



REVIEW

Transbronchial Lung Cryobiopsy in Idiopathic Pulmonary Fibrosis: A State of the Art Review

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease associated with significant morbidity and mortality. The diagnosis of IPF involves a combination of clinical history, radiological imaging and examination of histopathological samples in appropriate cases. Historically, transbronchial biopsy (TBB) has been used to obtain histological samples; however this lacks diagnostic accuracy. At present, surgical lung biopsy (SLB) is the gold standard technique for obtaining specimen samples; however this carries a significant mortality risk. Transbronchial lung cryobiopsy (TBLC) is a new

technique that has been pioneered in the management of lung malignancy and offers a potential alternative to SLB. The technique employs a freezing probe, which is used to obtain lung tissue samples that are larger and better quality than traditional TBB samples. This affords TBLC an estimated diagnostic yield of 80% in interstitial lung disease. However, with limited evidence directly comparing TBLC to SLB, the diagnostic accuracy of the procedure has been uncertain. Common complications of TBLC include pneumothorax and bleeding. Mortality in TBLC is low compared with SLB, with exacerbation of IPF frequently reported as the cause. TBLC represents an exciting potential option in the diagnostic pathway in IPF; however its true value has yet to be determined.

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INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders causing inflammation and scarring of the lung interstitium. Idiopathic pulmonary fibrosis (IPF) is the commonest form of ILD, characterised by progressive fibrosis of the lung parenchyma. It is associated with

significant morbidity and mortality, with a reported median survival of 3–5 years post diagnosis [1]. Distinguishing IPF from other forms of ILD is of great importance as there are significant implications for treatment options and prognosis. Two novel antifibrotic agents, pirfenidone and nintedanib, have been shown to slow the progression of IPF and now represent first-line therapeutic options [2, 3]. Conversely, immunosuppressive therapy, formerly the mainstay of treatment and a common treatment option in other forms of ILD, has been associated with increased mortality in IPF [4].

Despite recent progress in the treatment of IPF, significant challenges exist, particularly regarding accuracy of diagnosis. The diagnosis of IPF involves a combination of clinical history, radiological imaging and examination of histopathological samples in appropriate cases. Clinical history is required to exclude known causes of lung fibrosis, such as occupational exposure and connective tissue disease, while imaging and biopsy specimens are examined for evidence of a usual interstitial pneumonia (UIP) pattern of disease. Two international consensus guidelines have recently been published, one by the joint thoracic societies and the other by the Fleischner Society, which update the description of UIP on both high-resolution computer tomography (HRCT) and surgical lung biopsy (SLB) specimen [5, 6]. The guidelines suggest that a diagnosis of IPF can be made on clinical history and HRCT scan alone if a definite pattern of UIP is seen, that is, fibrosis that has a subpleural and basal distribution with visible honeycomb cysts. If honeycomb cysts are not seen but the distribution is typical and other features of fibrosis are present, such as reticulation and traction bronchiectasis/bronchiolectasis, the pattern can only be described as “probable UIP”. Less typical patterns would be described as “indeterminate” or not UIP (“alternative diagnosis”) if features of an alternative ILD are seen. The American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) guidelines recommend that histological sampling should be considered in any case where a definite UIP pattern is not

seen on HRCT. In a large therapeutic clinical trial, only 53.4% of patients had evidence of honeycombing on HRCT [7]. Importantly, the Fleischner Society offer an alternative opinion regarding the role of biopsy [6]. These guidelines suggest that, in the appropriate clinical context, a diagnosis of IPF can be made if a probable UIP pattern is observed on HRCT, without the need for histological examination.

A histological diagnosis of UIP relies upon the identification of alternating areas of preserved lung architecture and advanced fibrosis with minimal inflammation, creating a variegated appearance. These are better appreciated at low magnification and require adequate tissue size and specimen quality. In the past, traditional transbronchial biopsy (TBB) sampling has been used to obtain histological samples in suspected IPF; however it has long been recognised that their value in the diagnostic process is extremely limited [1]. TBB samples are small in size and subject to significant crush artefact, preventing detailed study of tissue architecture [8]. Surgical lung biopsy (SLB) samples are ideal for histological examination as they are generally large, and the lung architecture is well preserved. In clinical practice SLB rates are low and it is common for a “working diagnosis of IPF” to be made solely on radiology and clinical history [9, 10]. This is particularly true in the context of a probable UIP pattern on HRCT, in line with Fleischner Society recommendations [6]. A recent study involving 404 physicians from around the globe found that 63% were prepared to prescribe treatment for patients with a “working diagnosis of IPF” without requesting an SLB [11]. In the UK, it is estimated that only 13% of IPF diagnoses included an SLB [12]. The primary reason for low SLB rates centres around concerns regarding high morbidity and mortality risks compared with standard diagnostic tests. The procedure can be performed either through an open thoracotomy or via video-assisted thoracoscopic surgery (VATS), which is generally the preferred option due to reduced length of stay [13, 14]. Mortality rates post-procedure have been variably reported with two recent studies noting 30-day mortality at 2.4% and 7.1% [15, 16]. Mortality is higher in patients undergoing a non-elective SLB but is

also higher in older, co-morbid patients. Death following an exacerbation of ILD is the most commonly reported cause of mortality in patients undergoing a diagnostic SLB [17–19].

There is a drive within the ILD community to develop safer diagnostic techniques with sufficient yield that they would provide a feasible alternative to SLB. Transbronchial lung cryobiopsy (TBLC) is seen by many as the most promising option. Cryosurgical techniques have been used in the airways since 1968, traditionally in palliative treatment of obstructive endobronchial tumours and the management of acute airway obstruction [20, 21]. Their role in lung biopsies has been relatively recent and has predominantly involved malignant sample retrieval [22]. TBLC represents an attractive diagnostic tool in ILD as it may allow large tissue samples to be extracted and improve histological architecture preservation compared with TBB [8]. In this review article we will discuss the technical aspects of this procedure, the evidence for its use as a method of obtaining biopsy tissue in IPF and potential risks associated with the procedure. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

TRANSBRONCHIAL LUNG CRYOBIOPSY: TECHNICAL ASPECTS

Flexible cryoprobes employ the Joule-Thomson effect of thermodynamics by which a gas, nitrous oxide in this context, is rapidly decompressed through a small nozzle leading to extreme drops in temperature. This freezing process leads to tissue adhering to the probe, which can subsequently be removed. There are no standardised methods for performing TBLC in ILD and a wide variety of techniques have been employed in the published data. A recent statement from an international expert panel has sought to provide some clarity regarding the optimum sampling technique [23]. Although TBLC has been performed under local anaesthetic, expert consensus is that the procedure should be performed under general anaesthetic, using either a flexible or rigid bronchoscope. A

bronchial blocker or Fogarty balloon may be employed to manage potential haemorrhage [24, 25]. The bronchoscope is positioned within the relevant area of interest, often guided by pre-procedure high-resolution CT thorax. The cryoprobe is advanced to its limit and then withdrawn 1–2 cm to a final position equating to approximately 1 cm from the pleura [24–29]. Some studies include the use of fluoroscopy to confirm the final position of the cryoprobe and one small prospective study reported safe use of a radial miniprobe to guide TBLC in ILD [30]. The cryoprobe is then cooled for 5–7 s and then withdrawn from the bronchoscope [24–27, 29]. The temperature reached by the probe varies from -45 to -89.5 °C [31]. The tip of the probe is placed in a saline bath and once the sample has thawed and fallen away from the scope it can be transferred to formalin for processing.

There is no consistent number of samples within the range of studies that have been conducted but typically between two and five samples were taken [27, 29]. In a prospective study of 46 patients, it was found that diagnostic yield increased with a second biopsy if the sample arises from two different segments within the same lobe (69% vs. 96%) [32]. The cryoprobes are available in different lengths, generally 900 mm or 1150 mm, with a diameter of 1.9 mm or 2.4 mm. There has been a suggestion that activation time, the point from which contact is made between probe and tissue, and probe size could affect the amount of tissue obtained via biopsy; however the smallest cryoprobe was still noted to provide a larger biopsy than a forceps biopsy [33]. The size of the sample obtained is important, as diagnostic yield appears to correlate with specimen size [24]. It has been suggested that specimen samples should be ≥ 5 mm to be considered adequate for histological examination [26].

TRANSBRONCHIAL LUNG CRYOBIOPSY: EVIDENCE FOR USE IN IPF

Table 1 summarises the published studies of TBLC in suspected ILD including IPF patients.

Table 1 Studies that report diagnostic yield and safety outcomes in transbronchial lung cryobiopsy in patients with suspected interstitial lung disease including idiopathic pulmonary fibrosis

First author	Country	Year	N	Study design	No. of centres	Demographics		FVC % (mean)	Diagnostic yield (%)		Complications (%)		30-Day mortality (%)
						Age (mean)	Gender (%)		Histological	MDT	Pneumothorax	Bleeding	
Babiak [22]	Germany	2009	41	Retrospective	Single	NR	NR	NR	95.1	39.0	4.87	0.0	NR
Kropfski [48]	USA	2013	25	Retrospective	Single	57.1	52	75.3	76.0	28.0	0.0	0.0	NR
Casoni [24]	Italy	2014	69	Prospective cohort study	Single	60 ^a	51	81 ^a	93	57 ^d	28	1.4	1.4
Fruchter [38]	Israel	2014	75	Retrospective	Single	56.2	55	NR	70	9.3	0.0	0.0	NR
Griff [41]	Germany	2014	52	Retrospective	Single	63 ^a	69	NR	79	25	0.0	0.0	NR
Pajares [56]	Spain	2014	39	Prospective randomised control trial	Single	60.3	51	78.2	74.4	0.0	7.7	56.4	NR
Hernandez-Gonzalez [42]	Spain	2015	33	Retrospective	Single	64	33	69	79	12	12	21	NR
Cascante [51]	Spain	2016	55	Prospective	Single	58.8	58.1	79.7	NR	32.7	14.5	10.9	0.0
Echevarria-Uraga [50]	Spain	2016	100	Retrospective	Single	63 ^a	66	85 ^a	NR	11.0	3	13	1 ^c
Hagmeyer [64]	Germany	2016	32	Retrospective	Single	65.4	68.8	74.6	NR	NR	19	78	NR
Hagmeyer [63]	Germany	2016	19	Prospective	Single	67 ^a	63	80 ^a	NR	NR	26	79	5.3
Ravaglia [45]	Italy	2016	297	Retrospective	Single	60 ^a	57.9	86.0 ^a	82.8	NR	20.20	0.0	0.3 ^c
Tomassetti [49]	Italy	2016	58	Retrospective	Single	59 ^a	47	82 ^a	NR	50.0	33	0.0	1.7 ^c
Almeida [44]	Portugal	2017	100	Retrospective	Single	57.15	64	90.0 ^a	82	9.0	18.0	3.0	1.0
Bango-Alvarez [29]	Spain	2017	106	Prospective	Single	60	65	76.4	NR	20.8	4.7	16	NR
DiBardino [36]	USA	2017	17	Retrospective	Single	NR	NR	NR	53	5.9	11.8	17.6	0.0
Kronberg-White [27]	Denmark	2017	38	Retrospective	Single	61 ^a	58	87	84.2	26.3	26	16	0.0 ^c
Marçao [39]	Portugal	2017	90	Retrospective	Single	60	58.9	85 ^a	73.3	8.1	22.4	5.6	NR
Sriprasart [47]	USA	2017	74	Retrospective	Single	54	49	NR	87.84	14.9	6.8	4.1	4.1
Ussavarungsi [35]	USA	2017	74	Retrospective	Single	63	55	NR	51	79.7	1.4	12.2	0.0
Cooley [37]	USA	2018	159	Retrospective	Single	57	46	70	69	6.9	11	3.8	1.9

Table 1 continued

First author	Country	Year	N	Study design	No. of centres	Demographics		FVC % (mean)	Diagnostic yield (%)		Complications (%)		30-Day mortality (%)
						Age (mean)	Gender (%)		Histological	MDT	Pneumothorax	Bleeding	
Hagmeyer [72]	Germany	2018	42	Prospective	Single	66	57	82	NR	76.2	12	0	2
Lentz [34]	USA	2018	104	Retrospective	Single	58.2	55.8	70.2	44.2	68.3	2.9	3.8	NR
Cho [46]	USA	2019	40	Retrospective	Single	57.2	70	68.51	85	NR	0	10	0
Kuse [40]	Japan	2019	38	Retrospective	Single	71 ^b	68 ^b	NR	74	92	0.0	0.0	0.0 ^c
Ravaglia [54]	Italy	2019	699	Retrospective	Single	61 ^a	59.1	85.4	87.8	90.1	19.2	8.3	0.4
Romagnoli [61]	France/ Italy	2019	21	Prospective	Two	65 ^a	48	80.05	38 ^c	48	9.5	0.0	NR
Samitas [43]	Greece	2019	50	Retrospective	Single	61	58	69.7	80	76	10	24	NR
Wäscher [62]	Germany	2019	109	Retrospective	Single	64 ^a	66	77 ^a	73.4	83.5	11.9	28.4	0.0

IPF idiopathic pulmonary fibrosis, MDT multidisciplinary team, NR not reported

^a Reported as median

^b Mixed cohort of IPF and lung malignancy patients

^c Diagnostic accuracy

^d Includes possible IPF

^e Did not specify 30-day mortality

The majority of the evidence for diagnostic yield in ILD comes from retrospective cohort studies and case series. In the first study reporting the use of TBLC in ILD, 39 of the 41 patients undergoing the procedure received a definitive diagnosis at a multi-disciplinary team (MDT) meeting while the other two patients required a further SLB to confirm diagnosis [22]. Subsequent single-centre studies have reported variable diagnostic yields, ranging between 44.2 and 87.8 for histological diagnosis and 68.3–98% for an MDT diagnosis [27, 34–50]. A small prospective study reported that 87.5% of patients undergoing TBLC obtained an MDT diagnosis with high confidence [51]. Several meta-analyses have been published that consistently report a diagnostic yield for TBLC of approximately 80%, however with significant heterogeneity between the included studies [5, 45, 52, 53]. Most recently, a large multi-centre cohort study of 699 patients, including some previously published data, reported a diagnostic yield of 87.8%, which helped achieve a multidisciplinary diagnosis in 90.1% of cases [54]. IPF was the most common diagnosis in this cohort. In cases of UIP, interobserver agreement amongst three pathologists was moderate at 0.54. Similar levels of agreement have been noted in SLB specimen interpretation [55], reflecting the difficulty in making a diagnosis even with optimum pathological sampling. It has been suggested that TBLC significantly increases the confidence of making a diagnosis of IPF at the MDT level [49]. In a cross-sectional study assessing the impact of TBLC on the MDT diagnostic process in fibrotic ILD, the addition of TBLC improved the confidence of IPF diagnosis from 29% to 63% and was comparable to SLB. In 19% of cases the diagnosis was changed to IPF following the addition of TBLC samples. In another study [27], 20 patients with a radiological pattern of possible UIP as per previous international consensus guidelines [1] underwent TBLC. At MDT, nine subsequently received a diagnosis of IPF, three of hypersensitivity pneumonitis, two of non-specific interstitial pneumonia, five with alternative diagnoses and one did not receive a diagnosis.

As expected, TBLC compares favourably to TBB in diagnostic utility in ILD. A randomised

control trial comparing TBLC to TBB in 77 patients under an ILD diagnostic pathway found that the diagnostic yield was significantly higher in those patients who had TBLC (74.4% vs. 34.1%) [56]. A retrospective analysis of a cohort of 56 patients who underwent both TBB and TBLC for suspected ILD in a single centre reported that TBLC was diagnostic in 11 cases where TBB was non-diagnostic [57]. Interestingly, TBB was diagnostic in four cases in which TBLC was not and in 15 cases neither were diagnostic. A meta-analysis of eight studies, which included a total 916 patients, concluded that TBLC allowed for larger specimen sizes, fewer artefacts and superior diagnostic yield compared with TBB [58]. Despite a significant improvement in diagnostic yield in comparison to TBB, TBLC appears to fall short of SLB, which is still considered the gold standard method of obtaining adequate lung tissue for diagnosis in IPF and other forms of ILD. A retrospective analysis of 150 patients undergoing SLB and 297 having TBLC found that the diagnostic yield of SLB was 98.7% compared with 82.8% with TBLC [45]. Meta-analyses have estimated a diagnostic yield of 83.7–84.4% in TBLC and 91.1–92.7% in SLB [59, 60]. While the diagnostic yield of TBLC has been well reported, the diagnostic accuracy of TBLC in ILD is not as clear, as few patients will undergo both TBLC and SLB. Early data are emerging from prospective studies in patients receiving both procedures. A small two-centre study has recently been published in which 21 patients had TBLC and SLB from the same anatomical locations [61]. In only 38% of cases was the histological diagnosis concordant between the two biopsy methods. SLB was concordant with the final MDT diagnosis in 62% cases compared with 48% with TBLC. Another prospective study comparing TBLC, TBB and SLB in 20 patients is ongoing (NCT01972685).

TRANSBRONCHIAL LUNG CRYOBIOPSY: SAFETY IN IPF

A significant concern regarding the use of TBLC in the diagnosis of IPF is safety. Reported complication rates vary considerably, possibly

because of the heterogeneity of the sampling methods used and experience of the operator. The two most commonly reported complications are pneumothorax and bleeding. The reported rates of these complications are summarised in Table 1.

The rates of pneumothorax post-TBLC have been variably reported between 0% and 33% [22, 24, 27, 29, 34–51, 56, 61–64]. One meta-analysis reported an overall pneumothorax risk of 6% with a 3% risk of chest drain insertion [45]. More recent meta-analyses estimate the overall procedural pneumothorax risk to be closer to 10% [5, 59, 60]. Comparatively, these studies estimated pneumothorax risk post-TBB to be similar at 6–10%, while persistent air-leak post-SLB was 2–6%. A large multicentre retrospective study reported an overall pneumothorax rate of 19.2% in a cohort of 699 patients with suspected ILD undergoing TBLC of which 70% required drainage [54]. The impact this had on length of stay was not reported. Pneumothorax risk was significantly higher when the larger 2.4 mm probe was used as opposed to the 1.9 mm probe (21.2% vs. 2.7%). In addition, pneumothorax was also more common when multiple lobes were sampled and when three or more biopsies were taken. Pneumothorax was more common when biopsies were taken from the lower lobes. The risk of developing a pneumothorax is increased if pleural fragments are identified in the biopsy and declines if fluoroscopic guidance is used [24, 65]. Patients with IPF are more at risk of pneumothorax than other forms of ILD [23, 54]. In addition, patients who suffer from pneumothorax tend to have poorer baseline lung function, although an FVC of < 50% predicted does not appear to be a risk factor for developing a pneumothorax as a complication of TBLC [54].

Bleeding is common post TBLC; however overall bleeding risk is difficult to quantify as there is no internationally accepted severity scale, although a classification of mild, moderate and severe bleeding described by Ernst et al. is most commonly used [66]. Mild bleeding, not requiring intervention, has been reported in 30% of cases [56]. Pooled analyses of studies reporting moderate and severe bleeding estimate a risk of 4.9–39% [53, 59, 60]. Risk of

bleeding appears to be higher when the lower lobes are sampled, likely reflecting the basal predominance of UIP pattern fibrosis, but does not appear to be related to the number of sites sampled or the size of the probe [54]. Due to the risk of severe bleeding, it is recommended that a pre-emptive endobronchial blocker or occlusive balloon be placed in the airway [23]. The use of an occlusion balloon has been associated with a significantly lower incidence of moderate-to-severe bleeding (1.8% vs. 35.7%) [65]. To accommodate both a bronchoscope and a blocker/balloon simultaneously, a rigid bronchoscope or flexible endotracheal tube is required and would require general anaesthetic support. However, techniques using a deflated endobronchial blocker alongside a flexible bronchoscope have been described, obviating the requirement for rigid bronchoscopy or general anaesthesia [67].

The major concern that troubles both patients and physicians with regard to SLB in the diagnosis of IPF is the risk of mortality. Thirty-day mortality post-SLB has recently been reported to be as high as 7.1% [16]. Exacerbation of IPF following SLB is felt to be a leading cause of mortality [19]. In comparison, pooled-analyses estimated mortality rates post-TBLC to be 0.1–2.7% [5, 52, 59, 60]. Exacerbation of IPF remains a leading cause of death in these patients [24, 54, 65, 68]. The overall frequency of exacerbation post-TBLC is unclear as it is not commonly reported in the published data. This may reflect the lack of a universally recognised definition of an acute exacerbation. Length of stay has been estimated at 3 days for patients with IPF undergoing TBLC compared with 6 days for those undergoing SLB [49].

CONCLUSION

The use of TBLC in the diagnosis of IPF continues to divide opinion in the ILD community. This is apparent from the publication of the 2018 guidelines for diagnosis of IPF when the guideline panel did not make a recommendation regarding its use in the context of probable or indeterminate UIP on CT [5]. The panel were evenly split for and against the use. On one

hand, TBLC appears to offer the opportunity to obtain large-volume, well-preserved lung tissue allowing reasonable diagnostic yield with less mortality risk than SLB. However, on the other hand, morbidity post-TBLC is not insignificant and concerns regarding diagnostic accuracy have been raised [61]. Of concern is the fact that some complications, such as pneumothorax, are more common in patients with IPF [54]. The safety data published thus far for TBLC in suspected ILD may not be fully reflective of patients diagnosed with IPF. As shown in Table 1, the proportion of patients in the published work with an eventual diagnosis of IPF is commonly < 30%. In addition, the average age of patients included in a recent large retrospective analysis was 61 with a forced vital capacity of 85.4% predicted and transfer factor of 61.2% [54]. Registry data suggest the average age of IPF patients is closer to 70 with significantly poorer lung function [69]. The risk of TBLC in this group needs further examination to determine whether the technique is significantly safer than SLB. While these concerns need to be addressed, there are other areas such as cost in which TBLC appears to carry significant benefit over SLB [60, 70, 71]. In addition, as expertise and experience grow, the accuracy and safety of the technique will also improve.

While the body of evidence regarding the use of TBLC in IPF grows, the quality remains low. The majority of publications are retrospective single-centre studies, which suffer from significant risk of bias. The reported diagnostic yield varies considerably within the study set. This reflects intrinsic differences in patient selection based on clinical characteristics, such as age and co-morbidities, and disease features, such as radiological extent of disease. There has been a dearth of protocolised prospective work in the field to date; however, change is on the horizon. In addition to the recently published prospective comparison study between TBLC and SLB [61], there are a further 11 studies registered to *clinicaltrials.gov* assessing the utility of TBLC in ILD. However, at present it remains unclear as to the eventual role of TBLC in the diagnosis of IPF and there remains a definite need to identify

novel tests that have high diagnostic accuracy and are minimally invasive.

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