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The role of video-assisted thoracoscopic surgery in the diagnosis of interstitial lung disease

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Abstract. *Background:* When a clinical context is indeterminate for idiopathic pulmonary fibrosis (IPF), or a chest high-resolution computed tomography (HRCT) pattern is not indicative of typical or probable usual interstitial pneumonia (UIP) in patients with interstitial lung disease (ILD), surgical lung biopsy should be considered to make a confident diagnosis on the basis of multidisciplinary diagnosis (MDD). *Aim:* The aim of this study was to evaluate the role and safety of video-assisted thoracoscopic surgery (VATS) in patients with ILD. *Methods:* A total of 143 patients with ILD underwent VATS at Toho University Medical Center Omori Hospital between March 2004 and April 2017. We conducted a retrospective study on the usefulness and safety of VATS in the diagnosis of ILD under MDD. *Results:* The 30-day mortality was 0%. The postoperative complication rate was 12.6%, which included 5 cases of pneumothorax after discharge (3.5%), 4 cases of prolonged air leakage (2.8%), and 2 cases of acute exacerbation (1.4%). Three of 9 cases (33.3%) complicated by pneumothorax after discharge or prolonged air leakage were resected specimens of pleuroparenchymal fibroelastosis (PPFE). Two patients had acute exacerbation, who were ultimately diagnosed as having idiopathic unclassifiable IP and had histologically significant irregular dense fibrosis and numerous fibroblastic foci. The comparison between chest HRCT and histopathological findings revealed 55 cases of possible UIP [UIP (45%), NSIP (25%), and unclassifiable IP (29%)] and 21 cases of inconsistent with UIP [UIP (10%), NSIP (33%), organizing pneumonia (10%), unclassifiable IP (24%), and PPFE (24%)]. *Conclusion:* VATS can be safely performed to obtain a confident diagnosis for appropriate treatment strategies in patients with ILD. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (2): 148-156)*

Key words: interstitial lung disease, video-assisted thoracoscopic surgery, complication, survival, multidisciplinary discussion diagnosise

Abbreviations List:
SLB: surgical lung biopsy
VATS: video-assisted thoracoscopic surgery
OLB: open lung biopsy
HRCT: high resolution computed tomography
ILD: interstitial lung disease
MDD: multidisciplinary discussion diagnosis
IIPs: idiopathic interstitial pneumonias
IPF: idiopathic pulmonary fibrosis
NSIP: nonspecific interstitial pneumonia
UIP: usual interstitial pneumonia
CHP: chronic hypersensitivity pneumonia
PPFE: pleuroparenchymal fibroelastosis
AE: acute exacerbation
KL-6: Krebs von den Lungen-6
SP-D: surfactant protein-D
FVC: forced vital capacity
DLco: diffusing capacity for carbon monoxide

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Introduction

In recent years, the necessity of surgical lung biopsy (SLB) for the purpose of diagnosis of interstitial lung disease (ILD) has been questioned not only because of the development of the chest high-resolution computed tomography (HRCT) but also because of the high morbidity and mortality associated with the procedure. More recently, Lynch, et al. (1) emphasized in a Fleischner Society White Paper that a confident diagnosis of idiopathic pulmonary fibrosis (IPF) can be made in a correct clinical context without SLB when CT imaging shows a pattern of typical or probable usual interstitial pneumonia (UIP). However, it is very important and challenging work-up for pulmonologist to make a correct diagnosis from over 100 different ILDs (2). When a clinical context is indeterminate for IPF, or a chest HRCT pattern is not indicative of typical or probable UIP in patients with ILD, surgical lung biopsy should be considered to make a confident diagnosis on the basis of multidisciplinary discussion diagnosis (MDD). Indeed, the chest HRCT findings do not always represent typical features of patients with ILD. Sverzellati et al. (3) reported that 34 out of 55 patients diagnosed as IPF on biopsy had received a diagnosis of NSIP, CHP, or sarcoidosis on SUGINO, The role VATS in ILD chest CT. In addition, Morris et al. (4) described that only 54% of patients who received a consensus diagnosis of UIP after video-assisted thoracoscopic surgery (VATS) lung biopsy, had received a diagnosis of probable UIP on chest HRCT. Therefore, VATS can be considered as one of necessary tool for the accurate diagnosis of ILD.

It has been reported that in general, risk factors of SLB are male sex, increasing age, increasing comorbidity, unstable condition such as rapidly progressive ILD requiring mechanical ventilation, severely impaired pulmonary function, coexisting of pulmonary hypertension in patients with ILD, undergoing open lung biopsy (OLB), and a provisional diagnosis of IPF or connective tissue disease–related ILD (5-8). VATS is generally considered as a safe procedure to provide adequate lung tissue samples for definitive histological diagnosis. However, postoperative complications may outweigh the potential benefits in patients with ILD because postoperative acute exacerbation (AE) or prolonged air leakage is one of the particularly critical and significant complications. According to a comprehensive literature review by Nguyen and Meyer (9), the overall 30-day mortality for OLB was 4.3% versus 2.1% for VATS biopsy, and non-lethal complications appeared to occur more frequently with OLB (18.1%) vs. VATS (9.6%) procedures. Given that VATS reduces risks of morbidity and mortality in this study, we aimed to assess the usefulness and postoperative complications of VATS in patients with ILD at our institution.

Methods

Patients

This study cohort included a total of 143 consecutive patients underwent VATS for suspected ILD at Toho University Omori Medical Center between March 2004 and April 2017. We conducted a retrospective review of the usefulness and postoperative complications of VATS in the diagnosis of ILD under MDD. All patients underwent a preoperative work-up including spirometry, blood gas analysis, electrocardiogram, and ultrasonic cardiogram. The data collected include: baseline patient characteristics, pulmonary function test findings, chest HRCT images, surgical parameters such as biopsy site, location, operation and anesthesia time, duration of chest drainage, postoperative complications, and 30-, 60-, and 90-day mortality. All scans were reviewed by consensus by 2 clinicians (S. H., K. Su.) and 1 radiologist (K. M.) with vast experience in ILD, who were blinded to histopathology results and clinical information. All patients were reviewed and interpreted by 2 expert pulmonary pathologists (K. S., T. U.). The postoperative diagnosis of ILD was determined at MDD. Patients excluded for VATS had a definite UIP pattern on chest HRCT, which was determined in accordance with the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) consensus statement (10). In addition, patients with diffusion capacity <30% predicted, AE-IPF and mechanical ventilation were excluded from VATS in the present study.

Informed consent for VATS was obtained from all patients. The study protocol was approved by the institutional ethics committee of Toho University Omori Medical Center (IRB No. M16266).

Surgical lung biopsy

A number of 2 or 3 biopsy sites, which were mild or moderate lesions adjacent to normal lungs avoiding severely affected areas, were determined through discussion with respiratory physicians, surgeons, and radiologists. Basically, VATS was performed with 3-port access under general anesthesia using a double-lumen endotracheal tube for single-lung ventilation as a standard procedure. In a case of severe pleural adhesions, conversion to a minithoracotomy was performed. As a result, triangle-shaped specimens with 3 to 5 cm in each margin were obtained. All biopsy specimens were inflated with formalin using a syringe and a needle after removing staples. Tissue samples for microscopic analyses were embedded in paraffin after being fixed with 10% formaldehyde. Sections with a thickness of 4 μm were routinely stained with hematoxylin and eosin and elastic van Gieson stains.

Definitions of postoperative complications

All complication occurred within 30 days after VATS. Postoperative AE was diagnosed by modified criteria for AE of IPF proposed by Collard et al. (11) and all of the following 3 conditions had to be fulfilled: i) worsening or development of dyspnea within 30 days after undergoing VATS; ii) chest HRCT scan with new bilateral ground-glass opacities and/or consolidation superimposed on a background ILD; iii) no evidence of pulmonary infection, heart failure, pulmonary embolism, and alternative causes for acute lung injury. Prolonged air leak was defined as a status requiring chest tube placement for 5 days or more. In addition, pneumothorax after discharge indicated that there was no evidence of air leak during hospitalization.

Measurement of the levels of the serum markers

The serum level of Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D were measured using a KL-6 enzyme-linked immunosorbent assay (ELISA) kit (Eisai Co. Ltd., Tokyo, Japan) and a SP-D ELISA kit (Yamasa, Tokyo, Japan), respectively. These were both commercially available kits. The cut-off levels of serum KL-6 and SP-D were <500 U/ml and <110 ng/ml, respectively.

Chest CT scan

A helical CT scanner (Aquilion 16, Toshiba, Tokyo, Japan) was applied. Thin-section CT scans were obtained at full inspiration and CT images were reconstructed by 1-2-mm collimation sections with a high spatial frequency algorithm and photographed at window settings appropriate for viewing the lung parenchyma (window level from -600 Hounsfield Units (HU); width from 1600 HU).

Statistical analysis

Data were expressed as median value and range for continuous variables, and as number and percentage for categorical variables. Data analyses were performed using statistical software (JMP, version 10.0.0, SAS Institute, Cary, NC, USA).

Results

Baseline patient characteristics

Baseline patient characteristics of this study are summarized in Table 1.

The study population consisted of 143 patients. There were 69 male (48%) and 74 female (52%) patients with a median age of 64 years (range 33-81 years). In 90 patients (62.9%), arterial blood gas analysis showed a ≥PaO_2 of 80 Torr. The median serum KL-6 and SP-D were 743 U/mL and 127 ng/mL, respectively. The pulmonary function test revealed that a ≥ forced vital capacity (FVC) of predicted of 60% and a ≥ diffusion capacity for carbon monoxide (DLco) of predicted of 50% were seen in 128 patients (89.5%) and 122 patients (89.1%), respectively (Table S1).

Surgical parameters in VATS

Characteristics of VATS lung biopsy procedure are summarized in Table S2.

While 3-port approach was carried out in 139 patients (97.2%), 4 patients were converted to minithoracotomy because of extensive pleural adhesion. The number of biopsy sites was 2 in 109 patients (76.2%). One biopsy was taken in 13 (9.0%) patients, and 3 biopsies were taken in 21 (14.7%) patients.

Table 1. Baseline demographic characteristics of 143 patients with ILD

Variable	Median or number	Range
Age, yrs	64	33-81
Sex, male/female	69/74	
Smoking history, Never/Former/Current	52 (36.4%)/76 (53.1%)/15 (10.5%)	
PaO_2, Torr	81.5	54.9-112
$PaO_2 \geq 80$	90 (62.9%)	
$70 \leq PaO_2 < 80$	36 (25.2%)	
$60 \leq PaO_2 < 70$	15 (10.5%)	
$PaO_2 < 60$	2 (1.4%)	
KL-6, U/ml	743	147-7580
SP-D, ng/ml	127	29.5-1530

ILD; interstitial lung disease, PaO_2; partial pressure of arterial oxygen, KL-6: Kreb von den Lungen-6, SP-D: surfactant protein D

The most common locations of biopsy sites were right lower lobe (32.3%) and left lower lobe (33.0%). Mean operation time was 96 min, and mean anesthesia time was 169 min. Intraoperative blood loss was extremely low (median; 0 mL, under 40 mL). The median duration of chest drainage and hospital stay was 1 and 6 days, respectively.

Complications of VATS

Total of 18 patients (12.6%) experienced postoperative complications such as pneumothorax after discharge in 5 (3.5%), prolonged air leakage in 4 (2.8%), AE of ILD in 2 (1.4%), and other complications in 7 patients. Three patients with pneu-

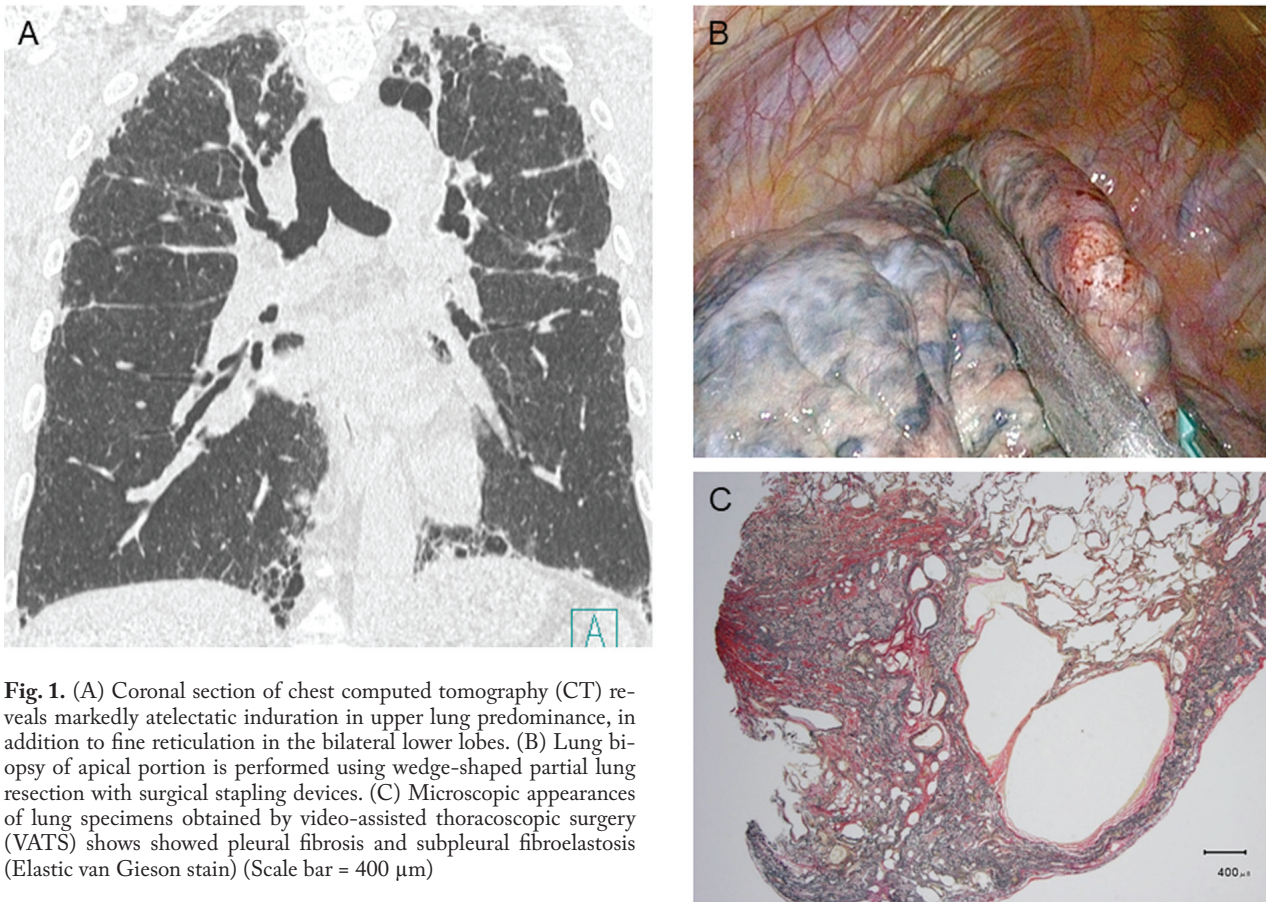

Fig. 1. (A) Coronal section of chest computed tomography (CT) reveals markedly atelectatic induration in upper lung predominance, in addition to fine reticulation in the bilateral lower lobes. (B) Lung biopsy of apical portion is performed using wedge-shaped partial lung resection with surgical stapling devices. (C) Microscopic appearances of lung specimens obtained by video-assisted thoracoscopic surgery (VATS) shows showed pleural fibrosis and subpleural fibroelastosis (Elastic van Gieson stain) (Scale bar = 400 μm)

mothorax after discharge required re-drainage and the remaining 2 patients had to undergo operation to close pulmonary fistulas. Prolonged air leakage in 2 patients resolved with continuous drainage, and the leakage in 2 other patients resolved with re-drainage. Three of 9 patients, who had a complication associated with pneumothorax after discharge along with a prolonged air leakage, underwent a biopsy for pleuroparenchymal fibroelastosis (PPFE) lesions in upper lobes (Figure 1, 2). The clinical characteristics of 2 patients who developed postoperative AE are summarized in Table 2. AE were observed on the second and fifth day after VATS. Additionally, locations of GGO accompanied by AE were primarily seen in the non-operated lungs of the present 2 cases. These histopathological findings were consistent with unclassifiable IP, including significant irregular dense fibrosis and numerous fibroblastic foci (Figure 3). Two patients complicated by AE were treated with 3-day intravenous administration of methylprednisolone (1000 mg/day). Thereafter, the dose was tapered based on their respiratory condition. Furthermore, synthetic neutrophil elastase inhibitor and cyclosporine A were added to the treatment. The both patients were consequently discharged at least once (Figure 4). No patients died 30 days after VATS. Although 1 patient died as a result of the second onset of AE within 90 days, this patient was classified as non-procedure related mortality (Table 3).

MDD of ILD

All 143 patients of ILD received a definite diagnosis after VATS under MDD. The most common diagnoses were IIPs (52.4%), including IPF (21.7%), NSIP (15.4%), and unclassifiable IP (10.5%), in addition to IP related collagen tissue disease (CTD) and chronic hypersensitivity pneumonitis (CHP) (Table 4). The comparison between chest HRCT and histopathological findings revealed 55 cases of possible UIP [UIP (45%), NSIP (25%), and unclassifiable IP (29%)] and 21 cases of inconsistent with UIP [UIP (10%), NSIP (33%), organizing pneumonia (10%), unclassifiable IP (24%), and PPFE (24%)] (Table 5).

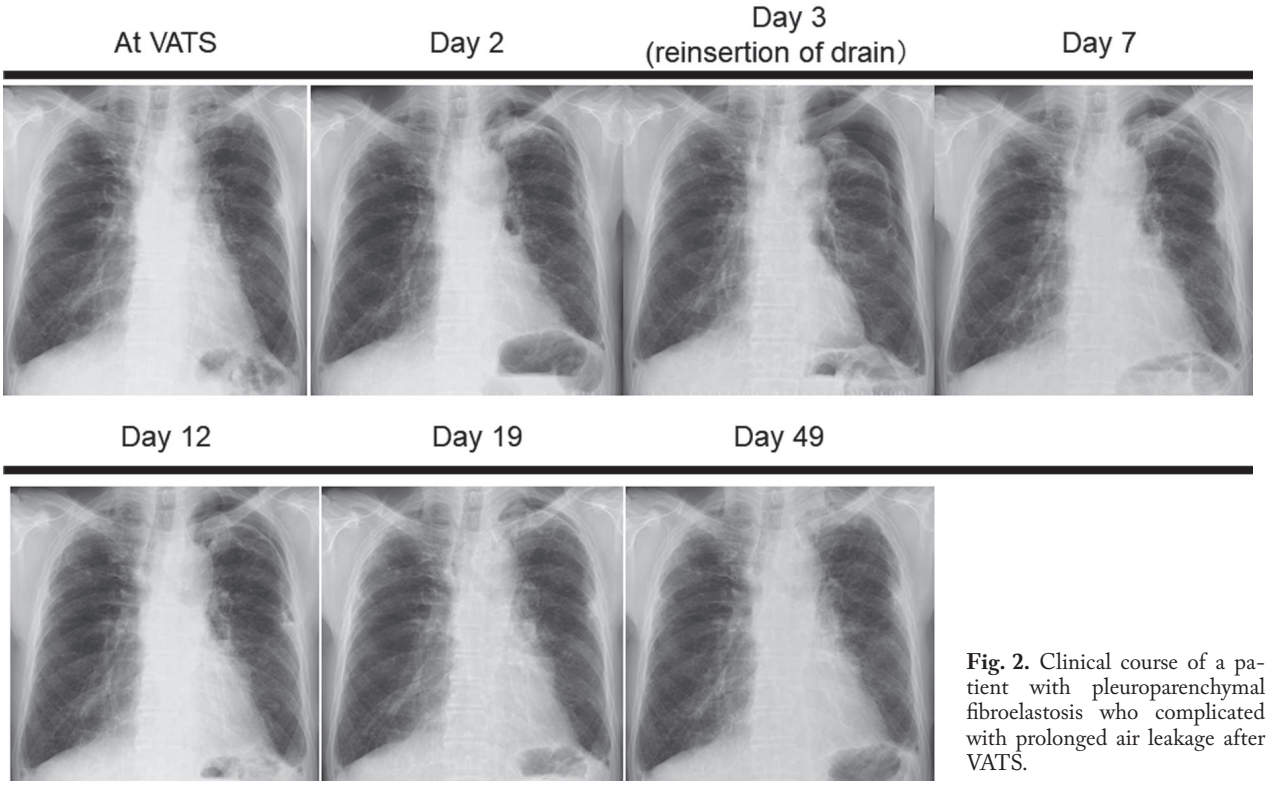

Fig. 2. Clinical course of a patient with pleuroparenchymal fibroelastosis who complicated with prolonged air leakage after VATS.

Table 2. Clinical characteristics of patients who developed postoperative acute exacerbation

No.	Age	Sex	%FVC	%DLco	PaO_2	Operation time (Days)	Pathological diagnosis	Duration from onset of AE	Cause of death	Survival time (days)
1	70	F	49.1	55.4	95.2	51	Unclassified (fibrotic NSIP + irregular fibrosis)	2	2nd AE	76
2	71	F	72.2	61.2	67.3	99	Unclassified (UIP + irregular fibrosis)	5	2nd AE	656

F; Female, FVC; forced vital capacity, DLco; diffusing capacity for carbon monoxide, PaO_2; partial pressure of arterial oxygen, NSIP; non-specific interstitial pneumonia, UIP; usual interstitial pneumonia, AE; acute exacerbation

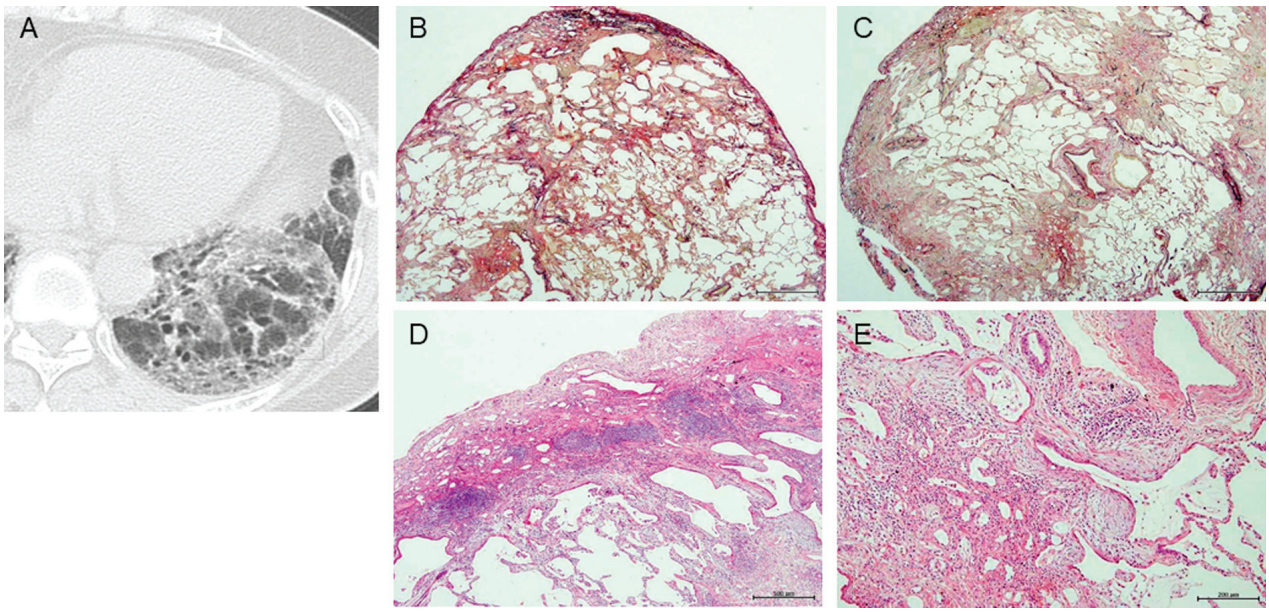

Fig. 3. (A) Chest CT scan shows diffuse reticulation and widespread ground-glass opacity accompanied by traction bronchiectasis predominantly in the bilateral lower lobes. (B) Lung biopsy specimens from the left lingula obtained by VATS reveals prominent uniform thickening of alveolar septa by fibrosis (nonspecific interstitial pneumonia; NSIP pattern) (Elastic van Gieson stain) (Scale bar = 1 μm). (C) Lung biopsy specimens from the left lower lobe reveal subpleural and perilobular fibrosis adjacent to relatively normal alveoli (usual interstitial pneumonia; UIP pattern) (Elastic van Gieson stain) (Scale bar = 1 μm). (D) There are marked inflammatory cell infiltration and lymphoid hyperplasia within dense collagen fibrosis (Hematoxylin-Eosin stain) (Scale bar = 200 μm). (E) Fibroblastic foci are sporadically present in dense collagen fibrosis and lymphocytes and plasma cells infiltration is mainly observed (Hematoxylin-Eosin stain) (Scale bar = 200 μm)

Discussion

In this single center retrospective study, we aimed to assess the usefulness and postoperative complications of VATS in patients with ILD at our institution. The usefulness of SLB for the purpose of diagnosis of ILD remains still controversial not only because of the development of the chest HRCT but also because of the high morbidity and mortality associated with the procedure. Moreover, in several institutions, SLB has been replaced with cryobiopsies; however, according to the latest IPF guideline, in cases without typical UIP pattern on chest HRCT, VATS is recommended (conditional recommendation) to be performed for a confident diagnosis (12).

The biopsy number and site may affect the diagnostic efficacy of VATS. In the present study, the site of biopsy was determined by the abnormalities on chest CT images of major lesions and intermediate or minor lesions. There is histologic discordance between lobes in 13-26% of patients with IIPs (13, 14). Therefore, a single site of biopsy cannot be suffi-

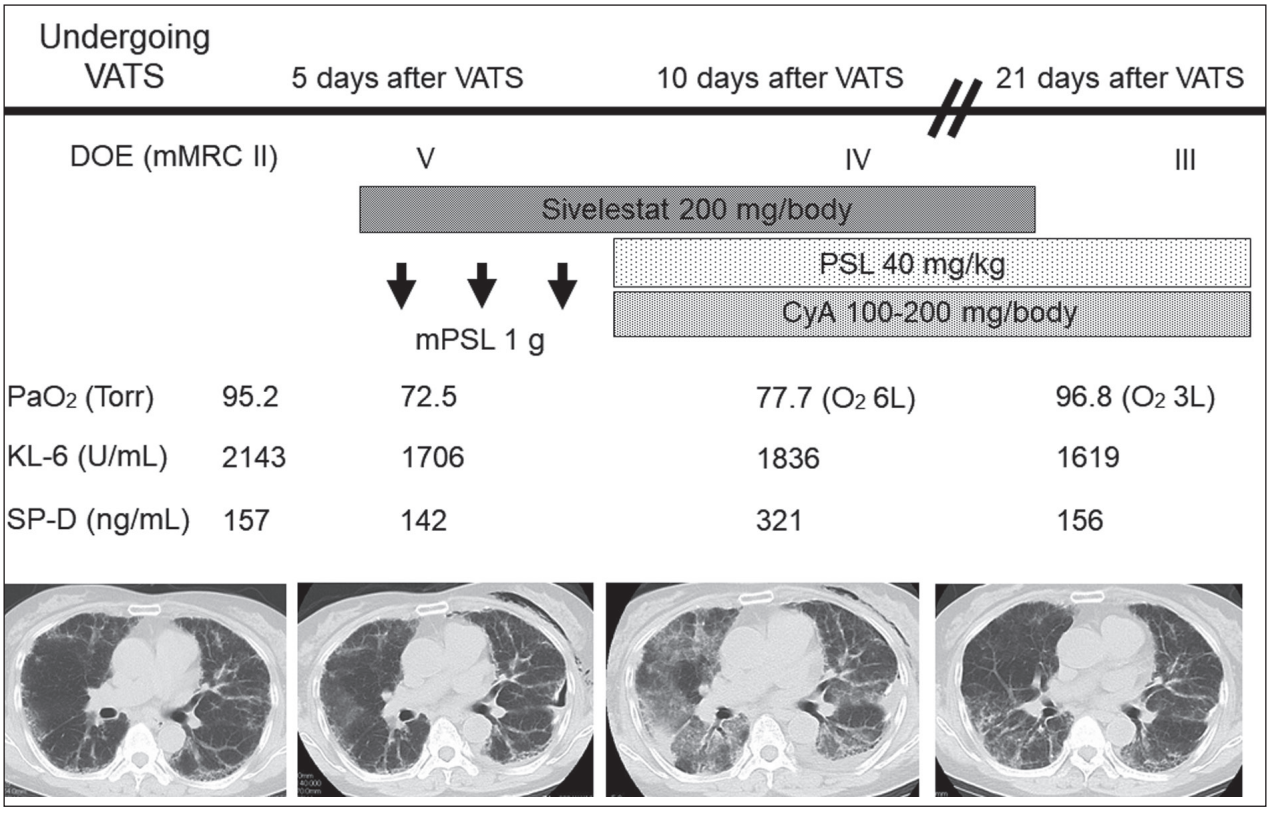

Fig. 4. Clinical course of a patient with idiopathic unclassifiable interstitial pneumonia who developed acute exacerbation after VATS

Table 3. Postoperative complications and operative mortality

Variable	Number	%
Postoperative complications	18	12.6
Pneumothorax after discharge	5	3.5
Prolonged air leakage (≥5 days)	4	2.8
Wound infection	3	2.1
Atelectasis	2	1.4
Acute exacerbation of interstitial pneumonia	2	1.4
Hemothorax	1	0.7
Pneumonia	1	0.7
Operative mortality		
30 days	0	0
60 days	0	0
90 days	0	0

Table 4. MDD of ILD

Variable	Number	%
Idiopathic interstitial pneumonia	75	52.4
Idiopathic pulmonary fibrosis	31	21.7
Nonspecific interstitial pneumonia	22	15.4
Cryptogenic organizing pneumonia	2	1.4
Unclassifiable interstitial pneumonia	15	10.5
Pleuroparenchymal fibroelastosis	5	3.5
Interstitial pneumonia related collagen vascular disease	49	34.3
Chronic hypersensitivity pneumonitis	11	7.7
IgG4 related lung disorder	2	1.4
Sarcoidosis	1	0.7
Langerhans cell histiocytosis	1	0.7
Leukemia	1	0.7
Diffuse panbronchiolitis	1	0.7
Common variable immunodeficiency	1	0.7
HTLV-I associated bronchiolo-alveolar disorder	1	0.7

MDD; multidisciplinary discussion diagnosis, ILD; interstitial lung disease, HTLV-1; Human T-cell leukemia virus type 1

cient to obtain a definite diagnosis for ILD patients. In this study, 2 or 3 biopsies were obtained from approximately 90% of our patients. More than half of our patients (61.5%) underwent a biopsy on both the upper and lower lobes.

It has been reported that in general, risk factors of SLB are male sex, increasing age, increasing comorbidity, an unstable condition such as rapidly progressive ILD requiring for mechanical ventilation, severely impaired pulmonary function, coexisting of pulmonary hypertension in patients with ILD, undergoing open lung biopsy (OLB), and a provisional

Table 5. Comparison between chest HRCT images and histological findings in IIPs

Histologic pattern	Chest HRCT pattern		MDD
	Possible UIP (n = 55)	Inconsistent with UIP (n = 21)	
UIP	25 (45%)	2 (10%)	IPF
NSIP	14 (25%)	7 (33%)	NSIP
OP	0 (0%)	2 (10%)	COP
Unclassifiable	16 (29%)	5 (24%)	Unclassifiable IP
PPFE	0 (0%)	5 (24%)	PPFE

HRCT; high resolution computed tomography, IIPs; idiopathic interstitial pneumonias, UIP; usual interstitial pneumonia, NSIP; nonspecific interstitial pneumonia, OP; organizing pneumonia, PPFE; pleuroparenchymal fibroelastosis, MDD; multidisciplinary discussion diagnosis, IPF; idiopathic pulmonary fibrosis, COP; cryptogenic organizing pneumonia

diagnosis of IPF or connective tissue disease-related ILD (5-8). In the present study, 30-, 60-, and 90-day mortality were 0%. However, %FVC of predicted of ILD patients with postoperative complication tend to decrease (79.2±20.7% vs. 88.2±21.1%). Moreover, one patient of postoperative AE had lower %FVC of predicted of 49.1% and %DLco of predicted of 55.4%, and the other had component of histological UIP. VATS is generally considered as a safe procedure to provide enough lung tissue samples for definitive histological diagnosis. However, postoperative complications may outweigh the potential benefits in patients with ILD because postoperative AE or prolonged air leakage is one of the particularly critical and significant complications. Sigurdsson et al. (15) reported that a 30-day mortality for SLB in 73 ILD patients was 2.7% and its complication rate was 16%. Moreover, Kreider et al. (16) demonstrated that a morbidity rate was 19% and a 60-day mortality rate was 4.4% in 68 patients with ILD undergoing VATS lung biopsy. According to a comprehensive literature review by Nguyen and Meyer (9), 9.6% of patients with ILD who underwent VATS experienced one or more postoperative complications. Additionally, the overall 30-day mortality was 2.1% for VATS lung biopsy. In this study, the 30-day mortality was 0%. Importantly, the low mortality rate may be related to appropriate patient selection criteria and operation by trained chest surgeons. The postoperative complication rate was 12.6%, including 5 cases of pneumothorax after discharge (3.5%), 4 cases of prolonged air leakage (2.8%), and 2 cases of acute exacerbation (1.4%). Three of 9 cases (33.3%) were complicated by either pneumothorax after discharge or prolonged air leakage, which were resected specimens of PPFE lesions. Probably, we should avoid resection of specimens of PPFE lesions in the upper lobes. As reported by Kreider et al. (16), 3 patients with pathological UIP and a low DLco value (19, 27, 30%) died after VATS lung biopsy. Postmortem examination in 2 of these 3 patients revealed diffuse alveolar damage on a background of UIP, consistent with AE of UIP. Thus, patients with definite UIP pattern on chest HRCT were excluded in this study. Interestingly, 2 cases developed postoperative AE in our study were histologically diagnosed with unclassifiable IP with significant irregular dense fibrosis and numerous fibroblastic foci. Unfortunately, it was impossible to predict these findings before undergoing VATS. Incidences of postoperative AE were too few to compare characteristics of ILD patients with or without AE.

Sverzellati et al. (3) reported that 34 out of 55 patients diagnosed as IPF on biopsy had received a diagnosis of NSIP, CHP, or sarcoidosis on chest CT. In addition, Morris et al. (4) described that only 54% of patients who received a consensus diagnosis of usual UIP after VATS lung biopsy had received a diagnosis of probable UIP on chest HRCT. In contrast, Raghu et al. (17) reported that the positive predictive value of possible UIP pattern on chest CT was 94% for the finding of histologic UIP. However, there has been a selection bias noticed in this study because the entire cohort of patients had histologic UIP and previously selected for participation in a clinical trial of IPF. Fell et al. (18) found that in patients without honeycomb change on HRCT, older age and a higher HRCT interstitial score are highly predictive of a diagnosis of IPF. A recent study by Gruden et al. (19) showed that a pattern of patchy heterogeneous basilar-predominant reticular abnormality without honeycombing was strongly associated with histologic UIP. In our study, approximately 50% of patients with possible UIP on chest HRCT was consistent with UIP; however, about 30% of patients was diagnosed with idiopathic unclassifiable IP. Some patients, who were considered as unclassifiable IP at initial diagnosis would ultimately be diagnosed as IPF through the clinical course under MDD. Therefore, we believe that MDD will be vitally necessary to make a more precise diagnosis for ILD.

The limitations of this study are as follows. Firstly, this study included retrospectively short

follow-up period and small number of patients at a single center. Therefore, our results may not represent the usefulness and safety of VATS in the entire ILD population. In the future, longer and larger observation prospective studies are needed to confirm our results. Secondly, patients with IP related to connective tissue diseases usually do not need to undergo a biopsy under VATS in clinical setting. However, we suppose that this attempt is useful to select whether anti-fibrotic agents or anti-inflammatory agents such as corticosteroid or immunosuppressants should be applied. Thirdly, patients with a definite UIP pattern on chest HRCT were excluded from indication of VATS based on their risk of AE-IPF in this study. However, we should pay attention to referring patients with possible UIP pattern for VATS, because many patients with possible UIP could have histologic UIP as reported by Raghu et al. (17) and because patients with a provisional diagnosis of IPF including patients with possible UIP pattern also have an increased mortality after SLB, as described by Hutchinson et al. (8).

In conclusion, although VATS is not required in patients with suspected IPF who had typical UIP pattern on chest HRCT, in other ILD patients, VATS is safely performed to obtain a confident diagnosis for appropriate treatment strategies.

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Author Contributions:

KSu, SH: study design, data analysis, manuscript preparation, guarantor of paper

KSu, HO, TM, YM, YN, KM, KSi: data collection, data analysis

KSu, HO, YM, YN, KM, YA, TM, AI, KSi, SH: manuscript preparation and review

All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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