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ORIGINAL ARTICLE

THORACIC

Impact of interstitial lung disease on short-term and long-term survival of patients undergoing surgery for non-small-cell lung cancer: analysis of risk factors†

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Abstract

OBJECTIVES: The study aimed to determine the impact of interstitial lung disease (ILD) on postoperative morbidity, mortality and long-term survival of patients with non-small-cell lung cancer (NSCLC) undergoing pulmonary resection.

METHODS: We performed a retrospective chart review of 775 consecutive patients who had undergone lung resection for NSCLC between 2000 and 2009. ILD, defined by medical history, physical examination and abnormalities compatible with bilateral lung fibrosis on high-resolution computed tomography, was diagnosed in 37 (4.8%) patients (ILD group). The remaining 738 patients were classified as non-ILD (control group). We also attempted to identify the predictive factors for early and late survival in patients with ILD following pulmonary resection.

RESULTS: There was no significant difference between the two groups in terms of age (69 vs 66 years), sex (79 vs 72% male), smoking history (93 vs 90% smokers), forced expiratory volume in 1 s % of predicted (89 vs 84%), predicted values of forced vital capacity (FVC)% (92 vs 94%), types of surgical resection and histology. Patients with ILD had a higher incidence of postoperative acute respiratory distress syndrome (ARDS; 13 vs 1.8%, $P < 0.01$) and higher postoperative mortality (8 vs 1.4%, $P < 0.01$). The overall 5-year survival rate was 52% in the ILD and 65% in the non-ILD patients, respectively ($P = 0.019$). In the ILD group, at the median follow-up of 26 months (range 4–119), 19 (51%) patients were still alive and 18 (49%) had died in the ILD group. The major cause of late death was respiratory failure due to the progression of fibrosis ($n = 7$, 39%). In the ILD group, lower preoperative FVC% (mean 77 vs 93%, $P < 0.01$) and lower diffusing capacity of the lung for carbon monoxide (DLCO%; 47 vs 62%; $P < 0.01$) were significantly associated with postoperative ARDS.

CONCLUSIONS: In conclusion, major lung resection in patients with NSCLC and ILD is associated with an increased postoperative morbidity and mortality. Patients with a low preoperative FVC% should be carefully assessed prior to undergoing surgery, particularly in the presence of a lower DLCO%. Long-term survival is significantly lower when compared with patients without ILD, but still achievable in a substantial subgroup. Thus, surgery can be offered to properly selected patients with lung cancer and ILD, keeping in mind the risk of respiratory failure during the evaluation of such patients.

Keywords: Lung cancer • Acute respiratory distress syndrome • Postoperative care • Interstitial lung disease • Morbidity • Long-term survival

INTRODUCTION

The incidence of lung cancer is reported to be higher among patients who have interstitial lung disease (ILD) compared with that of the general population [1, 2]. The appropriate selection of patients with lung cancer and ILD for major lung resection is a challenge as a consequence of reduced cardiopulmonary reserve. Although most studies have shown inferior results in patients with ILD compared with patients without, there is a wide variation in reported postoperative morbidity and mortality (ranging from 0 to 18.2%) and also in long-term survival (5-year survival rate 0–65%) [3–8]. Moreover, the predictors of short- and long-term survival are not well defined. It is also unknown what type of ILD carries a higher risk of postoperative morbidity and mortality.

The aim of this study was to detail our experience with lung resections for non-small-cell lung cancer (NSCLC) in patients

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with ILD in order to determine the impact of ILD on postoperative morbidity and mortality and long-term survival. We also attempted to identify the predictive factors for early and late survival in patients with ILD following pulmonary resection.

MATERIALS AND METHODS

Population

We performed a retrospective analysis of 775 consecutive patients operated on for NSCLC at the University Hospital of Siena from January 2000 to December 2009, in order to identify all patients also affected by ILD. This 10-year interval was chosen because the staging tools, surgical techniques, surgical team and postoperative care did not change during this time frame.

Thirty-seven (4.8%) patients carried a preoperative diagnosis of ILD, based on medical history, physical examination and abnormalities compatible with bilateral lung fibrosis on high resolution computed tomography (HRCT) (honeycombing with basal and peripheral predominance, peripheral reticular shadow or ground-glass opacity) and constituted the study group (ILD group). The remaining 738 patients who did not show any preoperative evidence of ILD served as the control group (non-ILD group). The types of ILD were classified according to recently reclassified American Thoracic Society/European Respiratory Society criteria [9].

The Institutional Review Board of the University Hospital of Siena approved this retrospective study. The patients had undergone surgery after providing informed consent, and the need for individual consent of patients whose records were evaluated was waived because they were not identified in the study. Information about preoperative patient characteristics, disease status, surgical procedures, postoperative complications, pathological findings and outcome of treatment was collected.

Patient selection and management

Assessment included a detailed medical history, physical examination, routine blood tests, electrocardiogram, echocardiography, blood gas analysis, spirometry and estimation of the carbon monoxide diffusion capacity of the lung (DLCO).

Cardiac stress tests and coronary angiography were performed when indicated by a history of angina pectoris or by significant ischaemic signs in the basal electrocardiogram; cardiorespiratory tests and/or lung perfusion scintigraphy were executed as second level tests in case of the predicted postoperative forced expiratory volume in 1 s <40%.

Clinical staging was based on bronchoscopy, contrast-enhanced computed tomography (CT) of the chest, upper abdomen and brain; mediastinoscopy was carried out selectively in the case of enlarged mediastinal lymph nodes on CT (short axis >1 cm).

During the study period, the policy of our institution was to perform lobectomy as the procedure of choice whenever the predicted postoperative forced expiratory volume in 1 s was >1 l and the predicted postoperative DLCO was >30% reserving the sublobar resections for patients showing lower respiratory reserve.

The patients in the ILD group who were on steroids and/or immunosuppressants were given the same dose of steroids intravenously during the first two or three postoperative days of coming back to oral administration when an oral diet was resumed.

Pulmonary resections were performed via either a posterolateral thoracotomy or a lateral muscle-sparing thoracotomy. During the operation, the lung was kept inflated for as much time as possible and always during the dissection of fissures. Systematic lymph node dissection was performed in all patients.

After operation, transfusion was performed at a speed of 1.25 ml/kg/h, and oxygen administration was set at the level to maintain a Pulse Oximeter Oxygen Saturation of at least 93.

In our routine daily check-up of postoperative patients, chest X-ray is undertaken on postoperative days 0, 1, 4 and 7, reserving the CT scan and bronchoscopy in the case of a decreasing trend in pO_2 and a new infiltrating shadow on chest X-ray.

Postoperative complications

The incidence of postoperative pulmonary complications and that of hospital mortality (death from all causes during the same hospitalization or within 60 days of surgery) were analysed and compared between the ILD and non-ILD groups.

Pulmonary complications included pneumonia, prolonged air leak, atelectasis requiring bronchoscopy, bronchopleural fistula, empyema and acute lung injury (ALI)/acute respiratory distress syndrome (ARDS).

Pneumonia was defined as the presence of focal or diffuse infiltrate on chest X-ray associated with one or more of the following criteria: fever exceeding 38°C, purulent sputum, leukocytosis (>10 000/ml) or isolation of a pathogen in respiratory secretions.

Air leakage was defined as prolonged if it lasted for >7 days. ALI and ARDS were defined according to the American-European Consensus Conference on ARDS [10].

The final status of all patients was determined in January 2012 on the basis of either the patients' most recent clinic visit or hospitalization or by means of a telephone interview.

Statistical analysis

Statistical evaluation was performed by standard computer software (SPSS 9.0; SPSS, Inc., Chicago, IL, USA). All data are presented as mean ± standard deviation. Differences in continuous variables were tested by unpaired Student's *t*-test. Differences in categorical and dichotomic variables were tested by the χ^2 test and Fisher's exact test, respectively.

Survival was defined as an interval between the surgical resection and death or last contact and was calculated by means of the Kaplan–Meier method. Patients who were not reported as having died at the time of analysis were censored at the date they were last known to be alive (non-informative censoring). The comparison of survival between groups was made with the log-rank test.

In patients with ILD, the Cox multivariable proportional hazard regression model was used to identify the risk factors of late death. Clinical–pathological-related factors were quantified by univariable analysis, and all factors with *P*-values of <0.2 at univariable analysis were included in the multivariable Cox' proportional hazard model. A P-value of <0.05 was regarded as significant.

RESULTS

Demographics

The preoperative characteristics of all patients subdivided in the two groups are shown in Table 1. There was no statistically significant difference between the two groups in terms of age, gender, smoking history and preoperative pulmonary function.

The operative procedures were similar in the two groups. In the ILD group, 4 pneumonectomies, 30 lobectomies and 3 sublobar resections were performed.

The distribution of histological cell type of NSCLC and pathological stages were also similar in the two groups (Table 2). Twelve patients in the ILD group were on treatment with steroid and/or immunosuppressive drugs at the time of surgery, and 18 (49%) had a Borg dyspnoea score II–III.

Table 1: Preoperative characteristics of patients with and without ILD

	ILD group (n = 37)	Non-ILD group (n = 738)	P-value
Age	69.3 ± 8.8	66.2 ± 12.8	n.s.
Male sex	78.4%	74.8%	n.s.
Smoking history	93%	90%	n.s.
FEV1% predicted	88.8 ± 12.3	84.1 ± 0.4	n.s.
FEV1 (l)	2.24 ± 0.3	2.20 ± 0.59	n.s.
FVC% predicted	91.40 ± 12.01	94.59 ± 18.8	n.s.
FVC (l)	2.9146 ± 0.51	3.1350 ± 0.76	n.s.
DLCO% predicted	59.73 ± 14.34	65.53 ± 19.20	n.s.
Arterial basal pCO_2	37.1 ± 2.6	38.3 ± 2.1	n.s.
Arterial basal pO_2	79.1 ± 4.9	83.5 ± 3.8	n.s.

ILD: interstitial lung disease; FEV: forced expiratory value; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; n.s.: not significant.

Table 2: Operative procedures, histology and stage

	ILD group (n = 37)	Non-ILD group (n = 738)	P-value
Operative procedures			
Pneumonectomy	4 (10.8%)	90 (12.3%)	n.s.
Lobectomy	30 (81.1%)	528 (72.1%)	n.s.
Sublobar resections	3 (8.1%)	114 (15.6%)	n.s.
Histology			
Adenocarcinoma	16 (43.2%)	428 (48%)	n.s.
Squamous cell	13 (35.1%)	214 (29%)	n.s.
Other	8 (21.6%)	96 (13%)	n.s.
Stage I	16 (44%)	228 (33%)	n.s.
Stage II	10 (28%)	252 (37%)	n.s.
Stage III	7 (19.4%)	168 (24.6%)	n.s.
Stage IV	3 (8.3%)	36 (5.3%)	n.s.

ILD: interstitial lung disease; n.s.: not significant.

Relative risks in patients with ILD

Patients with ILD showed a significantly longer mean hospital stay (12 vs 9 days; $P < 0.01$) and developed postoperative ARDS more frequently than those without ILD (13.5 vs 2.3%; $P < 0.01$). The mean time from the operation to the diagnosis of ARDS was 2.2 ± 2.3 (range 2–5) days.

In the ILD group, the incidence of ARDS after pneumonectomy was 25% compared with 10% after lobectomy, and the ARDS was the cause of death in all 3 patients who died in the postoperative period for a hospital mortality of 8.1%. The hospital mortality was more common in patients with ILD than in patients without ILD (8.1 vs 1.4%; $P < 0.01$).

The analysis of the outcome related to specific surgical procedures also showed a significantly higher postoperative mortality for pneumonectomy (25 vs 3.3%; $P < 0.01$) and lobectomy (6.6 vs 1.3%; $P < 0.01$) in patients with ILD, compared with patients without ILD. No patient died after a sublobar resection in the ILD group (Table 3).

Except for the development of postoperative ARDS, there was no significant difference between the two groups, in postoperative pulmonary complications, including pneumonia, bronchopleural fistula, prolonged air leak and atelectasis requiring bronchoscopy (Table 4).

Table 3: Procedure-specific mortality and incidence of ARDS/ALI after pulmonary resection

	ILD group (n = 37)	Non-ILD group (n = 738)	P-value
Mean hospital stay	12.51 ± 5.5	9.58 ± 4.1	≤0.01
Total deaths	3 (8.1%)	10 (1.4%)	≤0.01
Pneumonectomy	1/4 (25%)	3/90 (3.3%)	
Lobectomy	2/30 (6.6%)	7/528 (1.3%)	
Sublobar resection	0/3	0/114	
ARDS/ALI	5 (13.5%)	17 (2.3%)	≤0.01
Pneumonectomy	1/4 (25%)	7/90 (7.8%)	
Lobectomy	3/30 (10%)	8/528 (1.5%)	
Sublobar resection	1/3 (33%)	2/114 (1.8%)	

ILD: interstitial lung disease; ARDS: acute respiratory disease syndrome; ALI: acute lung injury.

Table 4: Pulmonary morbidity

Pulmonary complications	ILD group (n = 37)	Non-ILD group (n = 738)	P-value
Prolonged air leak (≥1 week)	5 (13%)	112 (15%)	0.8
Pneumonia (fever and culture positive)	2 (5%)	18 (2%)	0.2
BPF	1 (2%)	6 (≤1%)	0.2
Atelectasis (FBS)	2 (5%)	77 (10%)	0.3
ARDS/ALI	5 (13%)	17 (2.3%)	≤0.01

ILD: interstitial lung disease; BPF: bronchopleural fistula; FBS: fibrobronchoscopy; ARDS: acute respiratory disease syndrome; ALI: acute lung injury.

Predictive factors for short-term outcome in patients with ILD

In the ILD group, preoperative characteristics were compared between patients who developed postoperative ARDS and those who did not. ILD patients with postoperative ARDS had significantly lower values of preoperative FVC% of predicted than those without postoperative ARDS (77.8 ± 6.3 vs 93.6 ± 11.1%, respectively; $P < 0.001$).

Furthermore, ILD patients with postoperative ARDS had significantly lower values of preoperative DLCO% than those without postoperative ARDS (47.6 ± 15.5 vs 61.9 ± 13.2%; $P < 0.001$).

There was no significant difference in age, gender, smoking history, other preoperative pulmonary function tests, pO_2, pCO_2, extent of pulmonary resection, histological cell type, the stage of NSCLC and type of ILD (idiopathic interstitial pneumonia [IP] vs pneumoconiosis; see Section 3.5) between ILD patients with postoperative ARDS and those without.

ILD patients with a preoperative FVC% of predicted >80% had 50% incidence of postoperative ALI/ARDS, while those with FVC % of predicted >90% had no incidence.

Long-term outcome

In the ILD group, at the median follow-up of 26 months (range 4–119), 19 (51.3%) patients were still alive and 18 (48.7%) patients had died. The most common cause of late death was respiratory insufficiency due to the progression of fibrosis (n = 7; 38.9%), followed by the development of second primary lung tumours (n = 4; 22.2%), tumour recurrence (n = 2; 11.1%) and other (n = 2; 11.1%). In the control group, at the median follow-up of 32 (range 3–120) months, 437 (60%) patients were still alive and 301 (40%) had died. Differently from the ILD group, the major cause of late death was tumour recurrence (local or distant recurrence documented in at least 50% of patients who had died).

The actuarial 5-year survival rate was 63 and 52%, and the median survival was 47 ± 4.2 and 29 ± 5.4 months in patients without and with ILD, respectively. Actuarial survival was significantly worse in patients with ILD than in patients without ILD ($P = 0.019$; Fig. 1).

In the ILD group, the actuarial 5-year survival rate was significantly higher in patients with N0 disease (n = 24; 70% 5-year survival) than in patients with N1–N2 disease (n = 13; 12% 5-year survival).

Outcome in patients with ILD related to histopathology

The histological examination of the resected specimens of patients with ILD showed that 19 (51.4%) patients had IP, including 11 (29.8%) cases of idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) and 8 (21.6%) cases of non-specific interstitial pneumonia, that was idiopathic in 4 (10.8%) patients and related to collagen vascular disease in another 4 (10.8%) patients. The remaining 18 patients had pneumoconiosis.

Among 5 patients with ILD who developed postoperative ARDS, 3 had pneumoconiosis and 2 had IPF/UIP.

The Kaplan–Meier survival analysis showed no significant difference between patients affected by pneumoconiosis (n = 18) and by IP (n = 19; Fig. 2).

Risk factors for late death in patients with ILD

No preoperative characteristics or operation data selected in the univariable analysis (Table 5) were identified as predictors of late death, according to Cox's proportional hazard model (Table 6).

DISCUSSION

This study was undertaken to evaluate the role of surgery in patients with concomitant lung cancer and ILD and to identify predictive factors for survival following lung resection.

Our study differs from most others in the fact that only patients with a preoperative diagnosis of ILD were included, with 12 of them already on steroid or immunosuppressive treatment at the time of lung cancer resection and 49% of them complaining of a Borg dyspnoea score II–III.

We found that patients with ILD present a significantly higher incidence of postoperative ARDS (13.5 vs 2.3%; $P < 0.01$) and consequently higher postoperative mortality (8.1 vs 1.4%; $P < 0.01$) than those without ILD.

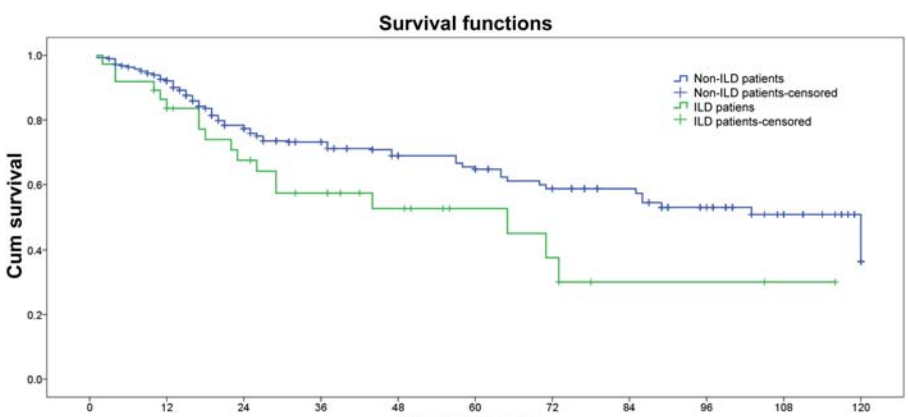

Figure 1: Survival curves after pulmonary resection for the non-ILD patients (n = 775) and the ILD patients (n = 37), ($P = 0.019$).

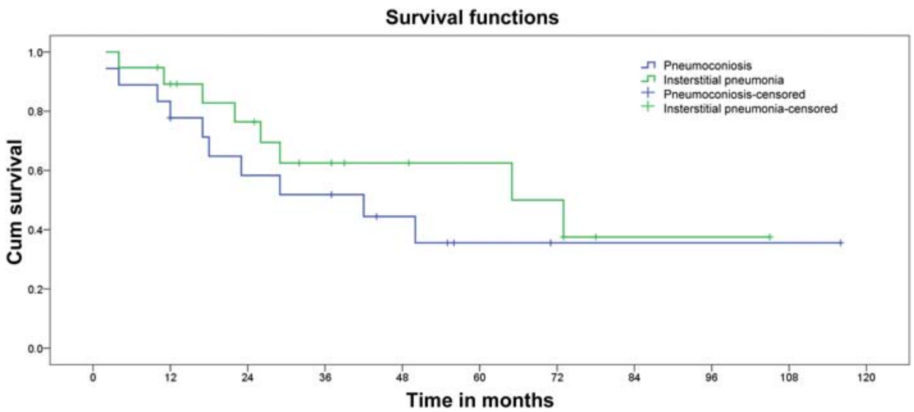

Figure 2: Survival curves after pulmonary resection in patients affected by pneumoconiosis ($n = 18$) and by IP ($n = 19$), (P = n.s.).

Table 5: Univariate comparisons between patients with late death and without late death

Variables	Alive ($n = 19$)	Death ($n = 15$)	P-value
Male sex	14	13	0.75
Age	68.8 ± 9.7	69 ± 7.1	0.96
Major co-morbidity	9	11	0.43
Procedure			
Lobectomy	18	10	0.50
Histological type			
Adenocarcinoma	9	6	0.31
Squamous cell carcinoma	5	7	
Pathological stage			
1	11	5	0.25
Type of ILD			
IIP	10	7	0.73
Pneumoconiosis	9	8	
Morbidity	6	5	0.92
Hospital stay	12.1 ± 6.4	11.7 ± 3	0.83
PaO_2	78.4 ± 4.9	78.2 ± 6.8	0.92
$PaCO_2$	36.6 ± 3.3	37.7 ± 1.4	0.3
FEV1 (l)	2.26 ± 0.43	2.25 ± 0.26	0.9
FEV1%	90.8 ± 14.9	84.2 ± 9.3	0.15
FVC (l)	3.02 ± 0.50	2.89 ± 0.48	0.44
FVC%	95.8 ± 12.4	89.4 ± 10	0.11
DLCO	61.7 ± 14.3	57.2 ± 15.6	0.42
DLCO/VA	72.5 ± 15.1	70.5 ± 22.4	0.78

ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; VA: alveolar volume.

Table 6: Predictors of late death by multivariate Cox regression analysis applied to patients with ILD

Variables	HR (95% CI)	P-value
FVC%	0.960 (0.889–1.036)	0.29
FEV1%	1.003 (0.924–1.088)	0.95

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; HR: hazard ratio; CI: confidence interval.

Even the analysis of the outcome related to the specific surgical procedures showed a significantly higher postoperative mortality for pneumonectomy (25 vs 3.3%; $P < 0.01$) and lobectomy (6.6 vs 1.3%; $P < 0.01$) in patients with ILD, compared with patients without ILD. In fact, the prognosis of postoperative ARDS particularly in patients with ILD is extremely poor, with mortality ranging from 50 to 100% [3–8]. In our study, 3 of the 5 ILD patients who developed postoperative ARDS died.

Excluding the study of Fujimoto *et al*. [6] showing no early postoperative mortality in patients with IPF and lung cancer, the incidence rates of postoperative morbidity and operative mortality are both significantly higher in patients with ILD, ranging from 32 to 54% and from 8 to 18.2%, respectively [3–6]. In particular, patients with ILD seem to be more prone to develop postoperative ARDS, with an incidence of 21–27% in several series [3–5, 11].

It has also been recently suggested that acute exacerbation of IPF may play a role in the pathophysiology of postoperative ARDS [8] and that subpleural honeycombing on HRCT is an independent risk factor for postoperative ARDS in patients without clinical evidence of ILD [12], reinforcing the concept that patients affected by ILD are at an increased risk of developing postoperative ARDS.

The pathogenesis of postoperative ALI/ARDS is not well understood, but it is likely that multiple influencing factors come into play, including excessive perioperative fluid administration [13], extent of resection [14], duration of operation [14], high-inspired oxygen concentration with the production of reactive oxygen species and capillary endothelial damage as a consequence of haemodynamic shear stress [15].

In addition, one-lung ventilation (OLV), used during lung resection, is considered to be one of the most important causative factors of postoperative ARDS, since the dependent lung is exposed to barotrauma and volutrauma and there is a conspicuous oxidative stress due to ischaemia–reperfusion resulting from collapse and reinflation of the operative lung [16–18].

Lungs with pre-existing interstitial disease have less elastic tissue and could therefore be more susceptible to volotrauma and barotrauma. These data indicate that shortening the OLV duration in patients with ILD may be useful in reducing the occurrence of postoperative ARDS.

We kept the time of OLV at a minimum in all patients with ILD, resulting in a mean time of only 25 min (data not shown); although we consider this an important prophylactic measure, no conclusions about this aspect can be drawn.

The extent of resection has been consistently reported as a risk factor for postoperative ARDS [14]. In this study, we found that ILD patients undergoing pneumonectomy showed an incidence rate of 25% of postoperative ARDS, although the extent of resection was not a statistically significant risk factor, probably because of the small sample size.

The patient who developed ARDS post pneumonectomy died, while no ILD patient undergoing sublobar resection died. Every staging tool, including Positron Emission Tomography, Endobronchial Ultrasound, Endoscopic Ultrasound and video mediastinoscopy, should be used in patients with ILD to better define the extent of a complete resection before intervention, in order to avoid operating on patients requiring a pneumonectomy. On the other hand, a sublobar resection, when technically feasible and oncologically appropriate, could be a good alternative to lobectomy in such high-risk patients.

The identification of risk factors for hospital mortality is then crucial, in order to select ILD patients for lung surgery properly.

Several reports suggest that a number of physiological parameters are useful in assessing disease severity and predicting survival in patients with ILD [19, 20]. To date, however, predicting the occurrence of postoperative morbidity and mortality based on preoperative baseline clinical variables has proved to be challenging [8–21]. A few studies have identified different prognostic risk factors for postoperative ARDS, including low DLCO and high preoperative composite physiological index [5], decreased FVC [3] and pre-existing co-morbidities [11].

We could demonstrate in this study that, in ILD patients, lower values of preoperative FVC% and DLCO% were both associated with postoperative ARDS. ILD patients with a preoperative FVC% of predicted <80% had 50% incidence of postoperative ALI/ARDS, while those with FVC% of predicted >90% had no incidence. The interpretation of the results of spirometry can be confounded by the presence of concomitant ILD and emphysema (not rare in heavy smokers), which may lead to spurious preservation of lung volumes [22]. Thus, the measurement of DLCO% is particularly important in patients with ILD, since the decreased diffusing capacity reflects the severity of ILD itself and significantly increases the risk of developing postoperative ARDS.

Although late outcomes after lung resection are uniformly worse in patients with ILD compared with patients without ILD, long-term survival is still achievable in a super-selected group.

In this study, we observed a 5-year survival rate of 52% in patients with ILD, which is within the range of survival rates reported in the last 10 years. Saito *et al*. [7] showed a 5-year survival rate of 54.2% in patients with stage IA NSCLC and IPF, and Watanabe *et al*. [8] showed a 5-year survival rate of 61.6% in patients with IPF and stage IA and IB NSCLC. Chiyo *et al*. [4] found a 5-year survival rate of 35.6%, with survival strongly related to the nodal stage. For patients with potentially surgically curable disease, lymph node metastasis is the most important prognostic factor. As expected, we observed a significantly higher 5-year survival rate in ILD patients with N0 disease compared with N1–N2 disease. However, only 13 patients had N1 ($n = 8$) or N2 ($n = 5$) disease, making this analysis less meaningful. No predictors of long-term survival in the ILD group were identified in the Cox proportional hazard model. Inasmuch as 7 (39%) patients died due to the progression of fibrosis, this result could be related to the fact that the ILD course in individual patients is highly variable, and predicting the prognosis in individual patients is challenging. We cannot also exclude a type II error. For instance, the FVC % was associated in the univariate analysis with long-term survival but failed to be a significant factor in the multivariable analysis. It must also be considered that important variables like pneumonectomy or N disease were not included in the univariate analysis because they were represented with a number of less than five in each subgroup. Of note, the 4 patients who had pneumonectomy were dead at the time of the last follow-up.

In the ILD group, the most common cause of late death was respiratory insufficiency due to the progression of fibrosis. Seven patients with pulmonary fibrosis displayed a rapidly progressive disease leading to respiratory failure and death with a mean postoperative survival of only 14 (range 4–27) months. We speculate that surgical trauma and mechanical ventilation would have activated the progressive phase of fibrosis. On the other hand, only 2 (11%) patients died of cancer recurrence, while at least 50% of non-ILD patients died of cancer recurrence. These results suggest that to improve the outcome in ILD patients, strategies for preventing postoperative ARDS and the progression of fibrosis should be implemented.

It has been shown that early administration of low-dose methylprednisolone significantly reduces mortality from ARDS after thoracic surgery [23]. In the long run, a balance should be found between the utility of a steroid or immunosuppressive therapy to control the progression of ILD and their side effects, which could contribute to the development of a second primary lung cancer (SPLC). Indeed, another important finding was the high rate of development of an SPLC (4 patients) in the ILD group. This event, in addition to the higher postoperative mortality rate and chronic respiratory failure occurrence, might explain the poorer long-term results compared with non-ILD patients. For such a high rate of SPLC in ILD patients, an intensive surveillance after curative pulmonary resection for lung cancer has been advocated. Unfortunately, the treatment is limited by the reduced pulmonary reserve. None of our 4 ILD patients who developed an SPLC underwent surgery, because in 1 case the tumour was a small-cell lung cancer, and in the other 3 cases the pulmonary reserve was considered inadequate to withstand a second resection. Even chemotherapy and/or radiotherapy are of difficult application because both can contribute to or determine the progression of fibrosis [24].

The prognostic value of different types of ILD after pulmonary resection is unknown. The prognosis of IPF/UIP is generally the worst among the ILD, with a median survival of only 2–3 years from the diagnosis [25]. We did not find any significant difference in the long-term survival between patients with idiopathic IP and with pneumoconiosis, although definitive conclusions cannot be drawn from our findings because of the small sample size. It is also possible that a longer follow-up could be necessary to find a difference.

The limitations of this study are inherent to its retrospective design, being susceptible to various sources of bias that may not have been identified and controlled.

First of all, we acknowledged that all patients of this study with ILD represent a selected group, as demonstrated by their well-preserved pulmonary function. Patients with severe impairment of pulmonary function were excluded from surgery. This selection bias certainly has a significant impact on survival.

Secondly, our long-term results come from a survival analysis based on a median follow-up of 26 months. However, since the follow-up was 100% complete and the censoring in survival analysis was ‘non-informative’, our results would not have been affected by such a follow-up. Finally, this is a single-institution study and the limited sample size did not allow us to define some important aspects, such as the identification of the predictors of long-term survival or the relative importance of the type of ILD. These results should be confirmed by prospective studies including larger series of patients.

In conclusion, major lung resection in patients with NSCLC and ILD is associated with an increased postoperative morbidity and mortality. Patients with a low preoperative FVC% should be carefully assessed prior to undergoing surgery, particularly in the presence of a lower DLCO%.

Long-term survival is significantly lower compared with patients without ILD. Pneumonectomy is substantially contraindicated in patients with ILD.

However, long-term survival is still achievable in a substantial subgroup. Thus, surgery can be offered to appropriately selected patients with lung cancer and ILD, keeping in mind the risk of respiratory failure during the evaluation of such patients.

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