

Peer Review File

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First Round Peer Review

Reviewer A

The manuscript of Otsuka and colleagues reports a retrospective study looking at the diagnostic yield and safety of surgical lung biopsy (SLB) in patients with so far unclassified interstitial lung disease (ILD). They analysed data of 129 patients who underwent SLB and found a 30- and 60-day mortality of 0%. Postoperative complications occurred in 10.1% of patients and in 74% of patients, SLB led to a specific diagnosis. Based on their data, the authors suggest that – if performed in the correctly selected patient population - SLB is a save procedure.

The study addresses a very crucial point which is the safety and diagnostic yield of SLB in patients with suspected ILD. A thorough, step-wise diagnostic work-up is the basis of a careful diagnosis and respective treatment in ILD-patients. According to the most current guidelines by Raghu G et al. (Am J Respir Crit Care Med 2018;198:e44-e68), SLB is - among others - suggested in “patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate for UIP, or an alternative diagnosis”. Furthermore, broncho-alveolar lavage is suggested for patients with a non-UIP pattern on HRCT. Importantly, transbronchial cryobiopsy has evolved as a valid diagnostic procedure with an excellent diagnostic yield and low morbidity/mortality. Of note, all patients with suspicion of ILD should be discussed in a multidisciplinary panel prior to SLB. Data on mortality after SLB show a considerable range/variability, and therefore, further data unraveling this issue by careful data reporting is urgently needed.

Thus, studying the diagnostic yield and safety of SLB in patients with ILD is important and adds to the current discussion concerning the validity of transbronchial cryobiopsy. The present manuscript reports data of a considerable number of SLB, it has, however, some shortcomings which limit the interpretability of the data.

Major comments:

Comment 1: The main neglect of the manuscript is the missing reporting of patient selection. Looking at the preoperative pulmonary function values of table 1, it seems that only patients with very early disease-stage with normal lung volumes and only slightly reduced diffusion capacity underwent SLB. Self-evident, this influences morbidity and mortality of the surgical procedure. Therefore, it is crucial to know what the selection criteria were, or – vice versa – what exclusion criteria were applied regarding the performance of SLB. As safety was the main research question of this

retrospective study, the issue of patient selection needs to be discussed in detail and compared with data from the literature.

Having said that, it is crucial to know in how many patients with suspected/so far unclassified ILD, SLB could not be performed due to the above mentioned selection criteria. Without this information, it is impossible to appraise the role of SLB – which is still considered the “gold-standard” in ILD-diagnostics - in the diagnostic procedure of patients with ILD.

In the same context, it is indispensable to know in how many of the patients broncho-alveolar lavage and/or transbronchial biopsy has been performed and what results these – less-invasive procedures – retrieved. According to current guidelines, the diagnostic procedure in patients with ILD should be a step-wise, with less invasive procedures preceding surgical interventions.

Likewise, it does not become clear whether patients have been discussed in a multidisciplinary board and whether decision for SLB has been made in this interactive panel.

Reply 1: Thank you for your insightful comments. In this study, the patients between 2007 and 2019 were included and the criteria of patient selection had been changed in this period. Therefore, we cannot show a single criterion of patient selection from the type of interstitial pneumonia. We always decide the indication of surgical biopsy through a multidisciplinary discussion. On the other hand, we excluded the patients whose respiratory status was worsening.

Changes in the text: We added these comments in the methods section.

Page 4 line 85: The indication of surgical biopsy was decided through a multidisciplinary discussion. Because this study included patients for a long period, the criterion of patient selection from the type of interstitial pneumonia is not unified throughout the study period. We excluded the patients whose respiratory status was worsening.

Comment 2: Diagnostic yield: Otsuka et al. report a diagnostic yield of SLB of 74% (26% of patients were diagnosed with unclassifiable ILD), which is considerably lower compared to previous reports in the literature. This issue and possible explanations should at least be discussed. It raises the question whether a safe procedure which does – however – not lead to a diagnosis in a quarter of the patients, is a “good” procedure.

Radiological patterns would be important to know: were patients with typical UIP-pattern undergoing SLB and if so, what was the histological diagnosis? Did patients with typical UIP-pattern on HRCT have more postoperative acute exacerbations?

Answers to these questions would be important for future patient selection.

Reply 2: Thank you for your insightful advice. We excluded patients with typical UIP pattern on chest HRCT. AE was found in 1 case of unclassifiable IP, HRCT finding of this case was alternative diagnosis. The reasons for the large number of unclassifiable ILD may be that (1) biopsies were not performed in cases with typical images, and (2)

many cases with multiple pathological findings were observed.
Changes in the text: We inserted this in the discussion section.

Page 8 line 186: In this study, 26% of patients were diagnosed with unclassifiable idiopathic interstitial pneumonia (IIP). The reasons for the relatively large number of unclassifiable IIP may be that (1) surgical biopsies were not performed in cases with typical HRCT images, and (2) many cases with multiple pathological findings were observed.

Minor comments:

Comment 3: Was the postoperative diagnosis – as mentioned in table 1 – a pure histopathological one or was this a diagnosis based on a multidisciplinary discussion integrating all clinical, radiological and histopathological information?

Reply 3: Thank you for your insightful question. The postoperative diagnosis was made based on a multidisciplinary discussion including physicians, pathologists, and radiologists.

Changes in the text: We inserted in the table 1. “Postoperative diagnosis based on MDD”

Comment 4: According to table 2, in 5 patients biopsies were taken from only one site and only 9% of patients had biopsies taken from three sites. As the current guidelines suggest biopsies from at least two lobes, the authors should explain, why in only 9% of patients biopsies were indeed taken from three sites.

Reply 4: Thank you for your good comment. In 96% of cases, biopsies were taken from two or more sites. As the guidelines suggest, the more biopsies are taken, the higher your diagnosis rate will be made. On the other hand, the more biopsies are taken, the more complications will occur. Therefore, only 9% of the cases were biopsied at 3 sites, which were carefully selected based on preoperative discussion.

Changes in the text: We inserted these comment in the discussion.

Page 8 line 173: As the guidelines suggest, the more biopsies are taken, the higher your diagnosis rate will be made. On the other hand, the more biopsies are taken, the more complications will occur. Therefore, only 9% of the cases were biopsied at 3 sites, which were carefully selected based on preoperative discussion.

Comment 5: Table 1: it would be more informative to mention how many of the patients were never-smokers, active smokers (with packyears), or ex-smokers (with packyears).

Reply 5: Thank you for your insightful comments. Unfortunately, we don't have more precise data about the smoking status on our database.

Changes in the text: None

Comment 6: In those patients with diagnosis of CVD-IP, was there a known/pre-existing positivity of autoantibodies suggesting CVD or even known CVD? This is even more important, as 32% of all patients were diagnosed with CVD-IP.

Reply 6: Thank you for your good advice. As you indicate, CVD-IP included many patients with preoperatively undiagnosed CVD. Unfortunately, we don't have data on whether undiagnosed CVD or known CVD on our database because the purpose of this study is to determine the surgical outcome.

Changes in the text: None

Reviewer B

Minor concerns:

Comment 1: Introduction:

TBLB is not recommended in diagnostic workout od IPF for very long time so there is no need to underline it's low diagnostic yeld in this area (especially with use of reserence no 7 were unexpetly high yield of TBLB was presented). Actually transbronchial lung cryobiopsy (TBLC) is considered as an alternative for SLB and this, in my opinion, should be presented in this section - for exampe S2K Guideline for Diagnosis of Idiopathic Pulmonary Fibrosis Respiration 2021;100:238–271

Reply 1: Thank you for your good advice. As you suggest, TBLC is currently an important option for biopsy. We inserted this in the introduction.

Changes in the text: We inserted a sentence in the introduction section.

Page 3 line 59: Currently, cryobiopsy is an important option for biopsy.

Comment 2: Are You sure that reference no 6 in line 64 is aproprate?

Reply 2: Thank you for pointing out. We fixed reference no 6 to the correct one.

Changes in the text: We fixed reference no 6.

Page 11 line 237: Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2001;164:193-6.

Comment 3: Results:

Considering very wide ranges of descriptive data presented in Table 1 (especially for preoperative function tests e.g. %DLco (%) 71.0% 21.0-126.5%) median with Q1 and Q3 may be better for presenting group characeristic in the table and in the text.

Reply 3: Thank you for your good advice. We fixed the data.

Changes in the text: We use quartile in Table 1

Comment 4: Discussion:

Is the reference no 13 in line 135 appropriate? - there are not recent guidelines presented in this paper

Reply 4: Thank you for your good advice. The correct reference number is [1].

Changes in the text: We change the reference number

Page 6 line 144: [1]

Comment 5:

in line 156 should be: 'in our study'

Reply 5: Thank you for your good comment. We fixed this.

Changes in the text: We fixed the sentence.

Page 7 line 167: seen in our study

Reviewer C

Thank you for the opportunity to review the manuscript. Although cryobiopsy has been introduced to the diagnostic process of LD and is replacing surgical lung biopsy (SLB), SLB is still an important diagnosing method of ILD. However, due to the risk of complications including death associated with SLB, it is important to identify risk factors related to these when selecting patients. This study was a retrospective study of 129 patients who had undergone SLB at a single institution for about 13 years and identified incidence and risk factors related to the postoperative complications. This study was conducted with a large number of patients and various clinical variables, including KL6, were considered in the analysis. However, the contents and novelty is limited because it showed only the results that verified the contents confirmed in previous reports. I have several comments for this manuscript as follows.

Comment 1: Although all patients included in this study underwent SLB, unclassifiable ILD accounted for 26.4%, and cvd-ip accounted for 32.6%. In general, considering that SLB is not perform for cvd-ipl, and all patients underwent SLB, the proportion of unclassifiable ILD and cvd-IP is very high. The author should explain this and check whether the subjects included in this study have been diagnosed with MDD.

Reply 1: Thank you for your good advice. CVD-IP included many patients with preoperatively undiagnosed CVD, which is why many CVD-IP patients were included. Unfortunately, we don't have data on whether undiagnosed CVD or known CVD on our database because the purpose of this study is to determine the surgical outcome.

Changes in the text: None

Comment 2: In the abstract or introduction, it is stated that SLB is performed on patients with suspected ILD, but this is an incorrect description - it is performed for differential diagnosis in patients with confirmed ILD. Also, although there is controversy over which patients should be applied with SLB in the ILD diagnosis process, the implementation of SLB in the diagnosis of ILD is not controversial.

Reply 2: Thank you for your good advice. As your advice, we fixed the sentence.

Changes in the text: We fixed this point in the abstract and introduction.

Page 2 line 28: a diagnostic surgical lung biopsy is recommended for differential

diagnosis in patient with confirmed ILD.

Page 3 line 54: a diagnostic surgical lung biopsy is recommended for differential diagnosis in patient with confirmed ILD.

Comment 3: It is appropriate to estimate LA pressure according to the presence of IVC plethora rather than applying 10 mmHg uniformly.

Reply 3: Thank you for your good advice. Unfortunately, we don't have the LA pressure data estimated according to the presence of IVC plethora.

Changes in the text: None

Comment 4: Please explain in more detail the patient selection and surgical procedure for ILD patients at this institution.

Please provide reasons for your preference for surgery on the left. Measures to prevent complications after surgery were mentioned in the discussion, which should be dealt with in more detail in the methods section.

Reply 4: Thank you for your insightful comments. In this study, the patients between 2007 and 2019 were included and the criteria of patient selection had been changed in this period. Therefore, we cannot show a single criterion of patient selection from the type of interstitial pneumonia. We always decide the indication of surgical biopsy through a multidisciplinary discussion. On the other hand, we excluded the patients whose respiratory status was worsening.

Changes in the text: We added these comments in the methods section.

Page 4 line 85: The indication of surgical biopsy was decided through a multidisciplinary discussion. Because this study included patients for a long period, the criterion of patient selection from the type of interstitial pneumonia is not unified throughout the study period. We excluded the patients whose respiratory status was worsening.

Comment 5: Please present multivariate results using logistic or cox analysis in the analysis of risk factors related to complications. Please provide a more detailed analysis method for the statistical section.

Reply 5: Thank you for your good advice. We made a multivariate analysis of our data. No significant risk factor was found.

Changes in the text: We added this in the result section.

Page 6 line 137: On multivariate analysis, no significant risk factor was found.

Comment 6: Please present the characteristics of patients with complications compared to those without.

Reply 6: Thank you for your good advice. Complications are as follows. Pneumothorax were found in 3 patients of PPFE, 3 patients of unclassifiable IIP, 1 patients of NSIP, and 1 patients of CVD IP. Pneumonia were found in 1 patient of CVD IP, and 1 patient of others. AE was found in 1 patient of unclassifiable IIP. Hemothorax was wound in 1 patient of CVD IP. Wound infection was found in 1 case of CVD IP.

Changes in the text: We added this in the result.

Page 6 line 129: The patient with postoperative acute exacerbation, once recovered and discharge after surgery, and died due to worsening of ILD 76 days after surgery.

Page 6 line 133: , including 3 cases of pneumothorax.

Comment 7: Please indicate how many patients who underwent upper lobe resection had PPFE.

Reply 7: Thank you for your insightful comment. Upper lobe resection was made in all patients with PPFE.

Changes in the text: We added this information in the result.

Page 6 line 137: Biopsy of the upper lobe was performed in all 5 PPFE cases.

Comment 8: Please suggest how the limitations mentioned in the description of limitations section can affect the interpretation of this study, and, explain why this study is important nevertheless.

Reply 8: Thank you for your good advice. We think this data is useful for selecting surgical biopsy or cryobiopsy.

Changes in the text: We added some comments to the discussion section.

Page 8 line 192: Currently, cryobiopsy for the diagnosis of ILD has become popular. To select surgical biopsy or cryobiopsy, our data should be useful, despite retrospective study.

Comment 9: In the conclusion section, it was mentioned that selection of biopsy sites is important to reduce complications. Considering that biopsy in the apex is usually performed in patients with suspected PPFE, biopsy in this area is thought to be inevitable.

Reply 9: Thank you for your good advice. As you commented, biopsy in the apex is inevitable in PPFE. In such cases, we recommend some other reinforcement such as fibrin glue. We inserted this in the end of discussion.

Changes in the text: We inserted a sentence in the discussion section.

Page 9 line 198: In the biopsy for apex, we should add some reinforcement technique such as fibrin glue covering.

Comment 10: Table 3 needs to be adjusted to make it easier for readers to understand.

Reply 10: Thank you for your good advice. We fixed Table 3

Changes in the text: We fixed Table 3

Reviewer D

Thank you for the opportunity to review this article on surgical lung biopsy for interstitial lung disease (ILD). This study performed by Otsuka H and collab. retrospectively assessed 129 ILD patients and aimed to evaluate the safety of video-assisted lung biopsy. The authors found a 10.1% rate of postoperative complications, with 0% mortality up to 60 days. A particular focus was made on the biopsy of the pulmonary apex, which was found a risk factor for postoperative pneumothorax, that occurred in 6.2% of the patients.

Comment 1:

Introduction:

In this section the authors introduce the indication of a surgical lung biopsy for ILD. After reading the section, one has the impression that, according to the guidelines, surgical lung biopsy is absolutely mandatory in the diagnosis of an ILD, which is not the case. They should be more specific about the necessity of lung sampling in ILD and, of course outline the surgical biopsy in comparison to other techniques (TBLB or trans bronchial cryobiopsy (TBCB)).

Moreover, as TBCB is a more recent, less invasive, technique that tends to spread widely to replace surgical biopsy, some comments regarding recent studies on TBCB or on comparing the surgical biopsy to TBCB are needed, either in this section or in the discussion.

On the other hand, authors correctly insist on the problem of postoperative complications in these frail patients and state some important risk factors found in the literature.

Reply 1: Thank you for your good advice. As you suggest, TBLC is currently an important option for biopsy. We inserted this in the introduction.

Changes in the text: We inserted a sentence in the introduction.

Page 3 line 59: Currently, cryobiopsy is an important option for biopsy.

Comment 2:

Methods:

It should be made clear if these surgical biopsies were performed in an acute or elective setting, although the reader gets the impression that there were elective interventions. Authors state that the site and the side of the biopsy were determined in a MDD, but they make no comments on the number of necessary samples in order to increase the chances of a correct diagnosis.

Reply 2: Thank you for your insightful comments. We excluded the patients whose respiratory status was worsening. In other words, all patients were performed in an elective setting. The number of the biopsy was also determined in an MDD.

Changes in the text: We added some comments to the methods.

Page 5 line 102: The site, side, and the number of the biopsy

Comment 3:

Results:

At the beginning of this section, certain results are stated that can also be found in Table 1. On my opinion, there is no need to show them twice.

Authors should also state the in-hospital mortality: it may have been 0%, but the reader may want to know what happened to the patient with acute exacerbation.

It was found that patients with a diagnosed PPF had significantly more complications than the other patients. It would be interesting to know which were the complications in these patients.

Reply 3: Thank you for your good advice. We have changed the results according to your advice.

Changes in the text: We changed the results, and added some comments to the results

Page 6 line 129: There was no case of hospital death after the biopsy. The patient with postoperative acute exacerbation, once recovered and discharge after surgery, and died due to worsening of ILD 76 days after surgery.

Page 6 line 133: , including 3 cases of pneumothorax.

Comment 4:

Discussion

There were some recent large retrospective studies on surgical lung biopsy (eg authors' reference n°6). It would be interesting that the authors position their results of mortality and morbidity also in comparison to those of these large series.

Some statement on decisions to use fibrin glue and/or oxidized cellulose, but also on the rehabilitation program, should also appear in the "Methods" section, as authors comment on this as a probable relation to their low mortality rate.

As KL-6 serum levels were included in the results section, a small comment on this result might be useful.

Authors may also want to comment on their patients' characteristics in terms of respiratory function, in the paragraph regarding the "appropriate selection of patients" and the low mortality rate (page 7, line 156).

The fact that a biopsy of the pulmonary apex was found a risk factor for postoperative pneumothorax is a very interesting finding that merits to be outlined throughout the article and the discussion section. More detailed explanations about the reasons, mechanisms of this occurrence and the state of the literature on the matter are needed.

Reply 4: Thank you for your insightful advice. According to your advice, we have changed the discussion and the methods.

Changes in the text: We added some sentences to the discussion and methods.

Page 7 line 165: Previous reports have been focused mainly on the patients' status [8-11]. We have improved the procedure of surgical biopsy for ILD and this study focused mainly on the procedure.

Page 5 line 107: To reinforce around the staple line, we used fibrin glue and an oxidized

cellulose sheet. Perioperatively, the patients were on a rehabilitation program to prevent respiratory complications.

Page 8 line 184: Although KL-6 is an indicator of interstitial pneumonia activity, it did not relate to the frequency of postoperative complications as far as our data.

Page 7 line 171: Surgical biopsy while the respiratory status is worsening causes postoperative respiratory complications and should be avoided.

Comment 5

Figures:

In figure 2C, the authors state that “some malformations were found on the staple line”. They should be more specific about this statement and clarify what these “malformations” were, as the explanation is not straightforward from the picture (parenchymal tear? etc)

Reply 5: Thank you for your good advice. We found small lacerations of visceral pleura. We added this information.

Changes in the text: We fixed the legend of figure 2.

Page 13 line 270: some small lacerations of visceral pleura were found near the staple line

Second Round Peer Review

Reviewer A

Comment 1: Authors should revise their statements in the introduction as it is difficult to follow with repeating sentences. The introduction of "cryobiopsy" doesn't seem to follow a common thread and the unity of this part of the article seems a bit lost.

Reply 1: Thank you for your insightful comments. As you pointed out, we repeatedly mentioned biopsy, so we deleted the following sentence “Currently, cryobiopsy is an important option for biopsy”.

Changes in the text: We deleted these comments in the introduction section.

Page 3 line 58: Currently, cryobiopsy is an important option for biopsy.

Comment 2: In the method section, the authors state that they “excluded the patients whose respiratory status was worsening”. It is not clear to me what “worsening” means and if they excluded these patients from the analysis or if the surgical biopsy was not performed in these patients.

Reply 2: Thank you for your insightful comments. We added an explanation regarding the part you pointed out

Changes in the text: We added these comments in the introduction section.

Page 4 line 89: 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.

Comment 3: Another new statement is not clear: “To reinforce around the staple line, we used fibrin glue and an oxidized cellulose sheet”. Did the authors used these products systematically or under which conditions?

Reply 3: Thank you for your good comment. We covered the staple line using fibrin glue and an oxidized cellulose sheet for all cases.

Changes in the text: We fixed the sentence in the methods section.

Page 5 line 111: we covered the staple lines in all patients with both fibrin glue and oxidized cellulose sheets.

Comment 4: In the discussion section, authors do not explain clearly why they make this statement: “To select surgical biopsy or cryobiopsy, our data should be useful, despite retrospective study”.

The meaning of this statement is unclear to me: “We have improved the procedure of surgical biopsy for ILD and this study focused mainly on the procedure”.

English also needs a bit of revision.

Reply 4: Thank you for your good comment. We fixed the sentence in the discussion section.

Changes in the text: We fixed the sentence in the discussion section.

Page 7 line 172: 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.

Page 8 line 199: 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.