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Is operation safe for lung cancer patients with interstitial lung disease on computed tomography?

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Abstract
Aims: Interstitial lung disease (ILD) is associated with the incidence of non-small cell lung cancer (NSCLC). Patients with ILD are at risk of acute exacerbation (AE) after pulmonary resection. However, there have been no recognized treatment guidelines for NSCLC patients with ILD on computed tomography (CT).
Methods: We reviewed the medical records of 156 consecutive patients with ILD on high-resolution CT who have undergone pulmonary resection and between 2014 and 2018. Data regarding general information, imaging features, perioperative indicators, and long-term prognosis of patients were compared.
Results: The mean patient age was 67.24 ± 6.80 years. Postoperative AE occurred in seven (4.5%) patients; five (71.4%) of the seven patients who had an AE died within 30 days. The incidence of postoperative AE was 5.3% among patients who underwent lobectomy ($n = 6$). Overall survivals (OS) was significantly poorer in patients with possible usual interstitial pneumonia (UIP)/UIP [hazard ratio (HR) 2.34, 95% confidence interval (CI) 1.11–4.95, $p = 0.026$] and severe postoperative complications (Grade $\geqslant 3$) (*versus* no complication: HR 2.58, 95% CI 1.11–6.02, $p = 0.028$; *versus* mild complications: HR 6.05, 95% CI 2.69–13.6, $p < 0.001$). Age (HR 1.071, 95% CI 1.006–1.137, $p = 0.030$) and ILD patterns (HR 2.420, 95% CI 1.024–5.716, $p = 0.044$) were independent prognostic factors for OS. Forced vital capacity (FVC) (odds ratio 0.351, 95% CI 0.145–0.850, $p = 0.020$) was an independent prognostic factor for patients who needed postoperative intensive care unit intervention.
Conclusion: Pulmonary resection for NSCLC Patients with ILD on CT is a safe procedure. However, surgical indications for lobectomy need to be more carefully for these patients, especially for possible UIP/UIP patients and patients with lower FVC.

The reviews of this paper are available via the supplemental material section.

Keywords: complications, interstitial lung disease, lung cancer surgery, surgery

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Introduction

Interstitial lung disease (ILD), such as idiopathic pulmonary fibrosis (IPF), have been described based on clinical, radiographic, and pathologic findings, and a correlation has been identified between ILD and the incidence of lung cancer. Lung cancer occurs approximately 3.34-fold more frequently among patients diagnosed with IPF than among the general population.[1]

Surgical operations performed on lung cancer patients with ILD may cause the rapid and progressive deterioration of the ILD, which is referred to as acute exacerbation (AE). The prognosis of AE is inferior, with an average survival time of approximately 2.2 months, and the mortality rate can reach as high as 80%.[2–4] The long-term survival rate of lung cancer patients with ILD is also poor, and the 5-year-survival rates after lung resection in non-small-cell lung cancer (NSCLC) patients with and without ILD have been reported to be 22.1–61.6% and 53.2–88.3%, respectively.[4–7]

The routine examination such as X-ray and computed tomography (CT) are difficult to make a definitive diagnosis of ILD. Especially for the NSCLC patients with ILD on CT; it is almost impossible to assess the risk of pulmonary resection after confirming the pathologic diagnosis of ILD by biopsy. So far, there have been some guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis, which accounts for a large proportion of cases of idiopathic interstitial pneumonia, (such as Diagnosis of idiopathic pulmonary fibrosis an official ATS/ERS/JRS/ALAT clinical practice guideline,[8] Japanese guideline for the treatment of idiopathic pulmonary fibrosis[9] and so on) based on evidence. However, few recognized treatment guidelines for NSCLC patients with ILD on CT have been reported.[8,10] In this study, we explored the factors associated with postoperative complications, including postoperative AE, and evaluated the long-term prognoses of lung cancer patients with ILD on CT. The results of this study will help clinicians to perform more accurate preoperative evaluation and surgical prognosis predictions for ILD patients.

Methods

Patients

The institutional review board of the participating institutions approved our study and waived the need for informed consent due to the retrospective nature of this study. We included NSCLC patients with ILD on CT who underwent pulmonary resection NSCLC at Shanghai Pulmonary Hospital without previous lung surgeries for lung tumors, between May 2014 and October 2018. Patients with neoadjuvant chemotherapy or radiotherapy, and those with benign tumors, small-cell cancer, or metastatic carcinoma based on pathologic diagnosis were excluded from further analyses. Patients lost to follow-up were also excluded from this study. Finally, clinical data of included patients were collected. Follow-up information was acquired from outpatient records and telephone interviews. Overall survival (OS) was defined as the time from the date of surgery to the date of death or last follow-up. All patients completed the follow-up survey up to October 2019.

Radiological and histological evaluation

High-resolution computed tomography (HRCT) was performed in all patients before the operation. The diagnosis and categorization of ILD were based on the evaluation of HRCT images by surgeons and radiologists, according to the criteria published by the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) in 2018.[8] We categorized ILD into the following three groups: usual interstitial pneumonia (UIP) pattern, possible UIP pattern, or indeterminate UIP pattern. NSCLC was pathologically confirmed and staged according to *The tumor, node, and metastasis (TNM) classification*, 8th edition, established by the Union for International Cancer Control.[11]

Surgical procedures

We performed lung resections using either video-assisted thoracoscopic surgery or thoracotomy. Lobectomy is the standard operation for radical resections of lung cancer. Sublobar resections (either wedge resections or segmentectomies) were the optional procedure, including intentional and compromised sublobar resections. For intentional sublobar resection, patients were required to meet the following criteria according to previous studies:[12,13] (i) location within the outer third of the lung parenchyma, (ii) pure ground-glass nodes less than 3 cm or with radiologically non-invasive appearance (consolidation/tumor ratio <0.5), (iii) adequate general condition and lung function, (iv) patients' age ranging from 20 to 79 years and (v) no prior chemotherapy or radiation therapy for any malignant diseases. Compromised sublobar resection was selected for patients who could not tolerate a lobectomy for any of the following reasons: (i) patients with poor lung function (% predicted forced expiratory volume in first second $\leqslant 70\%$), (ii) patient's age $\geqslant 80$ years, and (iii) patients with severe cardiovascular disease. Intraoperative frozen section analysis was used to assess the status of resection margins and lymph nodes. Lobectomy and segmentectomy were followed by systematic lymphadenectomy and wedge resections by lymph node sampling. When determining the site of resection, the surgeons did not determine whether the tumor was located in the area of radiographic ILD.

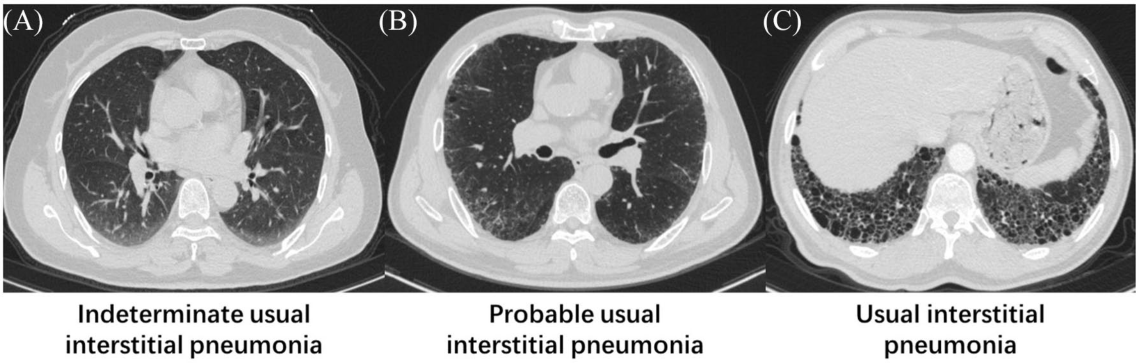

Figure 1. Representative interstitial lung disease patterns on computed tomography according to the criteria published by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association in 2018. (A) Indeterminate usual interstitial pneumonia, subpleural predominant ground-glass abnormality. (B) Possible usual interstitial pneumonia, subpleural and basal predominant reticular abnormality, without honeycombing. (C) Usual interstitial pneumonia, subpleural and basal predominant honeycombing abnormality.

Postoperative therapy and assessment

Routine postoperative management was performed for all patients. However, the administration of postoperative preventive steroid therapy (methylprednisolone or dexamethasone) was initiated on the day of the operation, at a dose of 40 mg/day (methylprednisolone) or 5 mg/day (dexamethasone), and was continued for 3 days in some patients. It is up to the surgeon to decide whether to give the steroid therapy according to the patients' condition.

All patients were followed up starting on the day of surgery. Postoperative complications were defined according to the Clavien–Dindo classification.[14] Postoperative follow-up procedures, including a physical examination and chest roentgenogram every 3 months and chest CT examinations every 6 months, were performed for the first year. After the first year, a physical examination and chest roentgenogram were performed every 6 months, and a chest CT examination was performed every year.

The criteria of AE included a clinical worsening within 30 days, the presence of new radiologic abnormality (e.g. bilateral ground-glass opacification/consolidation) on HRCT, and the exclusion of alternative etiologies (e.g. heart failure, pulmonary embolism).[15]

Statistical analyses

The demographics and outcomes of patients with postoperative acute exacerbation were analyzed using descriptive statistics. The Pearson χ^2 test was used to analyze categorical variables, and the two-sample Student's *t*-test was used to analyze continuous variables. We used the log-rank test to compare the survival curves. To assess the potential independent effects on OS, we used a Cox proportional hazards model. Factors that might predict patients' need of postoperative intensive care unit (ICU) intervention were evaluated using logistic regression. A two-sided *p*-value of 0.05 was considered to be significant. All analyses were conducted with SPSS 22.0 (IBM SPSS Statistics 22.0, IBM, New York, USA).

Results

Patient inclusion and characteristics

Out of a total of 5145 patients who were diagnosed with possible malignant lung lesions and underwent pulmonary resections, 256 patients presented with ILD features on HRCT. After exclusion criteria were applied, 156 patients were analyzed in this study. The process for determining patient inclusion is shown in Supplemental Material Figure 1 online. ILD patients were divided into three groups (indeterminate UIP, possible UIP, and UIP), according to the ATS/ERS/JRS/ALAT classification (Figure 1). Supplemental Figure 2 shows the relationship between the site of NSCLC and the site of the most severe ILD lesion. Patient characteristics, based on ILD patterns, are shown in Table 1. The mean patient age was 67.24 ± 6.80 years. Patients

Table 1. Characteristics of non-small cell lung cancer patients with interstitial lung disease.

Variables	All patients *N* = 156	Indeterminate usual interstitial pneumonia *n* = 60	Possible usual interstitial pneumonia *n* = 63	Usual interstitial pneumonia *n* = 33	*p*
Age, years	67.24 ± 6.80	66.32 ± 7.73	67.56 ± 6.37	68.30 ± 5.67	0.361
Sex, male	136 (87.2%)	42 (70.0%)	61 (96.8%)	33 (100%)	**<0.001**
Smoking history, yes	80 (51.3%)	21 (35.0%)	33 (52.4%)	22 (66.7%)	**0.010**
BMI, kg/m²	24.53 ± 2.68	24.42 ± 2.92	24.78 ± 2.35	24.26 ± 2.86	0.615
Pulmonary function					
FVC, L	3.07 ± 0.66	2.97 ± 0.71	3.14 ± 0.65	3.10 ± 0.55	0.319
%FVC, %	92.91 ± 17.30	93.97 ± 16.13	92.09 ± 19.68	92.55 ± 14.70	0.828
FEV1/FVC, %	78.57 ± 8.36	79.51 ± 9.00	78.52 ± 7.17	76.94 ± 9.26	0.368
Surgical procedures					0.713
Lobectomy	113 (72.4%)	43 (71.7%)	48 (76.2%)	22 (66.7%)	
Sublobar resection	31 (19.9%)	11 (18.3%)	11 (17.5%)	9 (27.3%)	
Others*	12 (7.7%)	6 (10.0%)	4 (6.3%)	2 (6.1%)	
Surgical path					0.772
Thoracotomy	33 (21.2%)	11 (18.3%)	14 (22.2%)	8 (24.2%)	
VATS	123 (78.8%)	49 (81.7%)	49 (77.8%)	25 (75.8%)	
p-stage					0.875
I	90 (57.7%)	37 (61.3%)	36 (57.1%)	17 (51.5%)	
II	34 (21.8%)	11 (18.3%)	15 (23.8%)	8 (24.2%)	
III	32 (20.5%)	12 (20.0%)	12 (19.0%)	8 (24.2%)	
Histology					**0.006**
Squamous cell carcinoma	62 (39.7%)	17 (28.3%)	24 (38.1%)	21 (63.6%)	
Adenocarcinoma	76 (48.7%)	38 (63.3%)	30 (47.6%)	8 (24.2%)	
Others	18 (11.5%)	5 (8.3%)	9 (14.3%)	4 (12.1%)	

*Others include bilobectomy and pneumonectomy.
BMI, body mass index; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; p-stage, pathological stage; VATS, video-assisted thoracoscopic surgery.

with possible UIP and UIP were more likely to be male ($p < 0.001$), and these patients were associated with more extensive smoking histories ($p = 0.010$) and higher rates of squamous cell carcinoma ($p = 0.006$). No significant differences were observed for age, body mass index (BMI), pulmonary function, or tumor stage among the groups.

Table 2. Perioperative outcomes of non-small cell lung cancer patients with interstitial lung disease.

Variables	All patients *N* = 156	Indeterminate usual interstitial pneumonia *n* = 60	Possible usual interstitial pneumonia/usual interstitial pneumonia *n* = 96	*p*
Operation time, h	2.21 ± 0.76	2.14 ± 0.65	2.26 ± 0.82	0.338
Estimated blood loss, mL	133.78 ± 194.05	96.50 ± 90.49	157.08 ± 234.36	**0.024**
Length of stay after surgery, days	6.66 ± 5.98	6.13 ± 4.82	6.99 ± 6.61	0.386
Postoperative ICU intervention, days of stay ⩾3	19 (12.2%)	6 (10.0%)	13 (13.5%)	0.511
Postoperative acute exacerbation	7 (4.5%)	2 (3.3%)	5 (5.2%)	0.878
Postoperative complications (Grade ⩾3)	13 (8.3%)	2 (3.3%)	11 (11.5%)	0.137
90-day mortality	7 (4.5%)	2 (3.3%)	5 (5.2%)	0.878

Perioperative outcomes among NSCLC patients with ILD

The perioperative outcomes for NSCLC patients with ILD are also shown in Table 2. We found that postoperative AE occurred in seven (4.5%) patients; five (71.4%) of them died within 30 days. The incidence of postoperative AE was 6.2% among patients who underwent lobectomy. There were 13 (8.3%) patients who developed severe postoperative complications (Grade ⩾3), and seven (4.5%) patients died within 90 days after surgery. The estimated blood loss in patients with possible UIP/UIP during the operation was larger than that for patients with indeterminate UIP ($p = 0.024$). No significant differences in operation times, length of stay after surgery, the rate of patients who needed postoperative ICU intervention (the days of stay in the ICU ⩾3), the incidences of postoperative AE and severe postoperative complications (Grade ⩾3), or mortality within 90 days were observed among groups. The general information, clinical features, and postoperative dynamic chest radiograph of patients with AE are shown in Table 3 and Supplemental Video 1, respectively. We summarize the postoperative complications of these patients and grading based on the Clavien–Dindo classification[14] in Supplemental Table 1.

Univariate logistic regression revealed that patients' need of postoperative ICU intervention was associated with age [odds ratio (OR) 1.107, 95% confidence interval (CI) 1.020–1.202, $p = 0.015$] and forced vital capacity (FVC) (OR 0.320, 95% CI 0.143–0.713, $p = 0.005$). Multivariate analyses demonstrated that FVC (OR 0.351, 95% CI 0.145–0.850, $p = 0.020$) was independent of prognostic factors for patients' need of postoperative ICU intervention, whereas age was not (Supplemental Table 2).

It is worth mentioning that we also compare the perioperative outcomes among different surgical procedures. Supplemental Table 3 compares the characteristics of patients among different surgical procedures. The patient characteristics were comparable between groups, except for the pathological stage ($p < 0.001$). Supplemental Table 4 compares the perioperative outcomes among lobectomy, sublobar resection and bilobectomy/pneumonectomy. In the operation time, estimated blood loss, length of stay after surgery, postoperative acute exacerbation, postoperative complications (Grade ⩾3) and 90-day mortality, sublobar resection was superior to the other two. The perioperative outcomes became relatively worse as the range of resection increased.

Long-term outcomes among NSCLC patients with ILD

In terms of long-term outcomes, we performed survival analysis of NSCLC patients with ILD based on ILD patterns and found that OS was significantly lower in patients with possible UIP/UIP than in those with indeterminate UIP [hazard ratio (HR): 2.34, 95% confidence interval (CI): 1.11–4.95, $p = 0.026$]. Also, when exploring

Table 3. Clinical Features of patients with postoperative acute exacerbation.

Case	Age	Sex	Smoking history	ILD patterns	FVC, L	FEV1/FVC, %	Histology (p-stage)	Size of tumor, cm	Preventive steroid therapy	Operation time, h	Surgical procedure	Surgical path	The main therapy for acute exacerbation	Follow-up
1	76	Male	Yes	Possible usual IP	1.55	83.25	SCC (T2aN0M0)	4.00	Yes	2.00	Lobectomy	Thoracotomy	Methylprednisolone	Died, 17 days
2	77	Male	No	Possible usual IP	3.22	58.19	SC (T1cN0M0)	3.00	No	2.00	Lobectomy	VATS	Methylprednisolone	Died, 21 days
3	59	Male	Yes	Usual IP pattern	2.94	68.40	SCC (T3N1M0)	6.00	No	4.00	Bilobectomy	Thoracotomy	Methylprednisolone	Died, 30 days
4	59	Male	Yes	Possible usual IP	3.94	78.01	SCC (T1cN0M0)	2.20	No	2.00	Lobectomy	VATS	Methylprednisolone	Died, 8 days
5	67	Male	Yes	Usual IP	2.52	69.37	SCC (T3N0M0)	5.50	No	3.00	Lobectomy	VATS	None	Died, 4 months
6	74	Male	No	Possible usual IP	2.23	71.84	Ad (T3N0M0)	6.50	No	3.00	Lobectomy	VATS	None	Alive, symptom-free, 21 months
7	84	Male	No	Indeterminate usual IP	2.69	77.53	SC (T3N0M0)	6.00	Yes	1.50	Lobectomy	VATS	Methylprednisolone	Died, 12 days

Ad, adenocarcinoma; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ILD, interstitial lung disease; IP, interstitial pneumonia; p-stage, pathological stage; SC, sarcomatous carcinoma; SCC, squamous cell carcinoma; VATS, video-assisted thoracoscopic surgery.

the influence of postoperative complications on long-term outcomes, we found that the OS in patients with severe postoperative complications (Grade $\geqslant 3$) (HR 2.58, 95% CI 1.11–6.02, $p=0.028$) or with mild postoperative complications (Grade 1–2) (HR 6.05, 95% CI 2.69–13.6, $p<0.001$) are both significantly poorer than in the patients without postoperative complications. The results of the survival analysis are shown in Figures 2 and 3.

The Cox proportional hazard models included age, sex, smoking history, BMI, ILD patterns, forced vital capacity, percent vital capacity, forced expiratory value in 1 s, pathological stage, operative procedure, and histology. Univariate analyses revealed that OS was associated with age (HR 1.061, 95% CI 1.008–1.117, $p=0.023$), ILD patterns (HR 2.339, 95% CI 0.835–4.947, $p=0.026$), pathological stage (HR 1.071, 95% CI 1.006–1.137, $p=0.030$) and histology (HR 2.436, 95% CI 1.271–4.670, $p=0.007$). Multivariate analyses demonstrated that age (HR 1.071, 95% CI 1.006–1.137, $p=0.030$) and the ILD patterns (HR 2.420, 95% CI 1.024–5.716, $p=0.044$) were both independent prognostic factors for OS, whereas the operative procedure was not (Table 4).

Discussion

The prognosis of lung cancer patients with ILD who undergo surgery is worse than that of lung cancer patients without ILD who undergo surgery, and as many as 21.2% of ILD patients experience postoperative AE.[16–18] A large-sample, multicenter, retrospective study examining lung cancer patients with ILD who underwent pulmonary resection showed that the incidence of AE among ILD patients was 9.3%, and the mortality rate associated with AE was as high as 43.9%, accounting for 71.7% of the total 30-day postoperative mortality.

However, the majority of research data comes from patients who have had the pathological examination or the multidisciplinary diagnosis. For patients with ILD on CT, our study suggests that postoperative AE occurred in seven (4.5%) patients, 13 (8.3%) patients developed severe postoperative complications (Grade $\geqslant 3$), and seven (4.5%) patients died within 90 days after surgery. The 90-day mortality of non-ILD patients after pulmonary resection ranged from 5.7% to 11.7%.[19–22] It is not difficult to find that the mortality rate of patients with ILD within 90 days after surgery was not significantly increased. Therefore, it is reasonable to assume that pulmonary resection is relatively safe in lung cancer patients with ILD on CT.

On the other hand, the risk of AE will increase with the area of resection. It was reported that the HR values for AE after segmentectomy, lobectomy, double lobectomy, and pneumonectomy were 3.675 ($p = 0.0024$), 3.861 ($p = 0.000$), 5.055 ($p = 0.001$), and 6.953 ($p = 0.000$) respectively, for the control group after wedge resection.[2] Our study reached a similar conclusion. For these patients, the operation time, estimated blood loss during operation, and length of stay after surgery in the lobectomy group were significantly worse than that in the sublobar resection group. Meanwhile, the incidence of AE after lobectomy was significantly higher than the sublobar resection (6.2% *versus* 0). Table 5 summarizes the incidence of AE for NSCLC patients with ILD that have been reported in recent studies. Because lung function in NSCLC patients with ILD is further reduced than in patients without ILD, the selection criteria used to determine treatment for patients with ILD should be different from the general NSCLC population, and stricter indications for surgery are recommended.

Also, the long-term survival of these patients is also considerable according to our study. As we know, both the oncological and ILD progression of these patients affect postoperative outcome. When the causes of death following pulmonary resection during the long-term were analyzed among lung cancer patients with ILD, most studies showed that the proportion of deaths caused by lung cancer was higher than the proportion caused by AE-induced respiratory failure.[4–7,24] Therefore, the postoperative AE risk and tumor stage should be comprehensively evaluated in patients with severe declines in pulmonary function. The safety and efficacy of surgical options should be considered. For lung cancer patients whose lung function conditions cannot tolerate lobectomies with early-stage tumors, restrictive resections (including segmentectomies and wedge resections) could be considered if a sufficient resection margin of the lesion can be ensured. Furthermore, in our findings, undergoing lobectomy was a significant risk factor for postoperative AE. Cox regression analysis of postoperative outcomes showed that UIP appearance on CT scans was an independent risk factor for long-term prognosis, whereas the choice of surgical procedure did not directly affect long-term postoperative survival.

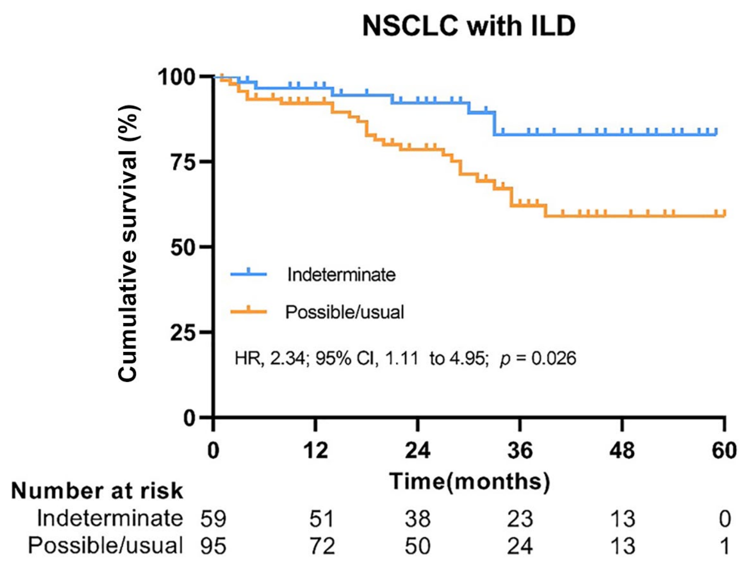

Figure 2. Relationship between overall survival and ILD pattern in patients with NSCLC and ILD after surgery. Indeterminate,= indeterminate usual interstitial pneumonia; Possible = possible usual interstitial pneumonia; Usual = usual interstitial pneumonia.
CI, confidence interval; HR, hazard ratio; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer;

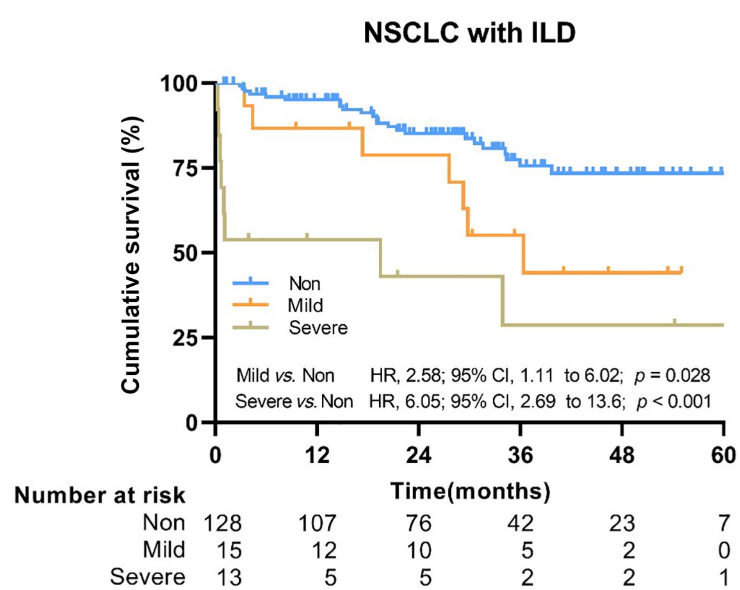

Figure 3. Relationship between overall survival and complications in NSCLC patients with ILD after surgery. Non = no complication; Mild, Grade 1–2 complications; Severe, Grade 3–5 complications.
CI, confidence interval; HR, hazard ratio; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer.

Table 4. Univariable and multivariable Cox analysis for overall survival in patients with ILD after surgery.

Variable	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years	1.061 (1.008–1.117)	**0.023**	1.071 (1.006–1.137)	**0.030**
Sex, male, *versus* female	25.586 (0.500–1309.573)	0.106		
Smoking history, yes, *versus* no	1.300 (0.685–2.464)	0.422		
BMI, kg/m²	0.943 (0.835–1.066)	0.350		
ILD patterns, possible usual IP/usual IP, *versus* indeterminate usual IP	2.339 (1.106–4.947)	**0.026**	2.420 (1.024–5.716)	**0.044**
FVC, L	0.760 (0.472–1.224)	0.260		
FEV1/FVC, %	0.987 (0.952–1.023)	0.464		
p-stage, I, *vs.* II+III	0.348 (0.176–0.690)	**0.003**	0.514 (0.235–1.124)	0.095
Surgical procedures, lobectomy, *versus* sublobar resection	3.856 (0.922–16.119)	0.064	2.472 (0.532–11.486)	0.248
Histology, squamous cell carcinoma, *versus* adenocarcinoma and others	2.436 (1.271–4.670)	**0.007**	1.455 (0.629–3.059)	0.322
Steroid, yes, *versus* no	0.739 (0.308–1.772)	0.497	0.773 (0.302–1.978)	0.591

CI, confidence interval; BMI, body mass index; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HR, hazard ratio; ILD, interstitial lung disease; IP, interstitial pneumonia; p-stage, pathological stage.

Table 5. The incidence of AE for non-small cell lung cancer in patients with interstitial lung diseases from recent studies.

Author (year of publication)[reference]	Surgical procedures	No. of cases	No. of AE (%)
Present study	Lobectomy	113	6 (5.3)
	Sublobar resection	31	0
Watanabe *et al.* (2008)[5]	Lobectomy/segmentectomy	48	4 (8.3)
	Wedge resection	7	0
Sato *et al.* (2014)[2]	Lobectomy/segmentectomy	995	100 (10.5)
	Wedge resection	202	10 (5.0)
Tsutani *et al.* (2017)[23]	Lobectomy	57	3 (5.7)
	Sublobar resection	50	3 (6.0)

AE, acute exacerbation; ILD, interstitial lung diseases; NSCLC, non-small cell lung cancer.

Currently, drugs towards ILD include pirfenidone,[25,26] nintedanib,[27] and ulinastatin.[28] For postoperative AE patients, steroid pulse therapy or high-dose steroid therapy combined with immunosuppressants (such as cyclophosphamide and cyclosporine A) are the primary treatment options.[29] However, no concrete evidence exists showing that steroid treatment can prevent postoperative AE based on prospective studies. The Japanese guideline for the treatment of IPF[9] does

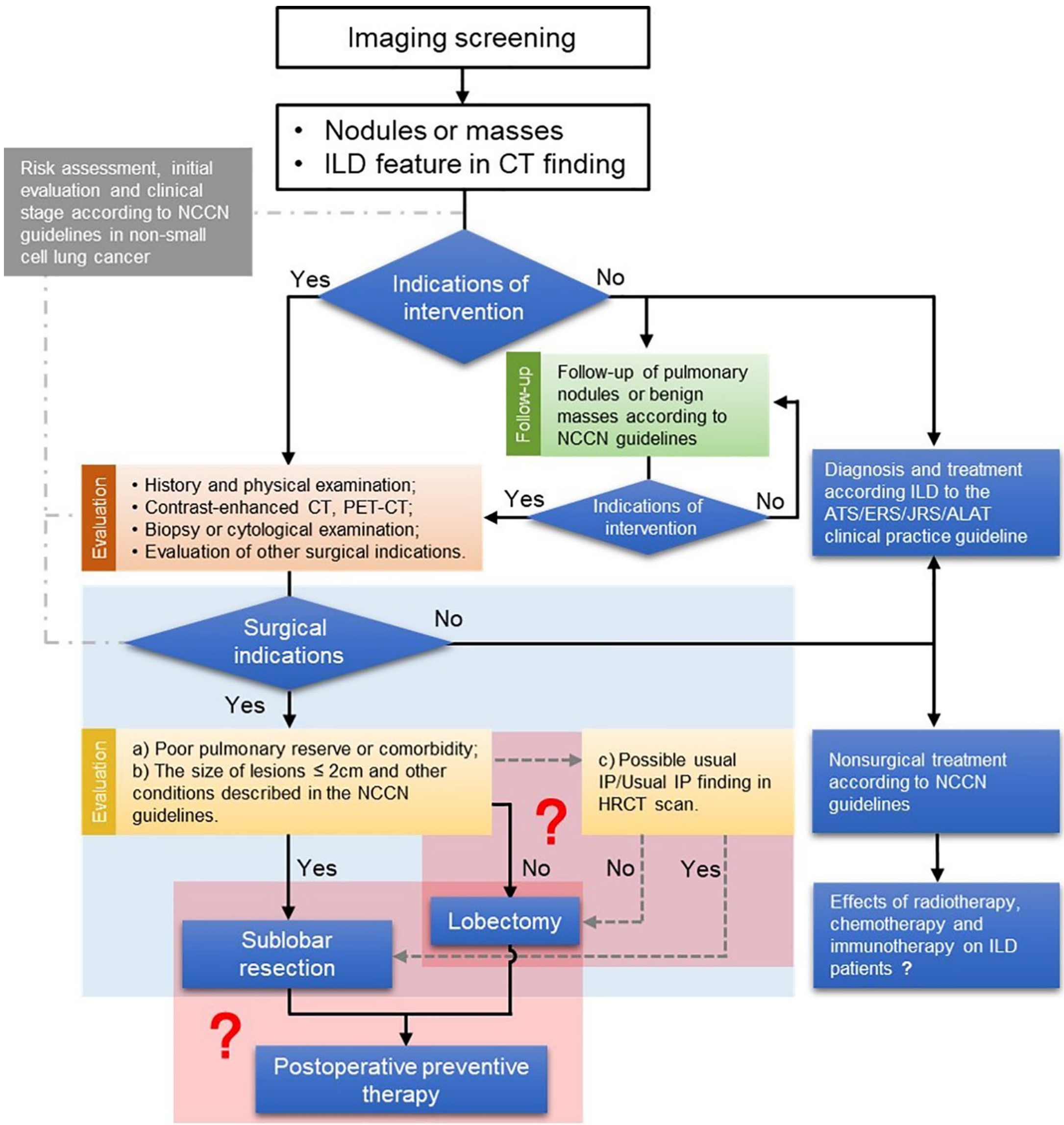

Figure 4. Algorithm for the perioperative management of non-small cell lung cancer in patients with interstitial lung disease on computed tomography.
ATS/ERS/JRS/ALAT, American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association; CT, computed tomography; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IP, interstitial pneumonia; NCCN, National Comprehensive Cancer Network; PET-CT, positron emission tomography-computed tomography

not recommend preventive drug administration for lung cancer patients with IPF or other forms of UIP to avoid postoperative AE, aside from antifibrotic drugs such as pirfenidone and so on. For high-risk lung cancer patients with ILD, Shanghai Pulmonary Hospital recently began the experimental treatment of postoperative preventive steroid therapy (methylprednisolone or dexamethasone), initiated on the day of operation and lasting for 3 days. Given the high mortality rate due to postoperative AE, a proven preventive strategy to reduced AE risk would be highly beneficial.

Based on the above scientific analysis and our previous experience with the management of NSCLC patients with ILD on CT, we have developed effective treatment protocols (Figure 4) for these patients. However, there are some limitations in this study: (1) it was a single-center, retrospective study. Previously unrecorded values cannot be added, such as carbon monoxide diffusing capacity (DLCO), which is a crucial spirometric value when surgeons evaluate the tolerability for surgery in patients with ILD. (2) Patients who received sublobar resections may have been highly selected (some sublobar resection patients did not undergo systematic lymph node dissection). (3) Because lung cancer and ILD lesions are often not found in the same location, the relation between ILD and operation cannot be evaluated directly.

In conclusion, pulmonary resection for NSCLC patients with ILD on CT is a safe procedure. However, surgical indications for lobectomy need to be more carefully for these patients. Also, because of the high mortality rate from postoperative AE, a great benefit would be likely if the reduced risk of AE through preventive administration was proven.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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