ORIGINAL ARTICLE

MAJOR PULMONARY SURGERY IN PATIENTS WITH COMPROMISED LUNG FUNCTION

Rita Gonçalves Pereira[1,2*], Joana Branco [1,3], Filipa Narciso Rocha [1,4], Catarina Figueiredo [1], Ana Rita Costa [1], João Santos Silva[1], João Eurico Reis[1], Paulo Calvinho [1]

[1] Thoracic Surgery Unit of the Department of Cardiothoracic Surgery, Centro Hospitalar Lisboa Central
[2] Department of General Surgery, Centro Hospitalar Barreiro-Montijo
[3] Department of Pneumology, Hospital Beatriz Ângelo
[4] Department of General Surgery, Unidade Local de Saúde do Baixo Alentejo

* **Corresponding author:** ritapereira.autor@gmail.com

Abstract

Introduction: *The risk stratification of lung resection is fundamentally based on the results of pulmonary function tests. In patients considered to be at risk, major surgery is generally denied, opting for potentially less curative therapies.*

Objective: *To evaluate the postoperative outcomes of major lung surgery in a group of patients deemed high risk.*

Methods: *We performed a retrospective review of clinical records of all patients submitted to lobectomy, bilobectomy or pneumonectomy in a 3-year period in a reference Thoracic Surgery Unit. The patients were then divided in two groups: group A composed of patients with normal preoperative pulmonary function and group B which included patients with impaired lung function, defined as FEV1 and/or DLCO ≤60%.*

Results: *A total of 234 patients were included, 181 (77.4%) in group A and 53 (22.6%) in group B. In group B, patients had more smoking habits, were more often associated with chronic obstructive pulmonary disease and were also more frequently submitted to thoracotomy. When surgery was motivated by primary lung cancer this group had a more advanced clinical stage of the disease. In the postoperative period, these patients had longer hospital stay, longer chest drainage time and greater need for oxygen therapy at home, however, no statistically significant difference was noted in morbidity or mortality.*

Conclusions: *Major thoracic surgery can be safely performed in selected patients considered to be high risk for resection by pulmonary function tests. A potentially curative surgery should not be denied based on respiratory function tests alone.*

Keywords: *respiratory function tests, thoracic surgery, forced expiratory volume, carbon monoxide, risk assessment, lobectomy, pneumonectomy*

INTRODUCTION

Surgical risk stratification complies the analysis of a multiplicity of variables in order to establish the relative risk of the procedure towards its benefits.

Risk stratification of anatomic lung resection is fundamentally based on the results of pulmonary function tests. Forced expiratory volume in the first second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) are the parameters that correlate most accurately with postoperative morbidity and mortality[1-4].

Patients defined as high operative risk by pulmonary function tests are often denied lobectomy and offered less invasive alternative therapies, but also potentially less curative such as sublobar resection or stereotactic body radiotherapy in patients with lung cancer or even conservative therapy in patients with benign disease [5,6].

OBJECTIVES

The aim of this study was to evaluate the postoperative outcomes of major lung surgery (lobectomy, bilobectomy or pneumonectomy) in patients considered to be at high risk according to pulmonary function tests, based on preoperative FEV1 and/or preoperative DLCO less than or equal to 60%.

MATERIALS AND METHODS

Patient population and methods

We performed a retrospective review of clinical records of all patients submitted to lobectomy, bilobectomy or pneumonectomy over a period of three consecutive years (between June 1, 2017 and May 31, 2020) in a Thoracic Surgery reference unit (Centro Hospitalar Lisboa Central). Then, patients were divided into two groups: group A composed of patients with normal preoperative lung function (FEV1 and DLCO> 60%) and group B which included patients with impaired lung function, defined as FEV1 and/or DLCO% ≤ 60%. The threshold of 60% was chosen based on previous studies that demonstrated that patients with these FEV1 or DLCO values were at increased risk of morbidity and mortality after lung resection [3,7-9]. We excluded patients without reference to FEV1 and DLCO in clinical process or missing follow-up.

The primary endpoints of this study were morbidity and mortality, defined respectively as any complication or death that occurred in the first thirty days after the surgery. The secondary endpoint was to assess patients who required home oxygen therapy after surgery.

The data collected for each patient included: sex, age, number of preoperative functional lung segments, respiratory function tests, pre-existing comorbidities and calculation of the Charlson comorbidity index 10, performance status according to the Eastern Cooperative Oncology Group [11], smoking habits, diagnosis that motivated the surgery, type of surgery performed and surgical approach, clinical and pathological stage in patients diagnosed with primary lung cancer, morbidity and mortality at 30 days of postoperative and respective Clavien-Dindo classification (Table 1)[12], length of hospital stay, chest drainage duration and need for home oxygen therapy.

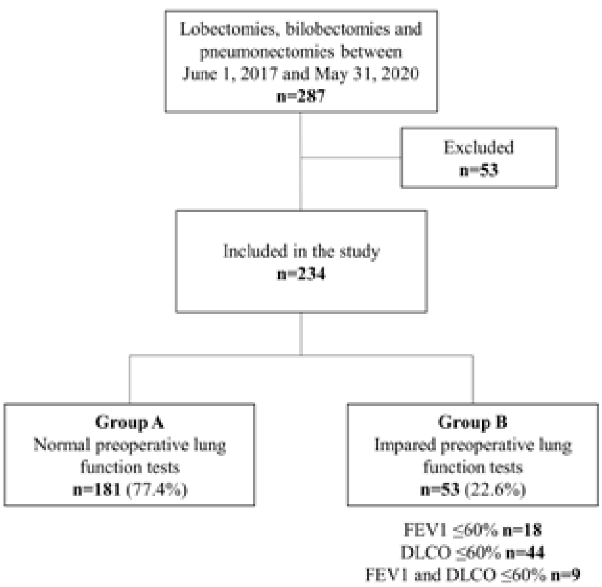

Figure 1 *Patients included in the study from June 1, 2017 to May 31, 2020. DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in the first second.*

Statistical analyses

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or medians and interquartile ranges for variables with skewed distributions. Normal distribution was checked using skewness and kurtosis.

Categorical variables were compared with the use of Fisher's exact test or the chi-square test, as appropriate. Logistic regression was also performed.

Continuous variables were compared with the use of unpaired Student's t-test or Mann-Whitney test, as appropriate. A p-value below 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA).

RESULTS

Preoperative results

During the study period, 287 patients underwent lobectomy, bilobectomy or pneumonectomy. After applying the exclusion criteria, we obtained a sample of 234 patients. A total of 181 (77.4%) had normal preoperative respiratory function tests (group A) and 53 (22.6%) were defined as patients with impaired lung function (group B). In group B, 18 patients had FEV1 ≤60%, 44 patients had DLCO ≤60% while 9 patients had FEV1 and DLCO ≤60% (Figure 1). Patient demographics, clinical and pathological stages, preoperative functional status and comorbidities of the 2 groups are summarized in Table 2.

In both groups we noted a higher proportion of men, a median age of 68 years in group A and 66 yearsin group B. In group B, patients had a statistically significant higher frequency of chronic obstructive pulmonary disease (12.7% vs 35.8%, $p < 0.001$), coronary heart disease (7.7% vs 17.0%, $p = 0.047$) and HIV (0.6% vs 5.7%, $p = 0.037$). The remaining co-morbidities were similar between the groups.

There was no significant difference between the groups when comparing the functional status according to the Eastern Cooperative Oncology Group performance status (ECOG PS) and when comparing the Charlson comorbidity index.

Table 1 **Clavien–Dindo classification of surgical complications**

I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
III	Requiring surgical, endoscopic or radiological intervention
III a	Intervention not under general anesthesia
III b	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
IV a	Single organ dysfunction (including dialysis)
IV b	Multiorgandysfunction
V	Death of a patient

Regarding smoking habits, we found that smoking was associated with compromisedlung function (p <0.001), while not smoking was associated with normal respiratory function (p = 0.009). Ex-smokers showed no significant difference.

Patients with impaired respiratory function most often underwent left pneumectomy (p = 0.011) and had more advanced clinical stages (p = 0.048) according to the 8th edition of the American Joint Committee on Cancer (AJCC). Comparing the clinical stage with the pathological stage, 43.1% of patients with impaired respiratory function had upstaging and 11.8% had downstaging, however, without statistical significance.

There was also a statistically significant association between the type of surgical approach and respiratory function. Group A was more frequently submitted to minimally invasive surgery while group B was more frequently submitted to classic surgery (p = 0.007).

The most frequent diagnosis in both groups was primarylungcancer(89.5%and96.2%,respectively).Adenocarcinoma was also the most frequent histological type (76.5% and 58.8%, respectively), without statistical significance.

Postoperative results

To assess postoperative (30-days) complications we used the Clavien-Dindo classification and found no statistically significant difference between the degrees of classification and pulmonary function.

When we compare the risk of having or not having complications after major pulmonary surgery, regardless of the type of complication that occurred, we found that there is an increased relative risk of 17.7% in Group B (37.0% vs 54.7%, OR 1.99 CI[1.08-3.67],p = 0.026). However, when the logistic regression is performed excluding minor complications (Clavien-Dindo I such prolonged air leak, pneumothorax and others), the higher risk of complications in this group ceases to be statistically significant (OR 2.02 CI [0.95-4.3], p=0.067).In both groups, the most frequent complication was prolonged air leak, however with no statistically significant difference between groups (p=0.584). Group A presented 1 death (0.6%) and there was no record of mortality in Group B.

Length of hospital stay and chest drainage duration were statistically significantly higher in patients with

Table 2 **Demographic data, functional status, co-morbidities, clinical and pathological stage**

Variables	Group A (n=181)	Group B (n=53)	*p*-value
Variables	111 (61.3)	40 (75.5)	0.058
Male gender, n (%)	68 (17-85)	66 (42-86)	0.060
Age (years), median (range)	19 (12-19)	19 (15-19)	0.583
Preoperative functional segments, median (range)	93 (61-178)	79 (45-117)	<0.001
FEV1%, median (range)	75 (33-131)	58 (27-99)	<0.001
ppoFEV1%, median (range)	79 (61-153)	55 (40-88)	<0.001
DLCO%, median (range)	63 (39-135)	44 (22-70)	<0.001
ppoDLCO%, median (range)	0 (0-2)	1 (0-2)	0.100
ECOG PS, median (range)	5 (0-10)	5 (2-11)	0.463
Charlson comorbidity index, median (range)			
Comorbidities, n (%)	100 (55.2)	24 (45.3)	0.201
Arterial hypertension	18 (9.9)	6 (11.3)	0.772
Uncomplicated diabetes mellitus	5 (2.8)	0	0.591
Complicated diabetes mellitus	14 (7.7)	9 (17.0)	0.047
Coronary disease	8 (4.4)	2 (3.8)	1.000
Acute coronary syndrome	4 (2.2)	2 (3.8)	0.620
Stroke	2 (1.1)	2 (3.8)	0.222
Cardiac insufficiency	23 (12.7)	19 (35.8)	<0.001
COPD	1 (0.6)	0	1.000
Hepatic failure	3 (1.7)	0	1.000
Chronic renal disease	1 (0.6)	3 (5.7)	0.037
HIV			<0.001
Smoking habits, n (%)	31 (17.1)	26 (49.1)	0.009
Smoker	73 (40.3)	11 (20.8)	0.106
Non-smoker	77 (42.5)	16 (30.2)	0.014
Ex-smoker			
Surgery, n (%)			
Right upper lobectomy	62 (34.3)	20 (37.7)	
Middle lobectomy	13 (7.2)	2 (3.8)	
Right lower lobectomy	26 (14.4)	5 (9.4)	
Left upper lobectomy	38 (21.0)	16 (30.2)	
Left lower lobectomy	36 (19.0)	4 (7.5)	0.036
Upper bilobectomy	2 (1.1)	0	
Lower bilobectomy	2 (1.1)	1 (1.9)	
Right pneumonectomy	2 (1.1)	2 (3.8)	
Left pneumonectomy	0	3 (5.7)	0.011
Systematic lymph node dissection, n (%)	173 (95.6)	53 (98.1)	0.688
Surgical approach, n (%)			0.007
Thoracotomy	62 (34.3)	29 (54.7)	
VATS	119 (65.7)	24 (45.3)	

Variables	Group A (n=181)	Group B (n=53)	*p*-value
Diagnosis, n (%)			
Primary lung cancer	162 (89.5)	51 (96.2)	0.175
ADC	124 (76.5)	30 (58.8)	
SCC	19 (11.7)	14 (27.5)	
SCLC	3 (1.9)	2 (3.9)	
Other	16 (9.9)	5 (9.8)	
Metastatic cancer	12 (6.6)	1 (1.9)	0.307
Infectious disease	5 (2.8)	0	0.591
Bronchiectasis	5 (100)	0	
Other	2 (1.1)	1 (1.9)	0.539
Hyaline fibrosis	1 (50)	0	
Inflammatory pseudotumor	1 (50)	0	
Synovial sarcoma	0	1 (100)	
Clinical stage, n (%)			0.048
IA1	8 (4.9)	2 (3.9)	
IA2	45 (27.8)	8 (15.7)	
IA3	39 (24.1)	7 (13.7)	
IB	21 (13.0)	11 (21.6)	
IIA	10 (6.2)	8 (15.7)	0.036
IIB	21 (13.0)	6 (11.8)	
IIIA	15 (9.3)	5 (9.8)	
IIIC	1 (0.6)	0	
IVA	2 (1.2)	4 (7.8)	0.025
Pathological stage, n (%)			0.180
No tumor	2 (1.2)	2 (3.9)	
IA1	8 (4.9)	2 (3.9)	
IA2	28 (17.3)	4 (7.8)	
IA3	35 (21.6)	5 (9.8)	
IB	27 (16.7)	11 (21.6)	
IIA	9 (5.6)	6 (11.8)	
IIB	22 (13.6)	10 (19.6)	
IIIA	21 (13.0)	6 (11.8)	
IIIB	5 (3.1)	1 (2.0)	
IVA	5 (3.1)	4 (7.8)	
Upstaging, n (%)	55 (34.0)	22 (43.1)	0.234
Downstaging, n (%)	23 (14.2)	6 (11.8)	0.659

ADC: adenocarcinoma; COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity of the lung for carbon monoxide; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FEV1: forced expiratory volume in the first second; HIV: human immunodeficiency virus; ppoDLCO: predicted postoperative diffusing capacity of the lung for carbon monoxide; ppoFEV1: predicted postoperative forced expiratory volume in the first second; SCC: squamous cell carcinoma; SCLC: small cell lung cancer; VATS: Video-assisted thoracoscopic surgery impaired respiratory function ($p = 0.003$ and $p = 0.005$, respectively).

When assessing the need for home oxygen therapy, we found that in group B, 3 patients needed this therapy, with statistical significance ($p = 0.011$). Of the 3 patients referred, 1 required oxygen for walking, 1 required oxygen therapy for 4 months and 1 required non-invasive ventilation by night.

The postoperative outcomes of the 2 groups are described in Table 3.

DISCUSSION

In this study, patients with FEV1 and/or DLCO ≤60% had more smoking habits, were more frequently associated with chronic obstructive pulmonary disease and had more advanced clinical stages when the main diagnosis that motivated the surgery was the primary lung cancer. Contrary to what might be expected, patients in group B did not have a statistically significant worse performance status or worse Charlson comorbidity index [1,5].

We also found that patients of group B were more frequently submitted to thoracotomy, while patients with normal respiratory function were more frequently submitted to minimally invasive video-assisted thoracoscopic surgery (VATS) with statistical significance. However, there are already studies including patients with impaired respiratory function, that conclude VATS lobectomy is associated with a lower risk of morbidity when compared to the conventional approach, especially in patients with early stages of lung cancer [7,13]. In our study, the authors believe that the compromised group had more often hilar nodal disease or central tumours that contributed to more thoracotomies. Furthermore, compromised lung function was more associated with previous infectious lung disease, such as pulmonary tuberculosis, that increased the risk of pleural adhesions that did not allow to proceed with a VATS technique. Unfortunately, this data and the conversion rate is not recorded in digital records. Although more than 60% of anatomical pulmonary resection surgeries are performed in this Thoracic Surgery Unit by VATS, the authors consider that it is still possible to increase the ratio VATS/thoracotomy approach, especially in patients considered at risk according to the respiratory function tests.

Patients with impaired lung function also had longer hospital stay, longer chest drainage duration and more need of supplemental oxygen therapy at home, which is in agreement with previous studies [5,6,14]. Despite this group of patients presenting, as expected, a higher relative frequency of complications in the postoperative period, in this study we found no significant difference between major complications and lung function. In fact, the most frequent postoperative complications do not jeopardize the patient's life. In 83.8% in group A and 82.8% in group B, complications were solved with conservative therapy such as respiratory physiotherapy, analgesia and antibiotics when justified.

The most important finding of this study is that patients with compromised lung function undergoing major thoracic surgery are not associated with statistically significant greater morbidity or mortality. Therefore, it is possible to perform this type of surgery in patients considered to be at risk and surgical treatment should not be denied based on respiratory function tests only, especially when surgery is considered the best option to treat the patient. These data are in accordance with the studies published by Bongiolatti and Subroto in 2020 and 2013, respectively[1,5]. It should also be noted that, although our study found no association with the performance status (ECOG PS) or comorbidities prior to surgery, these data should not be overlooked in the initial assessment of the patient since they have been associated with predictors of morbidity and mortality [15]. In fact, in our study, patients had excellent performance status and acceptable comorbidities, overcoming the impact that impaired lung function could have on postoperative recovery, as described in the literature[5]. That explains why patients at higher risk do not show a significant increase in morbidity or mortality.

In order to try to understand if the patient will tolerate major thoracic surgery, in addition to the assessment of performance status, comorbidities and respiratory function tests with FEV1 and DLCO, other preoperative studies can be performed in patients at risk, as ergometry, the 6-minute walking test or ventilation-perfusion lung scan[3,5]. However, these complementary studies are not always available and their performance often implies delaying surgical treatment, which can be harmful to the patient, so they are not usually performed and were not included in this study.

Finally, the authors would like to point out that most studies comparing postoperative results between groups with normal respiratory function and groups with impaired respiratory function were performed in patients diagnosed with lung cancer[1,2,4,5,13,16,17], however, it is also important to evaluate these results in patients with benign pulmonary pathology, since in these cases surgical treatment is more easily postponed, opting for alternative therapies that often do not completely resolve the pathology of the patient, implying greater relapse, more hospitalizations and worse quality of life. Thus, it is explained that in this study all lobectomies, bilobectomies and pneumonectomies performed in a period of 3 years were included, regardless of the diagnosis that justified the surgical need.

Limitations

Our study has some limitations. First, it has all of the inherent biases associated with a retrospective analysis. Second, the authors chose to define the group of patients with compromised lung function according to the values in percentage of FEV1 and DLCO (FEV1% and DLCO%) instead of the postoperative predictive values of

Table 3 **Postoperative results**

Variables	Group A (n=181)	Group B (n=53)	*p*-value
Clavien-Dindo classification, n (%)			0.395
I	44 (24.3)	17 (32.1)	0.257
II	13 (7.2)	7 (13.2)	0.171
III a	2 (1.1)	1 (1.9)	0.539
III b	5 (2.8)	3 (5.7)	0.385
IV a	3 (1.7)	1 (1.9)	1.000
V	1 (0.6)	0	1.000
Complications, n (%)	67 (37.0)	29 (54.7)	0.026
Impared lung function	0	2 (3.8)	0.051
Arrhythmia	1 (0.6)	2 (3.8)	0.129
Stroke	1 (0.6)	0	1.000
Thoracic empyema	3 (1.7)	3 (5.7)	0.131
Bronchopleural fistula	1 (0.6)	0	1.000
Bronchial fistula	0	1 (1.9)	0.226
Prolonged air leak	38 (21.0)	13 (24.5)	0.584
Haemothorax,	3 (1.7)	2 (3.8)	0.317
Other	6 (3.3)	3 (5.7)	0.427
Cardiac arrest	1 (0.6)	0	1.000
Pneumonia	9 (5.0)	3 (5.7)	0.737
Pneumothorax	3 (1.7)	0	1.000
Chylothorax	1 (0.6)	0	1.000
Deaths, n (%)	1 (0.6)	0	1.000
Chest drainage duration (days), median (range)	4 (1-30)	5 (2-33)	0.005
Length of hospital stay (days), median (range)	5 (2-33)	7 (2-36)	0.003
Home oxygen therapy, n (%)	0	3 (5.7)	0.011

DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in the first second.

FEV1 and DLCO (ppoFEV1% and ppoDLCO%), based on previous studies and because different studies that use ppoFEV1% and ppoDLCO% calculate these values with different formulas, making it difficult to compare them. Finally, the authors also decided not to include other parameters that can be used in the preoperative risk assessment, such as ergometry or the 6-minute walking test, since they are rarely available in clinical practice, reducing our population due to lack of data.

CONCLUSION

Patient's previous lung function is the main risk factor for morbidity and mortality in major thoracic surgery. The present study demonstrates the non-inferiority of surgery in the group of patients with impaired lung function. In summary, a potentially curative surgery should not be denied to these patients based only on respiratory function tests, but complemented with other cardiorespiratory functional tests, such as ergometry, or lung ventilation-perfusion scintigraphy, analysis of other comorbidities and global performance status, determining which patients will benefit from surgical treatment with acceptable morbidity and mortality rates.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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