Original Article

Contribution of fluorescence imaging to thoracoscopic anatomical segmentectomy: a multicenter propensity matching analysis

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Background: Thoracoscopic anatomical segmentectomy is increasingly recognized for managing early-stage lung cancer. However accurately identifying intersegmental planes (ISPs), especially in complex lung segments, remains challenging. In comparison to conventional methods, fluorescence imaging represents a novel solution. This study aimed to examine the potential benefits of fluorescence imaging in single-port thoracoscopic anatomical segmentectomy.

Methods: A multicenter (three regional hospitals), retrospective, comparative analysis was conducted using data from 402 consecutive patients who underwent single-port thoracoscopic anatomical segmentectomy from June 2020 to December 2022. The cohort included 191 patients treated with the fluorescence method and 211 patients treated with the modified inflation-deflation method. Among the cohort, 130 patients were placed in the simple segmentectomy group and 272 in the complex segmentectomy group. Propensity score matching (PSM) was used to adjust for baseline differences between the fluorescence and modified inflation-deflation subgroups in the complex segmentectomy group. Perioperative outcomes were compared between the groups.

Results: In the simple segmentectomy group, no significant differences were observed between the fluorescence and modified inflation-deflation methods regarding segmental resection time, intraoperative blood loss, postoperative chest tube drainage and duration, postoperative pain, length of hospital stay, complication rate, or hospital costs. In the complex segmentectomy group, however, fluorescence imaging significantly shortened segmental resection time (69.37±28.22 *vs.* 78.80±34.66 min; P=0.03), while reducing intraoperative blood loss (P=0.046); and improving visual analogue scale (VAS) pain scores on the first postoperative day (P=0.006). Both methods demonstrated comparable safety and oncologic effectiveness.

Conclusions: Fluorescence-guided single-port thoracoscopic anatomical segmentectomy demonstrated comparable perioperative safety and effectiveness to the modified inflation-deflation technique while offering advantages, such as shorter segmental resection time, for complex segmentectomies.

Keywords: Segmentectomy; fluorescence; indocyanine green (ICG); modified inflation-deflation

Submitted Jun 18, 2024. Accepted for publication Aug 21, 2024. Published online Aug 28, 2024.

doi: 10.21037/jtd-24-986

View this article at: https://dx.doi.org/10.21037/jtd-24-986

Introduction

Lung cancer is currently the most common cancer worldwide, Traditionally, lobectomy with systemic lymph node dissection or sampling has been the standard surgical treatment. Segmentectomy was considered only a "compromised" option for patients with poor cardiopulmonary reserve who could not tolerate a lobectomy. However, many groups have demonstrated that an intentional segmentectomy appears to be an equally effective alternative to lobectomy for a select subset of patients, while offering improved preservation of lung function (1-5). Three randomized controlled trials (CALGB140503/Alliance, JCOG0802, and DRKS00004897) (6-8) have confirmed the non-inferiority of segmentectomy compared to lobectomy for patients with peripheral early-stage (cIA <2.0 cm) non-small cell lung cancer (NSCLC).

For thoracic surgeons performing anatomical segmentectomies, accurately identifying the intersegmental plane (ISP) may pose significant challenges. Various intraoperative methods (9) are also available to delineate ISP including jet ventilation techniques, endobronchial methylene blue injection, modified inflation-deflation, and systemic injection of indocyanine green (ICG), three-dimensional (3D) simulation using multidetector computed tomography (CT) and virtual-assisted lung mapping. Multiple studies have investigated the application of systemic ICG injection for identifying ISP (10-12). However, data comparing the safety and effectiveness of this method with other techniques have been limited, In the following discussion, we will compare the results with the few similar studies (13,14) published to date.

To address this knowledge gap, we compared the safety and effectiveness of ICG fluorescence imaging with the modified inflation-deflation when performing single-port thoracoscopic anatomical segmentectomy. Surgical procedures were categorized operations into simple and complex segmentectomies based on the complexity of the lung segment resection site (15,16) and propensity score matching (PSM) was used to balance baseline characteristics between patients in the latter group. We subsequently analyzed and compared the perioperative and long-term outcomes between the groups. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-986/rc).

Highlight box

Key findings

- Single-port thoracoscopic anatomical segmentectomy with fluorescence visualization of intersegmental planes (ISPs) demonstrated safety and effectiveness comparable to the modified inflation-deflation method. In complex segmentectomies, specifically, fluorescence imaging conferred improved perioperative outcomes.

What is known and what is new?

- Fluorescence imaging is generally considered capable of shortening operative time and improving efficiency, but empirical data attesting to these benefits have been lacking.
- Compared to the traditional modified inflation-deflation method, fluorescence imaging shortened segmental resection time, reduced intraoperative blood loss and improved postoperative pain, albeit only for complex cases.

What is the implication, and what should change now?

- Fluorescence imaging is a viable option for identifying ISPs in single-port thoracoscopic anatomical segmentectomy and could be considered the method of choice for complex segmentectomies.

Methods

Patient population

This multicenter retrospective study included 402 patients [group a: 345 from Anhui Chest Hospital; group b: 29 from the First Affiliated Hospital of Wannan Medical College (Yijishan Hospital of Wannan Medical College); group c: 28 from the First Affiliated Hospital of Bengbu Medical University], who underwent single-port thoracoscopic anatomical segmentectomy between June 2020 and December 2022. Of these, 191 underwent the procedure using systemic ICG injection (fluorescence subgroup), while 211 patients underwent the modified inflation-deflation method (modified inflation-deflation subgroup). All three participating hospitals are regional medical centers with highly skilled thoracic surgeons, each performing more than 1,200 thoracic surgeries per year. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the leading institution Anhui Chest Hospital, Anhui, China (No. KJ2024-039) and informed consent was taken from all the patients. All participating hospitals/institutes were informed and agreed with the study.

Inclusion criteria

All consecutive patients who underwent thoracoscopic segmentectomy were included in the study. For malignant pulmonary nodules, segmentectomy was indicated based on the following criteria, as outlined by the National Comprehensive Cancer Network (NCCN) guidelines (17) and Asia expert consensus (16): (I) for stage 1A NSCLC with a favorable combination of tumor diameter, consolidation-to-tumor (C:T) ratio, and maximum standardized uptake value (SUVmax); (II) poor lung function or inability to tolerate lobectomy due to significant comorbidities; (III) CT findings suggestive of peripheral, noninvasive lung lesions with a maximum diameter of 2.0 cm or less, with intraoperative frozen section confirming atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), or invasive adenocarcinoma (IA) with clear resection margins; (IV) negative findings from intraoperative lymph node dissection/sampling; (V) CT follow-up over 1 year showing high suspicion of malignancy with a ground glass-like component ≥50%; and (VI) imaging-confirmed nodule volume doubling time ≥400 days. Additionally, patients with benign but central and segmentally confined lung nodules, which were not amenable to wedge resection, were also considered candidates for segmentectomy.

Exclusion criteria

Patients were excluded if they met any of the following criteria: (I) history of malignancy or thoracic surgery, or postoperative pathology confirming metastatic carcinoma; (II) known allergy to iodine or other contrast agents; (III) preoperative suspicion of lymph node metastasis; (IV) frozen section unable to determine whether the nodule was stage IA NSCLC with a tumor diameter of 2.0 cm or less; (V) centrally located malignant nodules for which adequate resection margins could not be ensured; (VI) frozen section suggesting malignancy within 2.0 cm of the surgical margin or less than the maximum lesion diameter, requiring additional margin sampling; and (VII) incomplete clinical data records unsuitable for statistical analysis.

Classification criteria

The 402 patients were categorized into two groups based on the complexity of the segmentectomy (16): simple segmentectomy group (n=130; n^a=123, n^b=4, n^c=3) and the complex segmentectomy group (n=272; n^a=222, n^b=25, n^c=25). Simple segmentectomy involved resection of segments forming only one ISP: LS1–3, LS4–5, LS6, and RS6 segments (65 patients in the fluorescence subgroup and 65 patients in the modified inflation-deflation subgroup). Complex segmentectomy included all other lung segments, requiring resection across two or more ISPs, including combined segmentectomies and sub-segmentectomies (126 patients in the fluorescence subgroup and 146 patients in the modified inflation-deflation subgroup).

Variables and outcomes

Demographic and clinicopathologic characteristics of the patients [sex, age, body mass index (BMI), forced expiratory volume in 1 second % predicted (FEV_1%), smoking history, comorbidities], as well as perioperative data (hook-wire localization, pleural adhesions, development of interlobar fissure, mediastinal lymph node dissection/sampling, segmentectomy site, and postoperative pathology) were collected and analyzed. It should be pointed out that we defined three degrees of pleural adhesions based on the relevant literature (18): A, no adhesions, existence of an interval space between the visceral and parietal pleura due to lung collapse; B, mild adhesions, adhesion area occupies 1–50%, blunt and sharp dissection required; C, severe adhesions, adhesion area occupies 51–100%, extrapleural dissection required because dissection between the visceral and parietal pleura is difficult. Similarly, development of interlobar fissure based on the Fissure Development Score (FDS) (19) and degree of completeness was defined as follows: grade 0, complete fissure; grade 1, fusion between 0 and 30%; grade 2, fusion between 30% and 70%; and grade 3, fusion more than 70%, and we divided the patients into three groups: A, well developed (grade 0); B, moderately developed (grade 1–2); C, undeveloped (grade 3). Outcomes included segmental resection time (i.e., time taken to perform dissection of the target segmental bronchovascular structures until the excision of the target segment), intraoperative estimated blood loss, chest tube drainage (volume and duration), visual analogue scale (VAS) pain scores assessed at 8:00 am for the first three postoperative days, complications, length of hospital stay, and total hospital costs.

Perioperative management

Preoperatively, patients were advised to cease smoking at least 4 weeks and received education regarding pre- and post-operative precautions, psychological counseling, and instructions on proper coughing and sputum clearance

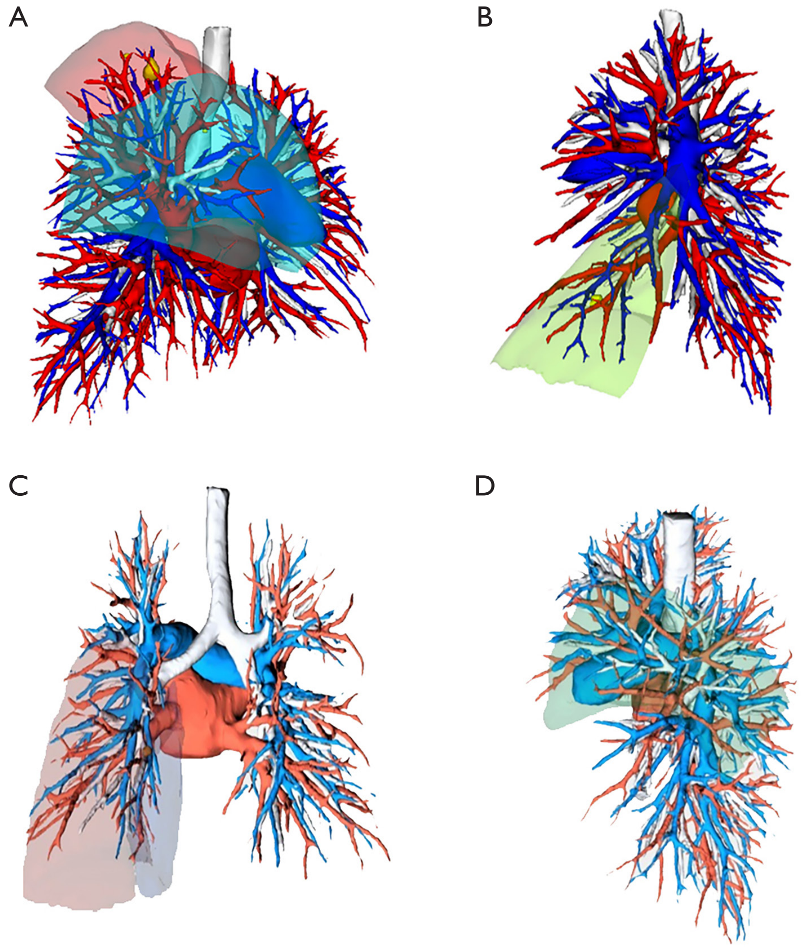

Figure 1 Preoperative 3D reconstruction of pulmonary segmental vasculature and bronchial to aid intraoperative identification: (A) RS1 and RS3 segments, (B) LS8 segment, (C) LS9 and LS10 segments, and (D) LS3 segment. 3D, three-dimensional.

techniques to reduce the occurrence of postoperative pulmonary complications. Patients with underlying lung diseases (e.g., infection, chronic obstructive pulmonary disease) underwent appropriate treatment, including antibiotics and bronchodilators, before proceeding with surgery after symptom resolution.

All patients underwent preoperative thin-section thoracic CT. For complex segmentectomies, chest imaging data were reconstructed using KINGSTAR 3D (Anhui King Star Digital S&T Co., Ltd., Hefei, China) or PVmed (Guangzhou Perception Vision Medical Technology Co., Ltd., Guangzhou, China) software to identify the target segmental vessels and bronchi (*Figure 1*). Moreover, 3D printed models of the tracheobronchial tree and pulmonary arteriovenous systems were created for select complex cases to aid in surgical planning and identification of segmental bronchovascular structures during surgery (*Figure 2*). For smaller, (size <1 cm), central (depth >1 cm), or predominantly ground-glass (C:T ratio <0.5) nodules preoperative CT-guided hook-wire localization was performed to precisely locate the pulmonary nodules for complete surgical resection.

Surgical procedures

All procedures were performed by a senior surgeon [a total of eight senior surgeons participated in this multicenter retrospective study, four senior surgeons from Anhui Chest Hospital, two senior surgeons from the First Affiliated Hospital of Wannan Medical College (Yijishan Hospital of Wannan Medical College), and two senior surgeons from the First Affiliated Hospital of Bengbu Medical University]

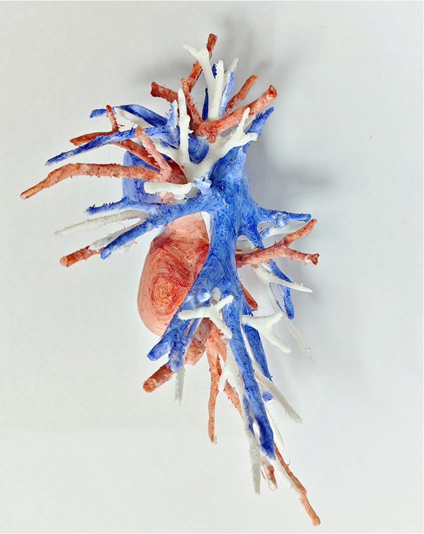

Figure 2 3D-printed model of the vascular and bronchial anatomy of the left lung. 3D, three-dimensional.

with an annual thoracoscopic anatomical segmentectomy exceeding 200 cases. Patients underwent general anesthesia with one-lung ventilation. A single 3–4 cm incision was made in the fifth intercostal space anterior to the midaxillary line, with the surgeon standing ventrally. A 30° high-definition thoracoscope/fluoroscope (Karl Storz Endoskope, Tuttlingen, Germany) was inserted through this incision to visualize the thoracic cavity. Following dissection and division of the target segmental pulmonary vessels, and bronchi, either fluorescence imaging or the modified inflation-deflation technique was employed to define ISP (which technique to take depended on the surgeon's habits or equipment conditions).

For the fluorescence method, 2 mL of diluted (5 mg/mL) Ridu ICG (25 mg/unit; Dandong Yichuang Pharmaceutical Co., Ltd., Dandong, China) was injected intravenously after the target segment arteriovenous and segmental bronchus were cut off. After 10–15 seconds, the lung tissue for preservation appeared green on the fluorescence mode of the thoracoscope, while the target segment for resection did not show green color (*Figure 3A,3B*).

For the modified inflation-deflation technique, consistent with the operation steps of fluorescence method before injected ICG, then double-lung ventilation with 20 cmH_2O airway pressure was initially used to achieve complete expansion of the operated lung. This was followed by transition to single-lung ventilation of the non-operated lung. After 15–20 min (it was generally necessary to wait for such a long time, but it was not ruled out that some patients have a slightly shorter or longer time to achieve resectable criterion), the target segment for resection appeared inflated and light pink in contrast to the deflated lung tissue for preservation (*Figure 3C,3D*).

In this study, we defined the criterion for inter-segmental visualizations as the display of ISP curve for more than 90% of the target lung segment using both techniques. Additionally, the target lung segment with a marginal bulge height >1 mm was required to meet through the modified inflation-deflation technique.

After ISP marking (surgeons decided whether to mark ISP if they choose the modified inflation-deflation method), energy devices or mechanical staplers were used to divide ISP. The specimen was removed in a bag and sent for rapid frozen section to assess the surgical resection margin. Subsequent lymph node dissection/sampling was performed if pathological examination revealed IA. If the lesion was reported as AIS or MIA, lymph node dissection/sampling was not undertaken. The operative field was inspected for bleeding, and the lung was assessed for air leaks following re-expansion. Air leaks from the lung surface were repaired with a polypropylene suture (PROLENE polypropylene monofilament non-absorbable suture with EVERPOINT cardiovascular needles, Ethicon, Johnson & Johnson, San Lorenzo, Puerto Rico, USA). A 24-French chest tube was then inserted through the incision and connected to a water-seal drainage system. Additionally, a microcatheter (8-French) was placed in the mid-axillary line of the seventh intercostal space and connected to a drainage bag to facilitate further postoperative drainage.

Postoperative management and follow-up

Routine postoperative care included administration antibiotics for a maximum duration of 72 hours. Pain control was achieved with a patient-controlled pump (including opioid analgesic, e.g., sufentanil; nonsteroidal analgesic, e.g., flurbiprofen axetil; antiemetic, e.g., tropisetron), which was supplemented by short-acting oral or intravenous analgesics for breakthrough pain as needed. Postoperative chest radiographs were monitored along with drainage output to guide chest tube removal. Patients without complications were discharged the day after chest tube removal.

Follow-up was conducted via telephone or outpatient clinic visits at 1 and 3 months postoperatively, then every 3 months up to 2 years, every 6 months from 2 to 5 years,

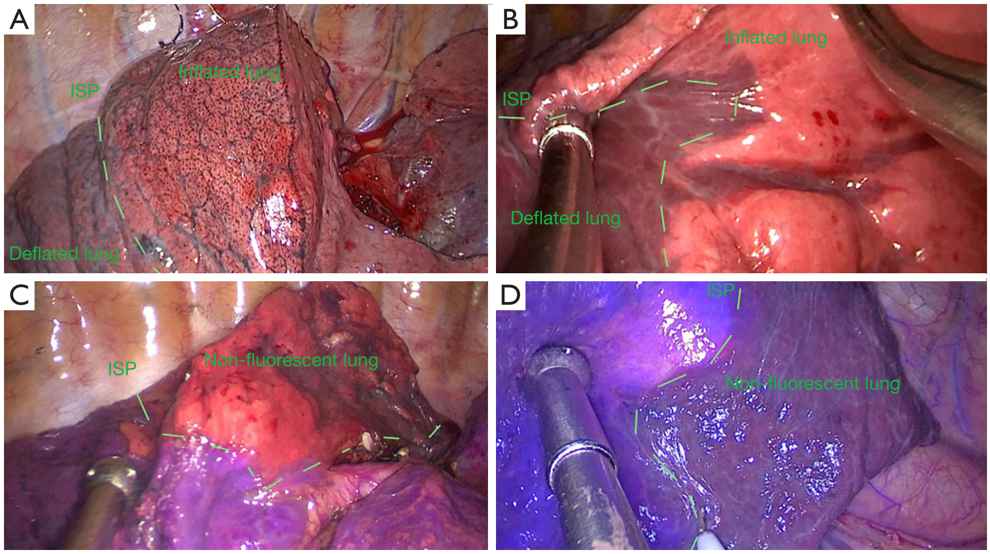

Figure 3 Intraoperative images during simple (A,C) and complex (B,D) lung segmentectomy. (A) Modified inflation-deflation method for RS6 segmentectomy, with the inflated RS6 segment being shown. (B) Modified inflation-deflation method for LS9+10 segmentectomy, with the inflated LS9 and LS10 segments being shown. (C) ICG fluorescence method for RS6 segmentectomy, with the nonfluorescent RS6 segment being shown. (D) ICG fluorescence method for LS10 segmentectomy, with the nonfluorescent LS10 segment being shown. ISP, intersegmental plane; ICG, indocyanine green.

and annually thereafter. Post-operative evaluation included blood laboratory investigations, tumor markers, chest radiography, thoracic CT, fiberoptic bronchoscopy, whole-body nuclear bone scan, brain magnetic resonance imaging, and positron emission tomography-CT, as indicated.

Statistical analysis

Normally distributed continuous variables were presented as mean ± standard deviation (SD), and groups were compared using Student's *t*-test or Welch's *t*-test based on the assumption of equal or unequal variances, respectively. Categorical variables were reported as frequencies and percentages, with between-group comparisons conducted using the Chi-squared test or Fisher's exact test for unordered variables, and the Wilcoxon rank-sum test for ordered variables. Statistical significance was set at P<0.05.

In real-world studies, the results were susceptible to bias due to broad inclusion and exclusion criteria as well as numerous confounding factors. To address this issue, the PSM was employed in this study. PSM was primarily utilized for subgroup analysis of observational clinical research or clinical trial data. The fundamental principle involved replacing multiple covariates with a single score to balance their distribution between the treatment and control groups, thereby equalizing confounding factors in nonrandomized studies in a randomization-like manner. Its advantage lies in transforming confounding factor control into propensity values, achieving 'dimensionality reduction', and controlling for confounding bias. Simultaneously, it could resolve the 'multi-dimensional' problem posed by various non-research factors and potential independent variable collinearity. Furthermore, we also understood that PSM was only useful for recreating randomization and cannot simulate true randomized complete block designs, the latter of which being stronger at removing imbalance and bias (20).

In the simple segmentectomy group, baseline characteristics were comparable between the fluorescence and modified inflation-deflation methods (all P>0.05), and thus no further matching was required (*Table 1*). In the complex segmentectomy group, however, significant differences were observed in BMI (P=0.042) and smoking status (P=0.043). PSM (1:1) was therefore performed, successfully matching 110 pairs of patients with comparable profiles in the complex fluorescence and modified inflation-deflation subgroups (*Table 2*).

All statistical analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA).

Table 1 Baseline characteristics of patients undergoing simple segmentectomy with the ICG fluorescence method *vs.* the modified inflation-deflation method

Characteristics	Fluorescence method (n=65)	Modified inflation-deflation method (n=65)	t/χ^2 value	P value
Sex			0.290‡	0.59
Male	24 (36.92)	27 (41.54)		
Female	41 (63.08)	38 (58.46)		
Age (years)	52.06±13.89	53.80±11.36	0.788†	0.43
BMI (kg/m^2)	23.12±3.00	23.11±2.72	−0.044†	0.97
FEV_1%	79.27±6.87	80.08±7.52	0.638†	0.53
Smoking history	5 (7.69)	11 (16.92)	2.566‡	0.11
Underlying lung diseases	4 (6.15)	5 (7.69)	0.000‡	>0.99
Hypertension	19 (29.23)	15 (23.08)	0.637‡	0.43
Diabetes	8 (12.31)	6 (9.23)	0.320‡	0.57
Cardiac disease	2 (3.08)	4 (6.15)	0.175‡	0.68
Hook-wire localization	5 (7.69)	11 (16.92)	2.566‡	0.11
Pleural adhesions			3.545‡	0.23
No adhesions	50 (76.92)	58 (89.23)		
Mild adhesions	10 (15.38)	5 (7.69)		
Severe adhesions	5 (7.69)	2 (3.08)		
Development of interlobar fissure			3.170‡	0.21
Undeveloped	6 (9.23)	8 (12.31)		
Moderately developed	32 (49.23)	22 (33.85)		
Well developed	27 (41.54)	35 (53.85)		
Mediastinal lymph node dissection/sampling	33 (50.77)	27 (41.54)	1.114‡	0.29
Site of segmentectomy			5.822‡	0.13
LS1+2+3	28 (43.08)	19 (29.23)		
LS4+5	8 (12.31)	11 (16.92)		
LS6	18 (27.69)	14 (21.54)		
RS6	11 (16.92)	21 (32.31)		

Data are presented as n (%) or mean ± SD. †, Student's *t*-test or Welch's *t*-test; ‡, χ^2 test value. ICG, indocyanine green; BMI, body mass index; FEV_1%, forced expiratory volume in 1 second % predicted; SD, standard deviation.

Results

The clinical and surgical characteristics of the patients in the simple segmentectomy group are summarized in *Table 1*. Postoperative pathology was predominantly MIA (53.85% and 43.08% in the fluorescence and modified inflation-deflation subgroups, respectively), with the remaining cases included precancerous lesions, IA, and benign nodules [organizing pneumonia (n=8), benign tumors (n=4), granulomatous inflammation (n=2), bronchiectasis (n=2), novel cryptococcosis (n=1), Castleman disease (n=1), tuberculosis (n=1)]. In the simple segmentectomy group, there were no statistically significant differences in perioperative outcomes, including segmental resection time,

Table 2 Baseline characteristics of patients undergoing complex segmentectomy before and after PSM by surgical method (ICG fluorescence *vs*. modified inflation-deflation)

Characteristics	Before PSM matching				After PSM matching			
	Fluorescence method (n=126)	Modified inflation-deflation method (n=146)	t/χ^2 value	P value	Fluorescence method (n=110)	Modified inflation-deflation method (n=110)	t/χ^2 value	P value
Sex			2.607‡	0.11			0.077‡	0.78
Male	57 (45.24)	52 (35.62)			41 (37.27)	43 (39.09)		
Female	69 (54.76)	94 (64.38)			69 (62.73)	67 (60.91)		
Age (years)	52.42±11.98	52.68±12.62	0.176†	0.86	52.15±12.44	51.63±12.49	0.908†	0.76
BMI (kg/m^2)	24.22±3.21	23.44±3.09	–2.044†	0.042	23.98±3.21	23.85±3.01	–0.313†	0.76
FEV_1%	79.29±8.56	80.95±7.57	1.694†	0.09	79.96±8.53	79.61±6.87	–0.328†	0.74
Smoking history	26 (20.63)	17 (11.64)	4.108‡	0.043	16 (14.55)	16 (14.55)	0.000‡	>0.99
Underlying lung diseases	11 (8.73)	6 (4.11)	2.464‡	0.12	5 (4.55)	5 (4.55)	0.000‡	>0.99
Hypertension	31 (24.60)	31 (21.23)	0.397‡	0.53	26 (23.64)	24 (21.82)	0.107‡	0.74
Diabetes	12 (9.52)	13 (8.90)	0.031‡	0.86	9 (8.18)	10 (9.09)	0.058‡	0.81
Cardiac disease	2 (1.59)	4 (2.74)	0.054‡	0.82	2 (1.82)	2 (1.82)	0.000‡	>0.99
Hook-wire localization	21 (16.67)	31 (21.23)	0.912‡	0.34	20 (18.18)	23 (20.91)	0.260‡	0.61
Pleural adhesions			3.151‡	0.21			0.103§	>0.99
No adhesions	98 (77.78)	103 (70.55)			85 (77.27)	84 (76.36)		
Mild adhesions	23 (18.25)	30 (20.55)			21 (19.09)	22 (20.00)		
Severe adhesions	5 (3.97)	13 (8.90)			4 (3.64)	4 (3.64)		
Development of interlobar fissure			0.522‡	0.77			1.046‡	0.59
Undeveloped	17 (13.49)	21 (14.38)			15 (13.64)	11 (10.00)		
Moderately developed	57 (45.24)	71 (48.63)			52 (47.27)	50 (45.45)		
Well developed	52 (41.27)	54 (36.99)			43 (39.09)	49 (44.55)		
Mediastinal lymph node dissection/sampling	59 (46.83)	69 (47.26)	0.005‡	0.94	54 (49.09)	40 (36.36)	3.641‡	0.056
Site of segmentectomy			9.033§	0.32			7.740§	0.46
LS1+2	26 (20.63)	36 (24.66)			22 (20.00)	29 (26.36)		
LS3	6 (4.76)	14 (9.59)			6 (5.45)	10 (9.09)		
LS8	1 (0.79)	2 (1.37)			1 (0.91)	1 (0.91)		
LS10	2 (1.59)	2 (1.37)			2 (1.82)	2 (1.82)		
RS1	31 (24.60)	30 (20.55)			26 (23.64)	25 (22.73)		
RS2	14 (11.11)	13 (8.90)			10 (9.09)	13 (11.82)		
RS3	8 (6.35)	18 (12.33)			8 (7.27)	10 (9.09)		
RS8	9 (7.14)	5 (3.42)			9 (8.18)	3 (2.73)		
Subsegments/combined segments	29 (23.02)	26 (17.81)			26 (23.64)	17 (15.45)		

Data are presented as n (%) or mean ± SD. †, Student's *t*-test or Welch's *t*-test; ‡, χ^2 test value; §, Fisher's exact test value. PSM, propensity score matching; ICG, indocyanine green; BMI, body mass index; FEV_1%, forced expiratory volume in 1 second % predicted; SD, standard deviation.

Table 3 Perioperative outcomes in patients undergoing simple segmentectomy with ICG fluorescence method *vs*. modified inflation-deflation method

Outcomes	Fluorescence method (n=65)	Modified inflation-deflation method (n=65)	t/χ^2 value	P value
Segmental resection time (min)	66.51±24.77	69.11±29.84	0.541†	0.59
Intraoperative blood loss (mL)	17.46±9.53	19.46±26.71	0.569†	0.57
Maximum nodule diameter (cm)	1.14±0.39	1.20±0.58	0.691†	0.49
Postoperative drainage (mL)				
Day 1	162.08±102.99	175.69±115.86	0.708†	0.48
Day 2	153.92±97.57	158.15±93.66	0.252†	0.80
Day 3	126.49±83.86	126.31±104.86	−0.011†	0.99
Mean drainage at 3 days after surgery (mL)	147.50±76.82	153.90±80.22	0.465†	0.64
Postoperative VAS pain score				
Day 1	2.97±0.35	3.03±0.39	0.939†	0.35
Day 2	2.68±0.53	2.66±0.59	−0.155†	0.98
Day 3	2.37±0.55	2.18±0.56	−1.909†	0.059
Postoperative chest tube duration (days)	5.38±2.60	4.78±1.80	−1.532†	0.13
Postoperative hospital stay (days)	6.42±2.62	5.78±2.18	−1.493†	0.14
Postoperative complications			4.819§	0.31
Pneumonia	6 (9.23)	2 (3.08)	1.199‡	0.27
Prolonged air leaks (>3 days)	7 (10.77)	8 (12.31)	0.078‡	0.78
Massive postoperative drainage (≥200 mL/day for 5 days)	2 (3.08)	7 (10.77)	1.910‡	0.17
Atelectasis	2 (3.08)	2 (3.08)	0.00‡	1.00
Lung lesion pathology			1.938§	0.78
AAH	1 (1.54)	2 (3.08)		
AIS	4 (6.15)	5 (7.69)		
MIA	35 (53.85)	28 (43.08)		
IA	17 (26.15)	19 (29.23)		
Benign	8 (12.31)	11 (16.92)		
Total hospital cost (CNY)	42,965.74±5,043.28	43,850.36±6,922.78	0.833†	0.41

Data are presented as mean ± SD or n (%). †, Student's *t*-test or Welch's *t*-test; ‡, χ^2 test value; §, Fisher's exact test value. ICG, indocyanine green; VAS, visual analogue scale; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; CNY, Chinese Yuan; SD, standard deviation.

between the fluorescence and modified inflation-deflation methods (all P>0.05) (*Table 3*).

Table 2 details the characteristics of the patients in the complex segmentectomy group before and after PSM by surgical method (fluorescence *vs*. modified inflation-deflation). MIA comprised over half of the postoperative pathologies (58.18% and 61.82% in the fluorescence and modified inflation-deflation subgroups, respectively). The remaining cases included precancerous lesions (n=13 *vs*. 13), IA (n=27 *vs*. 22), and benign nodules [organizing pneumonia (n=8), benign tumors (n=3), tuberculosis (n=2), granulomatous inflammation (n=1), and *Aspergillus*

Table 4 Perioperative outcomes in matched patients undergoing complex segmentectomy with ICG fluorescence method *vs*. modified inflation-deflation method

Outcomes	Fluorescence method (n=110)	Modified inflation-deflation method (n=110)	t/χ^2 value	P value
Segmental resection time (min)	69.37±28.22	78.80±34.66	2.212†	0.03
Intraoperative blood loss (mL)	17.00±8.84	20.64±16.83	2.007†	0.046
Maximum nodule diameter (cm)	1.06±0.39	1.08±0.43	0.247†	0.81
Postoperative drainage (mL)				
Day 1	144.59±86.00	128.77±82.38	–1.393†	0.17
Day 2	144.55±124.12	139.91±88.99	–0.318†	0.75
Day 3	100.27±91.80	104.50±82.37	0.359†	0.72
Mean drainage at 3 days after surgery (mL)	131.55±79.19	124.40±61.01	–0.749†	0.45
Postoperative VAS pain score				
Day 1	2.92±0.36	3.05±0.31	2.785†	0.006
Day 2	2.64±0.54	2.70±0.58	0.842†	0.40
Day 3	2.25±0.64	2.28±0.56	0.449†	0.65
Postoperative chest tube duration (days)	4.59±2.23	4.48±1.28	–0.445†	0.66
Postoperative hospital stay (days)	5.55±2.36	5.55±1.45	–0.413†	0.68
Postoperative complications			3.457§	0.66
Pneumonia	5 (4.55)	3 (2.73)	0.130‡	0.72
Prolonged air leak (>3 days)	7 (6.36)	5 (4.55)	0.353‡	0.55
Massive postoperative drainage (≥200 mL/day for 5 day)	3 (2.73)	7 (6.36)	1.676‡	0.20
Atelectasis	1 (0.91)	0 (0.00)	–§	>0.99
Other	2 (1.82)	2 (1.82)	0.000‡	>0.99
Lung lesion pathology			1.764‡	0.62
AIS	13 (11.82)	13 (11.82)		
MIA	64 (58.18)	68 (61.82)		
IA	27 (24.55)	20 (18.18)		
Benign	6 (5.45)	9 (8.18)		
Total hospital cost (CNY)	43,997.20±8,192.24	44,192.39±6,054.58	0.201†	0.84

Data are presented as mean ± SD or n (%). †, Student's *t*-test or Welch's *t*-test; ‡, χ^2 test value; §, Fisher's exact test value. ICG, indocyanine green; VAS, visual analogue scale; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; CNY, Chinese Yuan; SD, standard deviation.

infection (n=1)]. In the complex segmentectomy group, the fluorescence method demonstrated significant reductions in segmental resection time (69.37±28.22 *vs.* 78.80±34.66 min, P=0.03), intraoperative estimated blood loss (17.00±8.84 *vs.* 20.64±16.83 mL, P=0.046), and VAS pain scores on the first postoperative day (2.92±0.36 *vs.* 3.05±0.31, P=0.006) compared to the modified inflation-deflation technique. All other outcomes were comparable between the subgroups (P>0.05), and in particular no differences were identified between the two groups regarding overall complication rate and prolonged air leak (*Table 4*).

A total of 350 patients were included in both the

Table 5 Postoperative follow-up and complications in patients undergoing simple or complex segmentectomy with ICG fluorescence method *vs.* modified inflation-deflation method

Outcomes	Simple segmentectomy group		Complex segmentectomy group after PSM		Total (n=350)
	Fluorescence method (n=65)	Modified inflation-deflation method (n=65)	Fluorescence method (n=110)	Modified inflation-deflation method (n=110)	
Follow-up completion	61 (93.85)	60 (92.31)	94 (85.45)	102 (92.73)	317 (90.57)
Chest discomfort/dyspnea	1/61 (1.64)	4/60 (6.67)	1/94 (1.06)	4/102 (3.92)	10/317 (3.15)
Chronic cough (>3 months)	4/61 (6.56)	1/60 (1.67)	2/94 (2.13)	2/102 (1.96)	9/317 (2.84)
Chronic pain (>3 months)	1/61 (1.64)	0/60 (0.00)	1/94 (1.06)	1/102 (0.98)	2/317 (0.63)
Excessive sputum	1/61 (1.64)	0/60 (0.00)	0/94 (0.00)	0/102 (0.00)	1/317 (0.32)

Data are presented as n (%) or n/follow-up completion (%). ICG, indocyanine green; PSM, propensity score matching.

simple segmentectomy group and the matched complex segmentectomy group, with a follow-up deadline set for January 20, 2024, (range, 52 to 172 weeks). Of these, 33 patients were lost to follow-up, resulting in an overall follow-up rate of 90.57%. All patients who were followed up remained disease free. Long-term complications were observed in 22 cases, predominantly chest discomfort/dyspnea (n=10) and chronic cough (n=9) (*Table 5*).

Discussion

The use of ICG fluorescence imaging for surgical guidance dates back to 1948 when it was initially employed for the identification and localization of brain tumors (21). Since then, this technology has found applications across various surgical disciplines, including ophthalmic surgery, hepatobiliary surgery, gynecology, gastrointestinal surgery, and urology (22-26). The potential of fluorescence imaging to delineate lung ISPs was first demonstrated by Misaki *et al.* (27) through animal experiments in 2009. The following year, his team successfully identified ISPs using ICG in eight patients undergoing open segmentectomy (28), gradually expanding its application to thoracic surgical procedures. ICG is currently the sole contrast agent approved by the US Food and Drug Administration (FDA) for this purpose, owing to its established safety and effectiveness (29).

In the design of this multicenter study, we excluded the outcomes of operative time and intersegmental marking time which have been commonly used in similar studies (13,14). Operative time can be significantly affected by variations in intraoperative steps, including degrees of pleural adhesion, frozen section analysis, lymph node dissection/sampling, lung trauma repair, and hemostasis. Similarly, determining the endpoint for intersegmental marking time can be challenging, particularly with the modified inflation-deflation method. Instead, we selected segmental resection time as our comparison index since it is less influenced by the aforementioned and other external factors and can provide more relevant results.

Based on the study results, there was no statistically significant difference in any of the outcomes between the fluorescence and modified inflation-deflation methods in the simple segmentectomy group. This included segmental resection time, where the fluorescence method did not demonstrate an advantage. We hypothesize that this is due to the low anatomical complexity of the lung segment and the lower likelihood of arteriovenous and bronchial variants encountered during simple segmentectomy. The modified inflation-deflation technique likely resulted in faster lung deflation and greater operator familiarity with the plane of simple lung segments. This might have caused the surgeons to proceed with resecting the target segments before the surrounding segments were fully deflated, leading to shorter but statistically non-significant differences in resection times compared to the fluorescence method.

In the complex segmentectomy group, the fluorescence method (69.37±28.22 min) was associated with significantly shorter segmental resection time compared to the modified inflation-deflation technique (78.80±34.66 min, P=0.03). Considering the increased variance and irregularity of ISPs in complex lung segments, complete inflation and deflation is required to clearly delineate ISP when using this method. Among the 110 matched patients who underwent the modified inflation-deflation method, 17 patients with an inflation-deflation time exceeding 20 min still did not present a fully visible ISP. This may be attributed to emphysema or collateral ventilation between adjacent lung segments. In contrast, among the 110 matched patients who underwent fluorescence imaging, ICG revealed significantly enlarged ISP in five cases of RS1 resection, one case of RS2 resection, and one case of RS3 resection compared to experience-based observations. However, ISP revealed by ICG was found to be significantly reduced in three cases of LS1+2 resection. This discrepancy could be attributed to variations in right and left upper pulmonary arteries that were not detectable by preoperative 3D imaging techniques and incomplete intraoperative dissection.

The findings of our study also revealed that the fluorescence method resulted in significantly less intraoperative blood loss (17.00±8.84 mL) compared to the modified inflation-deflation method (20.64±16.83 mL, P=0.046). This suggests that during the complex procedure of modified inflation-deflation, there may be increased blood and interstitial fluid leakage due to arteriovenous stump and lung wound, as well as the release of inflammatory factors such as prostaglandins and cytokines during the prolonged operation time and lung inflation-deflation process, leading to systemic inflammatory response, pain, or hyperalgesia. This also could explain why the modified method yielded a higher VAS on the first postoperative day (3.05±0.31) compared to the fluorescence method (2.92±0.36, P=0.006). It is worth noting that, while these differences were statistically significant, they may have not necessarily translated into clinically meaningful improvements for all patients. The statistically significant but small reduction in blood loss and pain scores, although beneficial, may not substantially impact the overall clinical outcomes in every case.

For operations involving resection of lung subsegments or combined segments/subsegments, the fluorescence method seemed to be more accurate and efficient than the modified inflation-deflation technique. Due to the small number of lung subsegments or combined segments/subsegments cases, we did not conduct further comparative analysis, and only drew the above conclusion from the intuitive experience of these senior surgeons participating in this study. Indeed, the fluorescence method provides enhanced visualization that allows clear and immediate delineation of these complex borders, minimizing the risk of damage to adjacent healthy lung tissue. Additionally, this method reduces the likelihood of incomplete deflation, a common issue in the inflation-deflation technique, especially in subsegmental resections.

Other postoperative outcomes, including chest tube drainage and duration, complication rate, and length of hospitalization, showed no statistically significant differences between the fluorescence and the modified inflation-deflation methods in both the simple and complex segmentectomy groups. The three most common postoperative complications for the fluorescence and modified inflation-deflation methods were air leaks (n=14 and n=13, respectively), large fluid drainage (n=5 and n=14, respectively), and pneumonia (n=11 and n=5, respectively). Not only in the overall complications, but also in the individual complications, there was no significant difference between patients by the two methods in respective subgroups. In particular, the overall incidence of postoperative pneumonia appeared to be higher in the fluorescence subgroup (6.29%, 6+5/65+110) than in the modified inflation-deflation subgroup (2.86%, 2+3/65+110), but there was no statistically significant difference (χ^2 test value =2.358, P=0.13). Regarding massive postoperative drainage, the total postoperative incidence of 2.86% (2+3/65+110) in the fluorescence subgroup seemed to be lower than that of 8.00% (7+7/65+110) by the modified inflation-deflation subgroup, with statistically significant differences observed (χ^2 test value =4.508, P=0.03<0.05). Although such statistical analysis might be confused by surgical complexity assessment, resulting in unconvincing results, however, they did suggest potential advantages of using fluorescent techniques for reducing postoperative complications. Luckily, none of these complications were severe, and all patients with complications were discharged after extended hospitalization for symptomatic treatment. These findings indicate that the fluorescence method is comparable to the modified inflation-deflation technique in terms of safety. This finding is consistent with the results of another study (13).

An important consideration when adopting surgical technologies is cost-effectiveness, especially in healthcare settings with limited resources. Although a formal economic evaluation of the compared methods was outside the scope of this study, it is worth noting that there was no significant increase in the total cost of hospitalization with the fluorescence method in either groups [Chinese Yuan (CNY) ¥42,965.74±¥5,043.28 *vs.* ¥43,850.36±¥6,922.78, for the fluorescence and modified inflation-deflation methods, respectively, in the simple segmentectomy groups, P=0.41; CNY ¥43,997.20±¥8,192.24 *vs.* ¥44,192.39±¥6,054.58, for the fluorescence and modified inflation-deflation methods, respectively, in the complex segmentectomy groups, P=0.84]. Therefore, the fluorescence method does not impose a greater financial burden on patients and healthcare systems.

During long-term follow-up of approximately 90% of patients, no disease recurrence or cancer-related mortality was recorded. This demonstrates the sound oncological outcomes conferred by both the fluorescence and modified inflation-deflation methods, which ensured adequate resection margins. However, a small number of patients experienced long-term complications, such as chest discomfort/dyspnea and recurrent cough. These complications did not exhibit distinct associations with either method; rather, they were closely related to the extent of surgical resection and postoperative respiratory function recovery.

In a study by Liu *et al.* (14) comparing the near-infrared fluorescence method with the inflation-deflation method in segmentectomy for patients with chronic lung diseases, several advantages were observed including reduced operation time, improved clarity of ISPs, shorter chest tube drainage duration and length of hospital stay after surgery, as well as decreased incidence of prolonged air leak. However, it should be noted that because the patient population studied consisted of elderly individuals with chronic lung diseases, the benefit of near-infrared fluorescence over the inflation-deflation method have been accentuated in their study (e.g., in terms of chest tube drainage duration and length of hospital stay). One limitation of Liu's study was its small sample size and short follow-up period. In contrast, our multicenter study encompassed a larger sample size and broader range of indications within the study population. We also considered additional confounding factors to minimize statistical bias and conducted a longer follow-up observation period. Despite these differences, our results were overall fairly similar to Liu's findings, further highlighting the advantages of utilizing the fluorescence method.

Some limitations of this study should be acknowledged. First, the retrospective design of the study may introduce selection bias and limit the ability to establish causality. Furthermore, although we employed a multicenter design and used PSM to balance the baseline characteristics of complex segmentectomy patients and reduce confounding factors, certain data were not collected or compared. These include postoperative lung function tests, perioperative inflammatory markers, management measures for postoperative complications, and whether the techniques of ISP dissection were equivalent in the subgroups. Additionally, some patients were lost to follow-up, mainly due to changes in contact information, potentially resulting in missing adverse events related to either method. There has been an analysis of 5-year disease-free survival rate and risk factors of worse oncological in the study of simple and complex thoracoscopic segmentectomies for NSCLC (30), but our study was lacking in this regard. Future studies should aim to prospectively compare methods for identifying ISPs during segmentectomy, with long-term patient follow-up to better evaluate oncologic outcomes and late complications.

Conclusions

This multicenter retrospective study revealed no significant differences in short- and long-term outcomes between patients undergoing single-port thoracoscopic simple segmentectomy using the ICG fluorescence method *vs.* the modified inflation-deflation method. However, for complex segmentectomies, the fluorescence method demonstrated advantages in lung segmental resection time, intraoperative blood loss, and postoperative pain without compromising other perioperative or oncologic outcomes. These findings confirm the safety and effectiveness of systemic ICG injection for performing single-port thoracoscopic anatomical segmentectomy and support its application as the method of choice in complex cases.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-986/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-986/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-986/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-986/coif). B.H.O. reports honoraria from AstraZeneca, Bristol-Myers Squibb, Medtronic, MSD and Roche, and meeting support from MSD, outside the submitted work. The other 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). The study was approved by the Institutional Review Board of the leading institution Anhui Chest Hospital, Anhui, China (No. KJ2024-039) and informed consent was taken from all the patients. All participating hospitals/institutes were informed and agreed with the study.

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(English Language Editor: J. Gray)

Cite this article as: Wu F, Tao X, Wang A, Ge Q, Lampridis S, Maurizi G, Bongiolatti S, Ong BH, Ma D, Wang B. Contribution of fluorescence imaging to thoracoscopic anatomical segmentectomy: a multicenter propensity matching analysis. J Thorac Dis 2024;16(8):5299-5313. doi: 10.21037/jtd-24-986

