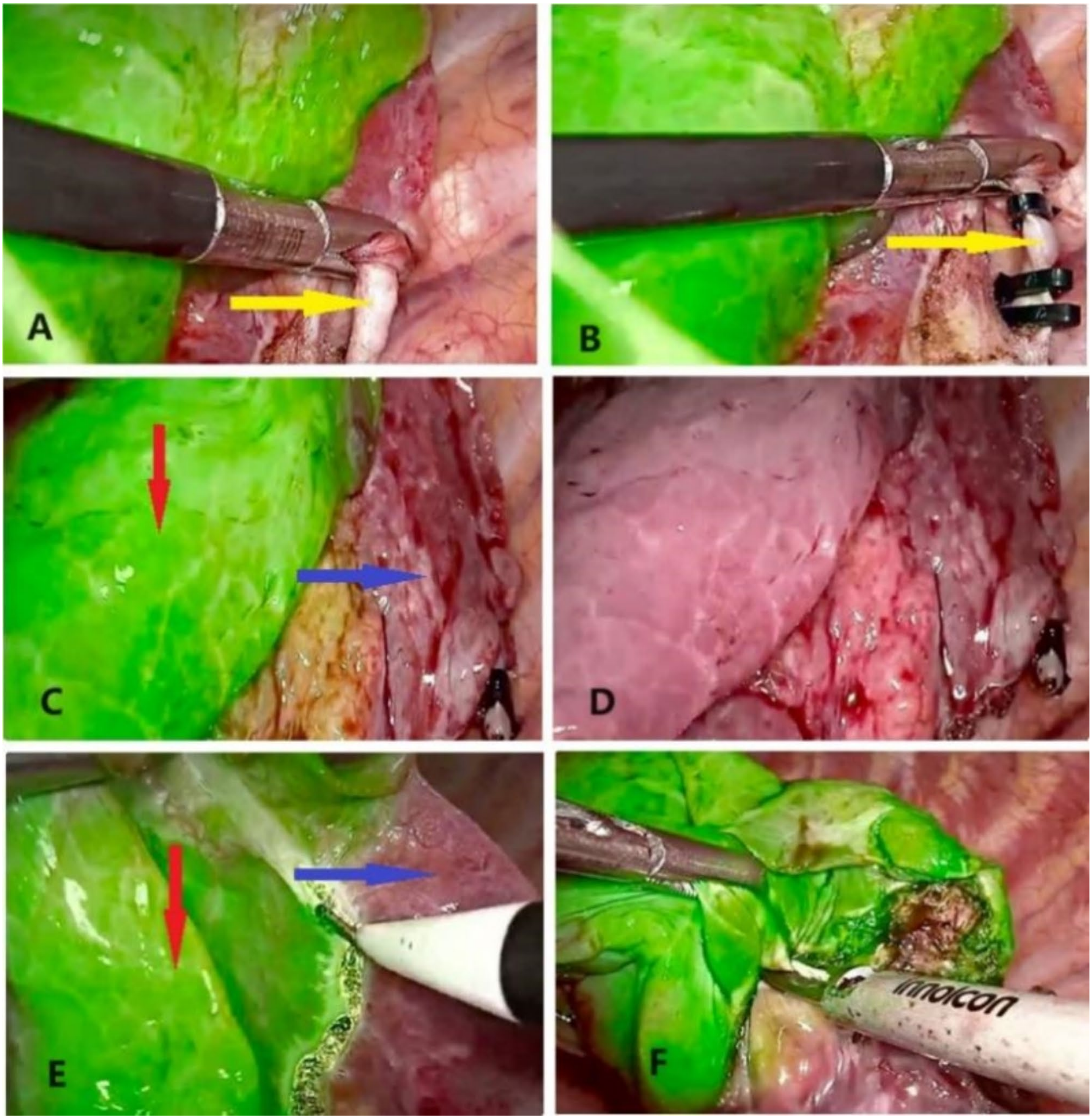

Fig. 1 Precise lesion resection of ILS under fluorescent thoracoscope. **A**. Isolation of systemic artery of ILS (yellow arrow); **B**. Resection of systemic artery of ILS by Hem-o-Lock and ultrasonic scalpel; **C**. Imaging of normal (red arrow) and lesion lung tissue (blue arrow) under fluorescence displaying; **D**. Imaging of normal and lesion lung tissue under normal displaying; **E**. Precise marking the lesion site by electrocoagulation hook; **F**. Removing of lesion ILS tissue

enter the thoracic cavity and identify anatomical landmarks. The target lung segment or lobe was exposed, and then a method from shallow to deep was used to continuously dissect and cut the blood vessels, bronchi, pulmonary arterioles, and venules using anatomical landmarks.

Postoperative follow-up

All patients were followed up in the outpatient department 3 to 6 months after surgery, including lung CT scan to assess the remaining lung tissue, whether there were any residual lesions, and the determination of pulmonary ventilation function.

Based on relevant literature reports [13–15], this study selected tidal volume (VT), minute ventilation (MV), time-to-peak ratio (TPTEF/TE), and volume-to-peak ratio (VPEF/VE) as key indicators for evaluating changes in pulmonary ventilation function. VT/kg is a reliable indicator for evaluating lung histopathology. It is usually

Table 1 The demographic and basic characteristics of each group

Characteristics	ICG group		Traditional group	
	n	%	*n*	%
Age (month), mean(SD)	12.24 ± 10.76		13.66 ± 13.62	
Gender				
Male	48	71.64	41	61.19
Female	19	28.36	26	38.81
Diseased region				
Right lower lobe lung	18	26.87	22	32.84
Left lower lobe lung	45	67.16	34	50.75
Right upper lobe lung	3	4.48	5	7.46
Left upper lobe lung	1	1.50	6	9.0

reduced in patients with restrictive or severe obstructive lesions. Minute ventilation (MV) is a reliable indicator for comprehensively assessing lung reserve capacity and an important criterion for assessing the tolerance of thoracic surgery. Time-to-peak ratio (TPTEF/TE) and volume-to-peak ratio (VPEF/VE) are important indicators for assessing small airway obstruction. In patients with obstructive ventilatory dysfunction, the severity of obstruction is negatively correlated with these ratios.

Statistical processing

The Kolmogorov-Smirnov test was used to determine the normal distribution of continuous variables. The t-test was used for inter-group comparison of pulmonary ventilation function-related values before and after surgery. The Mann-Whitney U test was used for comparison of continuous variables that did not conform to the normal distribution. The $\chi 2$ test was used for measurement data, with a two-sided 5% significance level. Statistical analysis was performed using Stata 16.0 software.

Results

All patients of children in this group successfully completed thoracoscopic non-anatomic lesion resection (ICG group), or thoracoscopic lobectomy or segmentectomy (traditional group), with no cases requiring conversion to open surgery.

The demographic and basic characteristics of each group are shown in Table 1. In the ICG group, there were 67 cases, including 48 males and 19 females; the average age was (12.24±10.76) months. The lesions were located in the lower lobe of the right lung in 18 cases, the lower lobe of the left lung in 45 cases, the upper lobe of the right lung in 3 cases, and the upper lobe of the left lung in 1 case. In the traditional group, there were 67 cases, including 41 males and 26 females; the average age was (13.66±13.62) months.

The comparison of intraoperative and postoperative results between the two groups is shown in Table 2. The operation time in the ICG group was (93.46±17.22) min, the intraoperative blood loss was (11.87±9.57) ml, there were 15 cases of postoperative complications (6 cases of postoperative pneumothorax and 9 cases of postoperative subcutaneous emphysema), the indwelling time of chest drainage tube was (53.19±8.15) h, and the postoperative hospital stay was (4.81±1.84) d. The operation time in the traditional group was (90.88±11.60) min; there was no significant difference between the two groups (P=0.311). The intraoperative blood loss was (12.87±8.26) ml, and the difference was not statistically significant (P=0.518). There were 12 cases of postoperative complications (3 cases of pneumothorax, 8 cases of subcutaneous emphysema, and 1 case of pleural effusion), and the difference was not statistically significant (P=0.465). The indwelling time of chest drainage tube was (73.25±15.51) h, and there was a significant difference between the two groups (P<0.001). The postoperative hospital stay was (6.72±1.31) d, and there was a significant difference between the two groups (P<0.001). The results showed that there was no significant difference in operation time, intraoperative blood loss, and postoperative complications between the ICG group and the traditional group. However, the drainage tube removal time was relatively earlier, and the postoperative hospital stay was also shorter.

There were no adverse reactions such as anaphylactic reactions, respiratory depression, or respiratory failure were observed, and no residual or recurrent lesions were found in two groups (Fig. 2). The pulmonary ventilation function indicators TPTEF/TE, VPEF/IE, VT (tidal volume), and MV (L/min) were analyzed and compared before and after surgery (Table 3). The preoperative TPTEF/TE (%) in the ICG group was 31.34±8.09, and the postoperative value was 39.27±5.52; the difference was statistically significant (P<0.001). The preoperative VTPEF/VE (%) was 32.74±7.84, and the postoperative value was 39.90±5.69; the difference was statistically

Table 2 Comparison of intraoperative and postoperative outcomes between the two groups

Group	Operative duration (min)	blood loss (min)	Complications	Period of thoracic drainage tubes (h)	Postoperation hospital stay(day)
ICG	93.46 ± 17.22	11.87 ± 9.57	15/67	53.19 ± 8.15	4.81 ± 1.84
Traditional	90.88 ± 11.60	12.87 ± 8.26	12/67	73.25 ± 15.51	6.72 ± 1.31
P	0.311	0.518	0.465	< 0.001	< 0.001

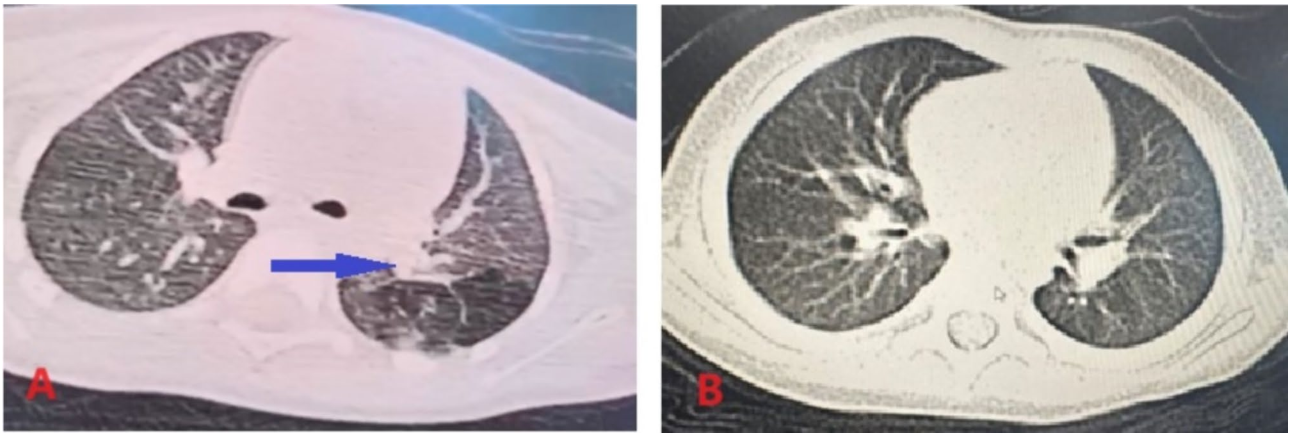

Fig. 2 : CT findings of ILS lesions in the lower lobe of the left lung before (**A**) and 6 months after surgery (**B**) (blue arrow showed systemic artery of ILS)

Table 3 Statistical data on preoperative and postoperative pulmonary ventilation function

Group		NO.	TPTEF/TE(%)	VPEF/IE(%)	VT/kg(ml/kg)	MV(L/min)
ICG	Preoperative	67	31.34 ± 8.09	32.74 ± 7.84	10.72 ± 1.49	4.85 ± 1.41
	Postoperative	67	39.27 ± 5.52	39.90 ± 5.69	12.00 ± 1.66	5.82 ± 1.48
	P-value		< 0.001	< 0.001	< 0.001	< 0.001
Traditional	Preoperative	67	33.84 ± 3.41	34.28 ± 2.92	9.71 ± 1.08	4.01 ± 1.32
	Postoperative	67	36.73 ± 1.81	37.08 ± 3.10	10.64 ± 1.36	4.43 ± 1.22
	P-value		< 0.001	< 0.001	< 0.001	0.058
	P*-value		< 0.001	< 0.001	< 0.001	< 0.001

significant ($P<0.001$). The preoperative VT/kg (ml/kg) was 10.72±1.49, and the postoperative value was 12.00±1.66, indicating a statistically significant difference ($P<0.001$). The preoperative MV (L/min) was 4.85±1.41, and the postoperative value was 5.82±1.48; the difference was statistically significant ($P<0.001$). This suggests that the pulmonary ventilation function of the children improved after surgery.

The postoperative pulmonary ventilation function of the ICG group was superior to that of the traditional group (Table 3): TPTEF/TE(%) (39.27±5.52 vs. 36.73±1.81, P*-value<0.001), VPEF/IE(%) (39.90±5.69 vs. 37.08±3.10, P*-value=0.013), VT/kg (12.00±1.66 vs. 10.64±1.36, P*-value<0.001), MV (5.82±1.48 vs. 4.43±1.22, P*-value<0.001), respectively. All P*-values were less than 0.05, indicating statistical significance.

Discussion

The goal of surgical treatment for ILS is to remove lung tissue changes to alleviate symptoms, improve the lung function of the remaining lung, prevent long-term complications, and enable compensatory lung growth [16]. In recent years, with the advancement of minimally invasive techniques, thoracoscopic treatment of ILS has gradually become mainstream. However, there is still a lack of standardized surgical methods. Although thoracoscopic lobectomy or segmentectomy is a recognized treatment method for localized peripheral lesions, complete resection of the lesion through lobectomy or segmentectomy can lead to the loss of a large amount of normal lung tissue. This may be detrimental to lung function recovery and long-term prognosis [17]. Some experts have proposed lung-preserving surgery, which aims to maximize the preservation of normal lung tissue after the removal of the lesion [18]. Currently, lung-preserving surgery includes two methods: wedge resection and lesion resection. ILS is a cystic lesion with a nonlinear internal boundary. The commonly used wedge resection uses a linear incision. If the resection margin is not sufficient, this method may lead to residual lesions. If the incision is too deep, there is a risk of continuous air leakage and possible damage to major blood vessels [6]. Lesion resection requires precise anatomical separation of pulmonary vessels and bronchi while removing the affected lung parenchyma. The determination of the resection interface depends on the visible changes on the lung surface. However, due to the cystic changes of the lesion, the lesion surface is often tense, and the distribution boundary in the lung parenchyma is different from that observed on the pleura surface. At the same time, the anatomical structure of pulmonary cystic lesions often involves poorly developed distal bronchi and blood vessels. The normal tissue adjacent to the lesion is more complex, with large individual differences and variations, making irregular and precise resection complicated [8].

In recent years, a few studies have reported the application of ICG in pediatric thoracoscopic lung resection [19, 20]. However, most of these operations involve intraoperative intravascular injection of ICG. The staining time is often short and may not be sufficient to fully treat the intersegmental plane. Therefore, its wide application is limited. In this study, the coloration time of ICG atomization inhalation in lung tissue can last at least 2 h, and it can provide a true vision through fluorescence thoracoscopy. The lesions directly observed during surgery are completely consistent with those shown on preoperative chest CT scans. Meanwhile, in basic study, we identified differentially expressed genes specific to bronchial cilia development by whole transcriptome sequencing of lesion and normal lung tissue in children with ILS. This provides a theoretical basis for reverse staining of lung malformations by atomization inhalation of ICG. The relevant research results will be submitted later.

The long-term recovery of lung function after the resection of malformed lung tissue has always been a concern for pediatric thoracic surgeons. Surgical removal of the lesion can prevent recurrent infection and potential canceration, while providing opportunities for compensatory growth of normal lung tissue [21]. However, the impact of surgery on lung function largely depends on the extent of normal lung tissue preserved [22]. Some studies have found that in the medium-to-long-term follow-up after lobectomy, the lung function of patients post-lobectomy is not significantly lower than that of normal children. Moreover, their activity levels and endurance in daily activities are essentially normal [23, 24]. However, it has also been found that 76.9% of patients have abnormal lung function, with 23.1% experiencing a decline in exercise oxygen tolerance [25]. This study uses TPTEF/TE, VPEF/VE, VT, and MV values as the evaluation criteria for postoperative lung ventilation function. Follow-up results show that the postoperative pulmonary ventilation function of patients has improved compared to preoperative levels. The postoperative lung function of the ICG group is also superior to the traditional group.

Previous reports have indicated that thoracoscopic lung resection may result in intraoperative bleeding, postoperative pneumothorax, hemothorax, bronchopleural fistula, and lesion residue as complications. In this study, there were no statistically significant differences in surgical duration, intraoperative blood loss, or postoperative complications between the two groups. However, the ICG group had a shorter indwelling time of thoracic drainage tubes and hospital stay, suggesting a faster recovery from surgery. Therefore, compared to traditional segmental or lobectomy, precise resection of lung malformations after ICG inhalation undoubtedly reduces the possibility of postoperative lesion residue, protects normal lung tissue to a greater extent, and has advantages over traditional surgery in promoting postoperative recovery and lung function.

In conclusion, preoperative atomization inhalation of ICG can facilitate precise lesion resection under thoracoscopy, maximizing the preservation of normal lung tissue and reducing complications. However, further large-scale prospective studies are still needed to assess the efficacy and safety of this procedure.

Abbreviations

ICG	indocyanine green
PS	pulmonary sequestration
ILS	intralobar pulmonary sequestration
CT	computed tomography
VT	tidal volume
MV	minute ventilation
TPTEF/TE	time-to-peak ratio
VPEF/VE	volume-to-peak ratio
MV	minute ventilation

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Author contributions

Tianqi zhu and Ye Yin: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed analysis tools and data; Wrote the paper. Jiexiong Feng: Conceived and designed the experiments; Guofeng Zhang, Wei LI, Didi Zhuansun, Xiaofeng Xiong, Yanan Li, Ying He, Wenjing Wang: Contributed and analyzed the data.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

This study was approved by the Ethics Committee of Tongji Hospital (TJ-IRB20230125) and registered at ClinicalTrials.gov (NCT06302985). All patients received informed consent from their guardians before surgery.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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