

# Thoracoscopic minimally invasive surgery for non-small cell lung cancer in patients with chronic obstructive pulmonary disease

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## ABSTRACT

**Objective:** To determine the incidence of peri-operative complications in non-small cell lung cancer (NSCLC) patients with co-existent chronic obstructive pulmonary disease (COPD) who undergo lung resection via traditional and minimally invasive techniques.

**Methods:** A retrospective analysis was conducted of 152 NSCLC patients with COPD who underwent thoracoscopic minimally invasive surgery. Particular attention is given to the relationship between disease severity or surgical approach and the incidence of complications.

**Results:** The prevalence of respiratory and cardiac complications was significantly higher in patients with severe/extremely severe COPD than those with mild to moderate COPD (respiratory complications: 37.3% vs. 20.4%,  $P=0.022$ ; cardiac complications: 16.9% vs. 6.5%,  $P=0.040$ ). Patients who underwent complete-video assisted thoracoscopic surgery (c-VATS) had a significantly lower overall morbidity of adverse reactions than those who had undergone VATS major resection (26.3% vs. 42.1%,  $P=0.044$ ). Among patients with severe/extremely severe COPD, there was no significant difference in the incidence of any complication between the lobectomy group and wedge resection group (38.8% vs. 70.0%,  $P=0.072$ ). Overall, the occurrence of adverse reactions was significantly lower in patients who underwent c-VATS than in those who had undergone VATS major resection surgery (34.2% vs. 61.9%,  $P=0.038$ ).

**Conclusions:** VATS techniques are suitable for COPD patients and are demonstrated here to lower the incidence of post-operative complications when compared with more invasive approaches.

## KEY WORDS

Non-small-cell lung cancer (NSCLC); chronic obstructive pulmonary disease (COPD); video-assisted thoracic surgery (VATS); thoracic surgery

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## Introduction

Lung cancer has been one of the leading causes of death in patients with chronic obstructive pulmonary disease (COPD). In the United States, the incidence of lung cancer in patients with COPD (16.7/1,000 person-years) is much higher than reported in the general population (76.4/1,000,000 in men

and 52.7/1,000,000 in women) (1). Whilst surgical resection remains the treatment of choice for patients with non-small cell lung cancer (NSCLC) and co-existing COPD, reduced lung function and poor respiratory reserve make these patients higher risk for surgery. Traditionally, this has resulted in thoracic surgeons adopting a more conservative approach in this patient group, a consequence of which is relatively strict selection criteria for surgical intervention (2). However, recent advances in the field of thoracic surgery, in particular video-assisted thoracic surgery (VATS), have led to a recent decline in the morbidity and mortality associated with surgery in NSCLC patients in comparison to ten years ago (3,4). There is an increasing body of evidence to suggest that surgery can be performed safely in individuals with both COPD and NSCLC, with emphasis on the need to revise the current selection criteria for these patients (5-7). The aim of this study was to determine whether minimally invasive techniques are beneficial for patients with NSCLC and co-existing COPD.

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**Table 1.** General data of the enrolled patients.

	No. (%)
Total	152
Age (years)	
<68 years	70
≥68 years	82
Mean (± S.D.)	66.6±8.04
Gender	
Men	140
Women	12
Histological type	
Squamous cell carcinoma	63
Adenocarcinoma	74
Other types	
Adenosquamous carcinoma	4
Large cell carcinoma	4
Bronchioloalveolar carcinoma	4
Pleomorphic carcinoma	3
TMN stage	
I	69
II	52
III	31
Surgical procedures	
VATS major resection	57
c-VATS	95
Resection	
Lobectomy	142
Wedge resection	10

## Patients and methods

### Patients

Between March 2000 and September 2010, 152 NSCLC patients with a diagnosis of COPD, in accordance with the Global Guidelines for the Diagnosis and Treatment of COPD (8), were enrolled in the study. Those enrolled included 55 cases of mild COPD [forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ≤70%, FEV1 ≥80% predicted], 38 cases of moderate COPD (FEV1/FVC ≤70%, 50% ≤ FEV1 <80% predicted), 46 cases of severe COPD (FEV1/FVC ≤70%, 30% ≤ FEV1 <50% predicted) and 13 cases of extremely severe COPD (FEV1/FVC ≤70%, FEV1 <30% predicted). All tumors were deemed operable based on anatomical location and staging as defined by the Union for International Cancer Control (UICC) guidelines 2007 [1]. Of the 152 patients with NSCLC Sixty-

two cases were stage I, fifty-nine were stage II with the remaining thirty-one stage IIIA. There were no patients with significant contraindications of cardiovascular, digestive, urinary, endocrine or other systemic disease. The same surgical team performed the operations, and all cases were divided in two groups with randomly: 57 patients underwent VATS major resection (VATS major resection, approach that used both direct vision and television monitor visualization) whilst the remaining 95 underwent c-VATS (complete VATS) (Table 1).

All patients received standardized COPD treatment for a minimum of one week, which included pharmaceutical therapy and chest physiotherapy to improve lung function. Intubation via a double-lumen endotracheal tube was used for all patients. Wedge resection was performed in 10 patients with severe/extremely severe COPD whilst the remaining 142 patients underwent standard lobectomy and lymphadenectomy. Patients were postoperatively managed with antibiotics, bronchial relaxation, spasmolytics, phlegm reduction techniques, oxygen therapy and physical expectoration. Patients with poor expectoration were managed with bronchoscopic suctioning, and those who experienced respiratory failure were treated with mechanical ventilation.

### Data collection

Preoperative pulmonary function testing, 6-minute walk tests, operation duration and postoperative respiratory complications (lung infections, air leakage, bronchospasm, respiratory function failure, mechanical ventilation and atelectasis) were recorded. Data was also collected regarding cardiac complications (myocardial infarction and arrhythmia), number of deaths, indwelling chest tube duration and length of hospital stay. A repeat 6-minute walk test was conducted four weeks following surgery.

### Statistical analysis

Postoperative complications were compared using paired t-test, and count data were compared using the chi-square test and Fisher exact test in the SPSS13.0. P-values of less than 0.05 were considered to be significant.

## Results

Postoperative pulmonary air leak was reported in twenty patients and managed with a prolonged (>14 days) indwelling chest tube, suction (where appropriate) and supportive treatment. Twenty-one patients experienced bronchospasm, which was treated with spasmolytic agents. Six patients were documented as having respiratory failure, hypoxia and carbon dioxide retention. Four of the six still required mechanical ventilation after symptomatic treatment. Two of these patients were discharged after removal

**Table 2.** Postoperative complications in the subjects.

Complication	n	%
Any complication	49	32.24
Any respiratory complication	41	26.97
Atelectasis	3	0.66
Pulmonary infection	9	5.92
Pulmonary air leak	20	13.16
Respiratory failure	6	3.95
Spasm	21	13.82
Mechanical ventilation	4	1.32
Any cardiac complication	16	10.53
Atrial fibrillation	6	3.95
Atrial flutter	3	1.97
Atrial premature	5	3.29
Ventricular premature	2	1.32
Myocardial infarction	1	0.66
Death	2	1.32

of ventilation (three and six days). The other two patients unfortunately passed away (Table 2).

Stratified analysis revealed significantly higher complication rates (Table 3) in severe/extremely severe COPD patients when compared to the mild to moderate COPD patients ( $P=0.040$ ). The incidence of any complication was significantly lower in the c-VATS groups than the VATS major resection group ( $P=0.044$ ). Additionally, there was a significantly higher incidence of any complication in the lobectomy group than in patients undergoing wedge resection ( $P=0.032$ ).

Patients with mild to moderate COPD had significantly shorter hospital stays than severe/extremely severe COPD patients ( $P=0.005$ ) (Table 4). There was no significant difference in performance pre and post-operatively in the 6 minutes walk tests in the c-VATS group ( $P>0.05$ ). A significantly reduced distance was observed in the VATS major resection group however ( $P<0.05$ ) (Table 5).

The impact of surgical approach and resection extent on postoperative complications for the 59 severe/extremely severe COPD patients is reported in Table 6. Because of the poor lung function, 10 patients underwent a wedge resection considering that they cannot tolerate a lobectomy. A lower incidence of both respiratory and cardiac complications was shown in the c-VATS group compared with the VATS major resection group ( $P<0.05$ ). No difference was found between the lobectomy group and the wedge resection group ( $P>0.05$ ).

## Discussion

The reported benefits of c-VATS over traditional muscle splitting

thoracotomy are many and include a reduction in post-operative pain and complications (9). The minimally invasive nature of the surgery reduces the adverse impact on pulmonary function; a result of limited damage to the chest wall and minimal trauma to the respiratory muscles. Therefore, for lung cancer patients with COPD in whom the risks of surgery are high, thoracoscopic minimally invasive surgery provides a safe alternative to conventional techniques. Even in individuals who can not tolerate radical lobectomy, partial resection via VATS may still be of therapeutic benefit.

In COPD patients who undergo surgery for NSCLC, the most common postoperative complication is parenchymal air leak (10). In the presented study, there was a difference in the morbidity mild to moderate COPD patients and those with severe/extremely severe COPD after surgery (20.4% vs. 37.3%,  $P=0.022$ ), which was mainly attributed to parenchymal air leak (8.6% vs. 20.3%). This is likely attributed to the poor quality of the lung parenchyma and the diminished elastic recoil in emphysema, which, in turn, delays healing of the lung tissue. Other complications between the mild to moderate and severe/extremely severe patients included bronchospasm (8.6% vs. 23.7% respectively), and respiratory dysfunction (2.2% vs. 10.2% respectively). In addition, the rates of cardiac complications differed between the two groups (6.5% vs. 16.9%,  $P=0.040$ ). This could be explained by chronic hypoxia, pulmonary hypertension and associated atrial volume-pressure function disorders in severe COPD patients. These disorders are known to precipitate arrhythmias and other cardiac complications in the presence of increased load in the right cardiopulmonary circulation.

Longer lengths of hospital stay were reported in the severe/extremely severe COPD group ( $16.0\pm 8.8$  vs.  $9.7\pm 4.1$ ,  $P=0.005$ ) as a result of an increase in complication rates. To minimize the effects of these complications, patients were encouraged to expectorate, undergo chest physiotherapy, and therapeutic agents which promote bronchial relaxation were administered during the post-operative period. Fiber-optic bronchoscopy and wound analgesia were also utilised to manage those having difficulty with expectoration. These active interventions are thought to be beneficial in the prevention of post-operative complications.

VATS major resection group and the c-VATS group, and revealed a significant difference (42.1% vs. 26.3%,  $P=0.044$ ). This was particularly evident in patients with severe/extremely severe COPD. In this subpopulation, the frequency of pulmonary and cardiac complications was significantly lower in patients who underwent resection via c-VATS than in the VATS major resection group. These findings reflect the advantages of c-VATS attributed to its minimally invasive nature and are particularly relevant to patients with poor respiratory function as a consequence of severe/extremely severe COPD. It has also been proved that minimally invasive thoracoscopic surgery is reported to have less of an adverse effect to the residual lung function,

**Table 3.** Stratified analysis of complications.

Stratification factors	Total cases	Any complication n (%)	P value	Respiratory complications n (%)	P value	Cardiac complications n (%)	P value	Death (n)
<b>Gender*</b>								
Men	140	44 (31.4)	0.525	37 (26.4)	0.605	15 (10.7)	P=1	2
Women	12	5 (41.7)		4 (33.3)		1 (8.3)		0
<b>Age</b>								
≤68 years	70	21 (30.0)	0.586	16 (22.9)	0.291	8 (11.4)	P=0.738	2
>68 years	82	28 (34.1)		25 (30.5)		8 (9.8)		0
<b>Severity of COPD</b>								
Mild to moderate	93	22 (23.7)	0.004	19 (20.4)	P=0.022	6 (6.5)	0.040	0
Severe/extremely severe	59	27 (45.8)		22 (37.3)		10 (16.9)		2
<b>Pathology</b>								
Squamous cell carcinoma	63	20 (31.7)	0.517	17 (27.0)	0.801	7 (11.1)	0.875	1
Adenocarcinoma	74	26 (35.1)		21 (28.4)		8 (10.8)		1
Others	15	3 (20.0)		3 (20.0)		1 (6.7)		0
<b>T stage</b>								
1	36	16 (44.4)	0.200	12 (33.3)	0.547	5 (13.9)	0.731	0
2	88	25 (28.4)		23 (26.1)		8 (9.1)		1
3	28	8 (28.6)		6 (21.4)		3 (10.7)		1
<b>Clinical classification</b>								
1	69	26 (37.7)	0.416	21 (30.4)	0.656	8 (11.6)	0.926	0
2	52	14 (26.9)		12 (23.1)		5 (9.6)		1
3	31	9 (29.0)		8 (25.8)		3 (9.7)		1
<b>Surgical approach</b>								
c-VATS	95	25 (26.3)	0.044	23 (24.2)	0.322	7 (7.4)	0.101	0
VATS major resection	57	24 (42.1)		18 (31.6)		9 (15.8)		2
<b>Resection</b>								
Lobectomy	142	42 (29.6)	0.011	32 (22.5)	0.064	14 (10.0)	0.284	2
Wedge resection	10	7 (70.0)		5 (50.0)		2 (20.0)		0

\*Fisher exact test. #The number of death was small, and no statistical analysis was performed.

**Table 4.** Influence of the severity of COPD on the surgery.

Severity of COPD	Mild to moderate	Severe/extremely severe	P value
N	93	59	
Surgical duration (min)	256±83.4	211±65.6	0.36
Hospital stay (days)	9.7±4.1	16.0±8.8	0.005
Indwelling chest tube duration (days)	3.6±1.7	6.8±6.5	0.119

whilst conventional thoracotomy is associated with a 30-50% decrease in pulmonary function (11-13).

The incidence of air leak in patients undergoing conventional thoracotomy for NSCLC has previously been reported at 52%

among 21 severe/extremely severe COPD (10). In the current study, only 13.2% of patients in the c-VATS were reported to have a post-operative air leak. This was potentially related to optimization of our surgical technique where division and suture

**Table 5.** Influence of surgical approach on the results of 6-minute walk tests.

Severity of COPD	Mild to moderate		Severe/extremely severe	
	VATS major resection	c-VATS	VATS major resection	c-VATS
Baseline 6MWT (m)	493±71	473±96	335±64	362±41
Post-operative 6MWT (m)	366±45	416±52	294±58	345±48
P value	0.023	0.327	0.038	0.876

**Table 6.** Impact of surgical factors on postoperative complications in patients with severe/extremely severe COPD.

Stratification factors	Total cases	Any complication n (%)		Respiratory complications n (%)		Cardiac complications n (%)	
			P value		P value		P value
<b>Surgical approach</b>							
c-VATS	38	13 (34.2)	0.038	11 (28.9)	0.033	2 (5.3)	0.048
VATS major resection	21	13 (61.9)		12 (57.1)		5 (15.8)	
<b>Resection</b>							
Lobectomy	49	19 (38.8)	0.072	19 (38.8)	0.228	4 (8.1)	0.259
Wedge resection	10	7 (70.0)		5 (50.0)		2 (20.0)	

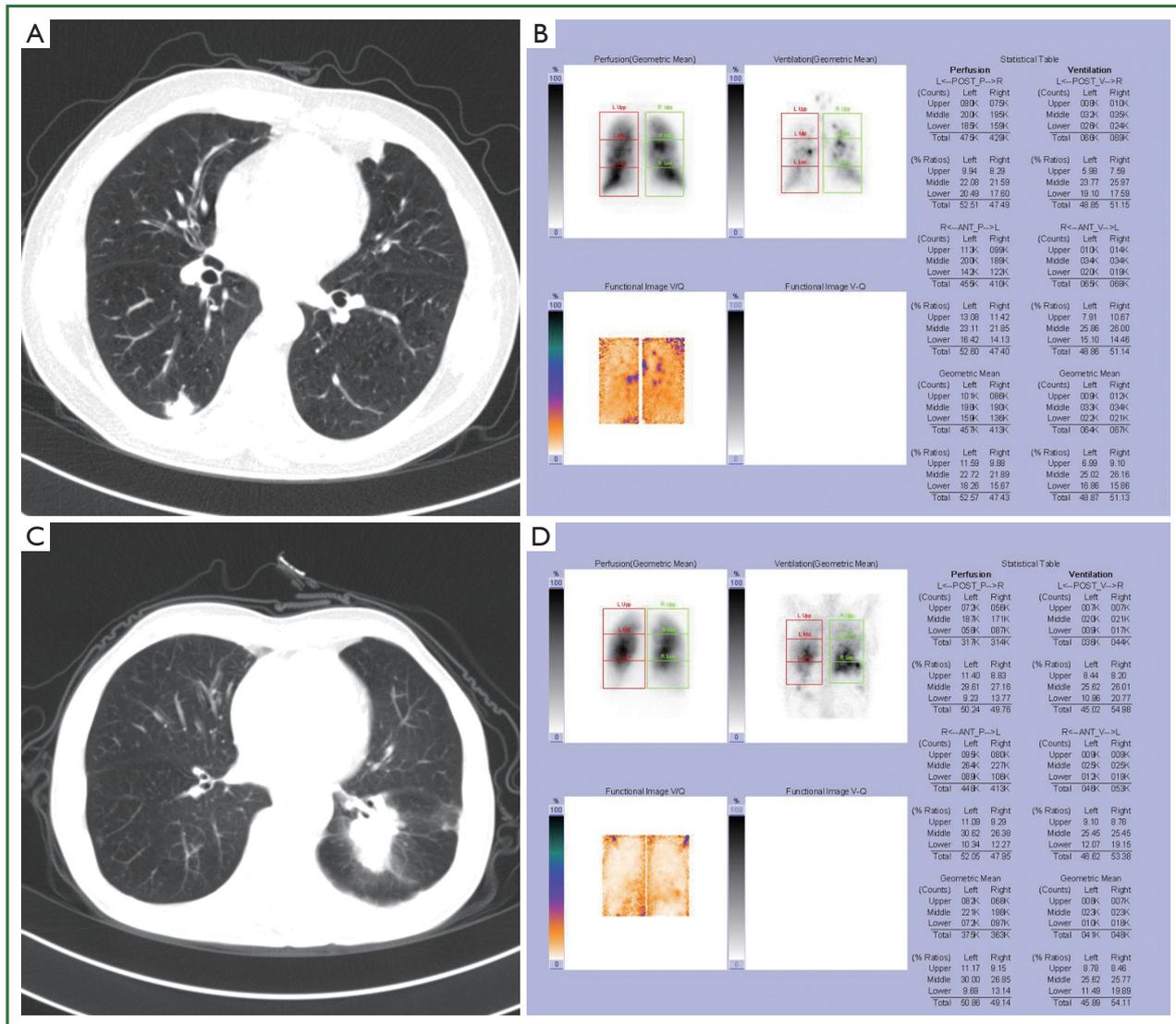
of pulmonary fissures was completed following the natural anatomical plane. Additionally, margins were trimmed in an inverted U-shape when dissecting the upper lung field. Vacuum suction and intensive bronchial relaxation were administered when appropriate, to improve postoperative lung compliance, reduced airway resistance and promote lung expansion. Optimization of post-operative nutrition was also employed to facilitate wound healing and prevent the occurrence of air leakage.

The c-VATS approach was also more efficacious in reducing selective cardiac complications. In the presented study, only 5.3% of the patients with severe/extremely severe COPD in the c-VATS group suffered a cardiac arrhythmia. We have hypothesized that this was related to reduced postoperative pain and improved oxygenation in this subpopulation.

To assess postoperative recovery, quality of life and cardiopulmonary function in our cohort, we performed 6-minute walk tests before and one month after surgery. We found a remarkable decline in performance in the VATS major resection group regardless of COPD severity. On the contrary, no difference was observed in the c-VATS group before and after surgery. We believe that lung volume reduction contributed to this finding. In patients with severe COPD lung volume reduction can improve elastic recoil, reduce resistance to blood flow and blood perfusion is appropriately redistributed with an associated improvement in the ventilation/perfusion ratio. This has the combined effect of raising the oxygenation capacity. This benefit is demonstrated to be particularly evident when the tumor is located in an area severely compromised by COPD (10,14).

Standard radical surgery for NSCLC includes anatomical

lobectomy plus lymph node dissection. It remains controversial however, as to whether patients with severe/extremely severe COPD can tolerate lobectomy. Sufficient residual lung function is a prerequisite for lung surgery, and good postoperative lung function can reduce both the risk of surgery and postoperative complications (15). Previous studies have suggested that eligibility for surgery in this population relies on a predicted FEV1 of not less than 0.8 L after surgery (16). In the general population a preoperative FEV1  $\geq$ 50% or predicted postoperative FEV1 of greater than 40% is generally considered acceptable (17,18). With improved surgical, anesthetic and perioperative care techniques however; the potential for curative surgery in patients with severe pulmonary insufficiency has become a reality. One study of 13 COPD patients undergoing lobectomy with a mean preoperative FEV1 of 49% reported a decline in lung function that was less than expected (19). In another study where radical resection of lung cancer for 29 severe COPD patients was performed, the authors concluded that patients with a predicted postoperative FEV1 of less than 40% could tolerate lobectomy if the tumor was located on the opposite side of emphysema with a perfusion of less than 10% (20). Taking advantage of the protective effects of thoracoscopic minimally invasive techniques, we can further expand the potential for curative surgery in patients with poor lung function. Following consideration of ventilation perfusion imaging, tumor location and size, and tracheal and vascular invasion, patients with preoperative FEV1 of less than 50% can be considered for surgery (Figure 1). These patients can be divided into two categories. The first group includes those who have lost the



**Figure 1.** Surgical options for patients with severe COPD. A,B. A 56-year-old man with longstanding COPD, FEV1 0.68 L, FEV1 35% of predicted, and a nodule of 1.2 cm × 1.0 cm in the right lower lung. Biopsy confirmed “invasive adenocarcinoma”. Considering the right lower field accounted for almost 20% of the overall ventilation function, the epo FEV1/predicted value =25% Preoperative assessment suggested that the patient could not tolerate lobectomy due to the significant impact on his pulmonary function. Therefore, wedge resection of the right lower lung was performed. The patient was safe and stable throughout the perioperative period. C,D. A 58-year-old man with longstanding COPD, FEV1 0.72 L, FEV1 38% of predicted, and an occupying lesion measuring 5 cm × 4.5 cm in the left lower lobe. Bronchoscopy confirmed squamous cell carcinoma. Radical resection of the lower left lung was conducted. The patient was safe and stable throughout the perioperative period.

pulmonary function of the lobe where the tumor is located. This is typically seen in larger lesions that occlude the corresponding bronchi and compress the vessels, resulting in reduced perfusion. These patients may tolerate thoracoscopic resection with a FEV1 of <50% or even <30%, as long as there are no signs of respiratory failure. The second group includes patients who have satisfactory pulmonary function in the lobe, which corresponds to the tumor. In these patients, the postoperative lung function is predicted by formal assessment of lung function (pre-operative

FEV1), heart function, pulmonary ventilation perfusion, chest CT examination, blood gas analysis, and calculation of the estimated postoperative FEV1 (epo FEV1) based on the BTS guidelines (21). With an estimated postoperative FEV1 of ≥35%, normal Ejection Fraction (EF) and PaCO<sub>2</sub> of <50 mmHg, the patients can generally tolerate c-VATS lobectomy. In the case of an estimated postoperative FEV1 <35%, normal EF and PaCO<sub>2</sub> of <50 mmHg, c-VATS partial resection is recommended to preserve postoperative pulmonary function. Surgery is

contraindicated however if PaCO<sub>2</sub> is ≥50 mmHg or contraction dysfunction is present at rest without oxygen administration. In this study, 49 patients (83.1%) successfully tolerated radical resection. This was less well tolerated in the patients with severe/extremely severe COPD. There was no significant difference in the incidence of any complication between those two groups (38.8% vs. 70.0%, P=0.072).

In conclusion, despite high incidence rates of postoperative complications in patients with NSCLC and COPD, VATS-guided approaches are suitable for the majority of patients and can significantly reduce post-operative morbidity. Controversy remains in regard to the selection criteria of patients with COPD for thoracoscopic lobectomy. In this population, radical or partial resection based on comprehensive evaluation can benefit patients with severe/extremely severe COPD and provide therapeutic opportunity for a wider subgroup of lung cancer patients with COPD.

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