Utility of Transbronchial Lung Cryobiopsy in Non-Interstitial Diseases

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Keywords

Interventional pulmonology · Cryobiopsy · Diagnosis · Lung cancer

Abstract

Background: Transbronchial lung cryobiopsy (TLCB), performed with a flexible cryoprobe, is an interventional pulmonology procedure that has proved its diagnostic value for interstitial pulmonary disease. However, it has not been explored extensively as a diagnostic tool for patients with non-interstitial lung pathology, including infectious and malignant diseases. **Objective:** To evaluate the diagnostic yield and safety of an interventional pulmonology approach that integrates TLCB and bronchoalveolar lavage (BAL) for the diagnosis of non-interstitial pulmonary disease. **Methods:** TLCB and BAL were performed under general anesthesia through the same bronchoscopic access on 103 adult patients (including immunocompromised HIV+ individuals) with clinical/radiological evidence of non-interstitial lung

disease admitted to the Interventional Pulmonology Service between May 2015 and April 2016. Samples obtained were sent to pathology and microbiology laboratories for standard diagnostic analysis. **Results:** Samples of TLCB allowed the diagnosis of 75.7% of patients, while 39.8% were diagnosed from BAL. The global diagnostic yield from the dual sampling was 92.2%. TLCB allowed the diagnosis of 94.7% of cancer cases and 60.0% of infectious cases, while BAL samples identified 77.5% of infectious cases and 21.2% of malignant lesions. The incidence of complications was 4.9% with full recovery in all cases. **Conclusions:** Simultaneous TLCB and BAL constitute a safe and useful diagnostic procedure for non-interstitial pulmonary disease, with a global diagnostic yield of 92.2%. Complementary advantages of samples obtained by each technique result in a robust diagnostic strategy for infectious and malignant disease in adults, including HIV+ individuals.

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Introduction

Transbronchial lung cryobiopsy (TLCB) was developed as a diagnostic tool for idiopathic interstitial pulmonary disease. The diagnostic sensitivity of TLCB has been compared with forceps biopsy (FB), showing a better diagnostic yield in several studies [1–4]. Samples obtained by TLCB are of larger size than those of FB and lack the mechanical crush artifacts, improving the quality of the histopathology sample [5–7].

Even though the surgical biopsy is still considered the gold standard, TLCB is associated with lower morbimortality rates and significant lower costs, and can be performed in an interventional pulmonology unit on an ambulatory outpatient basis [1, 8, 9]. TLCB could be the first choice for patients with high surgical risk and those who do not consent to surgery [10].

In populations with lung cancer, TLCB has been performed mainly on patients with endobronchial lesions, showing a high diagnostic yield [11, 12] and no significant differences in complications compared to standard FB.

In general, TLCB has shown to be a relatively safe lung sampling technique; however, patients can undergo complications, including bleeding and pneumothorax, the latter occurring in up to 20% of patients in some settings [10, 13].

There is a paucity of studies that describe the use of TLCB in patients without interstitial lung disease. The aim of this work was to document the usefulness and diagnostic yield of pulmonary cryobiopsies in non-interstitial pulmonary disease and describe the complications of the procedure.

Methods

This is an observational, retrospective, descriptive study on patients seen by the Interventional Pulmonology Unit between May 2015 and April 2016 in a dedicated respiratory hospital (INER) in Mexico City. This study was approved by the INER committee of research and ethics (code C38-16). Subjects were adult patients referred for diagnostic bronchoscopy after clinical and radiographic assessment. Patients' demographics are shown in Table 1.

All procedures were performed under general anesthesia, using a rigid bronchoscope (12-mm Tracheoscope STORZ®; Karl Storz GmbH & Co, Germany). For TLCB performed with a flexible cryoprobe, 3–5 samples per patient were taken with a cryoprobe of 1.9 mm in diameter and 90 cm of length (ERBOKRYO®; Erbe, Atlanta, GA, USA) and all these were fluoroscopy-guided. Tomographic images were analyzed with use of the Magic Web System.

Samples obtained from both TLCB and bronchoalveolar lavage (BAL) were sent to the Anatomical Pathology and Clinical Microbiology Laboratory for standard analysis (Table 1).

Table 1. General characteristics of patients and sample studies ($n = 103$)

<i>Patient population</i>	
Male	68 (66.0)
Mean age $\pm$ SD, years	50.9 $\pm$ 18.2
<i>Specific subgroups of patients</i>	
HIV+	30 (29.1)
Peripheral localized lesions, TLCB guided by radial EBUS and fluoroscopy	27 (26.2)
<i>Sample studies</i>	
<i>TLCB samples</i>	
Pathology results	102 (99.0)
Microbiology results	89 (86.4)
Total	103 (100.0)
<i>BAL samples</i>	
Pathology results	93 (94.9)
Microbiology results	89 (95.1)
Total	98 (100.0)

Values are shown as n (%), unless otherwise indicated. TLCB, transbronchial lung cryobiopsy; EBUS, endobronchial ultrasound; BAL, bronchoalveolar lavage.

Diagnoses were grouped as follows: 1 = malignant: (a) non-small cell carcinoma, (b) small cell carcinoma, (c) carcinoid, (d) metastatic, and (e) other; 2 = infectious (when a specific etiological microorganism was identified); 3 = mixed (diagnoses with findings of both group 1 and 2; there were 2 patients with cancer and lung infection diagnoses); 4 = other diagnoses (including pneumonia without identification of causal microorganism, chronic granulomatous inflammation, and alveolar hemorrhage). Finally, undetermined diagnosis constituted those patients where a conclusive one could not be established.

The global diagnostic yield of the interventional pulmonology procedure (simultaneous TLCB and BAL) as well as the diagnostic yield of each sampling technique in all mentioned groups were established.

The global diagnostic yield was calculated as follows: the sum of patients with a diagnosis of any group (1, 2, 3, and 4) divided by the total number of patients (group 1, 2, 3, 4 and undetermined diagnosis). Additionally, we measured the diagnostic yield in the subgroup of HIV+ patients and the subgroup of patients who underwent fluoroscopy-guided radial endobronchial ultrasound (EBUS) during TLCB, as indicated for peripheral lesions.

Comparison of the diagnostic yield between sampling techniques and diagnostic groups was analyzed statistically with IBM SPSS 21 software using the Wilcoxon signed-rank test to two related samples with a significance threshold of $p < 0.05$.

Results

One hundred and three patients with no evidence of interstitial lung disease underwent TLCB. Tomographic images were available for 99.0% of the patients (102/103).

Table 2. Diagnostic yield for sample type and diagnostic group

Diagnostic group		BAL			TLCB			<i>p</i> value ^c
		<i>n</i>	total	%	<i>n</i>	total	%	
1	Malignant	7	33	21.2	36	38	94.7	<0.001
2	Infectious	31	40	77.5	24	40	60.0	<0.001
3	Mixed ^a	1	2	50.0	2	2	100.0	–
4	Other diagnosis	1	19	5.3	18	19	94.7	<0.001
Global diagnostic yield according to sample type ^b		39	98	39.8	78	103	75.7	<0.001

BAL, bronchoalveolar lavage; TLCB, transbronchial lung cryobiopsy. ^a Two patients had simultaneous malignant and infectious diagnoses and were included in each respective group. ^b The global diagnostic yield is the sum of patients with diagnosis of group 1, 2, 3, and 4 divided by the total number of patients (group 1, 2, 3, 4 and undetermined diagnosis) ×100. ^c *p* value for Wilcoxon signed-rank test to two related samples.

Localized lesions were present in 52.9% (54/102) and diffuse in 44.1% (45/102). The most frequent tomographic images were consolidation in 13.7% (14/102), ground-glass opacities in 23.5% (24/102), and nodules in 18.6% (19/102).

Independently of the type of lesion obtained, all samples were studied histopathologically and 91.3% (94/103) were subjected to microbiological examination. Histopathological analyses were completed in 99.0% of the TLCB samples (102/103) and microbiological results were obtained from 86.4% (89/103). Of the BAL samples, 94.9% (93/98) had histopathological results and 95.1% (89/98) microbiological results. Regarding microbiological analysis of BAL samples, 88.8% (87/98) were processed for PCR and culture diagnostic methods to identify specific fungi, bacteria, and viruses (Table 1).

A subset of 54 samples (52.4%; 54/98) from patients with clinical findings consistent with tuberculosis was also processed on the MTB/RIF GeneXpert[®] platform for identification of *Mycobacterium tuberculosis*.

Overall, the strategy allowed us to find 38 (36.9%) patients with malignant disease, 40 (38.8%) patients with specific pulmonary infections, and other diagnoses were found in 19 (18.4%) patients.

Diagnostic yields were initially calculated considering TLCB and BAL samples separately; data are shown in Table 2. We found that both specific and global diagnostic yields were significantly higher for TLCB than for BAL: 75.7 versus 39.8%, respectively. There were differences in diagnostic yield for each technique according to the findings: TLCB was superior to BAL for malignant lesions (94.7 vs. 21.2%, *p* < 0.001), while BAL had a significantly

higher diagnostic yield for infectious cases (77.5 vs. 60%, *p* < 0.001) (Table 2).

We then took into consideration the results of both sampling techniques (shown in Table 3), finding a global diagnostic yield for simultaneous TLCB and BAL of 92.2%.

Among all patients, 26.2% (27/103) had localized peripheral lesions, so fluoroscopy-guided radial EBUS was performed to aid TLCB obtainment. As shown in Table 3, the global diagnostic yield in the EBUS subgroup was 88.9%, with TLCB significantly higher than BAL: 81.5 versus 18.5% (*p* < 0.001). Localized lesions were present in 52.9% (54/102), among which 50.0% (27/54) were localized with the use of fluoroscopy-guided radial EBUS. Solid lesions constituted 59.3% (15/27), while 14.8% (4/27) were subsolid. Specific information about lesion size was available from 15 patients. In 14 patients, a specific diagnosis was reached. The mean diameter of the lesions in this subgroup was 43.3 ± 17.7 mm, and a ≥ 30 mm diameter was present in 82.6% of them. Only 1 patient without diagnosis had a smaller lesion diameter (24.1 mm).

The studied population included 29.1% (30/103) HIV patients. The global diagnostic yield of TLCB and BAL in these patients was 93.3%. Interestingly, TLCB was superior to BAL (76.7 vs. 53.3%, *p* = 0.09), even though in these patients the predominant diagnoses were infectious in 63.3% (19/30). Consistent with the global experience on HIV+ populations, fungal infections were highly frequent: *Pneumocystis jirovecii* in 5 (16.7%) patients and histoplasmosis in 4 (13.3%) patients, *Mycobacteria* were identified in 7 (23.3%) occasions, 57.1% (4/7) of them

Table 3. Diagnoses established by the simultaneous TLCB and BAL strategy in the full series and specific subgroups

Diagnosis	Total (<i>n</i> = 103)		Radial EBUS ^a (<i>n</i> = 27)		HIV+ (<i>n</i> = 30)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
1 Malignant	38	36.9	11	40.7	2	6.7
2 Infectious	40	38.8	5	18.5	19	63.3
3 Mixed ^b	2	1.9	0	0.0	0	0.0
4 Other diagnosis	19	18.4	8	29.6	7	23.3
5 Not diagnostic	8	5.8	3	11.1	2	6.7
Global diagnostic yield for specific subgroups ^c	95/103	92.2	24/27	88.9	28/30	93.3

BAL, bronchoalveolar lavage; TLCB, transbronchial lung cryobiopsy; EBUS, endobronchial ultrasound. ^a Peripheral localized lesions, TLCB guided by radial EBUS and fluoroscopy. ^b Two patients had simultaneous malignant and infectious diagnoses and were included in each respective group. ^c The global diagnostic yield is the sum of patients with diagnosis of group 1, 2, 3, and 4 divided by the total number of patients (group 1, 2, 3, 4 and undetermined diagnosis)×100.

Table 4. Diagnoses of malignancy according to the sampling type

Malignant diagnostic group	BAL (<i>n</i> = 33)			TLCB (<i>n</i> = 38)			<i>p</i> value ^a
	<i>n</i>	total	%	<i>n</i>	total	%	
1 Non-small cell lung cancer							
Adenocarcinoma	6	21	28.6	23	25	92.0	<0.005
Squamous cell carcinoma	1	4	25.0	4	4	100.0	–
Subtotal	7	25	28.0	27	29	93.1	<0.001
2 Small cell carcinoma	0	2	0.0	2	2	100.0	–
3 Carcinoid tumors	–	–	0.0	1	1	100.0	–
4 Metastatic cancer							
Ductal adenocarcinoma	0	2	0.0	2	2	100.0	–
Bowel adenocarcinoma	0	3	0.0	3	3	100.0	–
Subtotal	0	5	0.0	5	5	100.0	–
5 Others							
Non-Hodgkin lymphoma	0	1	0.0	1	1	100.0	–
Total	7	33	21.2	36	38	94.7	<0.001

BAL, bronchoalveolar lavage; TLCB, transbronchial lung cryobiopsy. ^a *p* value for Wilcoxon signed-rank test to two related samples.

corresponding to *M. tuberculosis* complex. A cancer diagnosis was made in 6.7% (2/30): one pulmonary adenocarcinoma and another corresponded to a non-Hodgkin lymphoma.

We then focused on the specific cancer findings in the whole series, which was of 36.9% (38/103) of our series. Results are shown in Table 4. The most frequent diagnosis was non-small cell carcinoma in 76.3% (29/38). Spe-

cifically, the distribution was as follows: lung adenocarcinoma in 86.2% (25/29), followed by squamous cell carcinoma in 13.8% (4/29) and non-pulmonary cancer with lung metastasis in 13.2% (5/38) of the cases. Several other cancer types were identified in individual cases. Interestingly, only pulmonary adenocarcinoma and squamous cell carcinoma were diagnosed in both BAL and TLCB samples (Table 4). Diagnosis by BAL represented 18.4%

Table 5. Immunohistochemistry diagnosis of malignancy from TLCB

Malignant diagnostic group	TTF1+		NAPSINA+		p40+		Total
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Non-small lung cell cancer							
Adenocarcinoma ^a	21	84.0	11	44.0	3	12.0	25
Epidermoid	3	75.0	3	75.0	1	25.0	4
Small cell carcinoma	2	100.0	1	50.0	0	0.0	2
Carcinoid tumors	1	100.0	1	100.0	0	0.0	1
Metastatic cancer							
Ductal adenocarcinoma	2	100.0	2	100.0	0	0.0	2
Bowel adenocarcinoma	3	100.0	2	66.7	0	0.0	3
Others							
Non-Hodgkin lymphoma	0	0.0	1	100.0	0	0.0	1

TLCB, transbronchial lung cryobiopsy. ^a Two patients with pulmonary adenocarcinoma had molecular biology studies, both with EGFR subtype 21 present: cases 1 and 2, a male and a female of 47 and 65 years, respectively.

(7/38) of all diagnosed malignancies, while TLCB allowed diagnosis of 94.7% (36/38) ($p < 0.001$).

Immunohistochemistry was performed in all cases, and molecular biology analysis was done in both patients with lung adenocarcinoma. Results are shown in Table 5.

Details on the cases with infectious diagnoses are presented in Table 6. Isolation of a causal agent was attained in 38.8% (40/103) patients with pulmonary infection. A total of 48 microorganisms were identified. Mycobacteria were by far the most frequent pathogens, found in 35.4% (17/48), with *M. tuberculosis* complex in 70.6% (12/17). Fungal infections occurred in 29.2% (14/48), pyogenic bacterial infections were responsible for 22.9% (11/48) and viruses for 10.4% (5/48) of the infections. One case of *Entamoeba* and one of *Branhamella catarrhalis* were identified.

Other diagnoses were found in 19 (18.4%): pneumonia without characterization of the etiologic agent in 36.8% (7/19), granulomatous inflammation in 31.6% (6/19), and alveolar hemorrhage in 31.6% (6/19). Two patients had simultaneous malignancies plus infections. Representative examples are shown in Figure 1. Just a single case of pneumonia without pathogen identification was diagnosed by both BAL and TLCB, while the other diagnoses were only made with the use of TLCB (BAL 5.3% vs. TLCB 94.7%, p value for Wilcoxon signed-rank test to two related samples, $p < 0.001$).

An important finding was that the diagnostic yield of infectious lung diseases with our dual technique was mainly obtained by BAL samples rather than by TLCB:

72.9 versus 41.7% ($p < 0.05$). This is likely a consequence of the nature of the microbiological diagnostic tests and the higher suitability of BAL samples compared to frozen tissue.

Safety was a crucial concern for implementation of the TLCB procedure. Complications occurred in 4.9% (5/103) of patients. In total, they accounted for 6 events: in one patient (HIV+ plus *Cladophialophora* spp. infection), two complications were simultaneously present (moderate bleeding controlled with cold saline solution instillation and pneumothorax which required chest tube placement). Another HIV+ patient with the same infection developed a pneumothorax, requiring chest tube placement. The remaining three patients had moderate bleeding as complication, with the following diagnoses: pneumonia without pathogen isolation, classic carcinoid, and lung tuberculosis; the management of each one was argon plasma cauterization, balloon occlusion, and saline solution plus adrenaline instillation, respectively. All cases were fully resolved and no perioperative deaths occurred.

Discussion

Our study demonstrates the usefulness of TLCB for the diagnosis of pulmonary lesions in patients with non-interstitial disease. We obtained a global diagnostic yield of 75.7% for TLCB, comparable to the one reported by Pajares et al. [2] in patients with interstitial lung disease,

Table 6. Infectious diagnoses of etiologic agents according to sample type ($n = 40$ patients/ $n = 48$ etiologic agents identified)

Infectious diagnoses	BAL		TLCB		Total	Method	p value ^a
	n	%	n	%			
Mycobacterial	13	76.5	6	35.3	17		0.102
<i>Mycobacterium tuberculosis</i> complex	11	91.7	4	33.3	12	GeneXpert® MTB/RIF	–
Non-specific mycobacteria	2	50.0	2	50.0	4	Culture and genotyping PCR	–
<i>Mycobacterium avium</i> complex	1	100.0	0	0.0	1		–
Fungal	13	92.9	6	42.9	14		<0.05
<i>Pneumocystis jirovecii</i>	7	87.5	5	6.3	8	Immunofluorescence microscopy	–
<i>Histoplasma capsulatum</i>	4	100.0	1	25.0	4	Culture and microscopy	–
<i>Aspergillus</i> sp.	1	100.0	0	0.0	1		–
<i>Cladophialophora</i> sp.	1	100.0	0	0.0	1		–
Pyogenic	3	27.3	8	72.7	11		0.054
<i>Acinetobacter baumannii</i>	0	0.0	2	100.0	2	Culture and Vitek®2	–
<i>Haemophilus influenzae</i>	1	50.0	1	50.0	2		–
<i>Branhamella catarrhalis</i>	0	0.0	1	100.0	1		–
<i>Pseudomonas putida</i>	0	0.0	1	100.0	1		–
Anaerobes	0	0.0	1	100.0	1		–
<i>Pseudomonas aeruginosa</i>	1	50.0	1	50.0	2		–
<i>Streptococcus pneumoniae</i>	0	0.0	1	100.0	1		–
<i>Stenotrophomonas maltophilia</i>	1	100.0	0	0.0	1		–
Viral	5	100.0	0	0.0	5		0.066
Influenza A	1	100.0	0	0.0	1	Luminex® real-time PCR	–
Parainfluenza	2	100.0	0	0.0	2		–
Enterovirus/rhinovirus	2	100.0	0	0.0	2		–
Parasitic	1	100.0	0	0.0	1		–
<i>Entamoeba</i> sp.	1	100.0	0	0.0	1	Microscopy	–
Total etiologic agents	35	72.9	20	41.7	48		<0.05

BAL, bronchoalveolar lavage; TLCB, transbronchial lung cryobiopsy. ^a p value for Wilcoxon signed-rank test to two related samples.

shown to be superior to the one with standard FB (74.4 vs. 34.1%).

We find this diagnostic yield for TLCB in our population highly encouraging, considering the inherent heterogeneity of the patients' demographics, clinical background, tomographic patterns, and diversity of non-interstitial diseases.

To date, few studies have documented the use of TLCB in patients with non-interstitial disease. Some series compare the diagnostic yield of TLCB to FB or even to surgical biopsies. Reported series on lung cancer show the usefulness of cryobiopsy in central tumors, and the improved diagnostic yield of endobronchial cryobiopsies over FB, ranging from 89.1 to 95% and from 65.5 to 85%, respectively [11, 12, 14].

Peripheral localized pulmonary lesions represent a diagnostic challenge, considering the need for relatively

large tissue samples suitable for a whole set of immuno-histochemical and molecular biology assays. In our study, the diagnostic yield of the procedure in patients with peripheral lesions was 88.9% (radial EBUS column, Table 3) (TLCB alone, 81.5%; BAL alone, 18.5%). These results compare favorably with the findings of Schuhmann et al. [15] on EBUS-guided transbronchial biopsies of lesions up to 40 mm, with a global diagnostic yield of 74.2% for cryoprobes.

To our knowledge, there are no reports of the use of TLCB for routine microbiological analysis. Of the patients in our study population who had a pulmonary infection (38.8% of the total), 72.9% of microorganisms were identified on BAL samples. However, even though frozen tissue is suboptimal for microbiological techniques (or non-suitable, i.e., for GenXpert®), 41.7% of the infections were also diagnosed on TLCB samples.

Fig. 1. Histological appearance of tissue obtained by transbronchial lung cryobiopsy (TLCB) during the dual procedure. **a** Solid adenocarcinoma composed of dense clusters of medium-sized cells; the nuclei are large, with irregular borders and obvious nucleoli. H&E. $\times 10$. **b** Presence of granulomatous response. H&E. $\times 10$. **c** Auramine-rhodamine staining reveals the presence of my-

cobacteria. $\times 40$. **d** Epithelial tumor constituted by abundant glandular cells with broad eosinophil cytoplasm and nucleus rejected at the periphery. The diagnosis is adenocarcinoma. H&E. $\times 20$. This patient was additionally diagnosed with a *Branhamella catarrhalis* infection by microbiological techniques on BAL.

One of the main findings of our work is that the interventional pulmonology procedure resulted in a high diagnostic yield of 93.3% for patients with known HIV+ status. Other groups report diagnostic yields of 79.7 and 77.3% [16–20] in HIV+ patients. Our approach shows very encouraging results for this patient population. We are currently extending the study to a larger population of HIV+ patients.

Finally, complications from TLCB occurred in 4.9% of patients, irrespective of the type of lesions or diagnosis, even among HIV+ patients, for whom this figure was 6.7%. In all instances, they were promptly controlled. This complication rate is similar to what others have reported. The most frequent complication was bleeding, which was moderate in all instances and promptly controlled with appropriate instrumentation [1, 4, 9, 15].

Limitations

The following limitations must be recognized: due to the retrospective nature of the study, we were unable to standardize the number and location of TLCB sampled per patient. In addition, the histopathological reports did not provide specific information of the TLCB samples size. Furthermore, in some cases, BAL and TLCB samples were not sent simultaneously to both the pathology and microbiology laboratories. The diagnostic yield of our approach was not compared against surgical biopsies. In malignancy cases, not all were subjected to molecular biology studies as stated above. Finally, regarding the tomographic images of the lesions, the majority of the data were retrieved from the medical files and not from the original studies.

Conclusions

TLCB and BAL performed in an Interventional Pulmonology Unit constitute a useful tool for non-interstitial pulmonary disease, with a high diagnostic yield, especially for patients with suspicion of lung cancer. The interventional approach makes it also possible to diagnose specific infectious microorganisms, increasing results in cases when BAL samples alone might be insufficient or unsuitable for conclusive results.

Our findings demonstrate that the simultaneous TLCB and BAL strategy constitutes a relatively safe procedure with a low rate of complications when performed in a specialized Interventional Pulmonology Unit.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest to disclose.

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