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Impact of lobectomy for non-small-cell lung cancer on respiratory function in octogenarian patients with mild to moderate chronic obstructive pulmonary disease☆

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Abstract

Objective: To assess the long-term impact of standard lobectomy on respiratory function in octogenarian patients with mild/moderate chronic obstructive pulmonary disease (COPD). **Methods:** We reviewed all octogenarians ($n = 38$), who underwent lobectomy for stage I—II non-small-cell lung cancer (NSCLC) from 2000 to 2006. Inclusion criteria were: Tiffenau index < 0.7, no adjuvant therapies, smoking cessation after surgery, spirometric data available after 12 ± 3 months from surgery in the absence of relapsing disease. **Results:** After excluding 14 patients (three died perioperatively), 24 fulfilled the inclusion criteria. The median preoperative forced expiratory volume in 1 s (FEV1) was 80% (range 56.7—100%). The mean change in FEV1 after lobectomy resulted in a loss of 11% (range −32% to +7%, $p = 0.004$). Considering two groups on the basis of median FEV1 (group 1: FEV1 $\leq$ 80%, group 2: FEV1 $>$ 80%), mean FEV1 loss after surgery was 7.9% in group 1 and 14.9% in group 2, respectively ($p = 0.17$). No statistical differences were found between the two groups in changes after surgery of forced vital capacity (FVC), arterial oxygen and carbon-dioxide tension. Diffusion capacity of the lung for carbon monoxide (DLCO)% loss was significantly higher in group 2 compared with group 1 (−22.5% vs +1.5%, $p = 0.001$). Six patients showed an improvement of postoperative FEV1: all had a preoperative FEV1 less than 60%, an upper or homogeneous pattern of emphysema, and received an upper lobectomy. In group 2, the FEV1 loss was not affected by the type of lobectomy whereas in group 1, the resection of lower lobe was associated to a major FEV1 loss (−14.5% vs +5.3%, $p = 0.05$). **Conclusions:** Octogenarians with lower preoperative FEV1% have a better late preservation of pulmonary function after lobectomy. Upper lobectomy seems to produce a lung-volume reduction effect, leading to an improvement in the expiratory volume in patients with higher airflow obstruction.

Keywords: Lung cancer; FEV1; Octogenarians; Lobectomy; LVRS

1. Introduction

Lung cancer is actually the primary cause of death by malignancy in the world. To date, radical surgical resection offers the major chance of cure and among the types of lung resection, anatomical lobectomy represents the gold standard, even for small peripheral cancers.

The aim of the present study is to assess the long-term respiratory functional results in octogenarians with airflow obstruction, who had undergone lobectomy for non-small-cell lung cancer (NSCLC), to analyze factors predicting pulmonary function loss in these patients.

2. Patients and methods

The lung-cancer database of the Thoracic Surgery Unit at the University of Siena was reviewed to identify all patients aged more than or equal to 80 years, who underwent curative lung resection for NSCLC, from January 2000 to December 2007.

Functional assessment included medical history, physical examination, routine blood tests, electrocardiogram, echocardiography, blood gas analysis, spirometry, and estimation of diffusion capacity of the lung for carbon monoxide (DLCO). Cardiac stress tests and coronary angiography were performed when indicated by a history of angina pectoris, or significant ischemic signs in the basal electrocardiogram. Lung-perfusion scintigraphy was performed in case of predicted postoperative forced expiratory volume in 1 s percentage (ppoFEV1%) less than 40% (computed on the basis of pulmonary segments to be removed).

Inclusion criteria were Tiffenau index (FEV1%/forced vital capacity percentage (FVC%)) $\leq$0.7, standard lobectomy as surgical procedure (no combined chest-wall resection or

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sleeve resections), no adjuvant therapies, smoking cessation after surgery, spirometric data available after 12 ± 3 months from surgery in the absence of local relapsing disease, or exacerbation of chronic obstructive pulmonary disease (COPD).

Out of 96 patients operated on from 2000 to 2006, 24 fulfilled all inclusion criteria and formed the population of the study. No patients presented atelectasis or obstructive pneumonia of lobe to be resected. Pulmonary function tests (PFTs) were performed after bronchodilator inhalation to eliminate the variable component of airflow impairment. Airflow obstruction (COPD) was defined by a Tiffenau index <0.7.

Roentgenographic pattern of emphysema was established according to the criteria proposed by Goddard and colleagues for computed tomography (CT) scan [1]; the attenuation value of lung parenchyma (between −600 and −900 Hounsfield Unit) was used to compute the percentage of functioning tissue resected and to correct the ppoFEV1, as proposed by Wu and colleagues [2], because lung-perfusion scintigraphy was performed only in patients with worst preoperative PFT. This method had been demonstrated to be a valid substitute of lung-perfusion scintigraphy, with a good correlation of values found by the two methods [3].

Follow-up information was obtained either during out-patient visits or by telephone interviews with the patient or his/her relative, or physician. Follow-up was completed in all patients within June 2008.

Data were analyzed using Statistical Package for Social Science (SPSS) software 13.0 (SPSS Inc., Chicago, IL, USA). Unpaired *t*-test and Mann—Whitney *U*-test were used for comparison of means of continuous variables between groups, while paired *t*-test was used to assess differences within groups between preoperative and postoperative spirometric values. Chi-square or Fisher's exact test was used for categorical variables. Correlation with curve estimation was used for analysis of relationship between preoperative FEV1 (considered as continuous variable) and postoperative percentage of FEV1 loss. A *p* value less than 0.05 was considered statistically significant.

3. Results

Demographic, clinical, and pathologic characteristics are summarized in Table 1.

Patients were categorized into two groups (mild vs moderate COPD) according to the global initiative for chronic obstructive lung disease (GOLD) criteria [4]: group 1 (G1) FEV1% <80%; group 2 (G2) FEV1% ≥80%).

The two groups were homogeneous regarding the number of patients, gender, age, pathologic stage, co-morbidities, and histology. Table 2 shows the type of concomitant diseases of the two groups of patients. The cumulative rate of complications was 38% in group 1 and 25% in group 2 ($p = 0.04$), whereas the incidence of major complications was not different in the two groups (15% vs 12%; $p = 0.72$). Considering the whole population which this series of patients came from, combined perioperative and in-hospital death was 6.5% in group 1 and 11.5% in group 2 ($p = 0.35$).

All patients underwent posterior-lateral muscle-sparing thoracotomy, anatomical lobectomy, and mediastinal lymph-node dissection. At the time of repeated PFT, no patients suffered significant thoracic pain or exacerbation of COPD that could have worsened spirometric parameters. Post-operative Eastern Cooperative Oncology Group (ECOG) status (according to the criteria proposed by Eastern Cooperative Oncology Group) was not different between the two groups.

Comparing preoperative and postoperative PFT in group 1, we observed a statistically significant variation only for FVC% (81.7 vs 68.4, $p = 0.016$) and for residual volume percentage (RV%) (140.9 vs 105.2, $p = 0.048$), while FEV1% dropping from

Table 1. Main demographic, clinical and pathological data of population.

	Group 1	Group 2	*p* values
Age (mean ± SD)	80.6 ± 0.4 years	81.5 ± 1 years	0.88
Gender (%):			
Male	10 (83.3)	12 (100)	0.68
Female	2 (16.7)		
Smokers before surgery (%)	12 (100)	11 (91.6)	0.55
Co-morbidities (%)	8 (66.7)	6 (50)	0.49
Pts with more than one co-morbidity (%)	4 (33.3)	5 (41.6)	
Respiratory parameters			
FEV1 (mean % of predicted value ± SD)	67.8 (±8.6)	88.5 (±7.9)	<0.001
FVC (mean % of predicted value ± SD)	81.7 (±10.9)	96.8 (±5.2)	<0.001
RV (mean % of predicted value ± SD)	140.9 (±41.4)	133.2 (±25.5)	0.33
Motley index	1.33 (±0.22)	1.24 (±0.05)	0.26
COPD index	1.32 (±0.12)	1.54 (±0.13)	0.001
DLCO (mean % of predicted value ± SD)	104.5 (±19.9)	88.1 (±11.6)	0.49
PaO_2 (mean ± SD)	81.9 (±6.6)	76 (±1.9)	0.079
$PaCO_2$ (mean ± SD)	37.6 (±3)	41.3 (±2.8)	0.084
pH	7.41 (±0.01)	7.40 (±0.01)	0.27
Pathological stage (%)			
I	8 (66.7)	9 (75)	0.66
II	3 (25)	3 (25)	0.79
III	1 (8.3)	0	0.45
Histology			
Adenocarcinoma	8 (66.7)	4 (33.3)	0.09
Squamous cell c.	3 (25)	6 (50)	0.15
Other	1 (8.3)	3 (16.7)	0.22

Table 2. Co-morbidities.

Co-morbidity	Patients (Group 1)	Patients (Group 2)
Hypertension	4	6
CAD	1	1
Kidney failure (Creatinine>2 mg/dl)	2	2
Vascular disease	0	2
Diabetes mellitus	1	0
Chronic atrial fibrillation	1	0
Heart valvular disease	0	2

Table 4. Mean variations of spirometric and arterial blood gas values before and after surgery in Group 2.

	Before surgery	After surgery	*p* values
FEV1%	88.3 (±7.9)	73.7 (±4.7)	<0.001
FVC%	96.8 (±5.2)	90.6 (±17.1)	0.11
RV%	133.2 (±27.1)	96 (±25.3)	<0.001
DLCO%	88.4 (±11.6)	65.5 (±12.8)	0.001
DLCO/VA%	83 (±38.4)	91.3 (±22.7)	0.38
PaO_2	76 (±7.6)	69.3 (±5.1)	0.12
$PaCO_2$	41.3 (±4.9)	40.4 (±4.4)	0.87
pH	7.40 (±0.04)	7.38 (±0.01)	0.91

67.8 to 59.1 did not reach a significance ($p = 0.06$). In group 2, FEV1% (88.3–73.7, $p < 0.001$), RV% (133.2–96, $p < 0.001$) and DLCO% (88.4–65.5, $p = 0.001$) showed significant variations. Reduction of RV% was significant in both groups; see Tables 3 and 4.

Comparing the variation of PFT parameters between the two groups, we note that mean FEV1 loss after surgery was −7.9% in group 1 and −14.9% in group 2, although the statistical difference was not significant ($p = 0.17$); further, differences in FVC% between the two groups were not remarkable (−13.3% in group 1 and −6.7% in group 2; $p = 0.33$). DLCO% loss was much higher in group 2 than in group 1 (−22.5 vs +1.5, $p = 0.001$), but the difference was no more significant considering DLCO% corrected by alveolar ventilation (VA), (Table 5).

Six patients among 24 showed an improvement of actual postoperative FEV1%, ranging from +1.5 to +7.3 compared with the preoperative value. All of these patients had a preoperative FEV1% lower than 60% and had undergone an upper lobectomy. Type of lobectomy had no influence in FEV1% loss in group 2 (upper lobectomy: −14.5%; lower lobectomy: −15.6%, $p = 0.81$), while it reached statistical significance in group 1 (upper lobectomy: +5.4%; lower lobectomy: −14.5%, $p = 0.05$), (Table 6). Actual postoperative FEV1% (apoFEV1%) and ppoFEV1% ratio was calculated for each patient: mean apo/ppoFEV1% was higher in patients of group 1, who received an upper lobectomy (1.32), compared with the other three categories in which ratio was almost equal to 1.

It must be pointed out that the same six patients, who gained advantage from surgery, had a homogeneous or upper-lobe pattern emphysema as confirmed by both CT scan and lung-perfusion scintigraphy.

Considering FEV1 as a continuous variable, linear regression analysis showed a significant inverse correlation between preoperative value of FEV1% and FEV1 percentage loss after surgery (B: −0.63, R^2: 0.46; $p < 0.01$), thus confirming the lesser FEV1% loss in patients with lower preoperative FEV1% and *vice versa* (Fig. 1).

Regarding blood gas tests, in group 1, the difference in PaO_2, PCO_2, and pH before and after surgery was not significant. Patients of group 2 showed a significant PaO_2 decrease after surgery. No differences were found between the two groups at the time of follow-up (Tables 3 and 4).

4. Discussion

In recent years, the percentage of patients aged more than 80 years referred to our Institution has constantly grown from 2.3% in the early 1990s to 8% in 2000 and 14% in 2007. Advanced age and increasing prevalence of major co-morbidities have made patients with NSCLC even more difficult to be scheduled for surgery. Because of the common risk factors underlying the two diseases (smoking, age), many patients with resectable tumors also present COPD with various grades of airflow obstruction. It is well known that patients with severe emphysema and low preoperative FEV1 are at high risk of complications and a poor clinical outcome.

Octogenarians are often denied lobectomy in favor of sub-lobar resections as a compromise operation, mainly because of low preoperative respiratory function and co-morbidities as also because of their advanced age. In our experience, further, octogenarian patients with NSCLC in stage I and II, who have reached a remarkable long-term survival and life expectancy, are more often limited by relapsing disease rather than age or co-morbidities [5].

On the other hand, lung-volume reduction surgery (LVRS) has been demonstrated to improve lung function in properly selected patients with severe emphysema. McKenna and colleagues [6] reported in 1997 that improvement in ppoFEV1% and dyspnea score was more evident in patients aged under 70 years, although the differences were not statistically significant. A growing number of studies in the

Table 3. Mean variations of spirometric and arterial blood gas values before and after surgery in Group 1.

	Before surgery	After surgery	*p* values
FEV1%	67.8 (±8.6)	59.1 (±8.7)	0.06
FVC%	81.7 (±10.9)	68.4 (±13.1)	0.016
RV%	140.9 (±45.1)	105.2 (±39.9)	0.048
DLCO%	71 (±13.9)	72.5 (±12.1)	0.182
DLCO/VA	104.5 (±9.8)	112 (±34.6)	0.76
PaO_2	81.9 (±9.6)	68.4 (±6.6)	0.66
$PaCO_2$	37.6 (±3.7)	35.2 (±2.8)	0.71
PH	7.41 (±0.02)	7.43 (±0.01)	0.88

Table 5. Comparison in variations of spirometric parameters between the two Groups.

	Group 1	Group 2	*p* values
FEV1%	−7.9 (±13.1)	−14.6 (±10)	0.17
FVC%	−13.3 (±16.1)	−6.753(±16.2)	0.33
RV%	−35.2 (±48.7)	−36.700 (±9.2)	0.94
DLCO%	+1.5 (±1.7)	−22.5650 (±17.9)	0.02
DLCO/VA	21.4 (±28.3)	8.2733 (±31.4)	0.47
PaO_2	−3.5 (±5.1)	−6.7 (±4.3)	0.15
$PaCO_2$	−2.4 (±5.7)	−0.9 (±1.6)	0.46
PH	+0.02 (±0.2)	−0.02 (±0.1)	0.21

Table 6. Variations of FEV1.

		Number of patients	Mean (±SD)	Range	*p* values
Group 1	Upper lobectomy	4	5.35 (±2.25)	3.4—7.3	0.005
	Lower lobectomy	8	−14.55 (±10.86)	−24.6—2.2	
Group 2	Upper lobectomy	8	−14.05 (±11.77)	−32.1 to −3	0.806
	Lower lobectomy	4	−15.67 (±6.55)	−21.3—10	

recent years have reported an improvement of respiratory function after lobectomy in some patients with moderate/severe COPD [7], or at least a better apoFEV% than ppoFEV1%. In such cases, the authors have hypothesized that lobectomy could have a LVRS effect [8]. In the evaluation of patient candidates for surgery, spirometry is still considered the gold standard: ppoFEV1% is the most powerful predictor of medical postoperative mortality and morbidity as demonstrated by Kearney and colleagues [9]. The second-level assessments as inhalation-perfusion lung scintigraphy and cardio-respiratory exercise test may be useful in further evaluation of 'critical' patients: however, while they demonstrated valid predictors of postoperative complications, they did not clearly show a higher accuracy than simple ppoFEV1% obtained by calculation of broncho-pulmonary segments removed [3]. These data from literature suggested to us that even elderly patients with less severe COPD could obtain some benefit from resection of emphysematous parenchyma and, therefore, in the decision-making process that leads to schedule an octogenarian for lung surgery; additional considerations should be made in evaluating respiratory function: apart from preoperative FEV1%, even ppoFEV1% could be inaccurate in some cases in predicting the real post-surgical lung reserve loss.

It is now clear that lung-volume reduction benefits act throughout to augment elastic recoil of small bronchi in the remaining lung and favorable thoracic-wall remodeling with improved respiratory motion and use of diaphragm [10]. Dyspnea is also relieved by drop of total lung capacity and use of accessory respiratory muscles [11].

Patients of this series obviously did not accomplish the criteria for LVRS and, on the other hand, lobectomy is not the standard surgical option for lung-volume reduction. The removal of part of functioning lung tissue, together with emphysematous tissue, can explain why group 1 patients showed, after lobectomy, a significant FVC% loss that is not observed after LVRS. However, some physiological effects of LVRS remain and are responsible of the remarkable drop of RV% and the not-significant loss in FEV% after surgery in group 1: DLCO showed a gain of +1.5 at follow-up, probably due to improvement in the ventilation—perfusion ratio. On the contrary, in group 2 patients with better-preserved pulmonary function, lobectomy strongly diminished FEV1% and also DLCO%, because of the resection of a major portion of functioning lung. These results confirmed reports of other authors [12,13] that pointed out a better pulmonary function preservation in patients with major airflow obstruction.

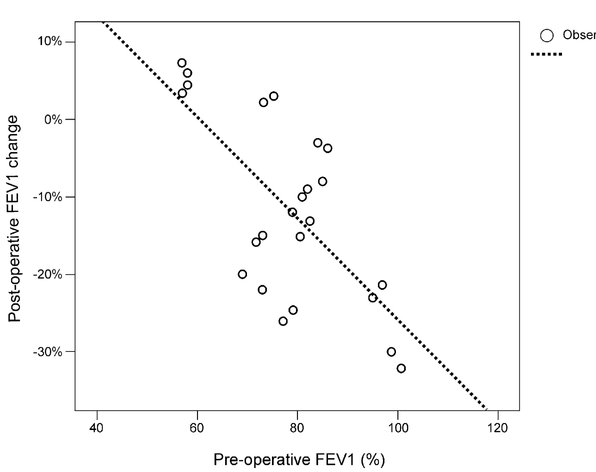

Fig. 1. Correlation between preoperative FEV1% and variations of FEV1% after surgery.

It must be noted that most of these studies report functional results after 1, 3, or 6 months: at this time, the post-thoracotomy pain could be still present in some cases, maybe causing a restrictive pattern and, consequently, a bias of the results [11]. In our series, all patients received a posterolateral muscle-sparing thoracotomy, reducing a possible factor conditioning the amount of thoracic pain.

The benefit of an upper lobectomy with regard to lower lobectomy in our series has emerged in patients with higher airflow impairment (group 1), even in case of homogeneous emphysema. This contrasts with the report of Sekine and colleagues [14], who found in their series a better preservation of lung function post-lower lobectomy. Nevertheless, they could not prove the reason adduced to this phenomenon, because the narrowing of lower lobar bronchus following anatomical repositioning after upper lobectomy has never been demonstrated. Probably, the better results after upper lobectomy simply reflect predominantly upper-lobe emphysema, and the same physiopathologic considerations should be valid in any case of resection of less-functioning lung lobe, but we have no data about this. Besides, it should be kept in mind that, even after LVRS with appropriate indication, in some cases, ppoFEV1% and FVC% are inaccurate and, on the other hand, clinical outcome and effort tolerance do not necessarily correlate with post-operative PFT. In another work on the same series of patients, we demonstrated that major complications were related to resection of more than one lobe or combined lung and chest-wall resections and mortality was acceptable after lobectomy (8.4%) [5].

ECOG status and dyspnea score did not differ significantly between preoperative and postoperative period neither in the original series nor in this smaller one: in particular, after surgery, global performance status and exercise tolerance seems to reach a similar level in both mild and moderate COPD patients (groups 1 and 2).

In conclusion, lobectomy, if necessary to achieve a radical resection, is a feasible option in octogenarian patients: in case of poor respiratory reserve, additional considerations should be made before excluding them from surgery because ppoFEV1% is inaccurate in particular cases. These more-compromised patients could benefit from a preoperative physiotherapic pulmonary rehabilitation program: in this way, it could be possible to minimize the rate of minor post-operative complications that are probably related to 1st day FEV1% as suggested by Varela and colleagues [15]. Lung volumes remodeling, in fact, takes at least some months to complete and favorable effects are not immediately available.

The present study suffers from some limitations. It is difficult to eliminate bias such as the preoperative optimization of respiratory reserve through medications (steroids, bronchodilators, and antibiotics) and the postoperative programs of physical rehabilitation. We tried to select a homogeneous cohort of patients with strict inclusion criteria to establish the pure effect of lobectomy after a long time, enough to allow the remodeling processes of lung and thoracic wall until the final steady result. This selection has produced a small series, often not sufficient to reach statistic significance in some tests.

Lung-perfusion scintigraphy was not routinely performed; hence, we had to use the CT scan estimation method to obtain corrected ppoFEV1%: the few cases that were studied with lung scintigraphy, however, demonstrated almost equal values.

Finally, the retrospective nature of the study itself implies that some patients were denied surgery; therefore, for example, we have no available data of patients with lower preoperative FEV1 and a homogeneous pattern of emphysema, who received a lower lobectomy; hence, the benefit of upper lobectomy could only be deduced on a physiological basis.

In conclusion, also in octogenarian patients with moderate COPD, there is a better preservation of pulmonary function than predicted. Upper lobectomy particularly seems to minimize the FEV1 loss in these patients and this could extend the indication to a curative lobectomy in a larger number of patients with higher airway obstruction.

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