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Original article

Impact of preexisting interstitial lung disease on outcomes of lung cancer surgery: A monocentric retrospective study

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ABSTRACT

Introduction: Interstitial lung disease (ILD) is a known risk factor for lung cancer (LC). However, the surgical risk of LC in patients with ILD remains unclear. Therefore, we conducted a single-center retrospective study to assess clinical features and outcomes of LC population who underwent surgery with or without ILD.

Methods: Patients who underwent surgery for LC between January 2006 and June 2023 in our center were assessed using data extracted from the nationwide EPITHOR thoracic surgery database. Suspicion of ILD was based on patients' records. Confirmation of ILD was then made on the patient's medical and radiological history. Patients were classified according to the pattern of ILD. The study aimed to describe the outcomes after lung cancer resection in patients with confirmed LC-ILD group compared to those without ILD (LC-non-ILD): post-operative complications, disease-free survival (DFS) and overall survival (OS). A subgroup analysis was also performed on patients with idiopathic pulmonary fibrosis and lung cancer (LC-IPF).

Results: 4073 patients underwent surgery for LC at Assistance Publique des Hôpitaux de Marseille between January 2006 and June 2023. Of these, 4030 were in the LC-non-ILD group and 30 were LC-ILD patients. In the LC-ILD group, the predominant CT scan pattern was probable UIP (50 %). OS was not significantly lower in the LC-ILD group (45 months versus 84 months, $p = 0.068$). Dyspnea and tumor size were identified as potential univariate predictors of OS. No significant differences were observed on post-operative complications or their severity. The most common post-operative complications in the LC-ILD group were prolonged air leak, respiratory failure, or pneumonia. 13 patients had cancer recurrence in the LC-ILD group.

Conclusion: Our study provides a comprehensive analysis of a LC-ILD population features and outcome when undergoing surgery for LC. Patients with LC-ILD appeared to have a reduced OS compared with LC-non-ILD. Further investigations with larger prospective studies could be useful to confirm and develop these preliminary findings.

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1. Introduction

Interstitial lung disease (ILD) is a rare group of chronic lung disease with an incidence of 20 to 42 cases/100,000 [1]. ILDs include

various subtypes with a wide range of expression: such as idiopathic pulmonary fibrosis (IPF) or connective tissue disease associated ILDs (CTD-ILD) amongst others.

ILD share common pathogenic pathways with lung cancer (LC) [2] and are already known as a risk factor for LC [3]. LC prevalence among the ILD population is various in the literature, from 2.7 % to 48 % [4]. In addition, a recent meta-analysis suggests that LC accounts for 7 %

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of mortality in the ILD population [5]. While adenocarcinoma is the leading LC subtype in the general population, there is an increasing prevalence of squamous cell carcinoma in the ILD population, especially in the IPF population [6].

LC management in patients with ILD is based on expert panel guidelines considering the lack of dedicated studies [7]. However, surgery in the LC-ILD population is associated with higher postoperative morbidity and mortality, partly due to ILD acute exacerbation [8]. Previous studies on surgery for localized LC-ILD have identified a shorter disease-free survival (5 years - 49 %) and overall survival (5 years - 52 %) [8,9]. These outcomes are attributed to several prognostic factors, including type of resection, disease stage, Performans Status (PS), age and comorbidities.

A French nationwide study from the Epithor cohort database, identified nine prognostic factors (sex, age, histology, stage, body mass index (BMI), comorbidities, WHO Performance Status (PS), ASA score and type of surgical procedure) after lung cancer surgery in the general population [10]. Because of the rare prevalence of ILD in general population, its specific outcomes were not described in this study.

There is a critical balance between the risk of early exacerbation underlined by a higher incidence of adverse events after lung surgery (9.6–13 %) and persistent challenge of achieving adequate oncological control [11,12,13]. To date only one European study has addressed this issue[8].

This single-center retrospective study aims to assess the features of the LC-ILD surgical population and outcomes after lung cancer resection compared with the LC without ILD population:

postoperative complications, disease free survival (DFS) and overall survival (OS). The secondary objective was to evaluate the outcomes of the LC-IPF subgroup.

2. Materials and methods

2.1. Patients

All patients who underwent surgery for LC at Assistance Publique des Hôpitaux de Marseille (APHM), Marseille, France, between January 2006 and June 2023 were included. All patients had a confirmed LC and postoperative staging was performed according to the 8th edition of the Tumor Node Metastasis (TNM) classification for LC [14]. TNM stage is automatically updated with the newest version of TNM in the EPITHOR database. LC-ILD patients were identified by hospital electronic health records matched with the LC surgical cohort, EPITHOR. To ensure complete reporting, CT scan reports of all patients with DLCO under 60 % in our center EPITHOR surgical database were also reviewed to identify interstitial lesions.

2.2. Data

Perioperative and surgical data were prospectively entered into the nationwide EPITHOR database at the time of surgery with postoperative data added after patient discharge. Additional data were obtained from patient’s medical records. Variables with more than 15 % of missing data were excluded. In the EPITHOR database,

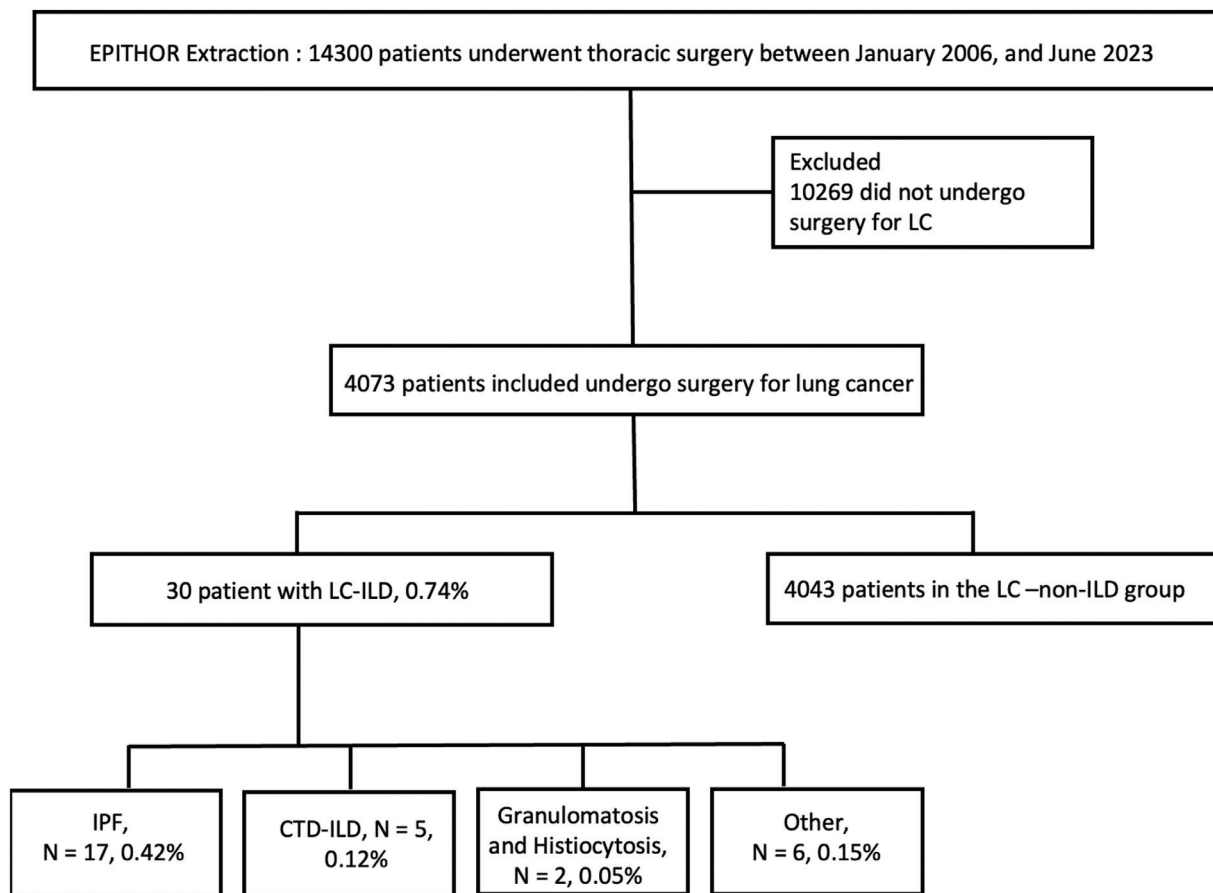


Fig. 1. a: Flowchart, LC-ILD cases in patients surgically treated for lung cancer. Prevalence of ILD subtypes specified in percentage. b: Representation of ILD diagnosis by year. LC: Lung cancer; LC-ILD: Lung cancer with interstitial lung disease, IPF: Idiopathic pulmonary fibrosis, connective tissue disease associated ILDs (CTD-ILD).

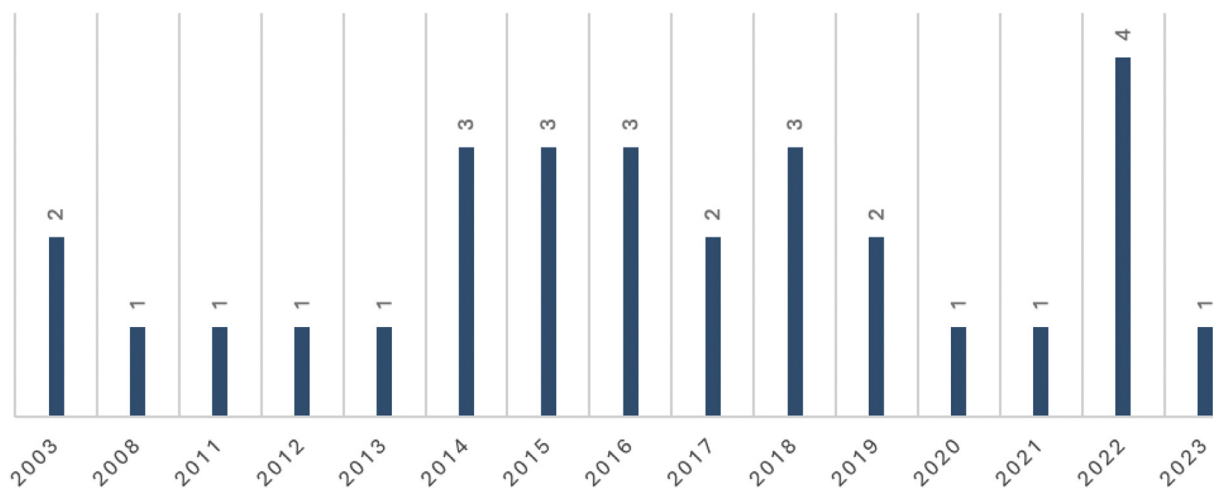


Fig. 1. Continued.

medical history is classified by systems, and a detailed list of comorbidities can be specified by the surgeon using a drop-down menu.

Peri-operative data included histology, adjuvant medical treatment details if available, cancer stage (TNM), localization, type of surgery, duration of surgery, length of hospital stay, ASA score (Physical Status Classification System), R0 resections, adverse events after surgery.

Demographics, clinical, and oncological data included sex, age, BMI, weight, height, PS, smoking history, country of birth, comorbidities (comorbidities in the EPITHOR database were defined as any medical event identified by the surgeon during the preoperative consultation), medical history, and occupational exposure. LC data included method of diagnosis, histology subtype, programmed Death-1 Ligand (PDL1) staining, molecular biology profile, completion of treatment plan, and detailed chemotherapy regimen.

Functional data included pulmonary functional test (PFT): Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC), FEV1/FVC, DLCO and six-minute-walk test (6MWT). GAP-Index was performed when possible.

Available preoperative and follow-up CT scans were reviewed by an experienced thoracic radiologist who confirmed ILD CT patterns [15].

In accordance with French regulation on retrospective observational studies, all patients received information stating that data could be anonymously analyzed for medical and epidemiological retrospective studies. No objection to the use of these data was identified. The computed patient study file was registered by our institution review board (registration number #RGPD 2019–01 PADS22–366).

2.3. Outcomes

This study assessed the outcomes after lung cancer surgery in patients with LC without ILD (LC-non-ILD) and patients with LC and ILD (LC-ILD). A subgroup analysis was also performed on patients with idiopathic pulmonary fibrosis and lung cancer (LC-IPF).

Baseline was set at day of surgery and the status of each patient (alive, dead, lost to follow-up, or relapse) was determined on the study end date set to June 30th, 2023. The overall survival was considered for all patients, and time to recurrence was only available for patients in the LC-ILD group.

Post operative complications were defined as adverse events (AEs) occurring within 90 days after surgery [16]. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) [17].

The objective of this study was to provide a clinical, functional and radiological description of LC-ILD population. Acute ILD exacerbation was defined as acute radiological or clinical worsening of ILD within 90 days of surgery. Chronic ILD progression was defined as clinical, functional or radiological deterioration within a year after surgery [7,18]. Functional decline was defined as a 5% decrease in predicted FVC or 10% decrease in predicted DLCO over 12 months [19].

2.4. Statistical analysis

Quantitative data were presented as mean, standard deviation (the assumption of normal distribution was assessed graphically using histograms and Q-Q diagrams) and compared using Student's *t*-test if valid (Mann-Whitney test otherwise). Categorical data were presented as numbers (percentages) and compared using the chi-2 test if valid (Fisher's exact test otherwise).

We first performed a univariate analysis using a logistic regression model, with odds ratios (OR) and their 95 % confidence intervals (95 % CI). Then, a multivariate logistic regression model with adjusted odds ratios (aOR) and 95 % confidence intervals (95 % CI) was performed: included data were selected based on their clinical relevance and the results of the univariate analysis. All tests were two-tailed and *p* values < 0.05 were considered statistically significant.

Survival analysis was conducted using Kaplan Meier curves and log rank test was used to compare survival curves.

The univariate Cox model was used to identify prognostic factors. Hazard ratios (HR) and their 95 % confidence intervals (95 % CI) were calculated for these factors. The multivariate Cox model was then performed with adjusted hazard ratios (aHR) and 95 % confidence intervals (95 % CI). The variables included in the multivariate model were selected based on their clinical relevance and the results of the univariate analysis. Statistical analyses were performed using RStudio software (Version 2023.03.0).

3. Results

3.1. Patients' characteristics

Between January 2006 and June 2023, 14,300 patients underwent thoracic surgery at Assistance Publique Hôpitaux de Marseille. Among them, 4073 underwent resection for lung cancer and 43 patients had LC with ILD suspicion. Of the 43 suspected LC-ILD cases, 30 patients were confirmed LC-ILD and 13 patients after radiological review were reclassified in the LC-non-ILD group. After reviewing the CT, it was found that the majority of these 13 patients (85 %) had

emphysema. Among the 30 patients in the LC-ILD group we identified 17 LC-IPF (Fig. 1).

First, we assessed the difference between the LC-ILD group and the LC-non-ILD group. The LC-ILD group was predominantly male (83.3 % versus 62 % $p = 0.02$) and were older (66.7 years old versus 65 $p = 0.002$). Mean pre-operative FEV1 % was higher in the LC-ILD group compared to the LC-non-ILD group (96 % versus 70 %, $p < 0.01$). FEV1/FVC ratio was higher in the LC-ILD group (81 versus 75, $p = 0.01$). DLCO was significantly lower in the LC-ILD group than in the LC-non-ILD group (61 % versus 69 %, $p < 0.01$). There were no significant differences found between the two groups in the six-minute walk test ($p = 0.7$) or dyspnea ($p = 0.5$).

Preoperative histology was performed more frequently in the LC-ILD group compared to the LC-non-ILD group (69 % versus 38 % $p < 0.01$). The LC-ILD group also exhibited more advanced post operative TNM stage, without significant difference in pre-operative stage. The proportion of squamous cell carcinoma was significantly higher in the LC-ILD group (40 % versus 20 %, $p = 0.004$) (Table 1).

3.2. Surgical data

There was no significant difference in the type of surgery: the most common procedure was lobectomy, and lymph node dissection was performed in the most of cases in both groups. Surgery duration

Table 1
Demographic and Clinical Characteristics of Patients Undergoing Lung Cancer Surgery with LC-ILD versus LC-non-ILD.

Variable	LC-non-ILD group n (%) or median [Q1-Q3]	LC-ILD group n (%) or median [Q1-Q3]	p value
Sex			0.016
	Female	1537 (38 %)	5 (17 %)
	Male	2505 (62 %)	25 (83 %)
PS			0.2
	0	2482 (61 %)	13 (43 %)
	1	1253 (31 %)	15 (50 %)
	2	242 (6.0 %)	2 (6.7 %)
	3	55 (1.4 %)	0 (0 %)
	4	11 (0.3 %)	0 (0 %)
Age	70 (61, 80)	78 (68, 90)	0.013
Weight	70 (61, 80)	78 (68, 90)	0.013
BMI	24.7 (22.0, 27.6)	26.1 (23.1, 28.7)	0.13
Tobacco (Pack Year)	35 (20, 50)	40 (15, 44)	0.7
Dyspnea			0.5
	0	1182 (29 %)	11 (38 %)
	1	1439 (36 %)	9 (31 %)
	2	1171 (29 %)	6 (21 %)
	3	214 (5.3 %)	3 (10 %)
	4	22 (0.5 %)	0 (0 %)
FEV1%	70 (58, 81)	96 (82, 114)	<0.001
FEV1/FVC ratio	75 (67, 82)	81 (75, 86)	0.010
DLCO	69 (58, 81)	61 (54, 68)	0.009
6 min-walk test	450 (405, 500)	441 (414, 525)	0.7
Comorbidities			<0.001
	None	138 (3.4 %)	8 (27 %)
	Yes	3905 (97 %)	22 (73 %)
Preoperative histology			<0.001
	None	2499 (62 %)	9 (31 %)
	Yes	1522 (38 %)	20 (69 %)
Preoperative treatment			0.7
	No	3679 (92 %)	27 (90 %)
	Yes	336 (8.4 %)	3 (10 %)
Preoperative stage			0.6
	Stage 0	7 (0.2 %)	0 (0 %)
	Stage I	2311 (58 %)	14 (48 %)
	Stage II	806 (20 %)	7 (24 %)
	Stage III	536 (14 %)	5 (17 %)
	Stage IV	308 (7.8 %)	3 (10 %)
Localization			0.012
	Inferior right	633 (16 %)	10 (33 %)
	Inferior left	532 (13 %)	7 (23 %)
	Superior right	1229 (30 %)	7 (23 %)
	Superior left	860 (21 %)	6 (20 %)
	Other	781 (19.6 %)	0 (0 %)
Definitive histology			0.004
	Invasive Adenocarcinoma	2623 (66 %)	18 (60 %)
	Squamous cell carcinoma	795 (20 %)	12 (40 %)
	Other	579 (14 %)	0 (0 %)
ASA score			0.2
	1	542 (13 %)	2 (7.4 %)
	2	2286 (57 %)	13 (48 %)
	3	1169 (29 %)	11 (41 %)
	4	42 (1.0 %)	1 (3.7 %)
	5	4 (<0.1 %)	0 (0 %)

¹n (%); Median (IQR).

²Fisher's exact test; Wilcoxon rank sum test.

Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC), FEV1/FVC, Diffusing Capacity of the lung for carbon dioxide (DLCO), patients with confirmed LC-ILD group (LC-ILD).

was significantly longer in the LC-ILD group (160 min) than in the LC-non-ILD group (120 min), $p = 0.004$. In both groups 10 % of surgeries were performed with robotic assistance ($p > 0.9$) (Table 2).

3.3. Oncological data

In the LC-ILD group pathological samples were obtained prior to surgery in most of patients and significantly more than in the LC-non-ILD group (69 % and 38 % respectively, $p < 0.001$). In the LC-ILD group it was commonly obtained by CT-guided biopsy in 59 % of cases, bronchoscopy in 25 %.

Median tumor size was 3 cm in both LC-ILD group and LC-non-ILD. In the LC-ILD group, tumor localization was mostly peripheral (93 %) and in abnormal parenchyma (73 %).

PDL1 expression in the LC-ILD groups was mostly between 1 and 49 % ($n = 9$, 33 %) and two patients (6 %) had PDL1 expression over 50 %. Molecular biology was available in 18 out of 30 patients. No alteration was identified in the epidermal growth factor receptor (EGFR), anaplastic lymphoma tyrosine kinase (ALK), or proto-oncogene tyrosine protein kinase 1 (ROS1) genes.

In the LC-ILD group, 52 % ($n = 16/30$) of patients had an indication for peri-operative treatment such as adjuvant chemotherapy. Two patients in the LC-ILD group did not follow the intended treatment protocol due to postoperative complications [20].

3.4. ILD data in LC-ILD groups

IPF was diagnosed in 46 % of patients and 17 % were identified as CTD-related ILD [21].

Regarding specific ILD therapies 23 % ($n = 7/30$) of LC-ILD cases received an antifibrotic agent, such as NINTEDANIB ($n = 3 = 43 %$) or PIRFENIDONE ($n = 4 = 57 %$). Another 30 % ($n = 7/23$) received immunosuppressive drugs.

The most common radiological patterns were probable Usual Interstitial Pneumonia (UIP) (50 %) or UIP (10 %). Table 3 shows the radiographic variables of the LC-ILD group.

In the LC-ILD group, only 50 % of patients ($n = 15$) had a previous CT scan before the preoperative CT scan, and none showed evidence of ILD worsening within the six months prior to surgery.

No clinical acute exacerbations were diagnosed. One patient exhibited acute CT worsening with no clinical symptoms.

Chronic radiographic worsening after surgery was found in 42 % of cases ($n = 12$). The main pattern of worsening in the LC-ILD was probable UIP accounting for 62% ($n = 8/12$) of cases, followed by UIP pattern in 23 % ($n = 3$) and fibrosing NSIP (non-specific interstitial pneumoniae) pattern in 1 case. 14 out of 30 patients with LC-ILD showed functional decline during the first year after surgery [22]. Table 3 shows the radiographic variables of the LC-ILD group. The median time between CT deterioration and surgery was 1 year (0.5 –2 years).

3.5. Overall survival (OS), disease free survival (DFS) and complications after surgery

Median OS in the LC-ILD group was lower than the LC-non-ILD group with no significant difference (45 (27 - NA) months versus 84 (80 – 91) months respectively $p = 0.068$) (Fig. 2). Cause of death was dominated by cancer related mortality (61 %)

The univariate Cox proportional hazards regression analysis highlighted preoperative dyspnea mMRC >1 (HR = 5.65 [1.09; 29.4], $p = 0.029$) and tumor size (HR = 1.13 [1.07; 1.60], $p = 0.011$) as potential predictive factors of overall survival. In the multivariable analysis, we combined these variables with the length of hospital stay and localization of LC, which were considered potential confounding variables. No independent predictive factors of overall survival were statistically significant. The median DFS of the LC-ILD group was 25

Table 2
Surgical Characteristics of Patients with LC-ILD versus LC-non-ILD.

Variable	LC-non-ILD group n (%) or median [Q1-Q3]	LC-ILD group n (%) or median [Q1-Q3]	p value
Surgery			0.5
Segmentectomy	386 (9.5 %)	5 (17 %)	
Lobectomy	2861 (71 %)	20 (67 %)	
Pneumonectomy	234 (5.8 %)	2 (6.7 %)	
Other	561 (14 %)	3 (10 %)	
Number of segments removed	4.00 (3.00 - 5.00)	4.00 (3.00 - 5.00)	0.77
Robotics surgery			>0.9
None	3609 (90 %)	26 (90 %)	
Yes	413 (10 %)	3 (10 %)	
Surgical approach			0.91
Thoracoscopy	1938 (43.9 %)	15 (52 %)	
Thoracotomy	2023 (50 %)	14 (48 %)	
Other	69 (1.71)	0 (0.00)	
Frozen section examination			0.8
Yes	1339 (33 %)	9 (31 %)	
No	2678 (67 %)	20 (69 %)	
Node dissection			0.6
None	324 (8.0 %)	2 (6.7 %)	
Biopsy	89 (2.2 %)	0 (0 %)	
Oriented	260 (6.4 %)	0 (0 %)	
Systematic	3370 (83 %)	28 (93 %)	
Length of surgery	120 (90, 156)	160 (115, 180)	0.004
Hospital Stay	8 (5, 13)	7 (6, 12)	0.4

Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC), FEV1/FVC, Diffusing Capacity of the lung for carbon dioxide (DLCO), patients with confirmed LC ILD group (c-LC-ILD).

Table 3
Clinical, functional and radiographic description of LC-ILD group.

Characteristic before surgery	LC-ILD group = 30
PFT :	
FVC (%)	94 (79.10)
KCO	70 (58.81)
PCO2	34 (32.37)
PO2	79 (77.87)
Antifibrosis treatment	7 (23)
NINTEDANIB	3 (43)
PIRFENIDONE	4 (57)
ILD GAP score	
0	3 (11)
1	3 (11)
2	3 (11)
3	12 (44)
4	5 (19)
5	1 (3.7)
CT pattern	
Fibrosing emphysema	3 (13)
UIP	8 (35)
Probable UIP	6 (26)
NSIP	3 (13)
Other	3 (13)
Emphysema	16 (53)
Evolution after surgery	
Chronic CT worsening	
No	7 (23)
Yes	12 (40)
CT pattern of worsening	
UIP	3 (23)
Probable UIP	8 (62)
NSIP	1 (7.7)

¹n (%); Median (IQR). PFT (Pulmonary Function Test), Forced Vital Capacity (FVC), Carbon monoxide transfer coefficient (KCO), partial pressure of oxygen (PO2), partial pressure of carbon dioxide (PCO2), Usual interstitial pneumonia (UIP), Non-Specific Interstitial Pneumoniae (NSIP).

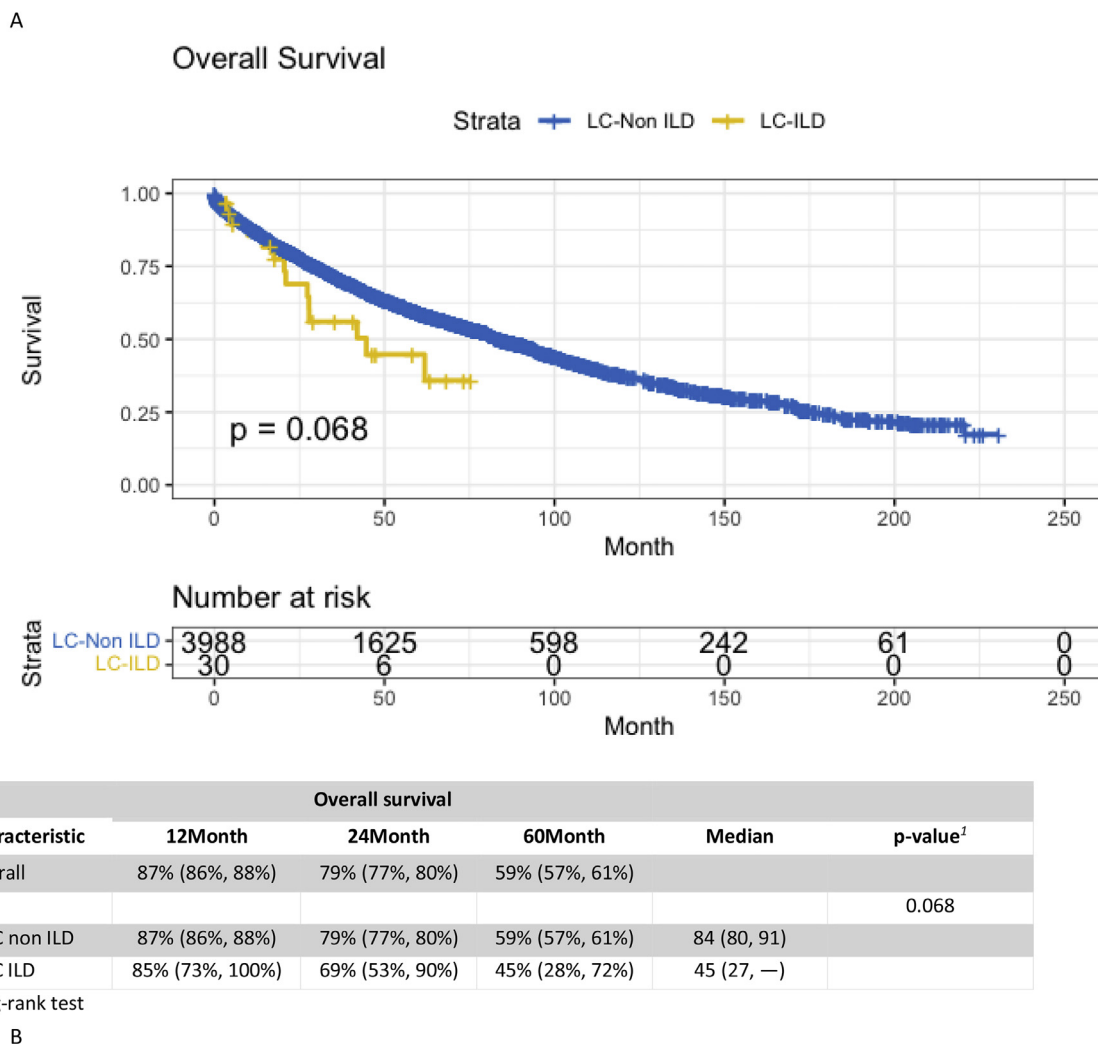


Fig. 2. Analysis of Overall Survival (OS) using Kaplan-Meier in LC-non-ILD versus LC-ILD (A) and log rank analysis in LC-non-ILD versus LC-ILD (B).

months. The median OS was 62 months and median DFS 27 months in the LC-IPF group (Fig. 3). In the LC-IPF group, the median survival was 38,4 months with antifibrotic treatment versus 29,7 months without, although this difference not statistically significant ($p = 0.13$).

In the LC-ILD group, the most frequent adverse events were prolonged air leaks (24 %), respiratory failure (12 %), and pneumonia (24 %). There were no significant differences in the frequency or types of adverse events. Moreover, the length of hospital stay did not differ significantly between the two groups ($p = 0.4$).

Fig. 4 illustrates the subsequent treatment strategies for 13 LC-ILD patients with recurrence: 2 patients were treated with radiotherapy, 8 with chemotherapy, 2 did not received specific treatment, for 1 patient data was not available.

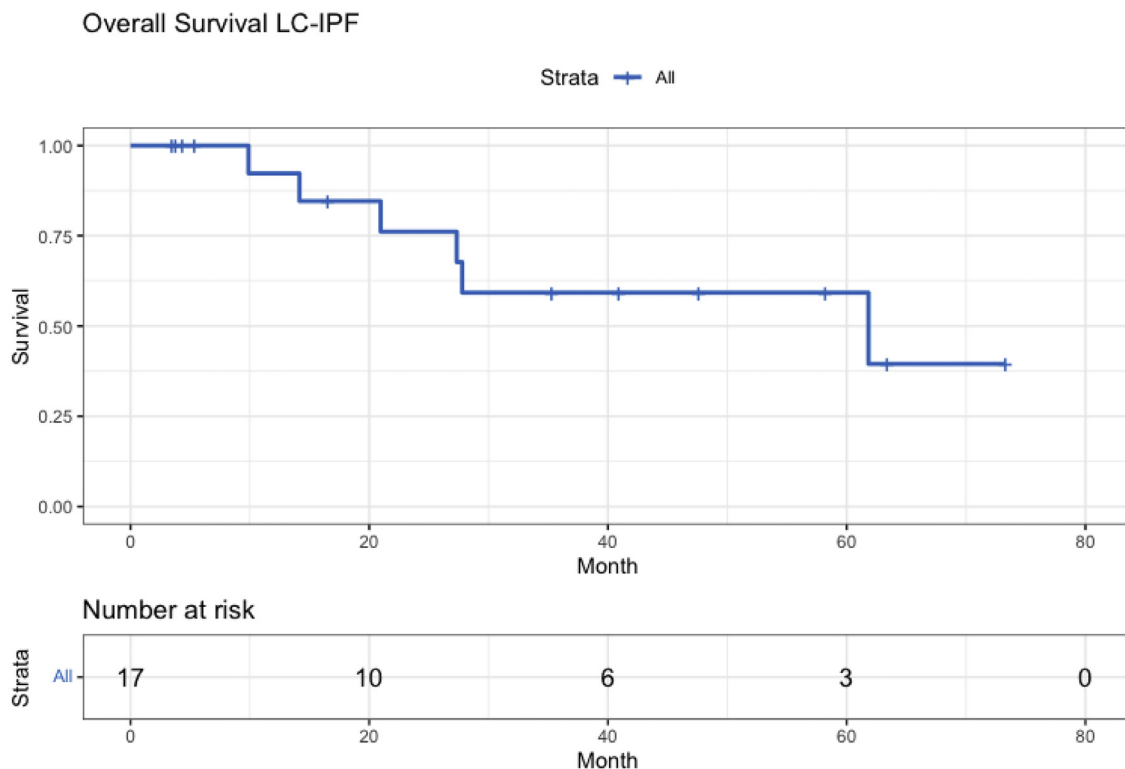
4. Discussion

Our study provides a detailed description of the clinical features and outcomes of a LC-ILD population undergoing surgery for lung cancer in an academic French center: in line with existing literature data, the LC-ILD group and especially LC-IPF were mostly older, male and heavy smokers [6]. ILD and LC are closely linked. We decided to focus on this thematic because of the high interaction of both LC and ILD disease, involving senescence and tobacco smoking induced inflammation [7]. The prevalence of ILD in LC population was lower than reported in the literature. This disparity highlights the

challenges in retrospectively identifying these patients and in the underdiagnosis of ILD. It could also be explained by the fact that patients were very cautiously selected for surgery. There were more stages II and III in the LC-ILD population and fewer stages I in the LC-ILD group compared with the LC-non-ILD group. Radiotherapy is generally contraindicated for patients with ILD due to the higher risk of severe radiation pneumonitis, regardless of LC stage [23]. This could explain why the indication for surgery was broader and could therefore have an impact on outcomes and survival [12,13]. Fukui and al [24] showed that ILD is a high risk for underestimating tumor size of LCs in preoperative staging and recommends careful pre-operative staging assessment.

Our findings in molecular biology support trends observed in other French studies, where activating driver mutations are rare in this population [25,26]. This was expected in this population of heavy smokers.

Our data suggest that the LC-ILD population was highly selected for surgery: preoperative histology was obtained more frequently. The LC-ILD population had better FEV1 while DLCO was lower, which we could only explain by mild to moderate ILD impairment, as DLCO decreases before FEV1 in ILD [19]. This also shows that surgeons were more likely to operate in early stages of ILD disease, with minor volume impairment. The lower DLCO in the LC-ILD group may be attributed to selection bias, as low DLCO% was one of the criteria used to identify LC-ILD patients in the surgical database. DLCO has been reported to be predictive of prognosis in UIP/IPF and other



A

Characteristic	OS LC-IPF			
	12Month	24Month	60Month	Median
Overall	92% (79%, 100%)	76% (56%, 100%)	59% (37%, 95%)	62 (27, —)

Characteristic	DFS LC-IPF				
	12Month	24Month	36Month	60Month	Median
Overall	71% (50%, 100%)	63% (41%, 95%)	45% (24%, 84%)	15% (2.7%, 83%)	27 (8.8, —)

Fig. 3. Analysis of OS and DFS using Kaplan-Meier in the LC-IPF group (A) and OS/DFS rates at different time points (1 year, 2 years, 3 years, and 5 years) DFS in the LC-IPF group (B).

progressive fibrosing ILDs [27,28]. Surgical data indicates that treatment did not deviate from the standard of care as undertreating patients with ILD is associated with higher mortality rates [13]. Our study underlines the fact that patient with LC-ILD should be cautiously selected by trained physicians.

Interstitial lung abnormalities (ILAs) are commonly discovered on CT scans, particularly in older individuals or smokers. They can also be identified during cancer diagnosis. ILAs independently predict mortality, with around 20 % progressing within two years and over 40 % progressing after five years [29]. Further research is needed to differentiate ILAs from genuine fibrosis prior to treatment, radiotherapy, or surgery [30]. These results suggest a proper identification of ILD is a necessity because of its impact on mortality. We classified ILA cases in the LC-ILD group.

Our study's key strength is the detailed examination of specific post-operative complications related to surgery among a surgical cohort, with expert radiological CT review, in a reference center. In contrast to Yotsukura et al. [31], who highlighted a prolonged air leak in only 4 % of their cases, our results show a higher frequency of

prolonged air leak. Conversely, our study found no significant difference in the type of post-operative adverse events between the two groups. This may indicate that the LC-ILD group was properly selected for surgery and cannot be explained by undertreatment in the LC-ILD as surgery was similar between the groups. This results significantly diverge from what is typically reported in the literature : a recent meta-analysis [32] indicated a wide range of acute exacerbation frequencies post lung resection surgery, varying from 4 to 32 %. Almost all data came from Asian studies in which patients were very well selected, but maybe Asian ethnicity is a risk factor of acute exacerbation for surgery as well as drug toxicity.

Our study found that median OS was not significantly lower in the LC-ILD group (45 months versus 84 months, $p = 0.068$). The five-year survival rate was 45 % in the LC-ILD group and 31 % in LC-IPF group, consistent with previous studies [8,9]. In our study, no independent predictive factors for overall survival were identified. The rate of post-operative complications did not differ significantly between the two groups. Post-operative complications may not be the major cause of lower survival in the LC-ILD group in our study compared to-

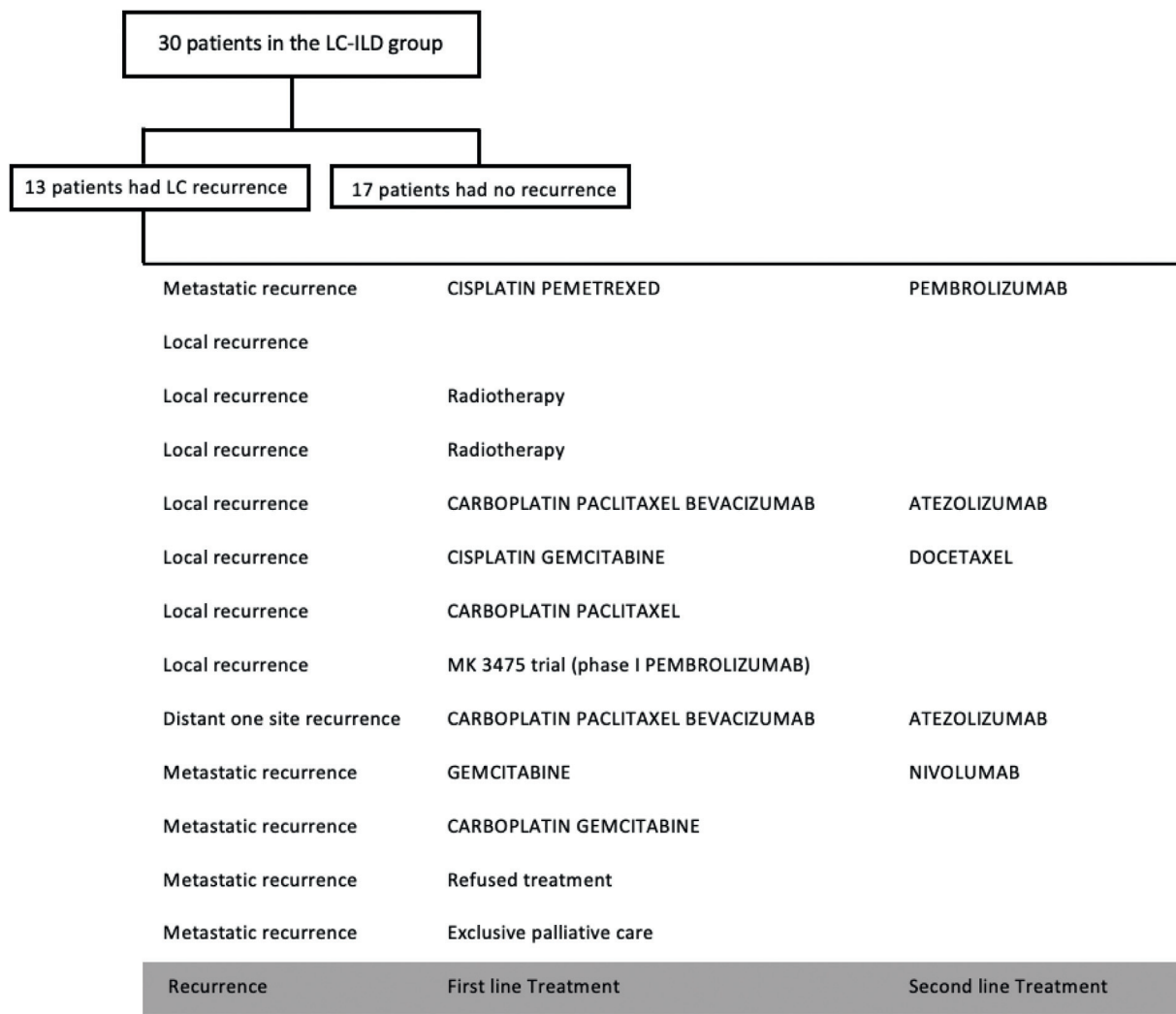


Fig. 4. Subsequent Treatment Strategies Following Recurrence After Surgery.

cancer related mortality. In a study by Song and al [9], the 5-year recurrence-free survival rate was significantly lower in the LC-IPF group than in the LC-non-ILD group (49.1 versus 69.1 %; $P < 0.001$), IPF and post-operative stage III were independent risk factors for recurrence. The higher mortality rate related to cancer may be related to several features, such as advanced stage, aggressive cancer patterns, lack of peri-operative treatments, lower response rates to treatment at relapse, or fewer treatment options available upon relapse.

Considering our findings, we would recommend careful selection of patients with ILD for surgery, with a focus on identifying such comorbidities to provide personalized care. These should guide the provision of appropriate interventions, including physiotherapy and rehabilitation, smoking cessation programs, and, when necessary, antifibrotic therapy for patients with fibrosing ILD. A better diagnosis of ILD would allow a better choice of therapies in case of lung cancer to prevent drug induced pneumonitis.

Specific guidelines for LC-ILD patients are needed. Our study suggests that selection of patients with good performance status, superior predictive postoperative FEV1, and significantly higher weight may lead to the absence of complications. The retrospective design may introduce potential bias and affect the results, especially in underestimating the frequency of some events. It is important to consider the potential limitations inherent in retrospective analyses when interpreting our findings. Managing the rare condition of LC-ILD in clinical practice presents challenges and issues. Identifying ILD patients is particularly challenging due to its rarity and frequent

underdiagnosis. The study highlights the significance of accurately identifying these patients to ensure appropriate follow-up, anti-fibrotic treatment, and rigorous patient selection.

Lung cancer screening may increase the prevalence of LC-ILD. Further prospective studies should focus on establishing guidelines for surgery in this particular group of patients.

5. Conclusion

This study assesses a French LC-ILD population who underwent surgery, covering demographic, clinical, functional, surgical, oncological, and radiological aspects. LC-ILD patients generally have a shorter OS compared to lung cancer (LC) patients without ILD. Patients selected for surgery had a low rate of complications and acute exacerbations, possibly due to the rigorous selection process at a referral center for ILD, LC and thoracic surgery. There is a lack of well-defined guidelines for addressing LC in this specific population. Larger scale or prospective studies are needed due to the unique challenges and characteristics of these patients and the rarity of this condition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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