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Impact of limited pulmonary function on the management of resectable lung cancer

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Summary *Aims:* Limited pulmonary function (LPF) related to obstructive disease and emphysema or due to significant lung toxicity resulting from chemotherapy regimens are frequent co-morbidity factors in lung cancer patients. Purpose of this study was to investigate the frequency of LPF in lung cancer and its impact of on surgical eligibility and postoperative outcome. *Materials and methods:* We analyzed a series of 255 consecutive patients with otherwise resectable lung cancer, admitted to our department between January 1998 and December 1999. Patients were considered affected by LPF if their forced expiratory volume in one second (FEV1%) and/or diffusing lung capacity for carbon monoxide (DLCO%) was less than 50% of predicted normal values. Perioperative mortality, major and minor complications were analysed according to lung function status. *Results:* A total of 42 (16.5%) patients presented with significant limitations of the pulmonary function (LPF). Of these, 11 (26%) cases were excluded from surgery because of the severity of pulmonary disease. In the group of 244 patients who underwent surgery, the 31 LPF cases showed a slightly higher frequency of preoperative induction therapies (42 vs. 30%) and sublobar resections (33 vs. 8%) in comparison with the other 213 resected cases. However, no difference was observed in median hospital stay (7 days in both groups), major morbidity (13 vs. 11%) or mortality (0 vs. 1.4%). *Conclusions:* A strict and careful selection of patients, guided by concurrent analysis of different functional tests, allowed to offer surgery with a very low complication rate to the majority of patients with limited pulmonary function. A volume reduction effect was evident in selected patients with severe emphysema.

1. Introduction

Complete surgical resection represents the best therapeutic option for patients with non-small cell lung cancer (NSCLC). However, many patients present with various degrees of obstructive pulmonary disease (COPD), which is reflected in

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impaired pulmonary function tests [1]. Chronic obstructive pulmonary disease (COPD) is a slowly progressive process over a period of years, and is by definition largely irreversible [2,3]. Lung resection in patients with limited pulmonary reserve has been associated in the past with an increased risk of postoperative complications, and sometimes prohibitive mortality rates [4,5]. However, recent data derived from the surgical treatment of emphysema demonstrated that a volume reduction effect can be achieved by curative resection of cancers arising in the most compromised areas of the lung (usually the upper lobes). Korst, by analysing the experience of Memorial Sloan Kettering, has demonstrated that patients with a very low preoperative FEV1 and FEV1 to forced vital capacity ratio are less likely to lose ventilatory function after lobectomy and may actually improve it [6]. Based on such experience, indications for surgery in emphysematous patients have been gradually extended.

Another form of impairment in lung function is that usually expected in patients receiving chemotherapy regimens. In fact, in the majority of patients, despite an improvement in spirometric volumes due to the drop in the airway resistance or to reduction of bronchial obstruction after treatment, a decline in the diffusing capacity is usually observed [7].

A wide range of tests have been proposed for the functional assessment of lung resection candidates but up to now there is no agreement as to which test is the most reliable, as no single diagnostic test can accurately predict the risk of postoperative complications [8–10]. In the last 4 years, we have routinely applied to every patients before lung resection: ECG, cardiologic examination, spirometry, diffusion capacity (DLCO) and in selected cases echocardiography, pulmonary perfusion scan or exertion test.

The purpose of this study was to retrospectively investigate: (1) the prevalence of limited pulmonary function (LPF) in a consecutive series of 255 patients with otherwise resectable NSCLC; (2) the number of patients excluded from surgery on the ground of pulmonary function; and (3) the ability of preoperative tests to adequately select appropriate candidates for surgery through the analysis of the postoperative outcome.

2. Material and methods

For the purposes of this study we considered at risk for limited pulmonary function those patients presenting with a forced expiratory volume in 1 s (FEV1%) and/or a diffusing lung capacity for carbon monoxide (DLCO%) which was less than 50% of predicted normal values.

These cut-off values were arbitrarily chosen, due to the considerations that in surgical papers there are not available commonly accepted criteria and/or established parameters to measure the degree of chronic obstructive pulmonary disease (COPD) and that the parameters used to measure a compromised pulmonary function are several (FEV1 value in litres, FEV/FVC percentage ratio, FEV1% or TLCO%, separately or combined).

As a result there is a big difference in the cut-off value chosen among available papers.

Patients presenting with these characteristics entered a 6-week period of rehabilitation with the aim to improve baseline tests.

They were asked for smoking cessation, for weight control and for a low-level home exercise programme (going up and down stairs and walking on flat surfaces, training on stationary cycle ergometer); they were introduced to a conventional medical treatment including beta adrenergic agonist and anticholinergic drugs at optimal doses (salbutamol, ipratropium bromide, and inhaled budesonide); antibiotics (b-lactam) were administered for the first 2 weeks.

Physiotherapist taught patients thoracic-mobility exercise, self-conscious breathing and diaphragmatic breathing control, abdominal muscle wall work and an effective cough.

After 6 weeks patients underwent a pulmonary function re-assessment that basically includes: (a) redo spirometry (focusing on FEV1, FEV1%, DLCO, DLCO% values); (b) repeated blood gas test; (c) improvement in the dyspnoea symptom.

A total of 266 consecutive patients candidate to surgical resection for NSCLC and admitted to the Department of Thoracic Surgery of the European Institute of Oncology of Milan between January 1998 and December 1999 were identified. Eleven (4.1%) of these patients had been excluded from surgery on the basis of severe non-pulmonary comorbidity, including: coronary artery disease ($n = 5$ cases), previous lung resection and/or a bilaterally located tumor ($n = 3$), significant toxicity due to neoadjuvant chemotherapy ($n = 2$) or poor performance status ($n = 1$), leaving 255 cases for the present analysis.

Data were collected from the Thoracic Service Database and for each patient included age, sex, histology and stage of the tumor, type of resection, neoadjuvant treatments if present, duration of hospital stay, duration of Intensive Care Unit (ICU) admission, time to removal of chest drainage, complications and pulmonary functional data. Pre-

Table 1 Functional features of the 255 patients

	Excluded from surgery	Resected with limited function	Resected with normal function
	11 patients (4.3%)	31 patients (12.2%)	213 patients (83.5%)
FEV1 (lt)	1.15 (0.8–2.3)	1.52 (0.9–3.8)[a]	2.39 (1.2–4.9)
FEV1 (%)	36 (28–68)	49.7 (29–109)[a]	84 (54–145)
TLCO (%)	46 (29–80)	46 (31–97)	77 (50–127)
Perfusion (%)[b]	49 (15–69)	47 (0–56)	
ppoFEV1 (%)	29 (12–41)	41 (27–65)	61 (34–111)
ppoTLCO (%)		36 (19–92)	59 (26–96)

[a] Upper limit of range refers to a 45-year-old patient with a locally advance NSCLC undergone preoperative chemotherapy treatment. Spirometric test revealed normal lung volumes with severely compromised diffusion capacity (TLCO 46%) potentially as expression of drug-related lung toxicity.
[b] Perfusion (%) is for percentage value of lung perfusion to the site containing the lesion and to be operated on.

operative respiratory function evaluation included blood gas test, spirometry, and DLCO measurement. Prediction equations for DLCO (single-breath technique) were obtained according to Gaensler and Wright method [11,12]. Diffusing capacity was corrected for hematocrit values and further for lung volume by the equation of Gelb et al. [13]. Echocardiography with evaluation of pulmonary artery pressure and lung perfusion scanning test were performed in selected cases. The number of lung segments removed, in addition to FEV1% and DLCO%, were used to calculate the postoperative predicted values (ppoFEV1%, ppoDLCO%) for each patient. Assuming that each of the 19 segments in normal lung contributes equally to respiratory function, predicted postoperative values for FEV1% and DLCO% were obtained multiplying percent values of predicted by the fraction of functional lung segments remaining after surgery. These estimates were corrected by the radioisotope perfusion studies when available. In patients undergoing wedge resections, the lung parenchyma excised was assumed to account for one bronchopulmonary segment. The anatomical resection of culmen and upper bilobectomy was considered in the group of standard lobectomies.

Complications were classified as follows: mortality (any postoperative death during hospital stay or within 30-day from surgery), major complications (surgical: re-thoracotomy for hemothorax, cardiac herniation; respiratory: ARDS, bronchopleural fistula, pneumonia, embolism, empyema, pulmonary oedema, tracheostomy or reintubation required; cardiovascular: myocardial infarction, ischemia or angina, cerebral vascular attacks, deep vein thrombosis; other: acute renal failure, acute gastric ulcer) and minor complications (atelectasis, prolonged air-leak exceeding 6th postoperative day, pleural effusion, atrial fibrillation or other arrhythmias, wound infection).

Data regarding the postoperative outcome and frequency of complications were analysed according to functional status. Comparisons were evaluated by χ^2-test and significance values considered relevant if $P < 0.05$.

3. Results

A total of 42 patients (16.5%) were classified as having limited pulmonary function (LPF). In 11 cases (26% of LPF, 4.3% overall) the pulmonary reserve was judged too severely damaged to tolerate the planned lung resection. Of the 31 cases (74% of LPF, 12.2% overall) who underwent surgery despite limited pulmonary performances, 13 showed an FEV1% $\leq$ 50% of predicted, 14 a DLCO% $\leq$ 50% of predicted, while in 4 case both parameters were decreased. Table 1 illustrates the functional features of the two LPF groups, as well as of the remaining 213 patients operated with relatively normal pulmonary function.

3.1. Patients excluded from surgery due to limited pulmonary function ($n = 11$, 4.3%)

These cases presented with a various combination of unfavorable features: impaired spirometric data (median FEV1 was 1.15lt vs. 1.52lt, median FEV1% was 36 vs. 49%), tumor located in unfavorable position (trachea, main bronchi or lower lobes in 10 patients out of 11, or 91%), a rather constant mismatch between the area of the lung to be resected (site of the tumor) and the distribution of the pulmonary perfusion (73%) and/or tumor located within the normally functioning or prevalent lung according to the radionuclide scanning test (75%).

These aspects are also reflected in a difference in the ppoFEV1% among the two subgroups (29 vs. 41%).

3.2. Patients resected with limited pulmonary function ($n = 31$, 12.2%)

Among the 244 surgical cases, 31 (12.7%) were classified as LPF patients (Table 2). There were 26 males (83%) and median age was 65 years (range 45–82). Thirteen patients (42%) had received an induction treatment (10 neoadjuvant chemotherapy and three chemo-radiotherapy). Preoperative pulmonary function tests showed a median FEV1% of 49.7%, a median DLCO% of 46.2%, a median ppoFEV1% of 41.3% and a median ppoDLCO% of 36.3% (Table 1).

Pneumonectomy was performed in 10 patients (32%), lobectomy in 11 (35%) and sublobar resections in 10 cases (seven anatomical segmentectomies and three wedge resections). There were three resections considered 'extended' (1 case left upper lobe wedge resection + chest wall resection, 1 case right upper lobectomy + superior vena cava replacement, 1 case right upper bilobectomy + superior vena cava and pulmonary artery double prosthetic replacement combined with bronchial sleeve) and three bronchial sleeve resections (one right upper sleeve bilobectomy, one right upper tracheal sleeve lobectomy with carinal reconstruction, one right tracheal sleeve pneumonectomy).

Histology was epidermoid carcinoma in 17 cases (55%) and adenocarcinoma in 14 (45%). Pathological staging showed stage I disease in 12 patients (38%), stage II in 2 (6%), stage IIIA in 11 (35%) and stage IIIB in 5 (12%). The only patient (3%) with stage IV disease, had undergone excision of a single brain metastasis from a lung adenocarcinoma followed by radiotherapy/chemotherapy and a left upper lobectomy was performed 2 years after neurosurgical intervention.

3.3. Patients with relatively normal pulmonary function ($n = 213$, 83.5%)

Two hundred and thirty-one patients were judged as having a relatively normal pulmonary function. There were 172 males (80%) and median age was 64 years (range 15–79). Sixty-two (30%) had received an induction treatment (48 neoadjuvant chemotherapy, five radiotherapy and nine a combination of chemo- and radiotherapy). Preoperative pulmonary function tests showed a median FEV1% of 84.2%, a median DLCO% of 77.3%, a

Table 2 Main characteristics of surgical patients

	Limited function 31 patients		Normal function 213 patients	
Age (years)	65	(45–82)	64	(15–79)
Sex (male)	26	83%	172	80%
Resection				
Pneumonectomy	10	32%	50	24%
Lobectomy	11	35%	145	68%
Sublobar resection	10	33%	18	8%
Segmentectomy	7		15	
Wedge	2		2	
Induction therapy	13	42%	62	30%
Chemotherapy	10		48	
Chemo + Radiotherapy	3		9	
Radiotherapy			5	
Histology				
Adenocarcinoma	14	45%	102	48%
Epidermoid	17	55%	92	43%
Large cell			11	5%
Other			8	4%
Stage				
I	12	38%	69	32%
II	2	7%	51	24%
IIIA	11	35%	81	38%
IIIB	5	16%	12	5%
IV	1[a]	3%		

median ppoFEV1% of 60.9% and a median ppoDLCO% of 59.3%.

Surgical treatment consisted of pneumonectomy in 50 cases (24%) and lobectomy in 145 (68%). Only a small minority received a sublobar resection ($n =$ 18, 8%) and only three patients (1%) received a non-anatomical wedge resection.

Histology was adenocarcinoma in 102 cases (48%), epidermoid carcinoma in 92 cases (43%), large cell carcinoma in 12 (5%). Pathological staging showed stage I disease in 69 patients (32%), stage II in 51 (24%), stage IIIA in 81 (38%) and stage IIIB in 12 (5%).

3.4. Postoperative outcome

No statistically significant differences were observed between the two groups of surgical patients with respect to postoperative outcome (Table 3).

Median hospital stay, calculated from the day of surgical intervention, was 7 days in both groups (range 4–21 and 4–62, respectively) and patients remained in the Intensive Care Unit (ICU) a median of 18 h (range 0–80) in the LPF group and a median of 18.5 h (range 0–44 days) in the normal pulmonary function group.

Analysis of complications revealed no mortality in the group with limited pulmonary function compared to three deaths (1.4%) in the other group of patients. The causes of death were ARDS after right pneumonectomy in two cases (one completion) and postoperative myocardial infarction after left lower lobectomy in one case.

Overall morbidity including major and minor complications was, respectively, 51% (16/31) vs. 35% (76/213). Separate analysis of complications showed no difference in major (13% vs. 11%, $P =$ ns) and a slight increase in minor events (38% vs. 24%, $P =$ ns) (Table 3). Major complications included: hemothorax after right upper lobectomy, early failure (on 5th postoperative day) of the bronchial stump in a patient undergone a left pneumonectomy after chemo-radiotherapy that was successfully repaired by reoperation, a transient cerebrovascular attack (TIA) after left upper lobectomy in a patient with a history of carotid artery disease and a pneumonia after anatomical resection of culmen which was medically treated.

In the compromised respiratory function group, there was a slight increase (38 vs. 24%) in minor complications: six cases of atrial fibrillation without clinical impact on postoperative course, three patients requiring aspiration bronchoscopy for sputum plugging and three patients with prolonged air-leak (air-leak was considered prolonged if chest drainage had to me maintained in place beyond the 6th postoperative day).

Table 3 Comparison of postoperative outcome and complications in the 244 operated cases

	Limited function 31 patients		Normal function 213 patients		
ICU stay (h)	18	(0–80)	18.5	(0–44)	
Drain removal (days)	4	(3–13)	4	(3–19)	
Hospital stay (days)	7	(4–21)	7	(4–62)	
Mortality	0		3	1.4%	$P = 0.84$
Overall morbidity	16	52%	76	35%	$P = 0.14$
Major complications	4	13%	23	11%	$P = 0.97$
Hemothorax	1		4		
Early bronch failure	1		1		
Bronch fistula			3		
Cardiac herniation			2		
ARDS			3		
Chylothorax			1		
Pneumonia	1		5		
Ischemia			2		
TIA	1		2		
Minor complications	12	38%	53	24%	$P = 0.17$
Prolonged air-leak	3		20		
Bronchoscopy	3		9		
Atrial fibrillation	6		24		

4. Discussion

The accurate prediction of postoperative outcome after surgical resection for lung cancer is crucial for the optimal selection of eligible patients, and is directly related to the risk of developing complications. For patients who appear to be anatomically resectable by staging and general oncological criteria, a multitude of procedures and tests have been proposed to evaluate their 'physiologic' operability. Routine pulmonary function studies, including spirometry and gas blood test, are nowadays primarily performed in all candidates to lung resectional surgery in order to assess and/or quantify an underlying severe COPD and accept these patients for surgery or indicate if further non-routine testing is advisable before any decision, taking into account that resection continues to offer the best prospect for long term survival in patients with non-metastatic lung cancer.

Spirometric values are still used in the routine clinical practice to select candidates since in 1955 Geansler et al. [12] reported that in a series of patients undergoing lung resection for tuberculosis a preoperative FEV1 less than 70% of predicted was associated with 40% mortality rate. Subsequent papers by Olsen et al. [5] and Boysen et al. [14,15] fixed the limit for surgery with an acceptable risk at preoperative FEV1 greater than 2 l or at predicted postoperative FEV1 (ppoFEV1) greater than 0.8 l. After these initial reports, in the last two decades some authors have implicated that a low preoperative FEV1 value is a risk factor for postoperative complications [15–17] while others showed no predictive value of FEV1 in determining the risk of lobectomy [18,19] and the superiority of the postoperative predicted percentage value (ppoFEV1%) [18].

The routine use of the estimated ppoFEV1 has been advocated as an important predictive factor [19–22] based on the findings that the overall morbidity and mortality risk was significantly increased when ppoFEV1 was less then 40% of predicted. Markos et al. [20] in prospective series of 55 consecutive patients demonstrated that the best predictor of death was the ppo-FEV1 expressed as percentage of predicted normal value. In their study a ppo-FEV1 greater than 40% of predicted normal was associated with no postoperative mortality, whereas a value below 40% was associated with a 50% mortality. Similarly Kerney et al. [18] studied prospectively a cohort of 331 patients and concluded that a low ppo-FEV1 was the best indicator of patients at high risks for complications and the only significant risk factors at a multivariate analysis, although the magnitude of risk did not appear to be prohibitive above the threshold of 0.6–0.8 l range.

On the other hand, the use of spirometric values to predict post-resectional ventilatory function (using simple anatomic calculation or alternatively functional lung scans) has resulted in adequate [18,20] or questionable accuracy [2,6,16]. In fact there are patients in which the ppoFEV1 can actually increase instead of being diminished, after surgical resection of damaged anatomical segments, due to a volume reduction effect [6].

Even the cut-off value of 800 ml for ppoFEV1 introduced by Olsen et al. [5] and generally considered a marker of prohibitive risk, should be questioned on the ground that selected patients with marked impairment of ventilatory function can tolerate limited resection with acceptable risk [18].

Ferguson et al. were the first to advocate the use of DLCO and the derived value ppoDLCO in the routine evaluation of patients candidate to surgical resection [23,24]. In a retrospective analysis of 237 patient operated for lung cancer they found that DLCO was the best predictor of mortality and the only predictor of complications. When DLCO was less than 60% of predicted, mortality was 25% and pulmonary complications occurred in 45% of the patients. Conversely, if DLCO was greater than 100% mortality was 0% and pulmonary complications 11%. They concluded that the lower limit for operability should be as DLCO around 60% of predicted normal and that DLCO measurement should be added routinely to the spirometry [23]. They later extended the study to 376 patients focusing on ppoDLCO value and the interactions between DLCO and ppoFEV and confirmed that a DLCO less than 60% and a ppoDLCO less then 50% were the most important predictors of postoperative pulmonary complications and mortality; ppoDLCO had to be regarded as the strongest single predictor of risk of complication and mortality [24].

The real impact of chronic obstructive lung disease or drug-induced lung toxicity on lung cancer surgery is difficult to assess, as surgical series do not usually provide data on patients excluded from surgery due to limited pulmonary function. Moreover, the degree of underlying COPD and emphysema may be difficult to assess in some cases, due to the bronchial obstruction determined by the tumor or to the acute pneumonic changes associated with it.

Our data demonstrate that a significant reduction of respiratory function, compatible with COPD and moderate to severe emphysema or a compro-

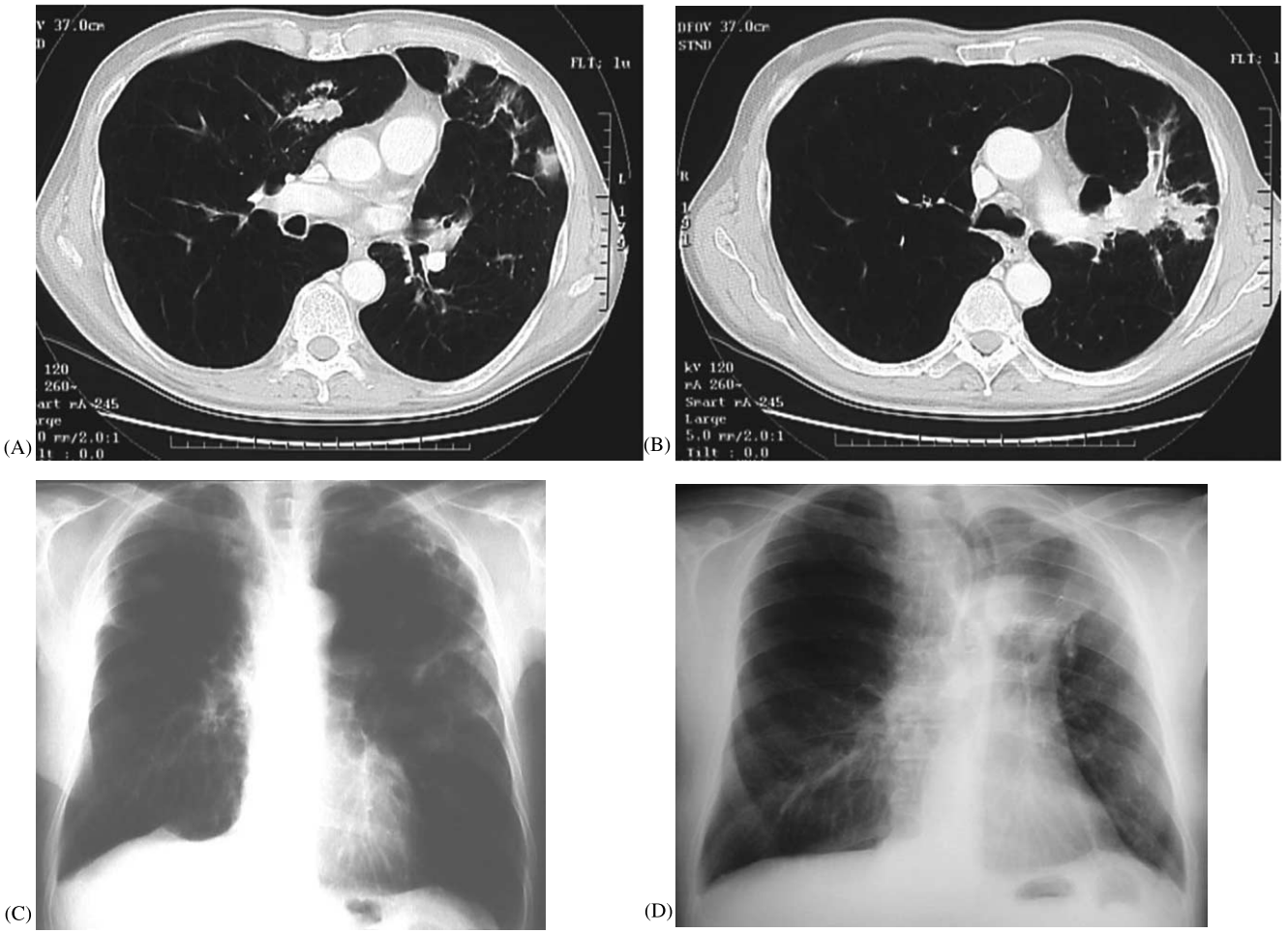

Fig. 1 Case of a 61-year-old patient presenting with a bilateral tumour (middle lobe (A) and left upper lobe (B)) and a severe obstructive lung disease characterized by FEV1 of 0.98 l, FEV1% of 28.8%, DLCO% of 46.6% and residual volume (RV%) of 163.3%. The patient first underwent lung volume reduction surgery combined with a middle lobectomy for a pT2N0 adenocarcinoma and 2 months later a left upper lobectomy with sparing of the lingula (culminectomy) for a pT2N0 squamous cell carcinoma. Both the surgical outcomes were uneventful. At the latest follow-up, 2 years after the first resection, patient is well without evidence of relapse and spirometric tests improved as follow: FEV1 = 1.57 l, FEV% = 49%, TLCO% = 67% and RV% = 123.5%. Chest X-rays 1 month after right lung resection (C) and 18 months after left surgery (D) are presented.

mised DLCO correlated with lung toxicity from chemotherapy regimens, is present in 16.5% (42/255) of otherwise resectable lung cancer patients. In approximately one quarter of LPF patients ($n = 11$), preoperative functional assessment resulted in exclusion from surgery. This group however represented only a small minority (4.3%) of the entire population.

The results of present study indicate that a panel of preoperative tests should be routinely applied to lung cancer patients in order to assess the severity of chronic lung disease and predict the risk of major complications after a given resection volume. These investigations include spirometric volumes, DLCO measurement, lung perfusion scans and their correlation with size as well as location of the tumor on CT scan, complete cardiologic work-up with echocardiographyc indirect assessment of arterial pulmonary pressure to detect an underlying subclinical pulmonary hypertension in selected cases.

As a consequence of such selection process, preoperative mortality was very low in the whole series and absent in the LPF group. The morbility profile appears particularly favorable taking into account that among these 31 patients about one third received a lobectomy (11 cases) and another third a pneumonectomy (10 cases). One has to consider however that all lobar resections were performed on upper lobe tumors where a lung volume reduction effect of the emphysema should be expected despite the critical spirometric values (Fig. 1 illustrates a case of surgical resection performed in a patient with a very severe emphysema). In 4 of these lobectomy cases, a bronchial or tracheoplasty procedure, with or without complex vascular reconstruction was performed, in order to achieve oncological radicality with maximum preservation of functional parenchyma. On the other hand pneumonectomy was performed only in patients with low ipsilateral perfusion (median 24%, range 0–36%) and high calculated ppoFEV% (48.5%), where some benefit from resection might be expected by removing the shunt of a non-ventilated and partially perfused lung.

5. Conclusion

The present series demonstrates that, a strict and careful selection of patients, guided by concurrent analysis of different tests (FEV1%, DLCO%, ppoFEV1%, perfusion scan studies, echocardiography) allowed to offer surgery with a very low complication rate to the majority of patients with limited pulmonary function. A volume reduction effect was evident in selected patients with severe emphysema.

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