The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease

Lars Hagmeyer[1]*, Dirk Theegarten[2]*, Jeremias Wohlschläger[2], Marcel Treml[1], Sandhya Matthes[1], Christina Priegnitz[1] and Winfried J. Randerath[1]

1 Clinic for Pneumology and Allergology, Center of Sleep Medicine and Respiratory Care, Bethanien Hospital, Solingen, Germany
2 Institute for Pathology and Neuropathology, University Hospital Essen, University Duisburg-Essen, Duisburg-Essen, Germany

Abstract

Background and Aims: It is not yet known if transbronchial cryobiopsy (TCB) is a reliable and safe diagnostic tool in the investigation of interstitial lung disease (ILD). To date, there have been no studies directly comparing the value of TCB with that of surgical lung biopsy (SLB). The study was initiated to determine whether the samples taken by TCB lead to a reliable diagnosis and whether SLB can be avoided in a relevant percentage of cases.

Methods: We analyzed 32 subjects with suspected ILD who underwent a TCB. Subjects' baseline characteristics, pathological findings after TCB and SLB, and complication rates were analyzed. The pathological inter-rater agreement was quantified statistically.

Results: The overall inter-rater agreement concerning TCB sample evaluation was good with a kappa value of 0.80. In 23/32 cases (72%), the findings from the TCB showed a strong congruence with all other clinical data, thereby enabling a definitive diagnosis. Eight of the remaining nine subjects gave their consent for an SLB, which led to a definitive histological diagnosis in six cases (75%). Following TCB, pneumothorax occurred in 6/32 subjects (19%) and endobronchial bleeding was moderate in 8/32 (25%) and was severe in 17/32 cases (53%).

Conclusion: This is the first study to correlate histological results and complications following TCB and SLB in ILD subjects, some of whom underwent both procedures. TCB is a suitable diagnostic tool in ILD, potentially completely dispensing with the need for an SLB in some cases. In all cases, an interdisciplinary case evaluation is necessary as a final step.

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Key words
bronchoscopy – diagnostic accuracy – histology – interstitial lung disease – surgical lung biopsy – transbronchial cryobiopsy

Correspondence
Lars Hagmeyer, MD, Clinic for Pneumology and Allergology, Center of Sleep Medicine and Respiratory Care, Bethanien Hospital, Aufderhöherstraße 169-175, 42699 Solingen, Germany.
Tel: 0049 212 63 6004
Fax: 0049 212 63 6005
email: lars.hagmeyer@klinik-bethanien.de

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Authorship and contributorship
Lars Hagmeyer (Solingen, Germany) and Dirk Theegarten (Essen, Germany) contributed equally to the work. Subjects were admitted to the hospital in Solingen for diagnosis of suspected interstitial lung disease. All the clinical diagnostic procedures, including transbronchial cryobiopsy, were performed in Solingen under the guidance of Lars Hagmeyer. The pathological analysis of all sampled biopsies was performed at the pathological institute in Essen under the guidance of Dirk Theegarten. Both authors, Lars Hagmeyer and Dirk Theegarten, contributed equally to the statistical analysis and interpretation of the data as well as to the writing of the manuscript.
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Dirk Theegarten: Substantial contributions to conception and design, analysis and interpretation of data, drafting the article and finalizing the version to be published.
Jeremias Wohlschläger: Analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.
Marcel Treml: Acquisition of data, analysis and interpretation of data, drafting statistics section and revising the article, and final approval of the version to be published.
Sandhya Matthes: Analysis and interpretation of data, revising the article critically forimportant intellectual content and final approval of the version to be published.
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Ethics
A waiver of consent was granted by the institutional review board, University of Witten-Herdecke, Germany.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abbreviations:
BAL bronchoalveolar lavage
COP cryptogenic organizing pneumonia
HP hypersensitivity pneumonitis
HRCT high-resolution computer tomography
IIP idiopathic interstitial pneumonia
ILD interstitial lung disease
IPF interstitial pulmonary fibrosis
NSIP nonspecific interstitial pneumonia
SLB surgical lung biopsy
TBB transbronchial forceps biopsy
TCB transbronchial cryobiopsy
UIP usual interstitial pneumonia

*Both authors contributed equally to the work.

Introduction

The interstitial lung diseases (ILDs) comprise of a broad variety of entities with different prognosis of the disease as well as guiding treatment options (1–3). Although clinical, radiological and bronchoalveolar lavage (BAL) findings help in determining the subentity of the ILD, in many cases, lung tissue samples are needed to confirm the diagnosis. In most ILDs, conventional transbronchial forceps biopsies (TBBs) are unhelpful because of the low yield of representative lung tissue and the high rate of compression artifacts (2, 4–7). TBB is therefore not routinely recommended, but rather to be implemented in specific cases (8–10).

Surgical lung biopsy (SLB) is the gold standard for tissue sampling in ILD (11). Many subjects cannot be referred for an SLB because of the increased risk of perioperative morbidity and mortality brought about by a combination of advanced age, comorbidity and severe respiratory insufficiency or the presence of secondary pulmonary hypertension in advanced disease. Furthermore, some subjects do not give their consent for a surgical intervention.

Transbronchial cryobiopsy (TCB) is an endoscopic technique that allows representative sampling of lung tissue. First data show the feasibility of the procedure and report a high diagnostic yield (12–16). It is yet to be investigated whether TCB is a suitable tool in the diagnostic workup of ILDs. This study was initiated to determine whether the samples taken by cryobiopsy lead to a reliable diagnosis and whether SLB can thus be avoided in a relevant percentage of cases.

Materials and methods

We retrospectively analyzed the data of all 32 subjects with suspected ILD who underwent a TCB at our tertiary care hospital during the period of July 2011 and December 2012. A waiver of consent was granted by the institutional review board, University of Witten/Herdecke, Germany. Relevant data of all subjects were registered including lung function status, findings of clinical investigations, high-resolution computed tomography (HRCT), BAL, histological findings and complication rates from TCB and SLB as well as the final diagnosis following interdisciplinary case evaluation. The routine diagnostic workup of ILDs in our institution includes a standardized clinical questionnaire, serological and lung function testing as well as an HRCT and BAL. In those subjects where the diagnosis remains equivocal after this first diagnostic step, we offer an SLB – in accordance with the guidelines (17) – to obtain a definitive diagnosis. Alternatively, we offer a TCB to subjects who either do not consent to a surgical intervention or are deemed to have an unacceptably high perioperative risk for an SLB (Fig. 1). In those subjects who initially do not consent for a surgical intervention and where the diagnosis remains equivocal following TCB, we advise the subject to reconsider an SLB – when perioperative risks are tolerable – as a step-up procedure. The final diagnosis was generated after an interdisciplinary case evaluation (pneumologist, radiologist, pathologist); for the diagnosis of idiopathic pulmonary fibrosis, the current consensus guidelines were used for clinical-radiologic-pathologic correlation (14). The TCB procedure was performed as rigid bronchoscopy (Storz, Tuttlingen, Germany) in combination with flexible bronchoscopy (Olympus, Hamburg, Germany) under general anesthesia using jet ventilation (Monsoon, Acutronic, Bubikon, Switzerland, working pressure 1.5–1.8 bar, jet frequency 100–120/min, positive jet pressure 22 mbar, oxygen 100%) or as flexible bronchoscopy under sedation (midazolam and disoprivan) using a cuffless 7.5 bronchoscopy tube (Rüsch, Teleflex Medical, Kernen, Germany). There were no set clinical criteria for preferring one of these procedures over the other. The TCB was performed with a flexible cryoprobe (Erbe, Tübingen, Germany), which was applied through the working channel of a flexible

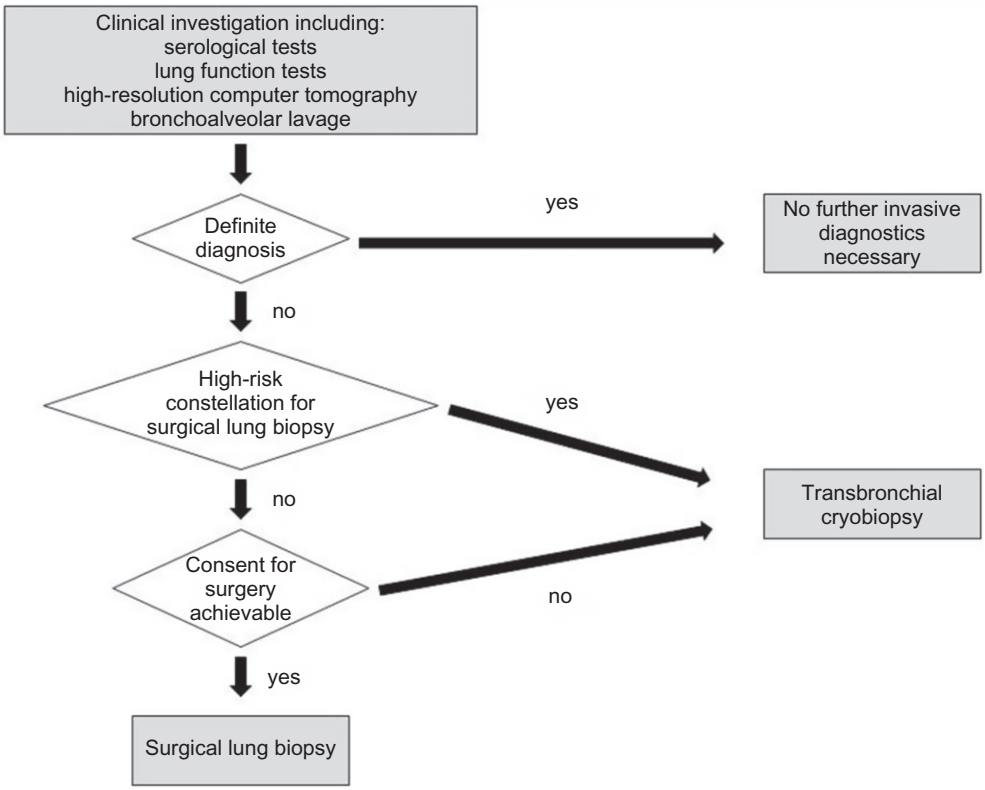

Figure 1. Diagnostic algorithm in interstitial lung diseases.

bronchoscope. The biopsy was taken under fluoroscopy control with the tip guided to a 1.0–1.5-cm subpleural position. The cryoprobe was cooled down to a working temperature of approximately −85 to −90°C for 4–5 s using liquid nitrous oxide, thus freezing the vital tissue in contact with the probe. The frozen area of tissue was subsequently extracted. In all subjects, two to four TCBs were taken from different ipsilateral segments. Biopsy sites were selected based on the distribution of the fibrosis patterns on HRCT scans. A chest X-ray was routinely performed on all subjects at the end of the procedure, in order to exclude an iatrogenic pneumothorax. Specimens were processed and stained for histology in the standard way (hematoxylin–eosin, Elastica-van Gieson and Prussian blue). Pathological findings from TCB and SLB were reported independently by two pathologists (DT and JW). The inter-rater agreement for the pathological evaluation of the TCB samples was statistically analyzed by calculating the unweighted kappa statistic. For further analysis, discrepancies between the pathologists were resolved by consensus evaluation. The histological results of the TCB and the SLB were correlated with the other findings in an interdisciplinary case evaluation as recommended by the guidelines (17). In order to evaluate the role of TCB in the diagnostic pathway of ILDs, congruence of TCB results with other findings (clinical, BAL, HRCT and if applicable SLB) and with the final diagnosis was categorized as having strong, approximate, weak or no congruence. Complications such as iatrogenic pneumothorax, post-interventional endobronchial bleeding and 30-day post-interventional morbidity and mortality were documented. Endobronchial bleeding was classified according to the BTS (British Thoracic Society) guidelines (18).

Results

We analyzed 32 subjects (10 female and 22 male) with suspected ILD who underwent a TCB. Mean age was 65.4 years (range 45–83). Lung function criteria showed: mean vital capacity of 74.6%pred (40–123), mean total lung capacity of 79.4%pred (44–127), mean diffusing capacity of the lung for carbon monoxide corrected for hemoglobin level (DLCO) of 52.4%pred (17–108), mean DLCO corrected for alveolar volume (DLCO/VA) of 75.5%pred (29–124) and mean oxygen partial pressure (PaO2) at rest on room air of 65.0

mmHg (47–87). In all cases, an SLB was initially not possible. Twenty-four subjects did not give their consent for a surgical intervention and eight subjects were not referred to the surgeon because of a high perioperative risk caused either by the advanced stage of ILD (19) or because of severe comorbidities. In all of these subjects, we attempted to obtain representative samples of lung tissue with a TCB. The bronchoscopy was performed under general anesthesia in 7 subjects and under intravenous sedation in 25 subjects. TCB samples could be obtained from all 32 subjects. The cryo-application time was 4 s in 17 subjects and 5 s in 15 subjects. The biopsies were always taken from different ipsilateral segments, but the total number of samples taken differed from patient to subject. A total of two cryobiopsies were taken in 11 subjects, three in 16 subjects and four in 3 subjects. In two subjects, only one biopsy could be taken because of prolonged endoluminal bleeding. Overall, the inter-rater agreement concerning the evaluation of a TCB sample was good with a kappa value of 0.80 (0.70–0.90, 95% confidence interval). The inter-rater agreement in the evaluation of an SLB sample also appeared to be good, although the number of subjects was too small for statistical evaluation (Supporting Information Table S1A and S1B).

In 23/32 cases (72%), TCB findings showed a strong congruence with the initially suspected diagnosis and no further investigations were necessary following interdisciplinary case evaluation. In 6/32 cases (19%), TCB findings showed only an approximate congruence with the initially suspected diagnosis. Pathological findings described possible honeycomb formations in two of these six subjects, but the samples were too small to diagnose a histological probable usual interstitial pneumonia (UIP) pattern according to the guidelines (17). In 3/32 cases (9%), TCB findings described an unspecific pattern so that the final diagnosis remained unclear. Altogether, in 9/32 subjects, TCB failed to lead to an unequivocal diagnosis following interdisciplinary case evaluation. Eight of these nine subjects subsequently gave their consent for an SLB. In this way, a definitive histological diagnosis could be generated in six of these eight subjects (75%). In the remaining two subjects (25%), the histological patterns, although suggestive for certain sub-entities of ILD, did not meet the criteria for a specific histological pattern. As a result, the histological diagnosis was classified as 'possible'. Interdisciplinary case evaluation following SLB resulted in a definitive clinical diagnosis in seven of the eight subjects (88%) and a probable diagnosis in one case (Table 1). TCB findings showed a strong congruence with the final diagnosis in 25/32 cases (78%), an approximate congruence in 6/32 cases (19%) and no congruence in 1/32 cases (3%). Subjects with the final diagnosis of a sub-entity of idiopathic interstitial pneumonias (IIPs) showed a strong congruence between the TCB findings and the final diagnosis in 14/20 cases (70%), an approximate congruence in 5/20 cases (25%) and no congruence in 1/20 cases (5%). Subjects with a non-IIP-ILD or excluded ILD showed a strong congruence between the TCB findings and the final diagnosis in 11/12 cases (92%) and an approximate congruence in 1/12 cases (8%) (Table 2A, Supporting Information Tables S2 and S3). Pathological findings from TCB showed a good congruence with the SLB in seven of the eight SLB subjects (88%). In these seven cases, SLB confirmed the suspected histological results obtained from TCB. In only one case did SLB show a completely different histological pattern than the one obtained from the TCB, therefore leading to a change in the clinical diagnosis (Table 2B). Considering the limited number of subjects, there was no

Table 1. Histological findings after TCB and SLB and final diagnosis in all 8 subjects who underwent both procedures

Patient #	TCB consensus	SLB consensus	Consensus interdisciplinary case evaluation
4	Probable NSIP, possible UIP	Definite UIP	IPF
6	Minimal changes, possible UIP	Definite UIP	IPF
8	Possible NSIP, inconsistent with UIP	Postbronchiolitic fibrosis, possible NSIP, inconsistent with UIP	NSIP (bronchiolocentric)
12	Possible UIP	Heterogeneous fibrosis, definite UIP and fibrotic NSIP	IPF
13	Interstitial granulomatous pneumonia, probable HP, eventually sarcoidosis	Interstitial granulomatous pneumonia, probable HP, eventually sarcoidosis	HP
14	Possible OP, inconsistent with UIP	OP	COP
31	Possible UIP	Definite UIP	IPF
32	Possible UIP	Bronchiolocentric fibrosis, possible UIP	Probable IPF

COP, cryptogenic organizing pneumonia; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; SLB, surgical lung biopsy; TCB, transbronchial cryobiopsy; UIP, usual interstitial pneumonia.

Table 2. (A) Congruence of TCB results with final diagnosis in all 32 subjects (21 IIP subjects, 11 non-IIP-subjects). (B) Congruence of histological findings after TCB and SLB in all 8 subjects who underwent both procedures (6 IIP subjects, 2 non-IIP subjects)

	Strong	Approximate	Weak	No
(A)				
All subjects	25	6	0	1
IIP subjects	15	5	0	1
Non-IIP subjects	10	1	0	0
(B)				
All subjects	4	3	1	0
IIP subjects	2	3	1	0
Non-IIP subjects	2	0	0	0

IIP, idiopathic interstitial pneumonia; SLB, surgical lung biopsy; TCB, transbronchial cryobiopsy.

clear evidence for a correlation between the TCB sampling procedure (cryotime, number of samples) and the congruence of TCB and SLB results.

Following TCB, a post-interventional pneumothorax was detected in six subjects (19%), which were successfully treated in all cases by the placement of a chest tube over a period of 2–3 days. Iatrogenic pneumothorax events were detected in three of seven subjects (43%) in whom invasive jet ventilation was used. Under conditions of sedation and spontaneous breathing over a bronchoscopy tube, pneumothorax occurred in 3 of 25 subjects (12%). Endobronchial bleeding following cryobiopsy was moderate in 8/32 cases (25%) and was severe in 17 subjects (53%). In 15 of these 17 subjects, bleeding could be stopped by intubation of the biopsied segment with the bronchoscope into the wedge position and the endobronchial application of adrenaline. In 2 of the 17 subjects, we switched to rigid bronchoscopy to extract blood clots. There were no cases where the endobronchial application of blocking devices or a surgical approach was necessary. No severe adverse event occurred within 30 days after TCB. SLB did not lead to any cases of prolonged chest drainage therapy and bleeding complications were not observed. However, two subjects died within 30 days following SLB because of an acute exacerbation of lung fibrosis. In both cases, histological findings from SLB described a definite UIP pattern with a final clinical diagnosis of idiopathic pulmonary fibrosis.

Discussion

SLB is the gold standard for obtaining histological tissue samples from the lung in the investigation of ILD (20–24).

Particularly in subjects where consent for an SLB is not given or where an SLB is associated with a high perioperative risk, up to now, less invasive alternatives have not been available.

Data analysis of the suspected diagnosis prior to TCB compared with the results obtained from the TCB together with the final clinical diagnosis shows that the results from the TCB in this study were valid. Even in cases where the obtained cryobiopsy only leads to a 'possible' rather than a 'definite' histological diagnosis, a valid final diagnosis may still be reached, providing that there is an overall consistency with all other noninvasive findings. In the case of initial honeycombing, TCB samples may show minimal nonspecific changes with predominantly bronchial structures. In cases where TCB shows an unspecific pattern, an SLB should be considered in order to enable a definitive final diagnosis. Pathological findings obtained via TCB showed a high level of congruence with SLB findings. Because of their larger size, SLB samples lead to a more definite histological diagnosis. In only one case however did SLB show a completely different histological pattern to the one obtained from TCB, thereby leading to a change in the final clinical diagnosis.

This is the first study correlating results of TCB with those from SLB in ILD subjects who underwent both procedures. SLB remains the gold standard for obtaining histological samples in ILD. But overall, the data from this study suggest that TCB results are valid and show a strong correlation with other clinical findings as well as with SLB results. Particularly in subjects who do not consent to a surgical intervention or those with high perioperative risk, TCB presents an interesting and reliable tool in the diagnostic workup of ILD. TCB may help to reach a definitive clinical diagnosis in cases where radiological and other noninvasive diagnostic findings remain inconclusive.

An SLB may be associated with a higher mortality rate than TCB. In this study, two subjects died following SLB because of an acute exacerbation of lung fibrosis. The SLBs were performed in an experienced thoracic surgery department with an overall post-SLB mortality rate of 4.8% in ILD patients (5/104 patients over a 5-year period). The number of subjects in this study is too small for a statistical mortality analysis. But it is worth noting that no subjects died after a TCB. Given this, TCB may be an attractive low-risk method of tissue sampling, which would potentially allow dispensing with an SLB altogether in the presence of valid histological findings. This approach could reduce the number of SLBs and the associated risks. An SLB would however still have its place as a step-up procedure recommended to subjects with equivocal results

following TCB. Relevant endobronchial bleeding following TCB occurred in most of the procedures but could be effectively managed in the endoscopy unit. These data correlate well with the results of recent feasibility studies (12–16, 25). Where standardized classifications for bleeding complications are applied in previous studies, bleeding is often classified as moderate or severe. In studies analyzing TCB, classification of bleeding complications is heterogenous. Blocking devices are used frequently as part of clinical routine (14, 26), suggesting that bleeding complications have to be classified as severe according to the BTS classification.

Two to four TCB samples seem to be sufficient to enable the pathologist to provide a report of high standard, which is comparable with those of SLBs. A high number of cryobiopsy samples may lead to a higher reliability of histological findings but may lead to more bleeding and pneumothorax complications. Futural prospective studies will have to determine the procedural conditions that provide a high diagnostic reliability under acceptance of low complication rates.

TCB can principally be performed under medical sedation with the preservation of spontaneous breathing conditions. Using this approach may reduce the cardiorespiratory complications associated with the use of general anesthesia. However, the use of general anesthesia may reduce the risk of complications from the TCB, which may occur as a result of patient movement or coughing. The method of choice should remain at the discretion of the endoscopist. Our data suggest that performing the TCB under medical sedation and spontaneous breathing leads to a lower risk of iatrogenic pneumothorax as compared with TCB under general anesthesia and invasive ventilation.

Analysis of the subjects' baseline characteristics showed only minor alterations in functional parameters in most cases. This suggests that particularly in cases where subjects suffer only mild symptoms, there is a reluctance to progress to the more invasive SLB and understandably a preference for less invasive procedures.

First results indicate that TCB is an effective technique with a place somewhere in between conventional TBB and SLB. Further prospective studies are necessary, in order to evaluate the diagnostic value and complication rate of TCB in comparison with the gold standard of SLB. It remains to be confirmed if the pathological findings following TCB are reliable enough to eventually be able to dispense with the need for an SLB completely.

Conclusion

First data suggest that TCB is a safe and reliable tool in the diagnostic workup of ILD. In subjects where an SLB cannot be performed, TCB is an alternative option. Histological findings from TCB show good congruence with results from SLBs. Valid histological results from TCB may potentially dispense with the need for an SLB altogether.

References

1. Demedts M, Costabel U. ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Eur Respir J. 2002;19: 794–6.
2. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ers executive committee, June 2001. Am J Respir Crit Care Med. 2002;165: 277–304.
3. Travis WD, Costabel U, Hansell DM, *et al*. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188: 733–48.
4. Shim HS, Park MS, Park IK. Histopathologic findings of transbronchial biopsy in usual interstitial pneumonia. Pathol Int. 2010;60: 373–7.
5. Romagnoli M, Bigliazzi C, Casoni G, Chilosi M, Carloni A, Dubini A, Gurioli C, Tomassetti S, Gurioli C, Poletti V. The role of transbronchial lung biopsy for the diagnosis of diffuse drug-induced lung disease: a case series of 44 patients. Sarcoidosis Vasc Diffuse Lung Dis. 2008;25: 36–45.
6. Morell F, Reyes L, Domenech G, De Gracia J, Majo J, Ferrer J. Diagnoses and diagnostic procedures in 500 consecutive patients with clinical suspicion of interstitial lung disease. Arch Bronconeumol. 2008;44: 185–91.
7. Berbescu EA, Katzenstein AL, Snow JL, Zisman DA. Transbronchial biopsy in usual interstitial pneumonia. Chest. 2006;129: 1126–31.
8. Mochimaru H, Kawamoto M, Enomoto T, Saitoh Y, Abe S, Nei T, Fukuda Y, Kudoh S. Transbronchial biopsy is clinically useful in classifying patients with interstitial pneumonia associated with polymyositis and dermatomyositis. Respirology. 2008;13: 863–70.
9. Popper HH. Which biopsies in diffuse infiltrative lung diseases and when are these necessary? Monaldi Arch Chest Dis. 2001;56: 446–52.
10. Kendall DM, Gal AA. Interpretation of tissue artifacts in transbronchial lung biopsy specimens. Ann Diagn Pathol. 2003;7: 20–4.

11. Theegarten D, Muller HM, Bonella F, Wohlschlaeger J, Costabel U. Diagnostic approach to interstitial pneumonias in a single centre: report on 88 cases. Diagn Pathol. 2012;7: 160.
12. Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, Hetzel M. Transbronchial cryobiopsy: a new tool for lung biopsies. Respiration. 2009;78: 203–8.
13. Franke KJ, Theegarten D, Hann von Weyhern C, Nilius G, Brueckner C, Hetzel J, Hetzel M, Ruhle KH, Enderle MD, Szyrach MN. Prospective controlled animal study on biopsy sampling with new flexible cryoprobes versus forceps: evaluation of biopsy size, histological quality and bleeding risk. Respiration. 2010;80: 127–32.
14. Casoni GL, Tomassetti S, Cavazza A, *et al*. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. PLoS ONE. 2014;9: e86716.
15. Pajares V, Puzo C, Castillo D, *et al*. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. Respirology. 2014;19: 900–6.
16. Fruchter O, Fridel L, El Raouf BA, Abdel-Rahman N, Rosengarten D, Kramer MR. Histological diagnosis of interstitial lung diseases by cryo-transbronchial biopsy. Respirology. 2014;19: 683–8.
17. Raghu G, Collard HR, Egan JJ, *et al*. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183: 788–824.
18. Du Rand IA, Blaikley J, Booton R, *et al*. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. Thorax. 2013;68(Suppl. 1): i1–44.
19. Park JH, Kim DK, Kim DS, Koh Y, Lee SD, Kim WS, Kim WD, Park SI. Mortality and risk factors for surgical lung biopsy in patients with idiopathic interstitial pneumonia. Eur J Cardiothorac Surg. 2007;31: 1115–9.
20. Bensard DD, McIntyre RC Jr, Waring BJ, Simon JS. Comparison of video thoracoscopic lung biopsy to open lung biopsy in the diagnosis of interstitial lung disease. Chest. 1993;103: 765–70.
21. Miller JD, Urschel JD, Cox G, Olak J, Young JE, Kay JM, McDonald E. A randomized, controlled trial comparing thoracoscopy and limited thoracotomy for lung biopsy in interstitial lung disease. Ann Thorac Surg. 2000;70: 1647–50.
22. Carnochan FM, Walker WS, Cameron EW. Efficacy of video assisted thoracoscopic lung biopsy: an historical comparison with open lung biopsy. Thorax. 1994;49: 361–3.
23. Ferson PF, Landreneau RJ, Dowling RD, Hazelrigg SR, Ritter P, Nunchuck S, Perrino MK, Bowers CM, Mack MJ, Magee MJ. Comparison of open versus thoracoscopic lung biopsy for diffuse infiltrative pulmonary disease. J Thorac Cardiovasc Surg. 1993;106: 194–9.
24. Glaspole IN, Wells AU, du Bois RM. Lung biopsy in diffuse parenchymal lung disease. Monaldi Arch Chest Dis. 2001;56: 225–32.
25. Hetzel J, Eberhardt R, Herth FJ, *et al*. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial. Eur Respir J. 2012;39: 685–90.
26. Pajares Ruiz V, Torrego Fernandez A, Puzo Ardanuy C, Gil de Bernabe A. Use of an occlusion balloon in transbronchial lung cryobiopsy. Arch Bronconeumol. 2014;50: 309–10.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. (A) Inter-rater agreement of histological findings after transbronchial cryobiopsy (TCB). (B) Inter-rater agreement of histological findings after surgical lung biopsy (SLB).
Table S2. Congruence of clinical, bronchoalveolar lavage (BAL), high-resolution computed tomography (HRCT) and histology results in idiopathic interstitial pneumonia (IIP) patients.
Table S3. Congruence of clinical, bronchoalveolar lavage (BAL), high-resolution computed tomography (HRCT) and histology results in non-idiopathic interstitial pneumonia (IIP) patients.