Outcomes of Video-Assisted Thoracic Surgical Lung Biopsy for Interstitial Lung Diseases

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**Purpose: Surgical lung biopsy (SLB) is an important diagnostic tool for interstitial lung disease (ILD), yet the risk factors for SLB are still debatable and long-term outcomes remain unknown.
Methods: We retrospectively reviewed the records of 85 consecutive patients with ILD who underwent SLB by video-assisted thoracic surgery (VATS) from 2008 to 2019. Risk factors for complications and differences of outcomes between idiopathic pulmonary fibrosis (IPF) and other ILDs were examined.
Results: All patients who underwent VATS had no mortality or acute exacerbation of ILD within 90 days of SLB. The rate of complication was 9.4%, and there were no statistically significant risk factors for complications. While the IPF group was not significantly different from the non-IPF group with regard to surgical parameters or complications, patients with IPF had significantly higher rates of mortality (50% vs. 9% in 5 years; p <0.001) and readmission due to acute exacerbation (75% vs. 8% in 5 years; p <0.001).
Conclusion: VATS lung biopsy for ILD can be a safe approach regardless of underlying phenotypes. An accurate diagnosis of IPF via SLB may be beneficial for correct patient management.**

Keywords: surgical lung biopsy, interstitial lung disease, video-assisted thoracic surgery, idiopathic pulmonary fibrosis

Introduction

Interstitial lung disease (ILD) is a heterogeneous group of disorders, ranging from acute inflammatory disorders to progressive fibrotic conditions. For ILD, surgical lung biopsy (SLB) is often beneficial for accurate clinicopathologic diagnosis and more informed decisions of treatment modality for ILD.[1] In particular, accurate diagnosis of IPF and distinguishing the disease from other ILDs are crucial in clinical practice with the development of antifibrotic drugs.[2,3] The American Thoracic Society/European Respiratory Society recommends SLB for most patients with ILD, who do not show a typical imaging pattern of idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT), for accurate estimates of prognoses, cessation of additional diagnostic testing, and the initiation of specific treatment.[4]

However, the risks of SLB should be carefully considered due to postoperative complications, especially acute exacerbation of ILD. Video-assisted thoracic surgery (VATS) has recently become a standard procedure for

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thoracic surgeons, and SLB for ILD by the VATS approach has reduced mortality, compared with a formal thoracotomy procedure.[5–8] Nevertheless, there is still potential risk in SLB by VATS approach for acute exacerbation and other complications. Although several studies have shown that male sex, increasing comorbidity, immunocompromised status, and preoperative respiratory failure are risk factors for perioperative mortality, other factors are still debated, such as clinicopathological diagnosis and increasing age.[1,6,9–15] In addition, long-term outcomes of patients who have undergone SLB for ILD remain unknown.

Here, we reviewed patients who received SLB for ILD by VATS approach in our hospital and analyzed the short- and long-term outcomes of patients depending on postoperative diagnosis.

Materials and Methods

Study population

Patients with suspected ILD from clinical and radiographic findings were indicated for SLB. We included a total of 85 consecutive patients who underwent SLB at the Toranomon Hospital from January 2008 to July 2019. We excluded patients with a confirmed diagnosis of IPF/UIP based on HRCT findings. All the analyses in this study were performed according to the ethical guidelines for clinical studies at the Toranomon Hospital with the approval of the Institutional Review Board (No. 1920).

Surgical procedure

All patients underwent VATS that was performed using the three-port approach in the lateral decubitus position with one-lung ventilation. The lung biopsy was performed using wedge-shaped partial lung resection with surgical stapling device, Echelon (Johnson and Johnson K.K., Tokyo Japan). Biopsy sites were determined after a preoperative discussion between chest physicians, thoracic surgeons, radiologists, and pathologists. One chest drainage tube was placed and was removed after confirming no air leak, no bleeding, and re-expansion of the lung.

Data analyses

Each patient was evaluated for the following factors: age, sex, smoking history, Charlson Comorbidity Index (CCI), serum levels of Krebs von den Lungen-6 (KL-6) and surfactant proteins A and D (SP-A and SP-D), spirometry results within 1 month before SLB, the side of the lung, number of biopsy sites, lymph node biopsy,

duration of operation, intraoperative blood loss, duration of chest tube drainage, and final postoperative diagnosis. Spirometry results included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and diffusing capacity of the lung for carbon monoxide (DL_{CO}). An agreement on final diagnosis was reached through a multidisciplinary discussion (MDD) among radiologists, pathologists, and pulmonologists. Furthermore, short- and long-term outcomes were assessed. Short-term outcomes were defined as postoperative length of stay, surgical complications, and mortality within 90 days of SLB. Surgical complications included prolonged air leak (7 days or more), pneumonia, hemothorax, pneumothorax after discharge, acute exacerbation of interstitial pneumonia, and readmission due to respiratory failure. Long-term outcomes included overall mortality and rehospitalization due to the first acute exacerbation after SLB. We used the following criteria for the diagnosis of acute exacerbation[16]: worsening dyspnea within 30 days; new ground-glass opacities on HRCT; and no clinical evidence of pulmonary embolism, congestive heart failure, or pneumothorax.

Statistical analysis

Pearson's chi-square test or Fisher's exact test was used for analyzing categorical data. The medians and ranges of continuous variables were compared using the nonparametric Mann–Whitney U test. Survival curves were generated using the Kaplan–Meier method and examined using the log-rank test. A multivariate regression analysis was performed using the Cox proportional hazards model to identify risk factors associated with overall survival. Clinically relevant variables according to literature[17] (age, sex, FVC % predicted, and DL_{CO} % predicted) and those with p <0.1 on univariate analyses (age, sex, CCI, acute exacerbation of ILD, and final diagnosis) were incorporated into the multivariate analysis. The included variables were assessed for collinearity and interactions. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using EZR, a modified version of R commander which adds statistical functions used frequently in biostatistics.[18]

Results

Patient characteristics and final diagnosis after SLB

Table 1 shows the patient characteristics. The median age at the time of SLB was 68 years (range: 19–80 years). In all, 50 (59%) patients were males, and 41 (49%) were

Table 1   Characteristic of 85 patients

Group	IPF (n = 17)	Non-IPF (n = 68)	p Value
Age, median (range)	71 (57–78)	65 (20–80)	0.021
Sex			0.784
Male, n (%)	11 (65)	39 (57)	
Female, n (%)	6 (35)	29 (43)	
Charlson Comorbidity Index			0.828
0, n (%)	5 (29)	23 (34)	
1, n (%)	7 (41)	29 (43)	
2, n (%)	3 (18)	12 (18)	
>3, n (%)	2 (12)	4 (6)	
Smoking			0.506
Never, n (%)	7 (41)	37 (54)	
Light (B.I. <1000), n (%)	7 (41)	19 (28)	
Heavy (B.I. ≥1000), n (%)	3 (18)	12 (18)	
Preoperative serum tests			
KL-6 (U/mL), median (range)	1242 (330–3030)	998 (221–7310)	0.839
SP-A (ng/mL), median (range)	66.0 (31.6–178.8)	58.8 (14.9–364)	0.924
SP-D (ng/mL), median (range)	354 (30.6–589)	225 (31.1–1108)	0.129
Preoperative spirometry tests			
FVC (L), median (range)	2.57 (1.33–3.96)	2.68 (1.33–5.47)	0.510
FVC (% predicted), median (range)	85.0 (52–120)	83.0 (48–129)	0.568
FEV_1 (L), median (range)	2.08 (1.19–3.11)	2.16 (1.10–4.41)	0.746
FEV_1/FVC ratio (%), median (range)	82.7 (62.8–93.2)	78.5 (54.7–95.1)	0.141
DL_{CO} (mL/min/mmHg), median (range)	12.8 (7.83–16.6)	12.7 (5.45–26.6)	0.470
%D_{LCO} (% predicted), median (range)	66.0 (44–87)	67.0 (35–154)	0.499

B.I.: Brinkman Index; DL_{CO}: diffuse capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; KL-6: Krebs von den Lungen-6; SP-A: surfactant proteins A; SP-D: surfactant proteins D

smokers. The diagnostic yield for this study was 100% and the final diagnosis after SLB is described in **Table 2**. Then, we divided patients into IPF and non-IPF groups based on postoperative MDD to assess the impact of the underlying disease on outcomes. There were no significant differences between the groups with regard to sex, CCI, smoking status, preoperative serum tests (KL-6, SP-A, and SP-D), or pulmonary function. Patients in the IPF group were significantly older than those in the non-IPF group (median age, 71 vs. 65 years; p = 0.021).

Surgical parameters and short-term outcomes of SLB

The three-port VATS approach was used for all patients, and none were converted to thoracotomy. The number of biopsy sites was one in only one patient, two in 65 patients, and three in 19 patients. The median time of operation was 88 minutes, and median intraoperative bleeding amount was 0 mL. The median durations of chest drainage and postoperative hospital stay were 1 and 4 days, respectively. No significant differences were found between the IPF and non-IPF groups in biopsy sites, side of the lung, lymph node biopsy, operation

Table 2   Final diagnosis after surgical lung biopsy

Diagnosis	n
Idiopathic interstitial pneumonia	
Idiopathic pulmonary fibrosis	17
Idiopathic nonspecific interstitial pneumonia	11
Cryptogenic organizing pneumonia	4
Acute or subacute hypersensitivity pneumonia	2
Chronic hypersensitivity pneumonia	12
Connective tissue disease-related interstitial pneumonia	
Amyopathic dermatomyositis	1
Anti-neutrophil cytoplasmic autoantibody-associated vasculitis	2
Polymyositis	2
Rheumatoid arthritis	7
Sjögren's syndrome	1
Systemic sclerosis	1
IgG4-related disease	5
Lipoid pneumonia	1
Mucosa-associated lymphoid tissue lymphoma	1
Pneumoconiosis	3
Sarcoidosis	1
Unclassifiable interstitial pneumonia	14

Table 3 Comparison of surgical parameters and short-term outcomes between the IPF and non-IPF patients

Group	IPF (n = 17)	Non-IPF (n = 68)	p Value
Biopsy sites, median (range)	2 (2–3)	2 (1–3)	0.078
Side			0.738
Right, n (%)	13 (76)	55 (81)	
Left, n (%)	4 (24)	13 (19)	
Lymph node biopsy, n (%)	0 (0)	7 (10)	0.336
Operation time (min), median (range)	92 (40–160)	86 (31–175)	0.947
Blood loss (mL), median (range)	0 (0–100)	0 (0–225)	0.737
Chest drainage (day), median (range)	1 (1–14)	1 (1–17)	0.762
Postoperative stay (day), median (range)	3 (2–16)	4 (2–23)	0.324
Complications, n (%)	2 (12)	6 (9)	0.658

IPF: idiopathic pulmonary fibrosis

time, blood loss, duration of chest tube drainage, postoperative length of stay, or rate of complications (**Table 3**).

Complications were observed in eight cases (9.4%), but there was no 90-day mortality or acute exacerbation of ILD. Five patients had prolonged air leak, two had a pneumothorax after chest tube removal, and one patient was readmitted due to dyspnea. There was no significant difference between complication and non-complication groups with regard to age, sex, CCI, smoking status, number of biopsy sites, lymph node biopsy, operation time, bleeding, or final diagnosis (IPF or non-IPF).

Long-term outcomes of SLB

After the median follow-up period of 45 months (range: 1–134), the overall 5-year survival rate of the study population was 82%. The 5-year mortality rate in the IPF group was 50%, which was significantly higher than that in the non-IPF group (9%; p <0.001) (**Fig. 1A**). Likewise, the probability of acute exacerbation after SLB in the IPF group was higher than that in the non-IPF group (75% vs. 8% in 5 years; p <0.001) (**Fig. 1B**). Multivariate regression analysis of prognostic factors for the overall survival after SLB was performed by the two models (**Table 4**). The model 1 incorporated variables which could be detected at the time of SLB (age, sex, CCI, FVC % predicted, DL_{CO} % predicted and final diagnosis) and notably showed that IPF as a final diagnosis was strongly associated with shorter survival rate (hazard ratio = 15.4; 95% interval, 3.99–59.1; p <0.001). In the model 2, acute exacerbation of ILD was added to variables considering that acute exacerbation has a serious impact on the overall survival of the patients with IPF.[19] This model also demonstrates that IPF as a final diagnosis was still a significant factor predicting shorter survival (hazard ratio = 14.7; 95% interval, 2.20–97.5;

p = 0.005), although acute exacerbation was most strongly correlated with shorter survival rate (hazard ratio = 32.6; 95% interval, 5.48–193.7; p <0.001).

Discussion

Our study demonstrates no 90-day mortality or acute exacerbation of ILD, but a morbidity rate of 9.4% in 85 consecutive patients who underwent SLB by VATS approach for diagnosis of an ILD. We found no statistically significant risk factors for complications. However, patients with IPF had significantly higher rates of mortality and readmission due to acute exacerbation in 5 years after SLB than non-IPF patients, despite no difference in surgical parameters or short-term outcomes. To our knowledge, ours is the first study to compare short-term and long-term results of SLB for ILD among patients with IPF or non-IPF groups.

Nguyen and colleagues showed in their review that postoperative mortality of SLB for ILD by thoracotomy was 4.3%, but it decreased to 2.1% with the development of thoracoscopic lung biopsy.[8] However, some studies demonstrated that even a VATS approach has potential risk of postoperative mortality and severe complications including acute exacerbation; these risks might be related to patients with older age, lower DL_{CO}, acute respiratory syndrome before surgery, and preoperative intensive care unit stay.[11,12,20,21] Our cohort included a relatively small number of patients who were over 75 years or had low DL_{CO}, and there were no patients with preoperative intensive care or on mechanical ventilation due to respiratory failure. This may explain why none of our patients had 90-day mortality or postoperative acute exacerbation.

We observed eight complications (9.4%) in our cohort, similar to those reported in previous studies.[8,9,22]

Table 4 Prognostic factors of patients for survival: the multivariate cox regression model

Variables	Hazard ratio	95% CI	p Value	Variables	Hazard ratio	95% CI	p Value
	Model 1				Model 2		
Diagnosis, IPF	16.1	3.96–65.2	<0.001	Diagnosis, IPF	14.7	2.20–97.5	0.005
Age	1.07	0.973–1.18	0.611	Age	1.03	0.919–1.15	0.620
Sex, male	4.94	0.888–27.5	0.0681	Sex, male	5.35	0.796–36.0	0.0844
CCI	1.20	0.591–2.45	0.611	CCI	1.01	0.483–2.11	0.979
FVC % predicted	0.984	0.956–1.01	0.268	FVC % predicted	0.898	0.794–1.02	0.086
DL$_{CO}$ % predicted	0.967	0.929–1.01	0.102	DL$_{CO}$ % predicted	0.998	0.959–1.04	0.923
				Acute exacerbation of ILD	32.6	5.48–193.7	<0.001

CCI: Charlson comorbidity index; DL$_{co}$: diffuse capacity of the lung for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis

Although some factors such as increasing age, male sex, low DL$_{CO}$, presence of significant comorbidities, and acute exacerbation at the time of SLB were thought to be risk factors for complications,[1,11,15] we found no significant risk factors for the complications in our cohort. Additionally, postoperative diagnosis of ILD was confirmed with SLB samples in all patients, and surgical parameters of our study including operation time, anesthesia time, and bleeding were not different from those described in previous reports.[10,11] Our results suggest that SLB for ILD should not be denied reflexively to patients because of their age, sex, or comorbidities.

We saw no difference in short-term results between IPF and non-IPF patients. The relationship between mortality and ILD subtypes is still controversial, as Tiitto and colleagues insisted that the mortality rate in patients with IPF was similar to that with other subtypes,[9] while Rotolo and colleagues reported significantly higher mortality in patients with IPF/UIP.[12] However, given that several studies showed that 19%–74% of cases finally diagnosed as IPF via SLB were not initially suspected on HRCT,[23,24] SLB may be indicated for patients with suspected IPF who do not exhibit the UIP pattern on HRCT as well as patients with other ILDs.

We revealed the long-term outcome of patients with ILD after SLB in this study. The estimated median survival of patients with IPF from the time of diagnosis has been reported to be 45 months,[13,25,26] which is comparable to our result (**Fig. 1A**). Although several studies have previously demonstrated that old age and low DL$_{CO}$ at the time of SLB are significant predictive factors for survival,[9,27] the final diagnosis and acute exacerbation of ILD after SLB were significant predicting factors for survival in our study. Furthermore, the exact frequency of acute exacerbation in ILD following SLB is still unknown although a few studies showed that the 1-year frequency of acute exacerbation was 4.2% in patients with ILD other than IPF[21] and 4%–19% in patients with IPF.[28,29] The obvious distinction of long-term survival and acute exacerbation rate between IPF and other ILDs in our study suggests that the accurate and definitive diagnosis of IPF is clinically relevant to proper patient management.

There are some limitations to our study that warrant discussion. First, this was a retrospective study; thus, clinical outcomes might be biased by patient selection. Since our cohort included small cases of severe respiratory failure, we were not able to evaluate these risk factors. Furthermore, selection bias may be responsible for lower 90-day mortality and morbidity in our study.
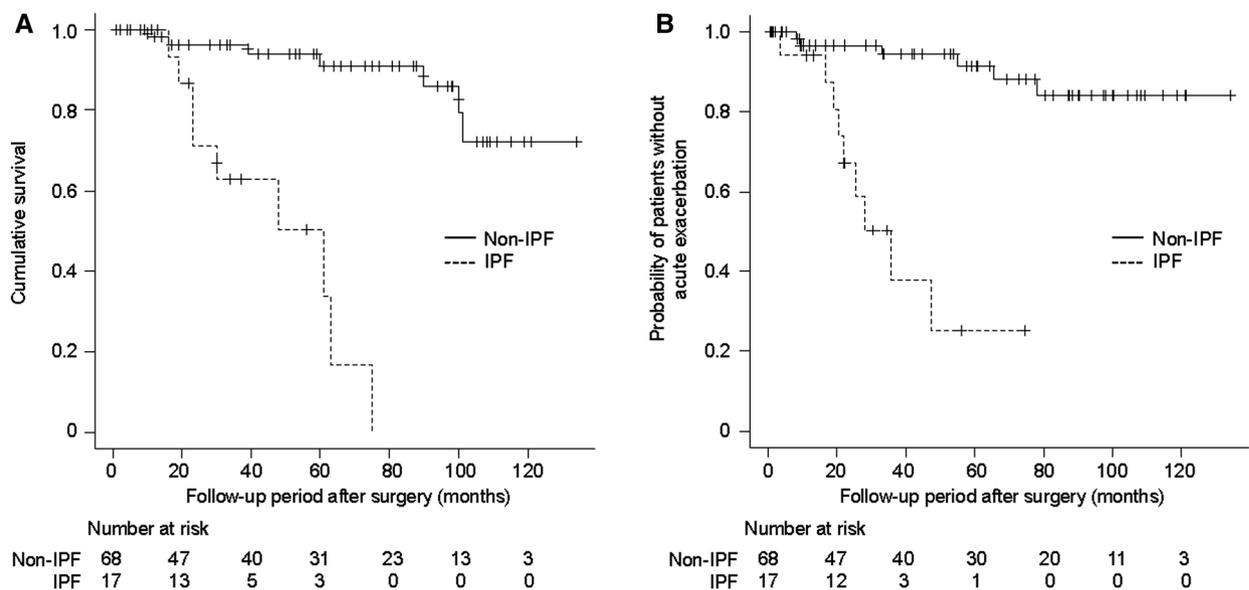
Fig. 1 Kaplan–Meier curves of patients with IPF and non-IPF groups. (**A**) Overall survival from surgical lung biopsy. (**B**) Time from surgical lung biopsy to the first acute exacerbation of interstitial lung disease. IPF: idiopathic pulmonary fibrosis

Another limitation of this study is the relatively small cohort. By design, it would be impossible to determine risk factors for 90-day mortality and morbidity in a cohort with no 90-day mortality and low rates of complications. However, the strength of our study is that we performed SLB with the same team, using a uniform surgical procedure (three-port VATS approach) that has been standardized over the last two decades, which we believe lead to excellent patient outcomes in this study. Third, we did not assess the differences of outcomes according to histopathology. Recently, several large clinical trials have been conducted in patients with progressive fibrosing ILD, demonstrating the efficacy and safety of antifibrotic therapy in the treatment of fibrotic interstitial pathology of other etiologies, as well as IPF/UIP.[30] Therefore, future research should determine what the impact of histological patterns determined by SLB might have on outcomes in patients with progressive-fibrosing phenotype.

In conclusion, this study indicates that SLB by VATS approach can be performed safely in patients with ILD, regardless of underlying phenotypes. The ability to differentiate IPF from other ILDs accurately by SLB may be beneficial for long-term patient management.

Authors' Contributions

M. N. designed the studies and wrote the manuscript. A.M., S. K., S. S., H. T., A.K., and T.F. collected and analyzed patient data. A.M. and S.F. revised the manuscript.

Disclosure Statement

The authors have no conflict of interests to declare.

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