



# Surgical lung biopsy for interstitial lung diseases—a single center study of 129 patients

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**Background:** According to guidelines for the diagnosis and treatment of interstitial lung diseases (ILDs), a diagnostic surgical lung biopsy should be used to obtain the differential diagnosis of an ILD in patients with ILDs, which are difficult to distinguish clinically. However, the risk of developing postoperative complications such as postoperative pulmonary fistula or acute exacerbation is a concern. The purpose of this study was to evaluate the safety of surgical lung biopsy for the differential diagnosis of ILDs.

**Methods:** From October 2007 to July 2019, 129 patients thought to have ILD underwent a surgical lung biopsy at Toho University Omori Medical Center. We conducted a retrospective study on the diagnosis and safety of surgical lung biopsy for patients with ILD.

**Results:** The 30- and 60-day mortality was 0%. Postoperative complications occurred in 13 of 129 (10.1%) patients. The complications included pneumothorax in 8 (6.2%) patients after removal of the chest tube, postoperative pneumonia in 2 (1.0%), and acute exacerbation in 1 (0.8%). Postoperative pneumothorax was observed in 4 of 13 patients (30.7%) who underwent a biopsy of the apex of the lung (right S1, left S1+2), which was a significantly higher rate of postoperative pneumothorax than seen for patients undergoing biopsy at other sites ( $P=0.0086$ ).

**Conclusions:** Surgical lung biopsy for the differential diagnosis of an ILD was performed safely. However, biopsy sites for ILDs need to be carefully selected to avoid postoperative complications.

**Keywords:** Interstitial lung disease (ILD); video-assisted thoracoscopic surgery (VATS); lung biopsy; complication

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## Introduction

Interstitial lung disease (ILD) consists of several lung diseases widely varying in etiology, pathological changes, treatments, and prognosis (1,2). Therefore, it is important to validate the diagnosis and classification of an ILD to select its treatment and determine the prognosis. According to guidelines for the diagnosis and treatment of ILDs, a diagnostic surgical lung biopsy should be used to obtain

the differential diagnosis of an ILD in patients with ILDs, which are difficult to distinguish clinically (1). However, with the development of chest high-resolution computed tomography (HRCT) and the high morbidity and mortality associated with a surgical lung biopsy, the utility of surgical biopsy for the diagnosis of an ILD remains controversial (3). Both the development of HRCT and the increasing use of diagnostic cryobiopsy have led to questions on the necessity

of surgical lung biopsy (4), since diagnostic cryobiopsy has also been reported to be effective for ILDs (5).

In most cases, a diagnosis can be established from the clinical information, the results of detailed laboratory tests, HRCT, and transbronchial lung biopsy (TBLB), all of which the patient's physician and radiologist or pathologist will discuss with each other. However, the sensitivity and specificity of such an approach for the diagnosis of idiopathic pulmonary fibrosis (IPF) has been reported to range from 60% to 80% (6). In addition, a TBLB may not be sufficient for a definitive pathological diagnosis, which depends on the sample volume and the biopsy site. A retrospective study of 21 patients with IPF found that only 32% of the TBLB specimens could be accurately diagnosed, compared with 95.4% of the surgical lung biopsy specimens (7).

The postoperative complications of surgical lung biopsy are a serious problem in ILD patients. Patients with a decreased diffusing capacity of the lungs for carbon monoxide [diffusing capacity for carbon monoxide (DLCO) <50% predicted value], who need mechanical ventilation (MV), or who have immunodeficiency or pulmonary hypertension, have been reported to have an increased risk of death after surgical lung biopsy (8-11).

Video-assisted thoracoscopic surgery (VATS) is generally considered a safe procedure for providing lung tissue samples that are sufficient for a definitive histopathological diagnosis (12). The purpose of this study was to evaluate the safety of surgical lung biopsy performed with minimally invasive procedures, including VATS, for patients with ILD. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1773/rc>).

## Methods

This was a retrospective study of 129 patients with suspected ILD, who consecutively underwent a surgical lung biopsy at Toho University Omori Medical Center between October 2007 and July 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of Toho University Omori Medical Center (No. M20122). Informed consent for VATS was obtained from all patients.

The indications for surgical biopsy were decided through a multidisciplinary discussion. Because this study included patients observed over a long follow-up period, the criteria of patient selection regarding the type of interstitial pneumonia

were not consistent. However, worsening respiratory status, such as the appearance of the signs/symptoms of dyspnea or an apparent decrease in a transcutaneous oxygen measurement were not indications for surgical biopsy.

Information was retrospectively gathered from the clinical case notes and included the following: demographic data (age, sex, and smoking status), results of pulmonary function tests (PFTs), estimated pulmonary arterial pressure as measured by echocardiography, surgical approach for biopsy, number of biopsy specimens, location of biopsy site, morbidity, 30- and 60-day mortality after biopsy, length of hospital stay, and postoperative diagnosis. The estimated pulmonary arterial pressure was calculated by adding the transtricuspid pressure gradient to the right atrial pressure (10 mmHg) (13). The transtricuspid pressure gradient was estimated with the use of the modified Bernoulli equation ( $4V^2$ , where V is the maximum velocity of the regurgitant jet of the tricuspid valve).

Surgical lung biopsy was performed with the patient under general anesthesia and consisted of intubation with a double-lumen catheter and single-lung ventilation. All the patients were placed in the lateral position. VATS was performed with 3 ports. A thoracotomy was performed for patients found to have severe adhesions during endoscopic exploration or for other reasons. The site, side, and the number of biopsy samples were planned after a multidisciplinary discussion (MDD) of physicians who performed careful clinical evaluations and assessments of the distribution of disease as shown on CT. In patients with homogenous bilateral disease and 1 to 3 different lobar targets, the left side was chosen preferentially. The biopsy specimen was obtained by a stapler and consisted of a triangular wedge of pulmonary tissue (*Figure 1*).

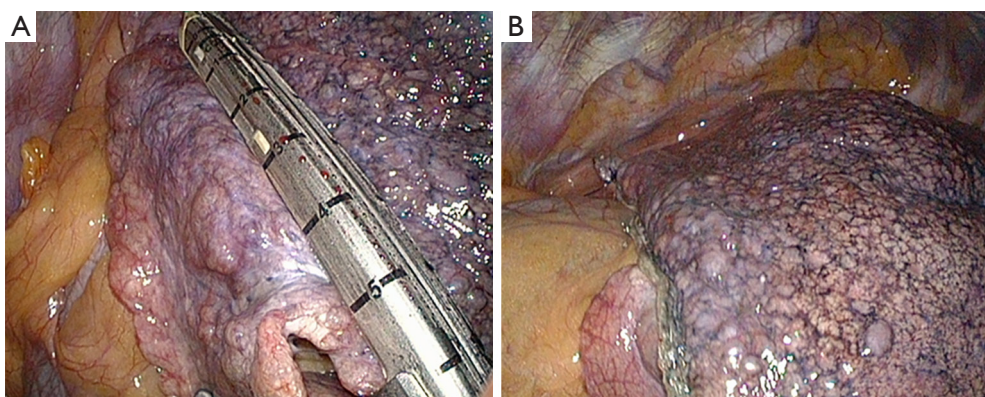
To reinforce the staple line, we covered the staple lines in all patients with both fibrin glue and oxidized cellulose sheets. The patients were enrolled in a rehabilitation program to prevent respiratory complications.

## Statistical analysis

Statistical analysis consisted of basic statistical analysis, with the two-tailed Fisher exact test used to compare complications. All statistical computations were performed with the use of a statistical software package (JMP, version 10.0.0; SAS Institute, Cary, NC, USA).

## Results

The characteristics of the 129 patients who underwent



**Figure 1** Procedure for performing a lung biopsy. (A) The peripheral region of the lung was selected as the biopsy site; (B) a triangular wedge of pulmonary tissue was taken with the use of a surgical stapler.

surgical lung biopsy are summarized in *Table 1*. The estimated pulmonary artery pressure as determined by echocardiography was determined in 111 (86%) patients.

*Table 2* summarizes the surgical parameters and complications after surgery. Biopsies of 2 or more sites were performed in 124 (96%) patients. The most common sites for biopsy were the left lower lobe (44%), left upper lobe (23%), and right lower lobe (22%). For the left upper lobe, the lingular division (17%) was selected more frequently than the upper division (6%) for biopsy. The mean operative time was 85.6 min. The mean duration of chest tube drainage and hospital stay were 1.2 and 5.1 days, respectively.

The 30- and 60-day mortality was 0%. Postoperative complications occurred in 13 of 129 patients (10.1%), which included 8 patients who developed pneumothorax after removal of the chest tube (6.2%), 2 who developed postoperative pneumonia, and 1 who developed postoperative acute exacerbation (AE) of interstitial pneumonia (0.8%).

There were no hospital deaths after the biopsy procedure. The patient who developed postoperative AE of interstitial pneumonia and subsequently recovered after surgery died 76 days after surgery after being discharged because of worsening ILD.

Patients who had been diagnosed with pleuroparenchymal fibroelastosis (PPFE) developed a significantly higher number of postoperative complications than other patients (*Table 3*), which included 3 cases of pneumothorax. Postoperative pneumothorax was observed in 4 of 13 (30.7%) patients who underwent biopsy of the apex of the lung (right S1, left S1+2) (*Figure 2*, *Table 4*). The

rate of pneumothorax occurring after biopsy of the apex was higher than the rate of biopsy occurring after biopsy of other sites ( $P=0.0086$ ). Biopsy of the upper lobe was performed in all 5 patients with PPFE. Multivariate analysis did not identify a significant risk factor for pneumothorax.

## Discussion

The usefulness of surgical lung biopsy for the diagnosis of ILD remains controversial, because of the use of chest HRCT. In addition, surgical lung biopsy has high morbidity and mortality. The latest IPF guidelines provide a conditional recommendation of VATS for the definitive diagnosis of patients without a typical UIP pattern on chest HRCT (1). VATS is generally considered to be a safe procedure that provides lung tissue samples that are sufficient for a definitive histopathological diagnosis. However, the postoperative complications are severe in patients with ILD, because the postoperative acute exacerbation of ILD is critical (11). The incidence of postsurgical lung biopsy complications has been reported to be 16–71%, with an overall postoperative mortality of 0–24% (14,15). It was reported that patients with decreased DLCO <50% of the predicted value, with requirement of MV, with immunocompromised status, and with pulmonary hypertension might be at increased risk of death after surgical lung biopsy (9–11). For selected patients with no risk factors, the overall postsurgical lung biopsy mortality rate was reported to be 1.5% (15). Sigurdsson *et al.* reported 30-day mortality and complication rate after surgical lung biopsy of 2.7% and 16%, respectively, for 73 patients with ILD (16). Moreover, Kreider *et al.* studied 68

**Table 1** Characteristics of 129 patients

Variables	Number or numerical value	Q1 and Q3 or %
Age (mean)	62.6 years	59.0 and 68.5
Male/Female	63/66	49%/51%
Smoking (pack-year: mean)	16.5	0 and 30.5
Preoperative pulmonary function		
VC (mean)	2.65 L	2.06 and 3.15
VC, % (mean)	91.1%	77.8 and 105.3
FEV1% (mean)	81.9%	77.4 and 86.7
DLCO, %	71.0%	55.5 and 82.9
Estimated pulmonary arterial pressure (mean)	30.4 mmHg	27.6 and 33.8
Serum KL-6 (mean)	1,217.6 U/mL	628 and 1,499
Postoperative diagnosis based on MDD		
Idiopathic interstitial pneumonia	72	55.8%
Unclassifiable idiopathic interstitial pneumonia	34	26.4%
Idiopathic pulmonary fibrosis	18	14.0%
Nonspecific interstitial pneumonia	15	11.6%
Pleuroparenchymal fibroelastosis	5	3.9%
CVD-IP	42	32.6%
Environmental lung disease	9	7.0%
Others	6	4.7%

VC, vital capacity; FEV1%, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; KL-6, Krebs von den Lungen-6; MDD, multidisciplinary discussion; CVD-IP, collagen vascular disease-associated interstitial pneumonia; Q1, quartile 1; Q3, quartile 3.

patients with ILD who underwent VATS lung biopsy and found a 60-day mortality and morbidity rate of 4.4% and 19%, respectively (15). A comprehensive literature review by Nguyen and Meyer reported that 9.6% of patients with ILD who underwent VATS developed 1 or more postoperative complications. They also reported an overall 30-day mortality of 2.1% for the VATS lung biopsy (17). In our study, the 30- and 60-day mortality was 0%.

In general, the risk factors of surgical lung biopsy in patients with ILD have been reported to be the following: male sex, increased age, increased number of comorbidities, unstable condition such as rapidly progressing ILD requiring mechanical ventilation, severely impaired pulmonary function, and coexisting pulmonary hypertension (9-11).

Previous reports have focused mainly on the status of a patient (8-11). We have improved the procedure of surgical biopsy for patients with ILDs to reduce their postoperative

complications. Therefore, this study focused mainly on the surgical procedure.

The low mortality rate seen in our study may be related to appropriate patient selection and specific surgical procedures such as applying fibrin glue to the partially resected stump and attaching an oxidized cellulose sheet for reinforcement of the residual resected stump. In addition to specific surgical procedures, we provide a perioperative rehabilitation program to reduce the risk of postoperative respiratory infections. A surgical biopsy performed for a patient with worsening respiratory status leads to postoperative respiratory complications and should be avoided.

As the guidelines have implied, the more biopsies are performed, the higher the yield of diagnoses, but the higher the rate of complications. Therefore, only 9% of the patients were biopsied at 3 sites, and these patients were

**Table 2** Surgical parameters and complications after surgery

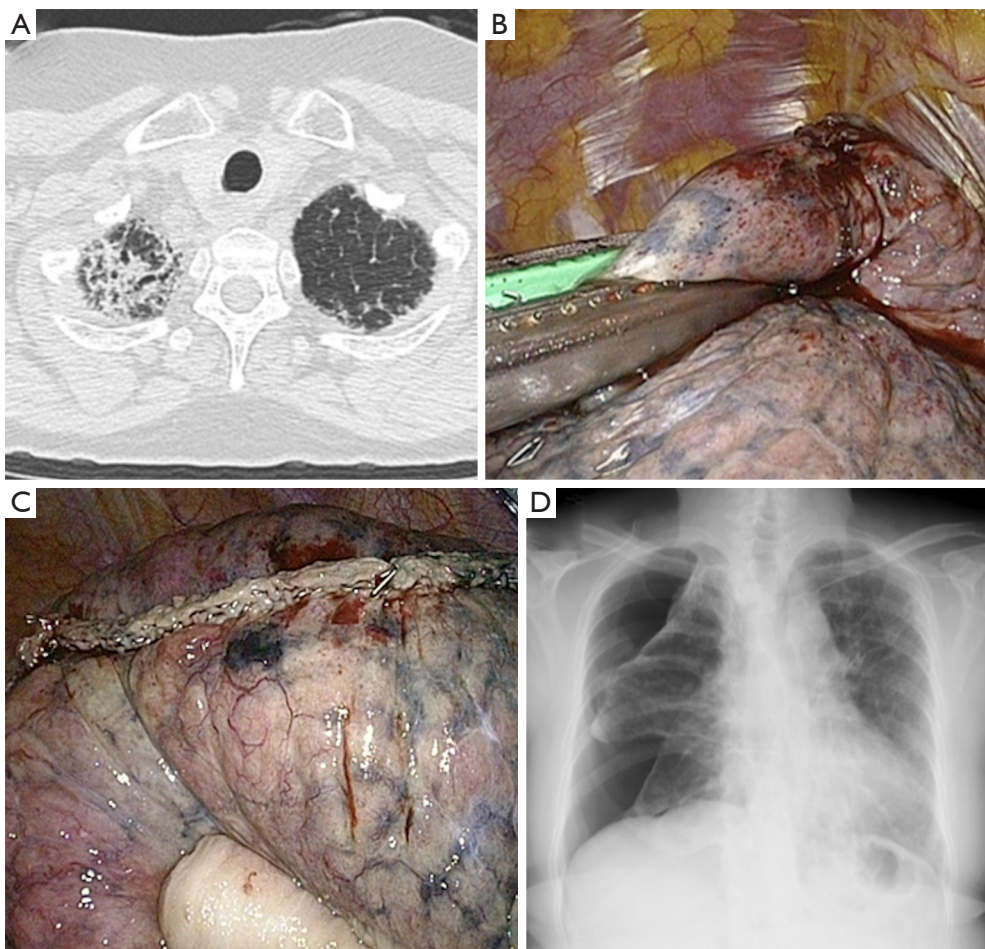
Variables	Number	Percentage, %
Surgical approach		
VATS/thoracotomy	120/9	93/7
Number of biopsy sites		
1/2/3	5/112/12	4/87/9
Location of biopsy site (total 266 specimens)		
Right upper lobe (apex)	19 (4)	7
Right middle lobe	10	4
Right lower lobe	59	22
Upper division of left upper lobe (apex)	17 (9)	6
Lingular division of left upper lobe	44	17
Left lower lobe	117	44
Complications	13	10.1
Acute exacerbation of interstitial pneumonia	1	0.8
Pneumothorax after removal of drainage tube	8	6.2
Postoperative pneumonia	2	1.6
Hemothorax	1	0.8
Wound infection	1	0.8
Postoperative mortality		
30 days	0	0
60 days	0	0

VATS, video-assisted thoracoscopic surgery.

**Table 3** Complications according to patients' factors

Preoperative factors (case number)	Case number of postoperative complications	P value
Male (n=63): female (n=66)	8:5	0.8000
<70-year-old (n=103): ≥70-year-old (n=26)	11:2	0.4897
Smoker (n=69): non-smoker (n=60)	5:8	0.3176
KL-6 <500 (n=15): KL-6 ≥500 (n=113)	1:12	0.5314
%DLCO <50 (n=21): %DLCO ≥50 (n=107)	1:12	0.3314
IPF (n=17): non-IPF (n=112)	0:13	0.2946
PPFE (n=5): non-PPFE (n=124)	3:10	0.0072
Apex (S1, S1+2) (n=13): others (n=116)	4:9	0.9961
1 or 2 sites (n=116): 3 sites (n=13)	11:2	0.8739

Data are missing for one case each of %DLCO and KL-6 (total 128 cases). DLCO, diffusing capacity for carbon monoxide; KL-6, Krebs von den Lungen-6; IPF, Idiopathic pulmonary fibrosis; PPFE, pleuroparenchymal fibroelastosis.



**Figure 2** Preoperative chest CT scan and intraoperative photos of a patient who developed pneumothorax after lung biopsy, and chest X-ray at the onset of pneumothorax. (A) The apex of the lung was selected as the biopsy site; (B) the “plane” of the region was strongly compressed by the surgical stapler; (C) small lacerations of the visceral pleura were found near the staple line; (D) one month after the biopsy, the lung collapsed because of staple failure. CT, computed tomography.

**Table 4** Comparisons of pneumothorax based on biopsy site

Biopsy site	Number of patients with postoperative pneumothorax/total case number	P value
Apex (S1, S1+2): others	4/13:4/116	0.0086
Lower lobe: others	1/41:7/88	0.2129

carefully selected based on preoperative discussions.

The postoperative complication rate was 10.1%, including 8 patients with pneumothorax after removal of the chest tube (6.2%), and 1 patient with acute exacerbation (0.8%). Four of 13 (30.8%) patients biopsied in the apex developed complications of pneumothorax after removal of the drainage tube. On the other hand, of the patients undergoing biopsy of the lower lobe only, one 1 showed

air leakage. It is thought that the reasons why air leakage is frequently detected after biopsy of the apex of the lung are that the “plane” region is strongly compressed and that a large number of patients had PPF. Although an increased expression of KL-6 is an indicator of interstitial pneumonia, an assessment of our data did not confirm a significant association between the finding and the frequency of postoperative complications.

In this study, 26% of the patients were diagnosed with unclassifiable idiopathic interstitial pneumonia (IIP). The reasons for the relatively large number of cases of unclassifiable IIP may be that (I) surgical biopsies were not performed in patients with typical HRCT images, and (II) many patients had multiple pathological findings.

This study has limitations. First, the study was retrospective. Second, this study included patients with various diseases. However, despite these limitations, we believe that our findings are important. Currently, cryobiopsy has become popular for the diagnosis of ILD. Despite the retrospective data, our findings should help in deciding between surgical biopsy and cryobiopsy. However, according to our data, surgical biopsy in the apex should be avoided, if possible.

In conclusion, surgical lung biopsy for patients with diffuse lung disease was performed safely. However, biopsy sites for ILD need to be carefully selected to avoid postoperative complications such as seen in patients undergoing biopsy of the apex of the lung, who had a significantly higher rate of postoperative pneumothorax than patients undergoing biopsy of other sites. When performing biopsies in the apex, we should add reinforcements such as fibrin glue and oxidized cellulose sheets.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1773/rc>

*Data Sharing Statement:* Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1773/dss>

*Peer Review File:* Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1773/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-21-1773/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work by ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of Toho University Omori Medical Center (No. M20122). Informed consent for VATS was obtained from all patients.

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