Physiologic assessment before video thoracoscopic resection for lung cancer in patients with abnormal pulmonary function

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Background: Impaired respiratory function may prevent curative surgery for patients with non-small cell lung cancer (NSCLC). Video-assisted thoracoscopic surgery (VATS) reduces postoperative morbility-mortality and could change preoperative assessment practices and therapeutic decisions. We evaluated the relation between preoperative pulmonary function tests and the occurrence of postoperative complications after VATS pulmonary resection in patients with abnormal pulmonary function.

Methods: We included 106 consecutive patients with ≤80% predicted value of presurgical expiratory volume in one second (FEV1) and/or diffusing capacity of carbon monoxide (D_LCO) and who underwent VATS pulmonary resection for NSCLC from a prospective surgical database.

Results: Patients (64±9.5 years) had lobectomy (n=91), segmentectomy (n=7), bilobectomy (n=4), or pneumonectomy (n=4). FEV1 and D_LCO preoperative averages were 68%±21% and 60%±18%. Operative mortality was 1.89%. Only FEV1 was predictive of postoperative complications [odds ratio (OR), 0.96; 95% confidence interval (CI), 0.926–0.991, P=0.016], but there was no determinable threshold. Twenty-five patients underwent incremental exercise testing. Desaturations during exercise (OR, 0.462; 95% CI, 0.191–0.878, P=0.039) and heart rate (HR) response (OR, 0.953; 95% CI, 0.895–0.993, P=0.05) were associated with postoperative complications.

Conclusions: FEV1 but not D_LCO was a significant predictor of pulmonary complications after VATS pulmonary resection despite a low rate of severe morbidity. Incremental exercise testing seems more discriminating. Further investigation is required in a larger patient population to change current pre-operative threshold in a new era of minimally invasive surgery.

Keywords: Lung cancer; video-assisted thoracoscopic surgery (VATS); pulmonary function testing; exercise testing; preoperative assessment

Introduction

Preoperative assessment before surgical resection of non-small cell lung cancer (NSCLC) is intended to identify patients with high risk of postoperative complications and to reduce mortality and morbidity. Different algorithms for risk assessment before lung resection have been published (1-4). However, all these algorithms are based on estimations of postoperative morbidity and mortality in conventional thoracotomy. These recommendations do not take into account current data on minimally invasive surgery.

In fact, surgical removal of NSCLC by minimally invasive video thoracoscopy seems particularly suitable for fragile patients (5-7). Scott *et al.* (8) showed in a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial that patients undergoing video-assisted lobectomy had fewer respiratory complications and shorter length of stay versus open lobectomy. In a retrospective study, Garzon *et al.* (6) reported 25 patients with altered function [expiratory volume in one second (FEV1) <0.8 L or <50% of the predicted value]. Thirteen of the 25 patients underwent lobectomy by video-assisted thoracoscopic surgery (VATS). No perioperative deaths were observed and postoperative morbidity was 29%. Moreover, to our knowledge, no study has specifically evaluated the association between the settings provided by cardiopulmonary exercise testing (CPET), other than peak oxygen volume (VO2peak) and the occurrence of postoperative cardiopulmonary complications in a cohort of patients undergoing lung resection by VATS. Given the very poor prognosis of lung cancer in absence of surgical treatment, preoperative evaluation should be optimised in patients with borderline respiratory function in order to provide them with a potentially curative intervention with acceptable risk.

This study aimed to evaluate the relation between preoperative pulmonary function and exercise tests and the occurrence of postoperative complications after VATS pulmonary resection in patients with abnormal pulmonary function. We also attempted to determine predictive FEV1 threshold value complications in VATS.

Methods

Study population

We analysed the clinical and surgical data of all consecutive patients who underwent lung resection surgery by VATS in the Thoracic Surgery department of Rouen University Hospital, France between September 2008 and April 2014 (prospective surgical database declared to the CNIL: the French Data Protection Authority; 1690770 v 0). All patients with the following criteria were included: (I) surgery for NSCLC performed during the study period; and (II) impaired preoperative respiratory function defined by a FEV1, and/or diffusing capacity of carbon monoxide (D_LCO) <80% of the predicted value. Clinical data, surgical data and perioperative outcome were prospectively recorded for each patient by a senior surgeon. Written informed consent was obtained from all patients, and the study was conducted according to the principles of the Declaration of Helsinki.

Pulmonary function tests, calculation of predicted postoperative values and cardiopulmonary exercise testing (CPET)

Spirometry, plethysmography and measurement of D_LCO were carried out according to European standards (Jaeger-Masterlab, Stuttgart, Germany). Forced vital capacity (FVC) and FEV1 were measured. Residual volume (RV), total lung capacity (TLC), D_LCO and transfer coefficient of carbon monoxide (KCO) were calculated. These values were expressed in absolute terms (litres, litres per second) and as a percentage of the theoretical values established for a European population (9).

We calculated predicted postoperative values (ppo), ppoFEV1, ppoD_LCO and ppoVO2peak for segmentectomy and lobectomy using the following formula: ppoFEV1=preoperative FEV1 × [(19– a) – b]/(19– a)] where a and b are the number of unobstructed and obstructed segments to be respectively resected, obstructed segments being identified by bronchoscopy. Patients underwent an incremental exercise test on an electromagnetic cycle ergometer (Ergoline 900, Sensor Medics, Anaheim, CA, USA). Oxygen pulse saturation (SpO2) was measured by a pulse oximeter (type Biox 3700, Ohmeda, Louisville, CO, USA). According to the protocol, patients started with a warm-up period of 3 minutes, and then work rate was increased each minute to obtain a 10-minute exercise duration.

The theoretical maximum heart rate (HR) was calculated from the patient's age according to the equation HRmax theoretical = 210–0.65× age. The maximum work rate corresponded to the highest work rate maintained for 1 minute. The VO2peak corresponded to the value of the

highest VO2 during the test. The theoretical VO2max and the theoretical maximum work rate were calculated from equations including age and sex. Reference values for maximum parameters of CPET were those of the study by Hansen *et al.* (10). Maximality was assessed on physiological and clinical criteria as recommended by the Société de Pneumologie de Langue Française (11).

Surgery by video thoracoscopy

Indication for lung resection and extend of resection was discussed in our multidisciplinary meeting. All stages were accepted for resection. We used VATS mainly in intent to treat with conversion if needed. Bulky or proximal tumour with indication of bronchial or vascular plasty was a relative contra-indication for VATS resection. Pre-operative CT-scan images were analysed and 3D-reconstruction was done for complex resections. Systematic dissection of mediastinal lymph nodes was performed for all tumours and radical for all lesions more than 2 cm. The technique used for VATS major resection was the anterior approach described by Hansen *et al.* (12).

Postoperative events

Operative mortality was calculated taking into account all deaths up to 30 days after the operation or during hospitalisation. Postoperative complications were classified according to Ginsberg (13): (I) major respiratory complications: atelectasis requiring bronchoscopy, pneumonia, respiratory failure, empyema and bronchopleural fistula; (II) minor respiratory complications: atelectasis requiring no fibro-aspiration, prolonged drainage (more than 5 days) and pneumothorax without clinical repercussions; (III) cardiovascular complications: cardiac arrest, myocardial infarction, heart failure, pulmonary embolism, cardiac conduction disorder and atrial fibrillation (AF); and (IV) various complications: postoperative bleeding, chylothorax etc.

Statistical analysis

We first conducted a univariate analysis. Quantitative variables were described by their mean and median. Dispersion was evaluated by standard deviation. Categorical variables were described by their frequency. Means were compared with a two-tailed Student *t*-test and percentages by Chi2 test. A P<0.05 was considered as statistically significant.

The Fisher exact test was used when conditions for applying Chi2 test were not met. To identify independent predictors of postoperative complications, significant variables with P<0.20 in univariate analysis were included in the multivariate analysis. Survival was estimated by Kaplan-Meier method. Significant differences in the probability of survival between strata were assessed by log-rank. A P value less than 0.05 was considered significant. The α risk was controlled by the method of Holm for ANOVA and Tukey HSD for Chi2.

Results

Demographics and clinical data

One hundred and six consecutive patients were included in the study. The average age at diagnosis was 64±9.5 years (range, 43–84 years). There were 87 men (82%). Ninety-seven percent of the patients had a history of smoking (*Table 1*). *Table 2* summarises respiratory and extra-respiratory comorbidities. Eighty-one patients (77%) had chronic obstructive pulmonary disease (COPD). Three patients were treated by long-term oxygen therapy. No COPD patient had FEV1 less than the 30% predicted. Four patients had a history of chest radiation and 10 had previous thoracic surgery including 3 pulmonary resections.

The NSCLC lesion was located in the upper lobes in 61% of cases [right (n=33) and left (n=32)]. Five patients had a lesion involving two lobes. Tumours were classified according to TNM stages (*Table 1*). Ten patients had neoadjuvant therapy: radiotherapy (n=7), chemotherapy (n=2) or concomitant chemoradiotherapy (n=1). Procedures included: lobectomy (n=80), lobectomy associated with wedge resection (n=10) or segmentectomy (n=1), segmentectomy (n=6), bilobectomy (n=4), and pneumonectomy (n=4) or segmentectomy associated with wedge resection (n=1). One hundred and two patients underwent lymphadenectomy: radical dissection for 64 and sampling for 38 patients. The resection margins (R1) were invaded in four patients.

PFT were performed on average 62±57 days (median, 42 days) before surgery. Mean preoperative FEV1 and D_LCO were 68%±21% and 60%±18% respectively. Data on preoperative PFT are presented in *Table 3*.

Short-term surgery outcomes

The average operation time was 175±54 minutes (range, 63–330 min). Sixteen intraoperative complications (15%)

Table 1 Demographics and clinical data of the 106 patients included

Variable	Outcome
Age, years	64±9.5
Male/female	87/19
Current/ex/never-smokers	33/59/14
BMI, kg/m²	25.5±5
Score of Charlson comorbidity index	4±1
Score of Charlson modified	6±2
Anaesthetic risk score: 1/2/3/4	6/37/61/2
Performance status: 0/1/2/3/4	0/49/28/8/0
Additional treatment (n): neoadjuvant therapy/adjuvant therapy	
Radiotherapy	7/26
Chemotherapy	2/3
Concomitant chemoradiotherapy	1/3
VATS operations	106
Lobectomy	80
Right upper/middle/lower lobe	33/4/24
Left upper/lower lobe	32/8
Bilobectomy	4
Lobectomy with: wedge/segmentectomy	10/1
Segmentectomy	6
Right/left pneumonectomy	2/2
Segmentectomy with wedge	1
Mean operative time, minutes	175±54
Histology	
Adenocarcinoma	69
Squamous cell carcinoma	30
undifferentiated carcinoma	4
Bronchioloalveolar carcinoma	2
Lymphoepithelioma like carcinoma	1
Pathologic staging (TNM): preoperative/postoperative	
IA	50 (47%)/37 (35%)
IB	18 (17%)/23 (21%)
IIA	10 (9%)/7 (7%)
IIB	6 (6%)/11 (10%)
IIIA	17 (16%)/22 (21%)
IIIB	0/1 (1%)
IV	5 (5%)/5 (5%)

Data expressed as n or n (%). BMI, body mass index; VATS, video-assisted thoracoscopic surgery; TNM, tumor-node-metastasis.

Table 2 Respiratory and extra-respiratory comorbidity of the 106 patients included in the study

Comorbidity	Number
Respiratory (n=154)	COPD (n=78): Gold 1 (n=11), Gold 2 (n=56), Gold 3 (n=8), Gold 4 (n=3)
	Emphysema (n=72)
	Obstructive sleep apnea (n=4)
Cardiac (n=37)	Ischaemic heart disease (n=18)
	Atrial fibrillation or flutter (n=12)
	Left heart failure (n=5)
	Pulmonary arterial hypertension (n=2)
Vascular (n=92)	Arterial hypertension (n=39)
	Peripheral vascular disease (n=29)
	Aneurysm of the abdominal aorta (n=11)
	Carotid stenosis (n=7)
	Stroke (n=6)
Other comorbidities (n=96)	History of chronic alcoholism (n=27)
	Dyslipidemia (n=26)
	Diabetes (n=16)
	HIV (n=2)
	System disease (n=4)
	History of solid cancer (n=17)
	Previous haematologic malignancy (n=3)
	Kidney transplantation (n=1)

COPD, chronic obstructive pulmonary disease; Gold, global initiative for obstructive lung disease classification for severity of COPD; HIV, human immunodeficiency virus.

were identified. No deaths were noted. The most frequently observed complication was intraoperative vascular tear (n=10). The overall conversion rate to thoracotomy was 17%. Mean and median drainage times were 5±3 days (range, 1–5 days) and 4 days respectively. Five patients required revision surgery: one lobectomy for necrotizing infectious pneumonitis, three re-drainages (two for prolonged bubbling and one for empyema) and one bubble resection with talc pleurodesis. Median hospital stay was 7 days (range, 1–67 days).

Thirty-seven patients had at least one postoperative complication. Overall morbidity was 34.9%. The number of complications was 0.6 per patient. Postoperative

Table 3 Preoperative pulmonary function tests of the 106 patients included

Variables	N=106	Min–max
FEV1 (L)	2.05±0.73	0.78–4.29
FEV1 (%)	68±21	33–130
FVC (%)	89±17	51–137
FEV1/FVC (%)	60±12	33–84
TLC (%)	110±23	65–158
RV (%)	153±50	59–292
D_LCO (%)	60±18	24–131
KCO (%)	68±18	30–105

Data expressed as mean ± SD. FEV1, expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; D_LCO, diffusing capacity of carbon monoxide; KCO, transfer coefficient of carbon monoxide.

Table 4 Postoperative complications

Complications	Number
Respiratory complications (n=43)	
Major respiratory complications (n=22)	Pneumonia (n=14)
	Atelectasis requiring fibro-suction (n=3)
	Acute respiratory distress (n=2)
	Bronchopleural fistula (n=2)
	Empyema (n=1)
Minor respiratory complications (n=21)	Prolonged air leak (n=14)
	Atelectasis not requiring fibro-suction (n=2)
	Pneumothorax (n=5)
Cardiovascular complications (n=10)	Myocardial infarction (n=1)
	Acute pulmonary embolism (n=1)
	Myocardial injury (n=1)
	Acute pulmonary oedema (n=4)
	Atrial fibrillation (n=4)
Other complications (n=7)	Dysphonia (n=2)
	Diaphragmatic paralysis (n=1)
	Megacolon requiring colorectal exsuflation (n=1)
	Urinary infection (n=1)
	Acute urinary retention (n=1)
	Confusion (n=1)

complications are summarized in *Table 4*. Operative mortality from all resections was 1.9%, two deaths occurred within 30 days following surgery. The first death was due to a cardiac arrest on myocardial infarction in a patient who had undergone left upper lobectomy and the second to a massive pulmonary embolism, on day 5 after right upper lobectomy.

Prognosis factors for outcomes

In univariate analysis, FEV1, expressed as a percentage of the predicted value, was associated with major postoperative respiratory complications (mean FEV1 equal to 59% in presence of complications *vs.* 70% in absence of complications; P=0.03). *Figure 1A* represents the predicted probability of major respiratory complications based on preoperative FEV1.

FEV1, expressed in absolute values, did not differ significantly according to the occurrence or non-occurrence of complications (1.74 *vs.* 2.12 L; P=0.06).

Contrary to FEV1, D_LCO was not related to major pulmonary complications (*Figure 1B*). In fact, mean D_LCO was 57% and 61% respectively in the groups of patients presenting and not presenting major pulmonary complications (P=0.41).

ppo values were calculated for 89 patients (84%) for lobectomy and segmentectomy. ppoFEV1 (L), ppoFEV1 (%) and ppoD_LCO (%) were respectively 1.65±0.58 L

(range, 0.57–3.02 L), 55%±17% (range, 31–116%) and 49%±15% (range, 20–97%). ppoFEV1 (L) and ppoFEV1 (%) were associated with major pulmonary complications. As with preoperative D_LCO, ppoD_LCO was not associated with postoperative morbidity.

Four predictive parameters were identified by multivariate analysis (*Table 5*). The most accurate logistic regression model performed best with the most contrasting odds ratio (OR) (4.16 and 0.96) and included a pulmonary function parameter FEV1. It was independently associated with major postoperative respiratory complications. OR are summarised in *Table 5*. Morbidity was less common when FEV1 was higher. However, the area under the ROC curve was 0.72, indicating average discrimination ability. We were unable to determine the FEV1 threshold that allowed staging of patients. Indeed, whatever the chosen FEV1 value, the capacity (sensitivity, specificity and Youden index) of FEV1
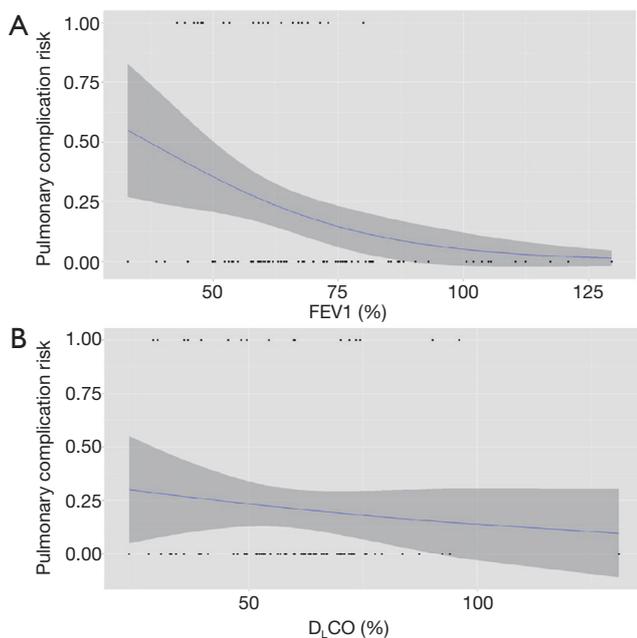
Figure 1 Predicted probability of major postoperative pulmonary complications according to preoperative FEV1 (A) or D_LCO (B). The regression line shows the predicted probability of major pulmonary complications in terms of FEV1 (A) or D_LCO (B). The shading around the regression line represents the limits of the confidence interval of 95 percent. The points at the top and bottom of the figure correspond to the actual occurrence observed (top of the regression line) or absence of occurrence (bottom of the regression line) of pulmonary complications and measurement of FEV1 (A) or D_LCO (B), for each patient in the study. FEV1, expiratory volume in one second; D_LCO, diffusing capacity of carbon monoxide.

Table 5 Parameters associated with the occurrence of major postoperative pulmonary complications by logistic regression method (multivariate analysis)

Variables	OR	95% CI	P
FEV1 (%)	0.96	0.93–0.99	0.016
Age	1.10	1.03–1.18	0.01
History of alcoholism	4.16	1.31–14.22	0.017
Dyslipidemia	3.84	1.23–12.67	0.022

OR, odds ratio; CI, confidence interval; FEV1, expiratory volume in one second.

Table 6 CPET data according to the occurrence or non-occurrence of postoperative cardiopulmonary complications

Variables	No postoperative complications (n=17)	Postoperative complications (n=8)	P
Work rate peak (watt)	82±39	81±15	0.46
Work rate peak (%)	72±16	59±12	0.05
VO2vt (mL/kg/min)	11.2±4.0	11.3±3.0	0.98
VO2vt/VO2max (%)	51.3±12.5	45.7±9.4	0.14
VO2peak (mL/kg/min)	16.4±5.9	16.2±4.5	0.90
VO2peak (%)	74±15	65±14	0.10
VE/VCO2 slope	31.5±6.8	38.4±10.3	0.32
VR (%)	16±13	14±13	0.62
Delta SpO2 (%)	2±2	4±3	0.05
HRmax (%)	82±9	74±18	0.41
HRR	71±31	44±19	0.049
Circulatory power peak (mmHg × mL/kg/min)	3,611±1,276	2,122±1,060	0.08

Data expressed as mean ± SD. CPET, cardiopulmonary exercise testing; VO2, oxygen consumption; vt, ventilatory threshold; VE, total ventilation; VE/VCO2, respiratory carbon dioxide equivalent; VR, ventilatory reserve; Delta SpO2 saturation transcutaneous oxygen (at peak exercise-rest); HR, heart rate; HRR, heart rate response [(HRpeak − HR at rest)/(VO2peak − VO2rest)].

to identify patients at risk of major respiratory complications remained identical.

Cardiopulmonary exercise testing (CPET)

Twenty-five patients (24%) performed incremental CPET, on average 39±18 days before surgery. Mean FEV1 and mean D_LCO were respectively 60%±14% and 54%±17%. The 25 tests conducted responded to maximum criteria. Six patients were treated with beta blockers, two patients in the group with complications and five in the group without postoperative complications. The patients presenting postoperative cardiovascular complications (n=8) were compared to patients not presenting complications (n=17) (*Table 6*). The aerobic work rate at peak exercise was

significantly lower in the group with complications (59% *vs.* 72%, P=0.05). VO2peak tended to be lower in the group with complications (65% *vs.* 74%; P=0.14). Desaturation

during exercise [OR, 0.462; 95% confidence interval (CI), 0.191–0.878, P=0.039] and heart rate response (HRR) (OR, 0.953; 95% CI, 0.895–0.993, P=0.05) were associated with postoperative complications.

Discussion

We found that FEV1 was independently correlated with postoperative pulmonary complications in major pulmonary resection by VATS, unlike D_LCO. However, we were not able to determine a consistent FEV1 threshold above which the risk of postoperative morbidity was lower, partly due to a weak association between FEV1 and postoperative pulmonary complications. We found that ppoFEV1 was associated with major postoperative pulmonary complications, unlike ppoD_LCO, but its value did not exceed FEV1 in terms of predictability of postoperative morbidity. Desaturation during exercise and HRR were associated with the occurrence of postoperative cardiopulmonary complications.

Our finding that D_LCO was not predictive of postoperative pulmonary complications was similar to that of Berry *et al*. (14). Indeed the latter determined the impact of preoperative pulmonary function on postoperative morbidity after VATS lobectomy in a retrospective analysis of 340 patients with pre-lobectomy FEV1 and/or D_LCO below or equal to 60%. The authors found that FEV1 and D_LCO were predictive of pulmonary complications when lobectomy was performed by thoracotomy but not by VATS. Other studies have shown similar results and did not report FEV1 and D_LCO as independent predictors of postoperative pulmonary complications (15,16).

We choice cut-off of 80% because current recommendations give a threshold of 80% for FEV1 and D_LCO, below which the risk of postoperative complications is high thereby justifying further explorations. Licker *et al*. (17) found that the best FEV1 threshold value for predicting respiratory complications was 60% in patients undergoing thoracotomy. In the study by Win *et al*. (18), the authors showed that FEV1 threshold may be lower (45–50% predicted). The literature also suggests that patients with poor respiratory function have perioperative outcomes similar to those with normal lung function when lung resection was performed by VATS (19-21). In view of data in the literature and the results of this work, the FEV1 threshold below which further explorations are indicated could probably be lowered.

VO2peak was lower in patients with postoperative cardiopulmonary complications but not significantly. This result is probably due to a lack of power. Indeed, many studies have shown that VO2max strongly correlated with postoperative morbidity and mortality (22,23). Desaturation during exercise was associated with the occurrence of postoperative cardiopulmonary complications as has already been shown for thoracotomy (24-26).

To date, no study has evaluated CPET parameters other than VO2max in patients operated by VATS lung resection. HRR was significantly higher for patients who presented postoperative cardiovascular complications. HRR corresponded to myocardial consumption of oxygen. Its elevation beyond 50 reflects the probable existence of a cardiomyopathy. This result highlights the importance of cardiac evaluation in preoperative assessment. HRR seems to be a promising prognostic marker of cardiopulmonary morbidity after lung resection.

The operative mortality in our study was 1.9%, which was similar to that reported in other series with mortality rates ranging from 0.6% to 5%. Morbidity was 34.9% and conversion rate 17% in our cohort which may seem high compared to current data in the literature (10% to 30%) (27-30), but the functional parameters of our study population were lower and we included patients who underwent supra-lobar lung resections.

Our study has limitations due primarily to its retrospective nature, but data collection was prospective, which implies no loss of information. Furthermore, we included all types of lung resection in our study population. Nevertheless, it comprised a majority of lobectomies and at least 1 segmentectomy. Finally, only 25 CPETs were performed in our cohort resulting in a lack of power.

In conclusion, FEV1 but not D_LCO was a significant predictor of pulmonary complications after VATS pulmonary resection for lung cancer in patients with abnormal pulmonary function. However FEV1 have little ability to predict pulmonary complications. CPET seems more discriminating, but a larger population of patients is necessary to support this hypothesis. Our results question the current decision-making algorithms and the necessity to validate in studies that take into account advances in thoracic surgery.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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