Εκπαιδευτική Ημερίδα

Hands-On Training

« Ο ρόλος της διαβρογχικής κρυοβιοψίας στις διάμεσες πνευμονοπάθειες »

ΕΤΑΙΡΕΙΑ ΝΟΣΗΜΑΤΩΝ ΘΩΡΑΚΟΣ ΕΛΛΑΔΟΣ

General principles of cryobiopsy

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Cryobiopsy in endobronchial tumor lesions

Cryoprobe biopsy increases the diagnostic yield in endobronchial tumor lesions

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Objective: Forceps biopsy is the standard method to obtain specimens in endoscopically visible lesions. It is common to combine forceps biopsy with cytology methods to increase the diagnostic yield. Although the flexible cryoprobe has been established for bronchoscopic interventions in malignant stenosis, the obtained biopsies, called ''cryobiopsies,'' have not been investigated in a large cohort of patients. The aim of this feasibility study was to prospectively evaluate the diagnostic yield and safety of cryobiopsy and forceps biopsy.

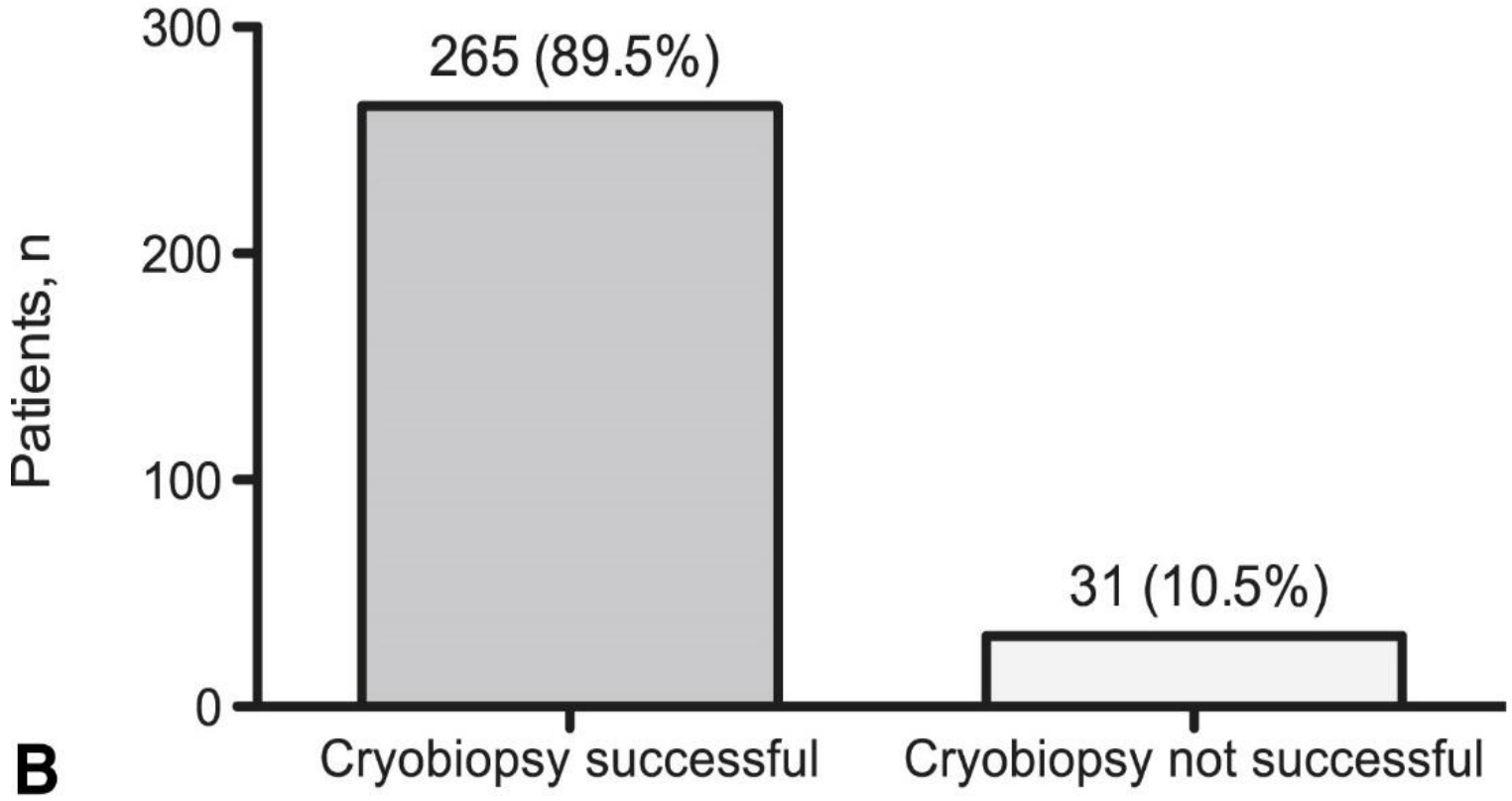
Methods: During a 6-year period, 296 patients with visible endoluminal tumor lesions were included in the study at the bronchoscopy unit of a university hospital. In the first consecutively conducted 55 cases, both techniques, forceps biopsy and cryobiopsy, were applied simultaneously. Pathologic and quantitative image analyses were performed to evaluate the size and quality of the obtained specimens. We evaluated the safety and diagnostic yield to describe the feasibility of cryobiopsy.

Results: Comparative analysis of the first conducted and randomly assigned 55 cases revealed a significantly higher diagnostic yield for cryobiopsy compared with forceps biopsy (89.1% vs 65.5%, $P < .05$). In this cohort, quantitative image analysis showed significantly larger biopsies regarding size and artifact-free tissue sections for cryobiopsy compared with forceps biopsy ($P < .0001$). The overall diagnostic yield of cryobiopsy was 89.5%. Mild bleeding occurred in 11 cases (3.7%), moderate bleeding occurred in 3 cases (1.0%), and severe bleeding occurred in 1 case (0.3%).

Conclusion: Cryobiopsy is safe and increases the diagnostic yield in endobronchial tumor lesions. The method also is feasible under routine conditions. (J Thorac Cardiovasc Surg 2010;140:417-21)

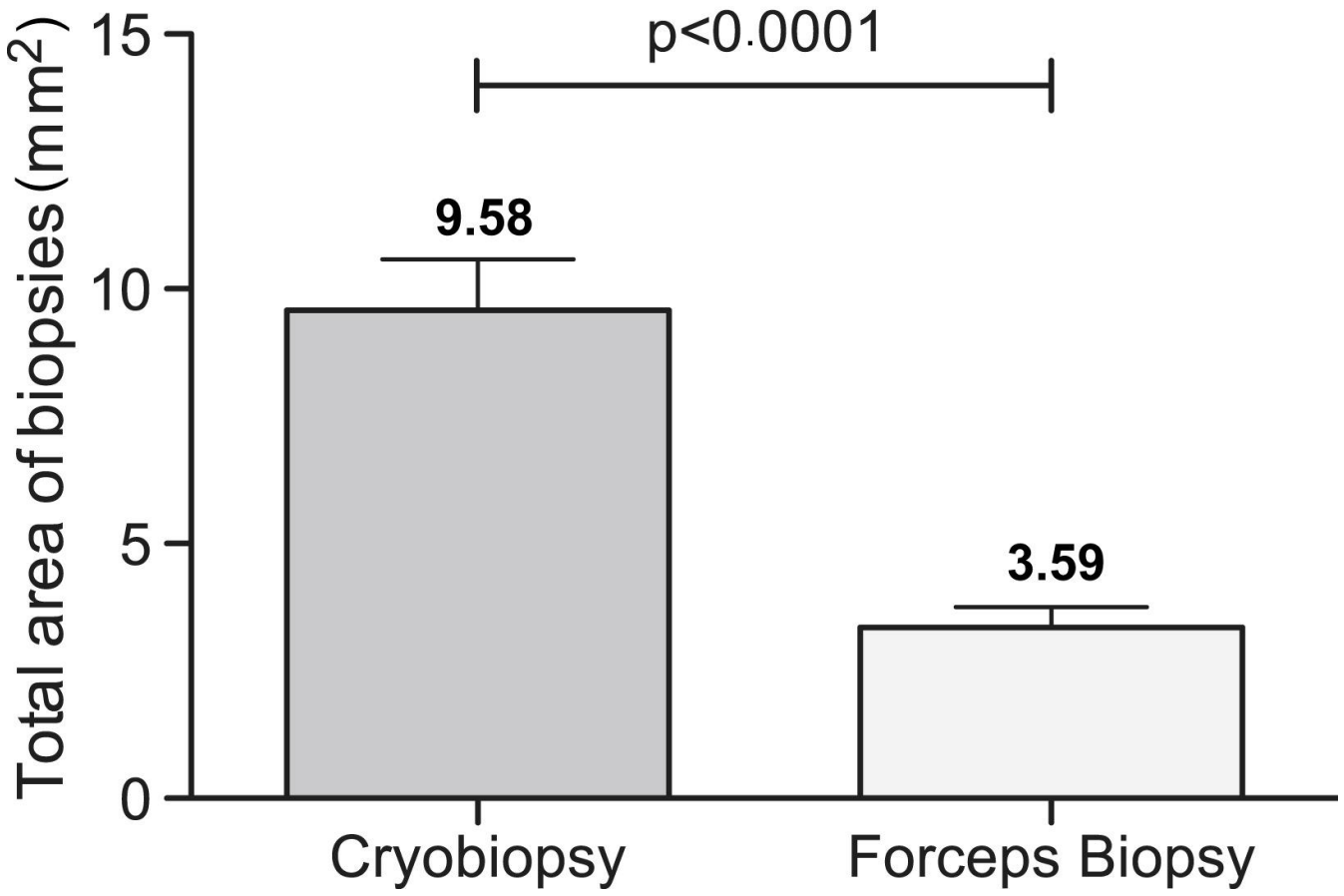
Schumann C. J Thorac Cardiovasc Surg 2010

Cryobiopsy in endobronchial tumor lesions



Schumann C. J Thorac Cardiovasc Surg 2010

Cryobiopsy in endobronchial tumor lesions



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Adv. Respir. Med. 2017; 85: 301–306

Cryobiopsy versus forceps biopsy in endobronchial lesions, diagnostic yield and safety

Introduction: This study aimed to evaluate the safety and diagnostic yield of cryobiopsy (CB) in comparison to forceps biopsy in endobronchial lesions.

Material and methods: Patients with suspected endobronchial lesions were enrolled. Two forceps biopsies and one cryobiopsy were done in the same patient with randomized sequence. The largest diameter of the samples was measured in mm by electronic caliper. Diagnostic yield of each technique and postbronchoscopy bleeding were evaluated.

Results: Samples obtained by CB was significantly larger than that of the forceps biopsy (5.9 ± 2.3 vs 2.5 ± 0.8, p = 0.001). Diagnostic yield of CB was significantly higher than forceps biopsy 74.5% versus 51.1% (p = 0.001). Mild and moderate bleeding grades were reported in both techniques with no significant difference (p = 0.063, p = 0.5), respectively. Severe bleeding was not recorded in both techniques.

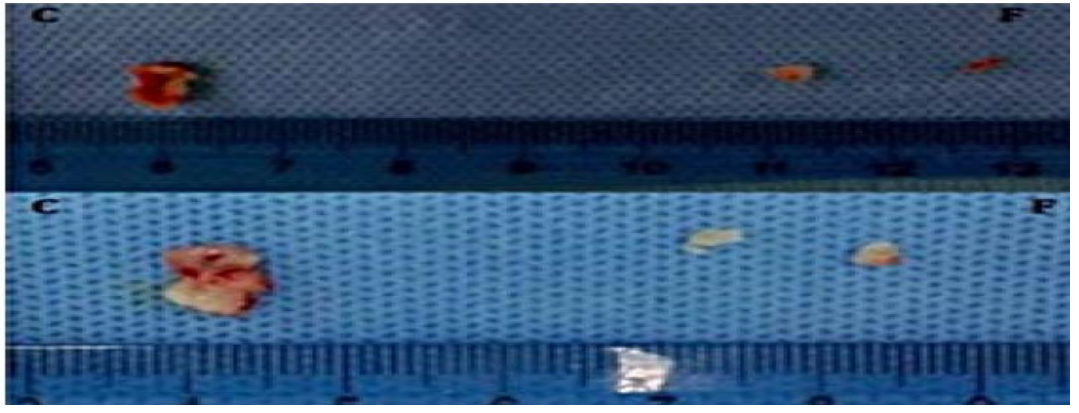
Conclusions: CB represents a safe and effective tool to obtain a larger tissue samples of a good quality with higher diagnostic yield in comparison to standard forceps samples. On the other hand, bleeding occurred more frequently after CB than forceps biopsy. However, without severe adverse effects.

Table 2. Sequence, number, site and size and diagnostic yield of bronchoscopic biopsies taken from the studied patients

	Total number of the patients: 47 (100%)		
	Forceps	Cryobiopsy	p
Sequence of biopsies	Forceps then cryo 23 (48.9%)	Cryo then forceps 24 (51.1%)	0.5
Number of the biopsies			
• Total biopsies number	94	47	–
• Biopsies per patient	2	1	≤ 0.001
Distribution of the biopsy site:			
• Rt main bronchus	8	4	
• Rt upper lobe	6	3	
• Bronchus intermedius	14	7	
• Middle lobe	8	4	–
• Rt lower lobe bronchus	4	2	
• Let main bronchus	18	9	
• Lt upper lobe	18	9	
• Lingula	4	2	
• Lt lower lobe	14	7	
Size of the biopsy in mm (mean ± SD)	2.5 ± 0.8	5.9 ± 2.3	≤ 0.001
Diagnostic yield	24 (51.1%)	35 (74.5%)	0.001

Table 4. Bleeding complication after forceps and cryobiopsy

	Total number of the patients: 47 (100%)		
	Forceps n(%)	Cryobiopsy n(%)	p
No bleeding	35 (74.5)	28 (59.6)	0.016
Bleeding			
• Mild	10 (21.3)	15 (31.9)	0.063
• Moderate	2 (4.3)	4 (8.5)	0.5



Respiration

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Transbronchial Cryobiopsy: A New Tool for Lung Biopsies

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Peter Moeller[d] Tahsin Balli[a] Martin Hetzel[a]

Table 1. Number of cases diagnosed using different biopsy techniques

Definitive diagnosis	History, lung function, CT, forceps biopsy, cryobiopsy	History, lung function, CT, forceps biopsy	History, lung function, CT[a]
IPF/UIP	15	11	11
NSIP	10	3	0
Desquamative interstitial pneumonia	3	3	0
Pulmonary lymphangioleiomyomatosis	1	1	0
Hypersensitivity pneumonitis	3	2	1[b]
Sarcoidosis	6	4	2[b]
Pharmacologically induced pneumonitis	1	0	0

[a] Two cases (one IPF and one NSIP) were diagnosed with surgical lung biopsy.
[b] Including laboratory testing and bronchoalveolar lavage.

Usefulness of simple transbronchial biopsy

Why TBBx is not used in fibrotic ILD diagnosis

Author	Diagnostic Bx	Comment
Anderson 1978 N=939	31%	Non Spec – 44% Normal/Inad – 25%
Poletti 1988 N=801	29%	Spec – 34%
Ensminger 2006 N=603	38%	Inad – 33%
Berbescu 2006 N=22	30%	Inad – 20%

Very Low Sensitivity (30% for Expert Pathologists)
Low negative predictive value (50%): the presence of TBB findings consistent with alternative diagnosis (ie. DIP, NSIP, ALI) does not rule out UIP

Recommendation: Transbronchial biopsy should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence).

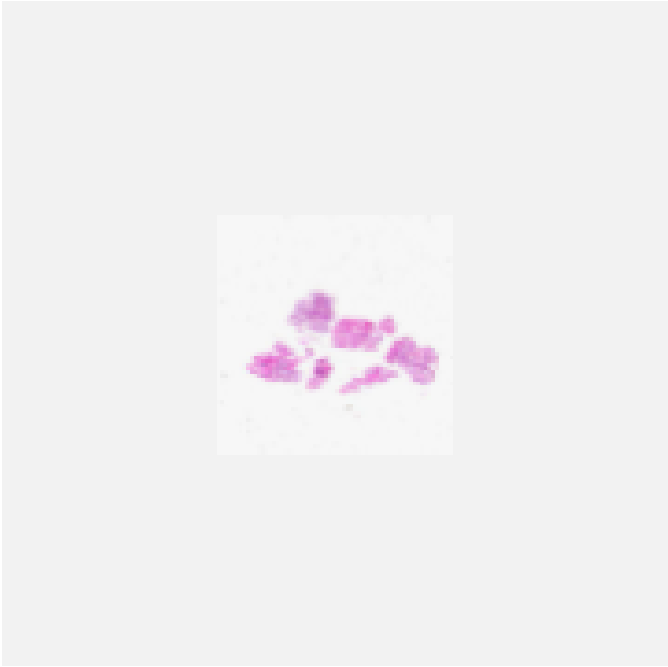
Raghu G, *et al. AJRCCM 2011*

Usefulness of simple transbronchial biopsy

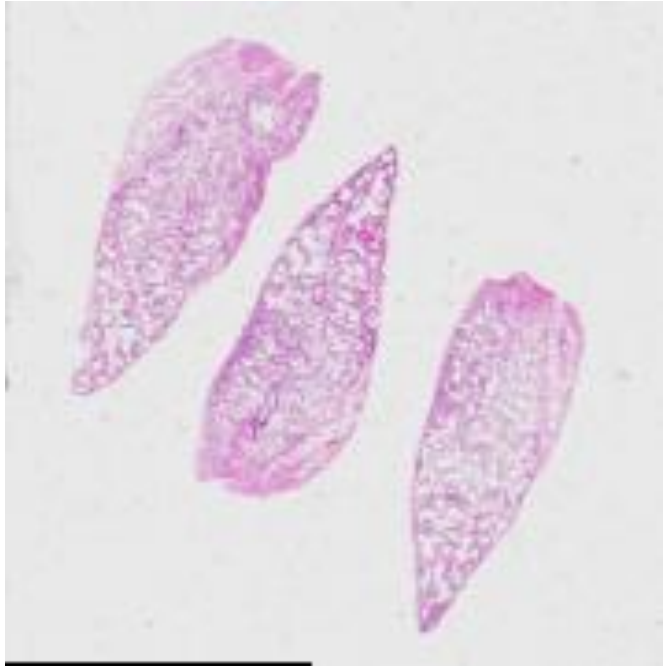
Why TBBx is not used in fibrotic ILD diagnosis

Size does matter

TBBx

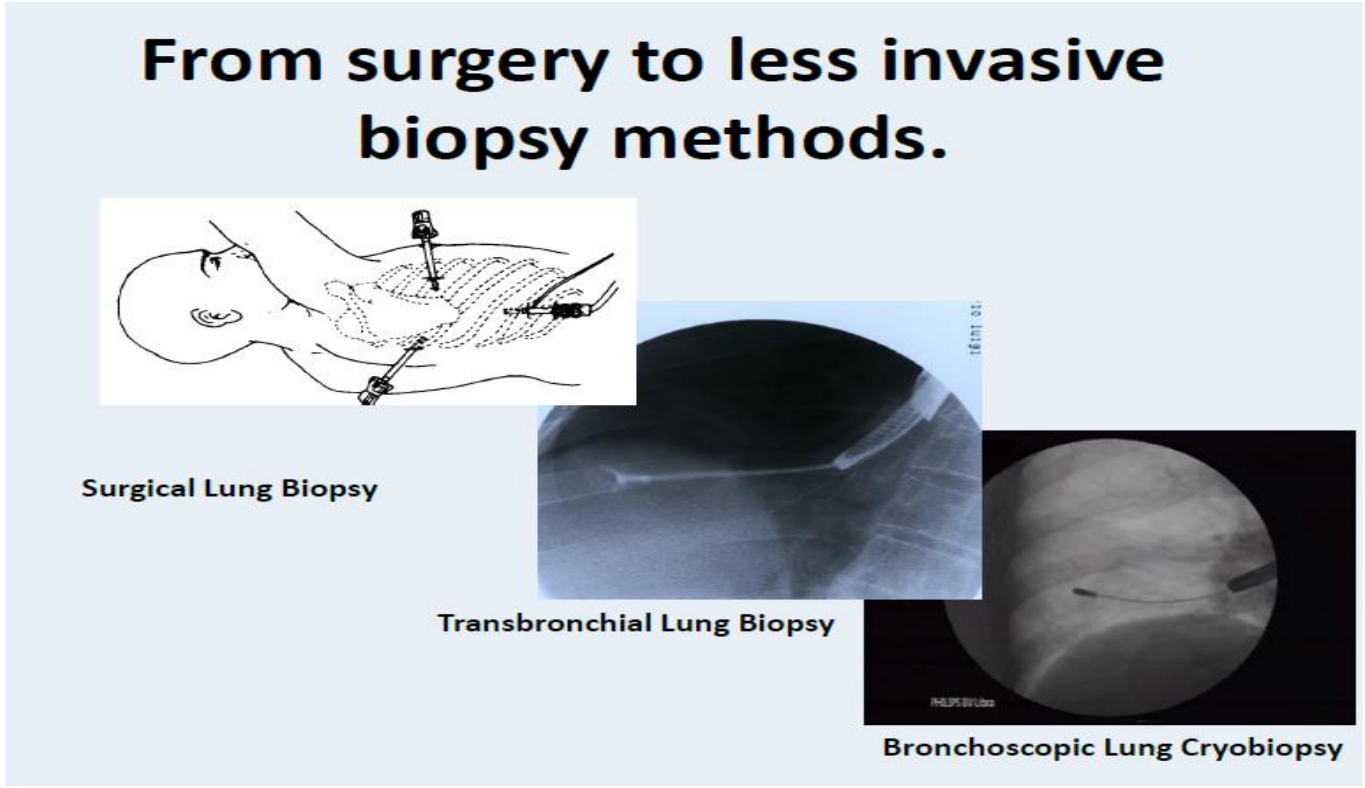


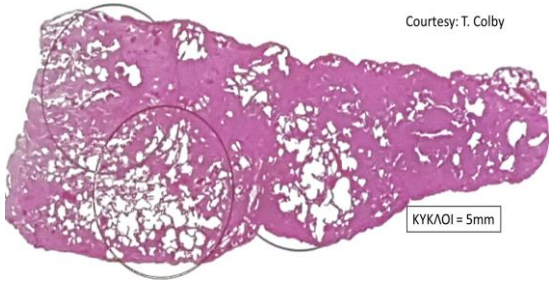
VATS Bx

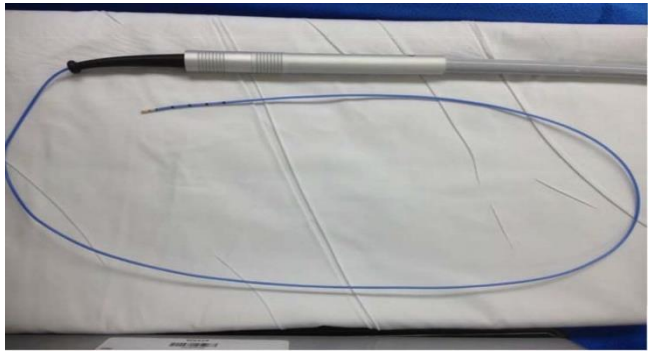


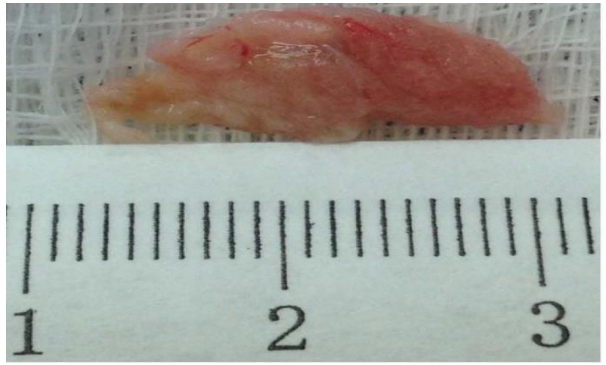
1X Magnification

Transbronchial cryobiopsy: The intermediate solution









Transbronchial cryobiopsy: The intermediate solution

Diagnostic yield

Cryobiopsy versus forceps biopsy

Study or Subgroup	cryobiopsy Events	Total	forceps biopsy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.2 Interstitial lung diseases						
Babiak et al	39	41	24	41	13.5%	1.63 [1.24, 2.12]
Pajares et al	29	39	13	38	7.3%	2.17 [1.35, 3.51]
Subtotal (95% CI)		**80**		**79**	**20.8%**	**1.77 [1.34, 2.32]**
Total events	68		37			
Heterogeneity: Tau² = 0.01; Chi² = 1.22, df = 1 (P = 0.27); I² = 18%						
Test for overall effect: Z = 4.08 (P < 0.0001)						
1.2.3 lung tumours						
Aktas et al	38	41	32	41	16.8%	1.19 [0.99, 1.43]
ChunLiang et al	75	75	52	75	18.1%	1.44 [1.24, 1.67]
Hetzel et al	268	282	239	281	21.0%	1.12 [1.06, 1.18]
Schuhmann M et al	19	31	15	31	7.7%	1.27 [0.80, 2.00]
Schumann et al	49	55	36	55	15.6%	1.36 [1.10, 1.68]
Subtotal (95% CI)		**484**		**483**	**79.2%**	**1.25 [1.10, 1.43]**
Total events	449		374			
Heterogeneity: Tau² = 0.01; Chi² = 12.99, df = 4 (P = 0.01); I² = 69%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
Total (95% CI)		**564**		**562**	**100.0%**	**1.36 [1.16, 1.59]**
Total events	517		411			
Heterogeneity: Tau² = 0.03; Chi² = 29.14, df = 6 (P < 0.0001); I² = 79%						
Test for overall effect: Z = 3.77 (P = 0.0002)						
Test for subgroup differences: Chi² = 4.87, df = 1 (P = 0.03), I² = 79.5%						

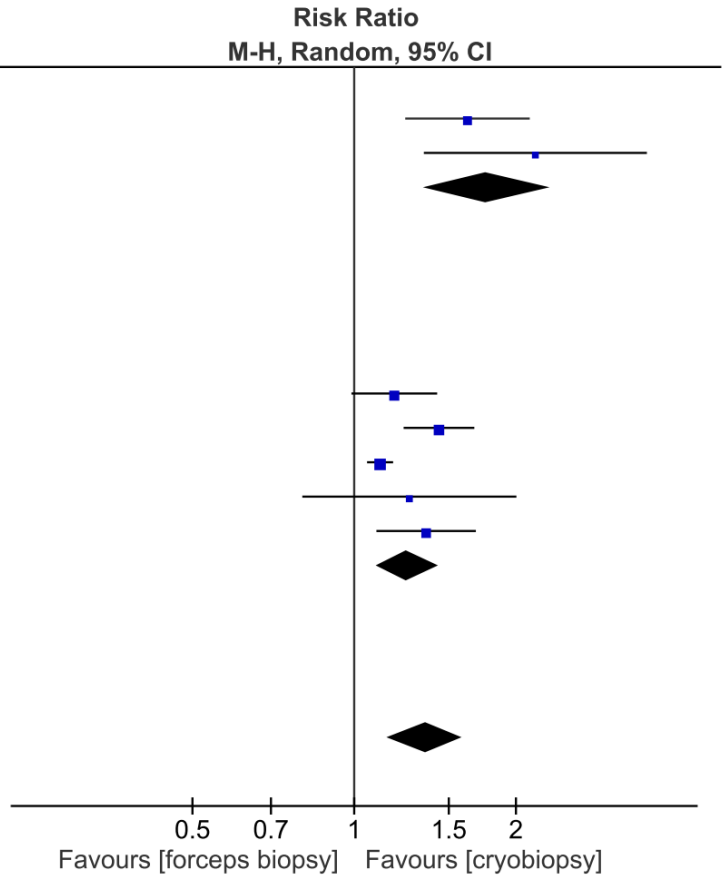
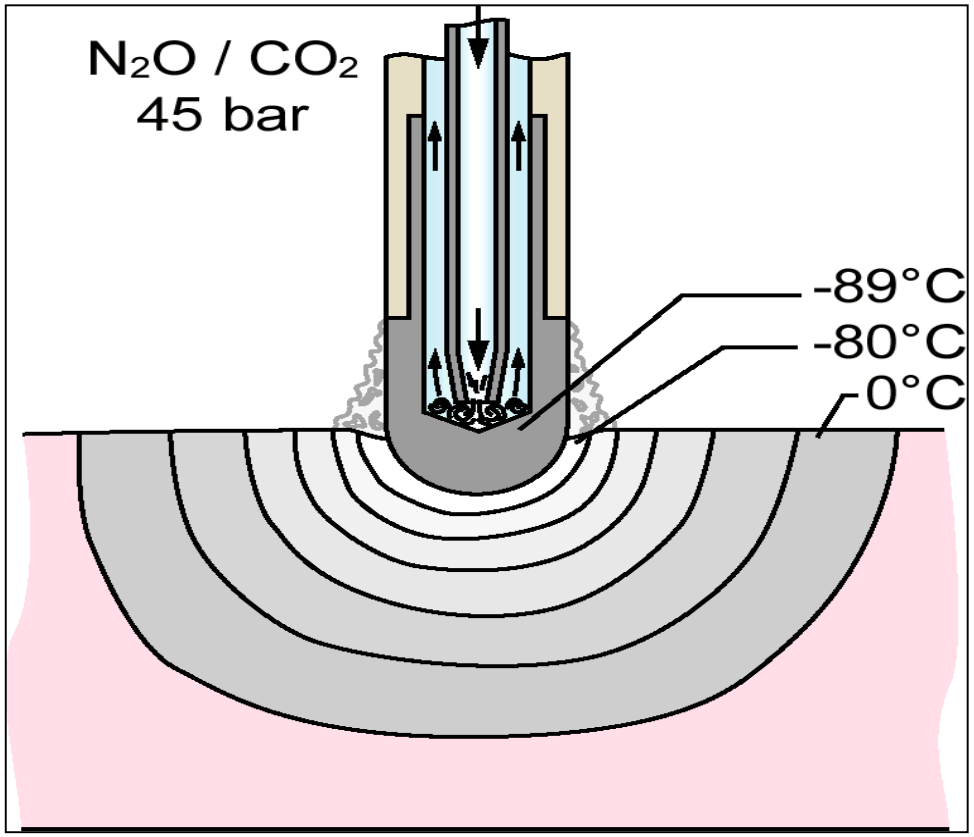


Figure 4 Diagnostic yield of cryobiopsy versus forceps biopsy. Fixed effects model of risk ratio (95% confidence interval). Events—number of patients diagnosed using this technique. Total—number of patients undergoing this technique.

Ganganah et al. Respirology 2016

Transbronchial cryobiopsy

The cooling agent is applied under high pressure (45 bar) through the central canal of the probe



The gas at the tip expands due to the sudden difference in pressure relative to the atmospheric pressure **(Joule-Thomson effect)**, resulting in a drop in temperature at the tip of the probe and subsequent freezing effect

Transbronchial cryobiopsy: Contra indications & complications

Absolute contraindications

- Known bleeding diathesis
- Anticoagulant therapy
- Antiplatelet drug
- Thrombocytopenia (<50x10^{9}/L)

Respiration

Thematic Review Series

Respiration
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Transbronchial Lung Cryobiopsy in Interstitial Lung Diseases: Best Practice

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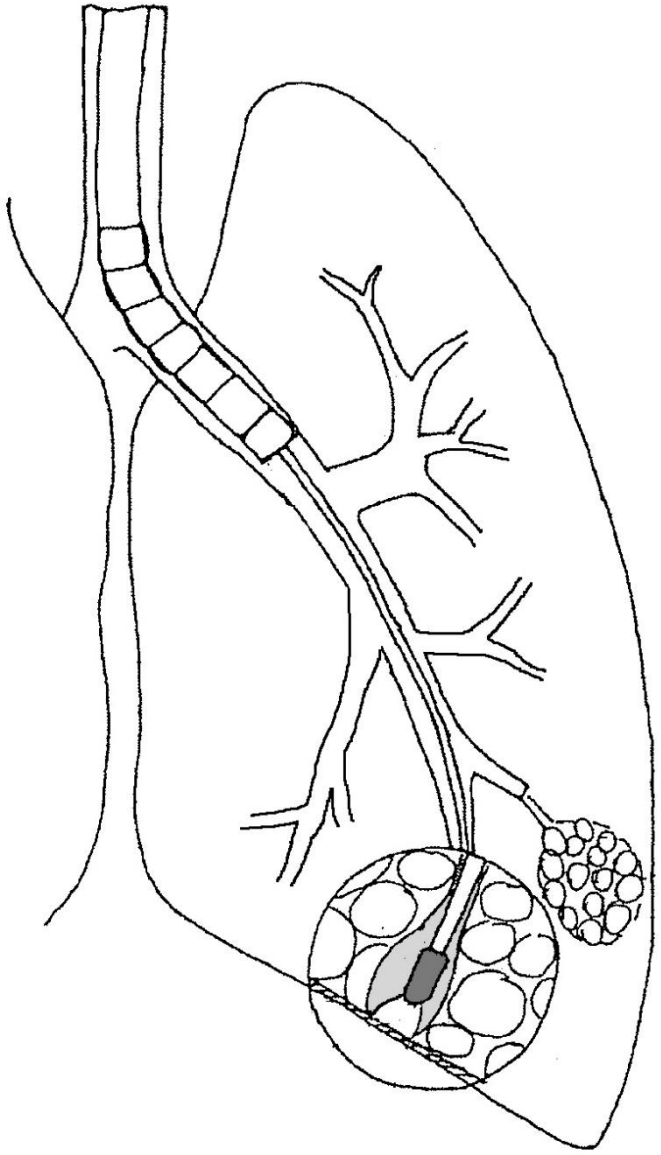
Relative contraindications:

- Rapid decline of pulmonary function
- FVC < 50% , FEV1 < 50% and DLCO < 35%
- RVSP > 50 mmHg
- No age limit is suggested

Complications:

- Pneumothorax (15-25%)
- Severe bleeding
- Acute exacerbation
- Air leak
- Infection

TRANSBRONCHIAL CRYOBIOPSY (MORGAGNI HOSPITAL RECIPE)

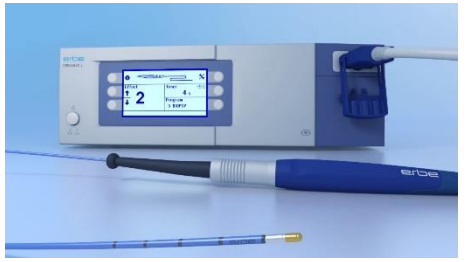


Poletti V; *et al Respirology* 2014

- General anesthesia (Propofol/Remifentanil)
- Spontaneous breathing
- Rigid Tracheochoscope (*Storz* 14 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)
- **Fogarty balloon**
- Fluoroscopic control (+/- radial EBUS)
- Erbokryo CA, ERBE, Tubingen, Germany (CO2)
- Cryoprobe 2.4 mm
- A distance of approximately <= 10 mm from the thoracic wall
- A perpendicular relation between the thoracic wall and the probe
- The probe is cooled for approximately 5-6 s

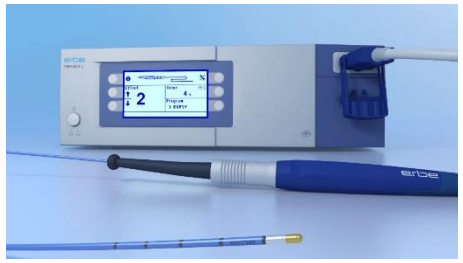
Cryobiopsy: Technical notes

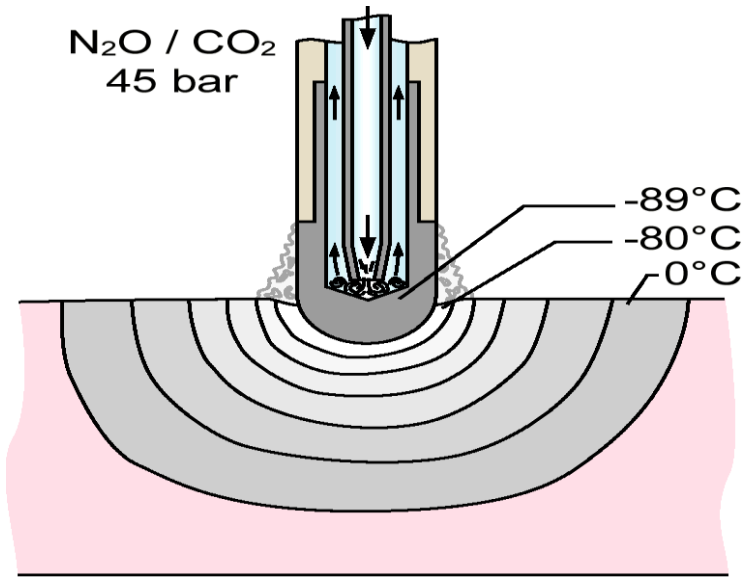
- General anesthesia (Propofol/Remifentanil)
- Rigid Tracheochoscope (*Storz* 14 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)



Cryobiopsy: Technical notes

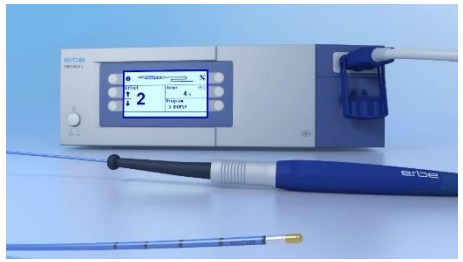
- General anesthesia (Propofol/Remifentanil)
- Rigid Tracheochoscope (*Storz* 14 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)
- Erbokryo CA, ERBE, Tubingen, Germany (CO2)

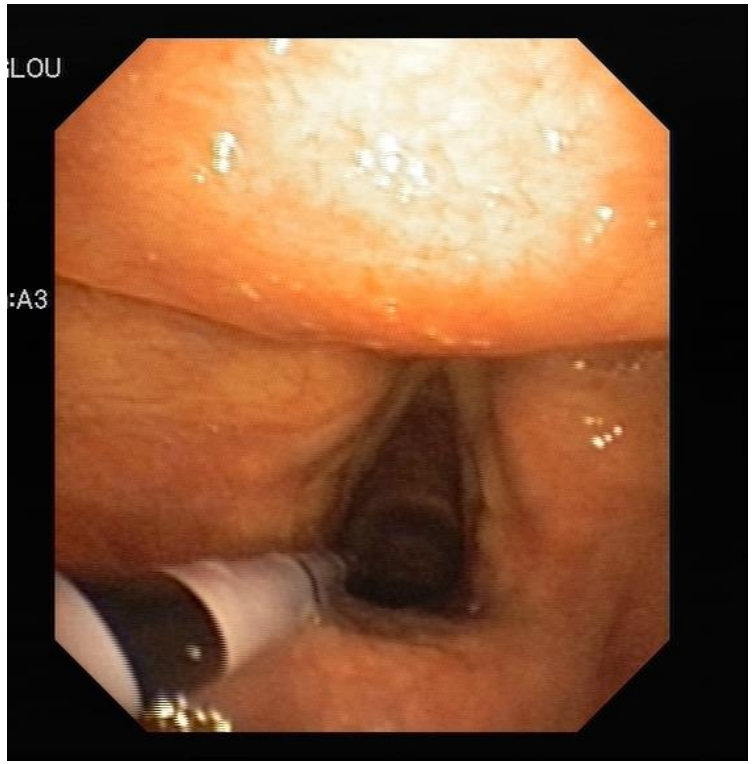




Cryobiopsy: Technical notes

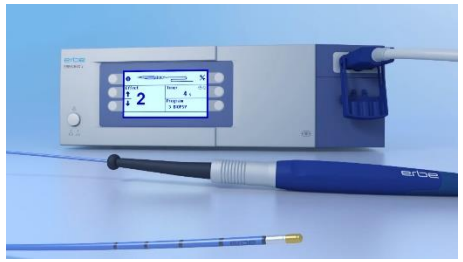
- General anesthesia (Propofol/Remifentanil)
- Rigid Tracheochoscope (*Storz* 14 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)
- Erbokryo CA, ERBE, Tubingen, Germany (CO2)
- **<u>Fogarty balloon</u>**

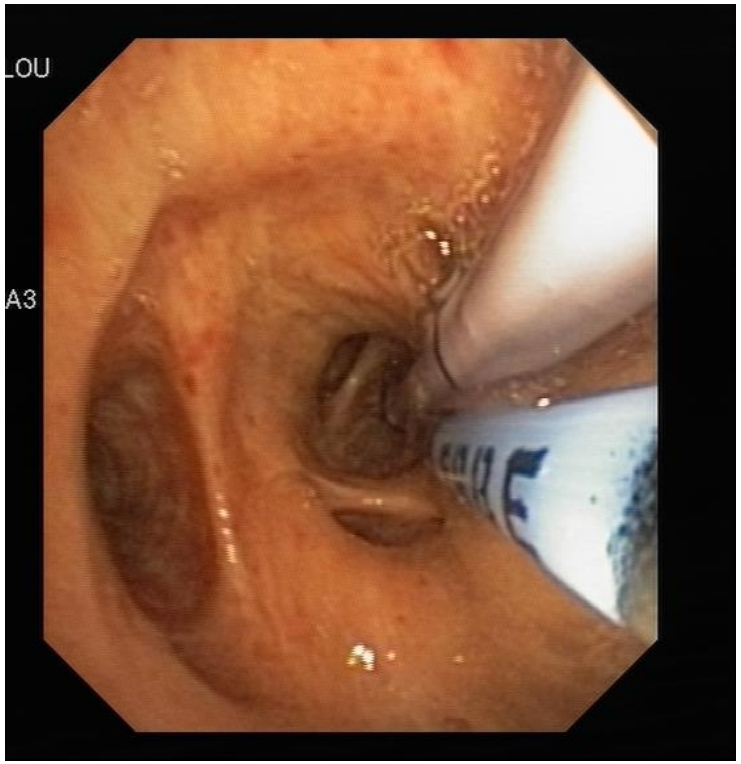


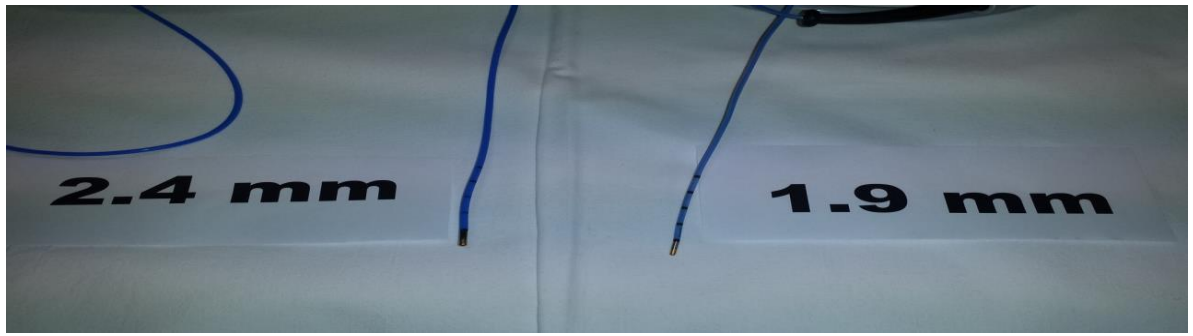


Cryobiopsy: Technical notes

- General anesthesia (Propofol/Remifentanil)
- Rigid Tracheochoscope (*Storz* 14 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)
- Erbokryo CA, ERBE, Tubingen, Germany (CO2)
- **<u>Fogarty balloon</u>**
- Cryoprobe 2.4 mm

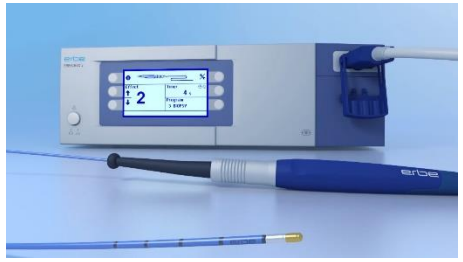


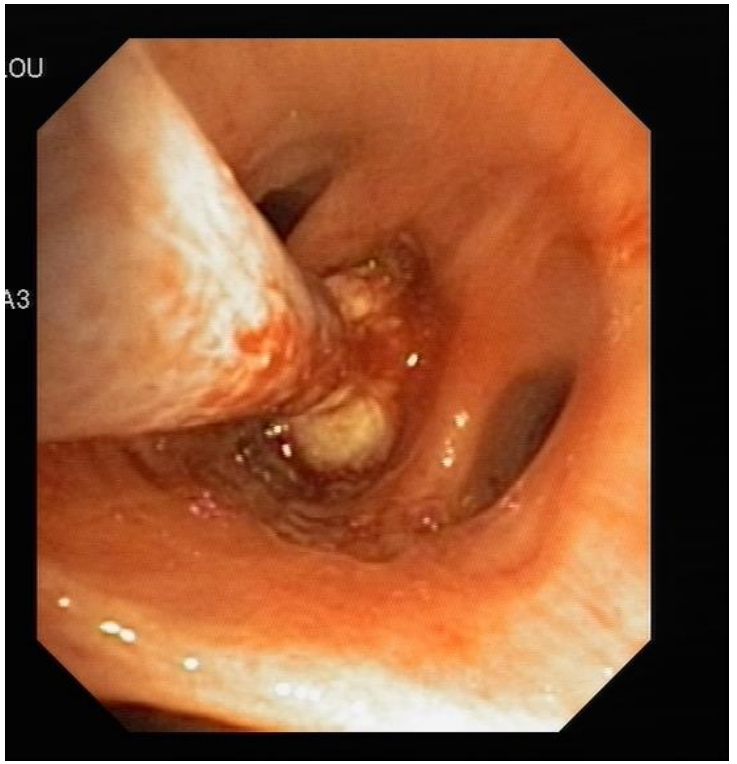




Cryobiopsy: Technical notes

- General anesthesia (Propofol/Remifentanil)
- Rigid Tracheochoscope (*Storz* 14 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)
- Erbokryo CA, ERBE, Tubingen, Germany (CO2)
- **<u>Fogarty balloon</u>**
- Cryoprobe 2.4 mm
- Taking biopsy and inflate the balloon





Cryobiopsy: Technical notes

- General anesthesia (Propofol/Remifentanil)
- Rigid Tracheochoscope (*Storz* 14 mm-33 cm)+fiberoptic bronchoscope (6.2 mm)
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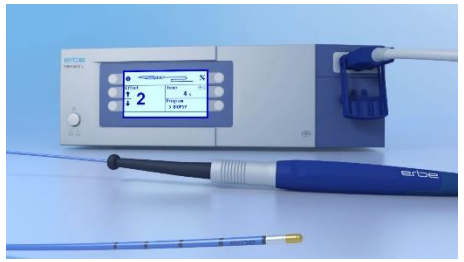
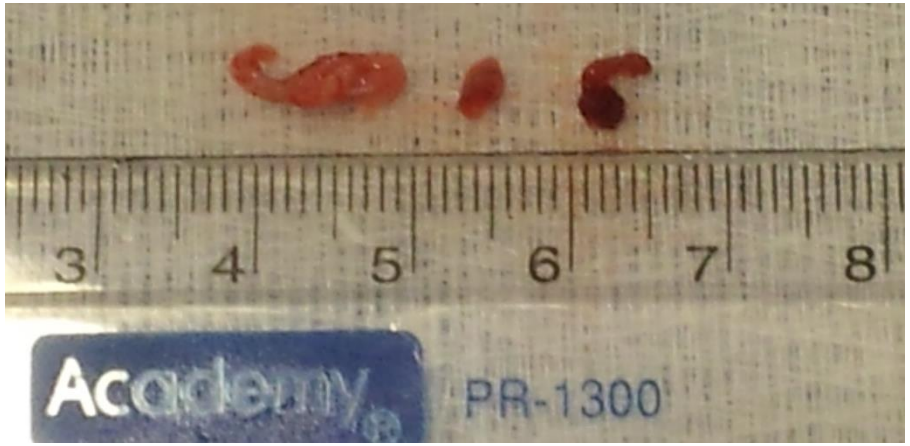
- **Fogarty balloon**
- Cryoprobe 2.4 mm





- Taking biopsy and inflate the balloon
- Carefully handling the specimens

Cryobiopsy: Technical notes

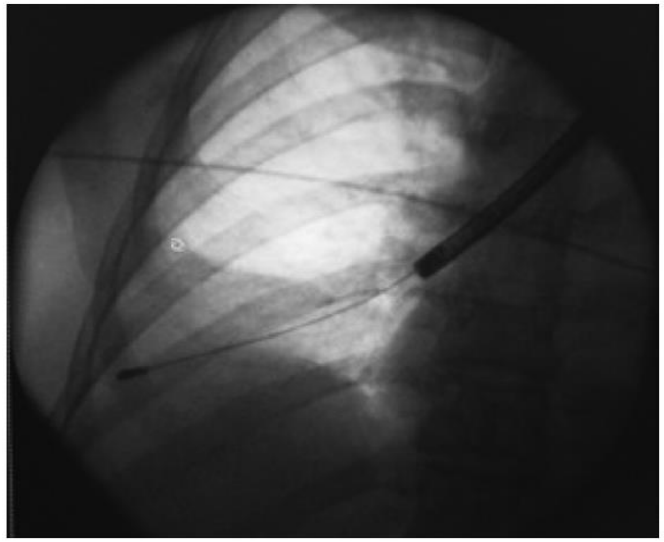


Figure 4.—Fluoroscopic view of the cryoprobe.

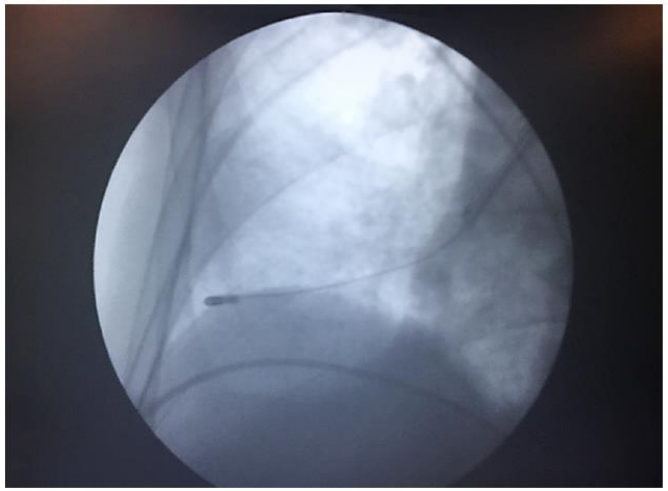


Fig. 4. The probe under fluoroscopic guidance.

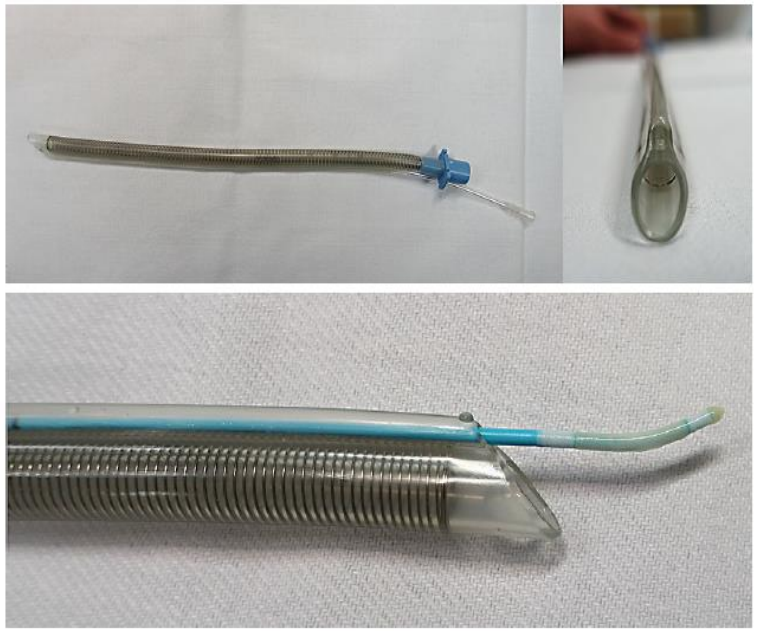


Fig. 3. Flexible tube with extra channel and angulated Fogarty balloon catheter.

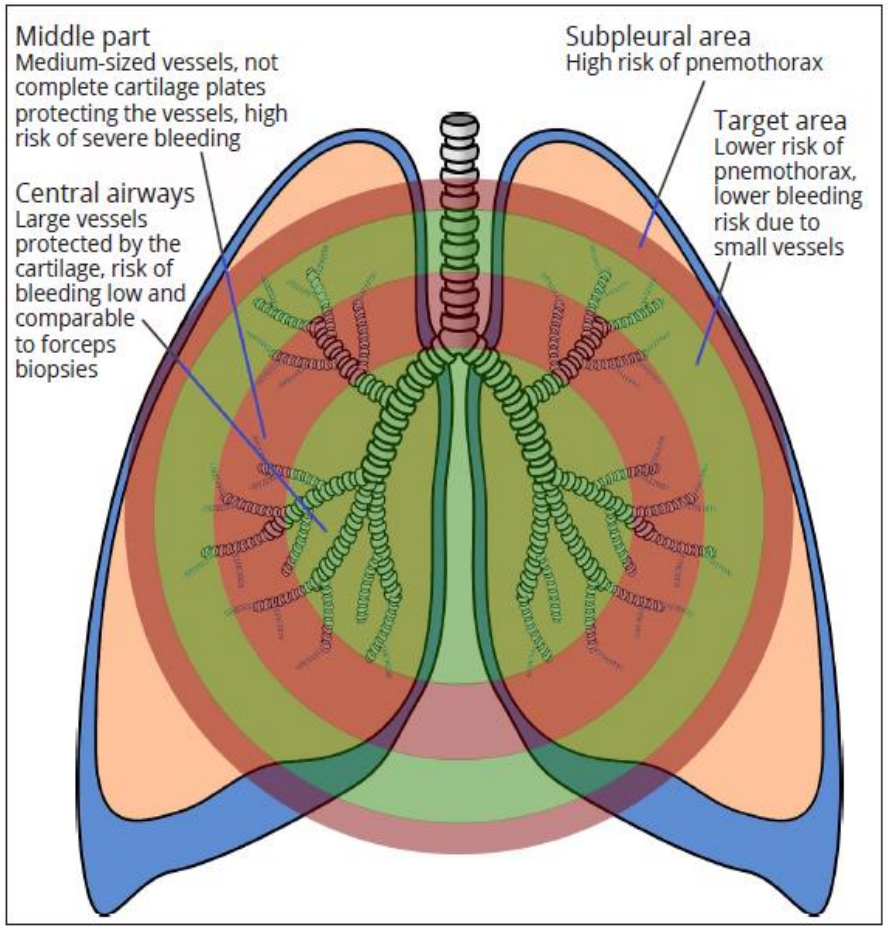


Figure 5.—The biopsies obtained in the periphery of secondary pulmonary lobule are more likely to get appropriate specimens for the histologic diagnosis of UIP. The area to perform the cryobiopsy with lower risk of pneumothorax or bleeding is the Target area. The major risk of pneumothorax is inside the Subpleural area, while the risk of severe bleeding increases if the biopsies are obtained in the middle third of lung.

Transbronchial cryobiopsy: Concerns and newer data

TBCB vs Surgical Biopsy???

Clinical Investigations

Respiration

Respiration
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Safety and Diagnostic Yield of Transbronchial Lung Cryobiopsy in Diffuse Parenchymal Lung Diseases: A Comparative Study versus Video-Assisted Thoracoscopic Lung Biopsy and a Systematic Review of the Literature

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Carlo La Vecchia[i] Stefano Gasparini[e,f] Venerino Poletti[a,o]

Ravaglia C. Respiration 2015

Transbronchial cryobiopsy: Concerns and newer data

TBCB vs Surgical Biopsy???

Cryobiopsy: Diagnostic yield in DPLD

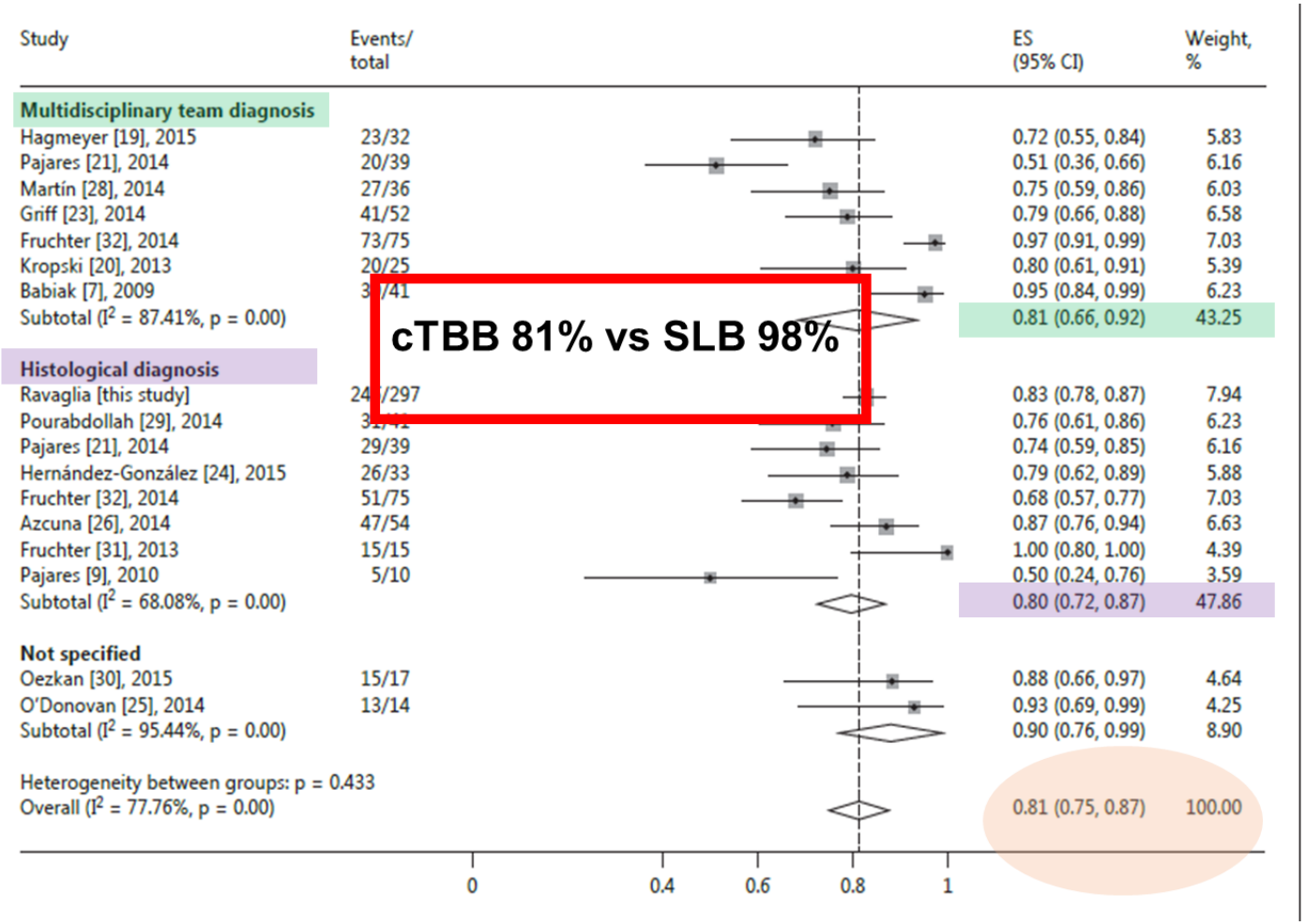

Fig. 2. DY overall and according to diagnostic criteria. ES = Effect size.

Ravaglia C. Respiration 2015

Transbronchial cryobiopsy: Concerns and newer data

TBCB vs Surgical Biopsy???

Cryobiopsy: Safety / Complications

	SLB (VATS) (n = 150)	TBLC (n = 297)	p value
Days of hospitalization	6.1 (3–48)	2.6 (0–17)	*<0.0001*
Adverse events			
Severe bleeding	0 (0.0)	0 (0.0)	
Persistent fever	7 (4.7)	0 (0.0)	
Prolonged air leak	5 (3.3)	1 (0.3)	
Acute exacerbation	5 (3.3)	1 (0.3)	
Pneumonia/empyema	3 (2.0)	0 (0.0)	
Transient respiratory failure	0 (0.0)	2 (0.7)	
Miscellanea	0 (0.0)	2 (0.7)	
Pneumothorax (in total)	NA (NA)	60 (20.20)	
Pneumothorax with drainage	NA (NA)	46 (15.50)	
Days of drainage	3.75 (2–40)	4.65 (2–15)	0.138
Patients with 0 adverse events	131 (87.3)	220 (74.1)	
Patients with 1 adverse event	16 (10.7)	75 (25.3)	
Patients with 2 adverse events	3 (2.0)	1 (0.3)	
Patients with 3 adverse events	0 (0.0)	1 (0.3)	
Time to 1st adverse event after biopsy, days	27.5±73.9	0.6±2.0	*<0.0001*
Mortality due to adverse event	4/150 (2.7)	1/297 (0.3)	*0.045*
	4/20 (20.0)	1/66 (1.5)	*0.01*

Ravaglia C. Respiration 2015

Transbronchial cryobiopsy: Concerns and newer data

TBCB vs Surgical Biopsy???

Am J Respir Crit Care Med. 2019 Mar 13. doi: 10.1164/rccm.201810-1947OC. [Epub ahead of print]

Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases.

Romagnoli M[1], Colby TV[2], Berthet JP[3], Gamez AS[4], Mallet JP[5], Serre I[6], Cancellieri A[7], Cavazza A[8], Solovei L[4], Dell'Amore A[9], Dolci G[9], Guerrieri A[10], Reynaud P[11], Bommart S[4], Zompatori M[12], Dalpiaz G[13], Nava S[14], Trisolini R[15], Suehs CM[16], Vachier I[17], Molinari N[18], Bourdin A[4].

Author information

Abstract

Rationale The diagnostic concordance between transbronchial lung cryobiopsy (TBLC) -- versus surgical lung biopsy (SLB) as the current gold standard -- in interstitial lung disease (ILD) cases requiring histology remains controversial. Objectives To assess diagnostic concordance between TBLC and SLB sequentially performed in the same patients, the diagnostic yield of both techniques, and subsequent changes in multidisciplinary assessment (MDA) decisions. Methods A two-center prospective study included ILD patients with a non-definite usual interstitial pneumonia (UIP) pattern (on HRCT scan) confirmed at a first MDA. Patients underwent TBLC immediately followed by video-assisted thoracoscopy for SLB at the same anatomical locations. After open-reading of both sample types by local pathologists and final diagnosis at a second MDA (MDA2), anonymized TBLC and SLB slides were blindly assessed by an external expert pathologist (TVC). Kappa-concordance coefficients and % agreement were computed for: TBLC-vs-SLB; MDA2-vs-TBLC; MDA2-vs-SLB, and blinded pathology versus routine pathology. Measurements and Main Results Twenty-one patients were included. The median TBLC biopsy size (longest axis) was 7 mm (interquartile range: 5-8). SLB biopsy sizes averaged 46.1 ± 13.8 mm. Concordance coefficients and % agreement were: TBLC-vs-SLB: K=0.22(95%CI: 0.01-0.44), %agreement=38%(95%CI: 18-62); MDA2-vs-TBLC: K=0.31(95%CI: 0.06-0.56), %agreement=48%(95%CI: 26-70); MDA2-vs-SLB: K=0.51(95%CI: 0.27-0.75), %agreement=62%(95%CI: 38-82)); Two pneumothoraces (9.5%) were recorded during TBLC. TBLC would have led to a different treatment if SLB was not performed in 11/21 (52%) of cases. Conclusion Pathological results from TBLC and SLB were poorly concordant in the assessment of ILD. SLBs were more frequently concordant with the final diagnosis retained at MDA.

Transbronchial cryobiopsy: Concerns and newer data

Cryobiopsy: Procedural standardization is needed

Interventional Pulmonology

Respiration

Respiration
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Transbronchial Cryobiopsies for the Diagnosis of Diffuse Parenchymal Lung Diseases: Expert Statement from the Cryobiopsy Working Group on Safety and Utility and a Call for Standardization of the Procedure

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Sara Tomassetti[c] Jay H. Ryu[f] Oren Fruchter[g] Sara Piciucchi[h] Alessandra Dubini[i]
Alberto Cavazza[j] Marco Chilosi[k] Nicola Sverzellati[l] Dominique Valeyre[m] Dimitri Leduc[n]
Simon L.F. Walsh[o] Stefano Gasparini[p] Martin Hetzel[q] Lars Hagmeyer[r] Maik Haentschel[a]
Ralf Eberhardt[s] Kaid Darwiche[t] Lonny B. Yarmus[u] Alfonso Torrego[v] Ganesh Krishna[w]
Pallav L. Shah[x] Jouke T. Annema[y] Felix J.F. Herth[s] Venerino Poletti[c, z]

7. Schleiter KE. Difficult patient-physician relationships and the risk of medical malpractice litigation. *Virtual Mentor.* 2009;11(3):242–246.

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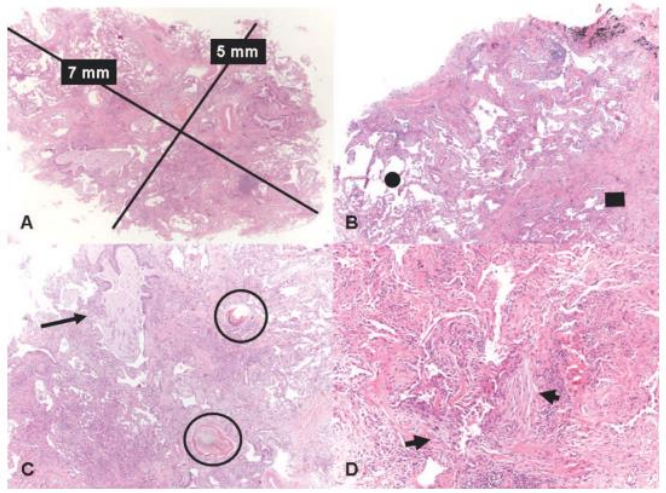
Report Standardization in Transbronchial Lung Cryobiopsy

To the Editor.—Transbronchial lung cryobiopsy (TLCB) is an increasingly accepted modality to obtain lung tissue samples, even in complex fibrotic interstitial lung diseases (ie, usual interstitial pneumonia [UIP] pattern, nonspecific interstitial pneumonia [NSIP] pattern) in which surgical lung biopsy (SLB) was the routine diagnostic approach.[1–3] TLCB is a safe proce-



A transbronchial cryobiopsy specimen with 7 mm × 5 mm in longitudinal and transversal diameters, respectively (A), showing usual interstitial pneumonia pattern with high confidence, characterized by patchy fibrosis consisting of relatively normal lung (B, black dot) abruptly passing to fibrotic tissue (B, black square), honeycombing change (C, arrow) with bone metaplasia (C, circles), and fibroblast foci (D, arrowheads) (hematoxylin-eosin, approximate original magnifications ×40 [A through C] and ×150 [D]).

Transbronchial cryobiopsy: Concerns and newer data

Cryobiopsy: Procedural standardization is needed

First author [Ref.]	Year	OT	RB	LM	NI	GA+JV	GA/DS	LA	Bronchial blocker	Cryoprobe size, mm	Freezing time, s
Babiak [10]	2009	x					x		N	2.4	4
Pajares [11]	2010	x					x		N	2.4	3
Griff [12]	2011		x		x		x	x			
Kropski [13]	2013	x					x			1.9	4
Yarmus [14]	2013		x (10)	x (11)		x	x		Y	1.8	3
Fruchter [15]	2013				x			x	N	2.4	4
Fruchter [16]	2013				x			x	N	2.4	4
Fruchter [17]	2014				x			x	N	2.4	4
Casoni [18]	2014		x				x		Y	2.4	5/6
Pajares [19]	2014	x					x		Y	2.4	3/4
Poletti [7]	2014		x				x		Y	2.4	5/6
Griff [20]	2014		x		x		x	x	N	1.9	3/5
Gershman [22]	2015				x			x	N	2.4	4
Hagmeyer [23]	2015	x	x			x			N	2.4	4/5
Hernández-González [21]	2015	x					x		Y	1.9	3/4

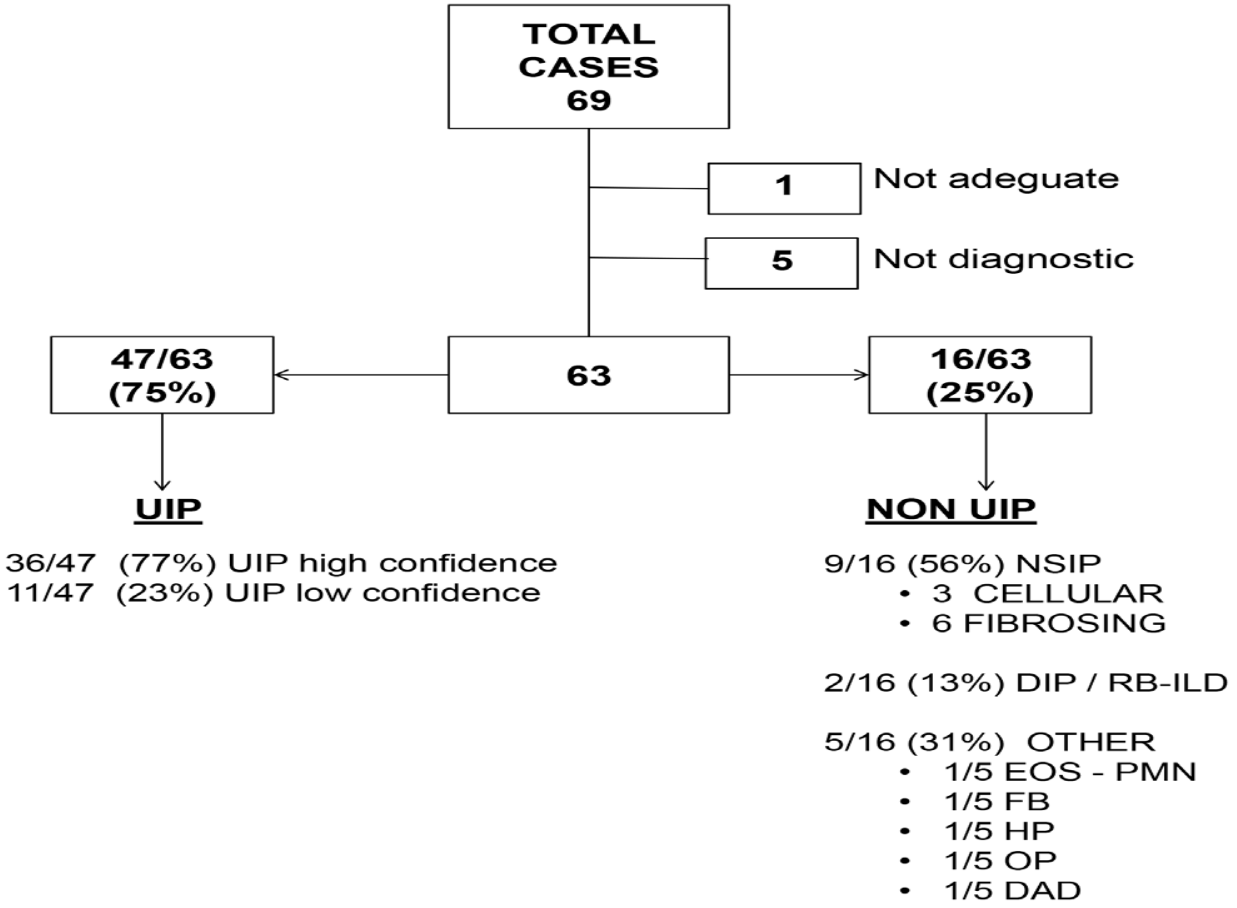
OT = Orotracheal tube; RB = rigid bronchoscope; LM = laryngeal mask; NI = no intubation; GA = general anesthesia; JV = jet ventilation; DS = deep sedation; LA = local anesthesia; Y = yes; N = no; x = method used.

Transbronchial cryobiopsy: Concerns and newer data

OPEN ACCESS Freely available online PLOS ONE

Transbronchial Lung Cryobiopsy in the Diagnosis of Fibrotic Interstitial Lung Diseases

Gian Luca Casoni[1,9], Sara Tomassetti[1,9], Alberto Cavazza[2], Thomas V. Colby[3], Alessandra Dubini[4], Jay H. Ryu[5], Elisa Carretta[6], Paola Tantalocco[1], Sara Piciucchi[7], Claudia Ravaglia[1], Christian Gurioli[1], Micaela Romagnoli[1], Carlo Gurioli[1], Marco Chilosi[8], Venerino Poletti[1]* PlosOne- 2014

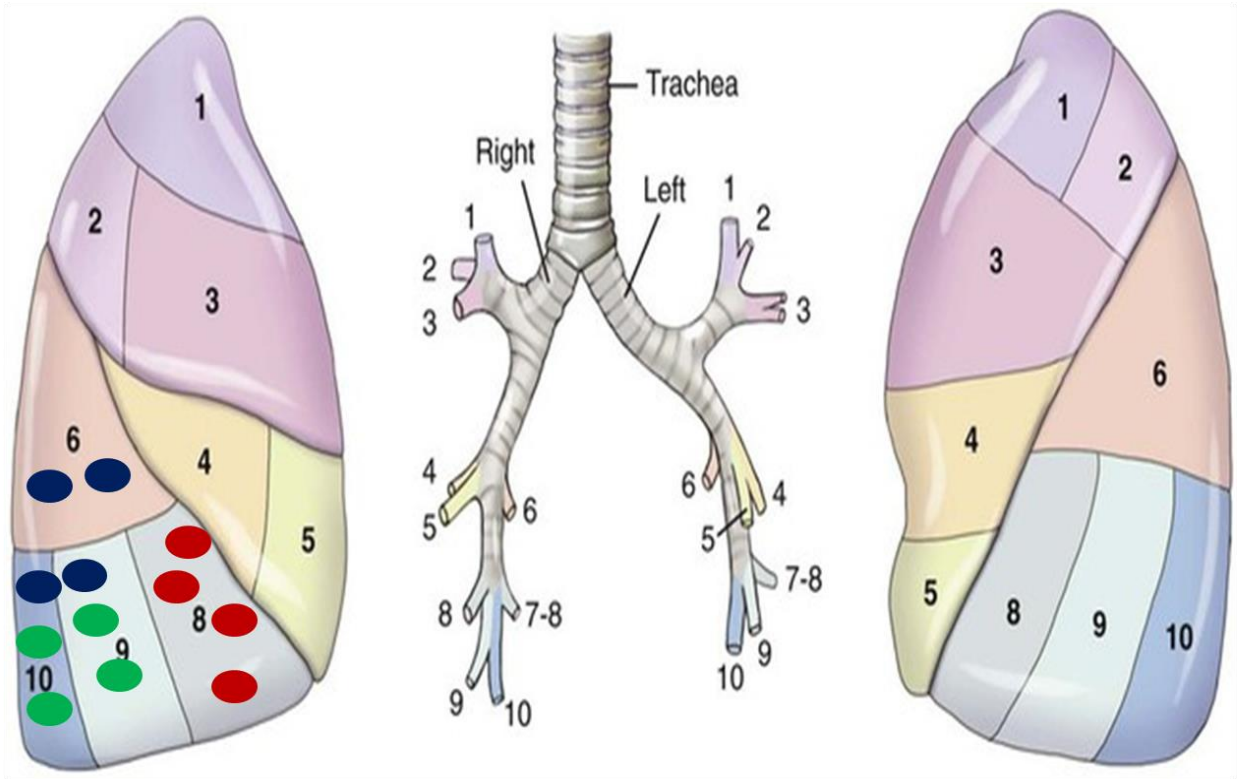


The area of fragments strongly correlates with the diagnostic yield, mean area was 41,99+/-14.73 mm^2 for diagnostic cases and 28.43+/-11.66 mm^2 for non-diagnosticcases, p = 0.038.

Transbronchial cryobiopsy: Concerns and newer data

Cryobiopsy: different strategies

Cryobiopsy: Procedural standardization is needed



Cryobiopsy: different strategies

Transbronchial lung cryobiopsy in diffuse parenchymal lung disease: comparison between biopsies in one segment or biopsies in two segments

[1]Claudia Ravaglia, [1]Sara Tomassetti, [2]Athol U Wells, [3]Alessandra Dubini, [4]Alberto Cavazza, [5]Sara Piciucchi, [6]Nicola Sverzellati, [1]Carlo Gurioli, [7]Ulrich Costabel, [1]Paola Tantalocco, [8]Jay H Ryu, [9]Marco Chilosi, [10]Angelo Carloni, [1,11]Venerino Poletti

Cryobiopsy: different strategies

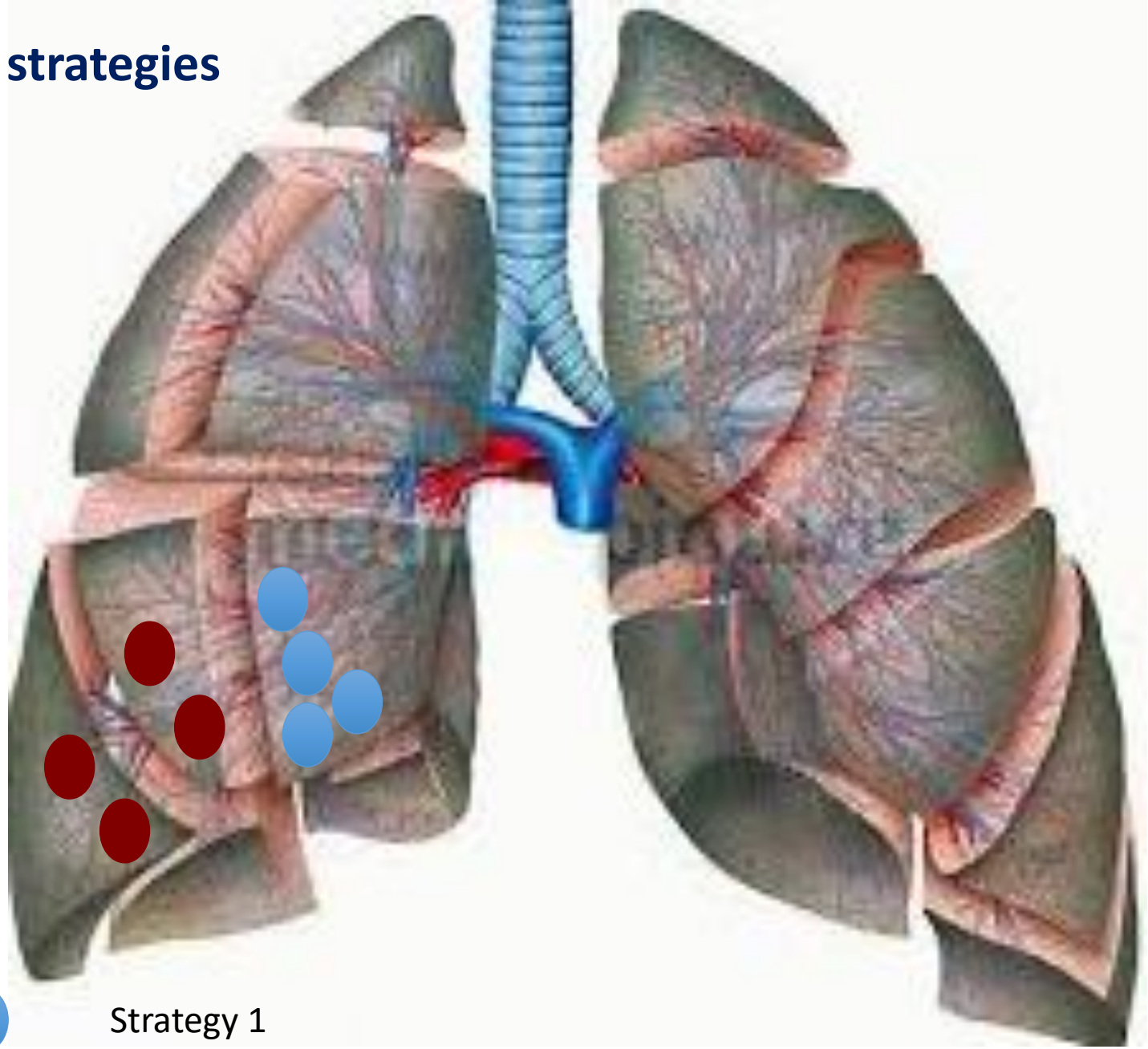
Study design

In the first arm **(arm 1) four samples from the same segment** were obtained ; in the second arm **(arm 2) two samples from one segment and two other samples from another segment of the same lobe were taken.**

In order to assess the minimum number of samples needed to reach a morphological diagnosis each cryobiopsy sample was processed individually.

Analysis of samples by pathologists was performed in a sequential way (from the first to the last sample) providing the identification of a pattern, or of characteristic morphologic features or, in the worse scenario, just a descriptive report for any single sample analyzed. Adding the next sample on top pathologists were also required to reformulate the report.

Cryobiopsy: different strategies



Strategy 1

Strategy 2

Cryobiopsy: different strategies

Table 4.

	I° sample	II° sample	III° sample	IV° sample
GROUP A				
UIP	**3**		**1**	
PF + FF + HC	1			
PF + FF	2		1	
GROUP B				
UIP	**5**	**1**	**4**	**1**
PF + FF + HC	3	1	1	
PF + FF + HC + ancillary findings of HP	0		1	1
PF + FF	2		2	

Ravaglia et al. BMC Pulmonary Medicine (2019) 19:16
https://doi.org/10.1186/s12890-019-0780-3

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients

Claudia Ravaglia[1*], Athol U. Wells[2], Sara Tomassetti[1,1], Carlo Gurioli[1], Christian Gurioli[1], Alessandra Dubini[3,3], Alberto Cavazza[4], Thomas V. Colby[5], Sara Piciucchi[6], Silvia Puglisi[1], Marcello Bosi[1] and Venerino Poletti[1,7]

Background: Standardization of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases is imminent; however, the majority of published series on cryobiopsy include a limited number of patients and are characterized by several differences in procedural technical details.

Methods: This is an observational, retrospective cohort study. Aim of the study was to suggest some sampling strategies related to transbronchial cryobiopsy in the diagnostic work-up of patients with diffuse parenchymal lung diseases.

Results: Six hundred ninety-nine patients with suspected diffuse parenchymal lung disease were recruited. A specific pathological diagnosis was achieved in 614/699 cases (87.8%) and a multidisciplinary diagnosis was obtained in 630/699 cases (90.1%). Diagnostic yield was significantly influenced by the number of samples taken (1 vs ≥ 2 biopsies, $p < 0.005$). In 60.4% of patients, biopsies were taken from one site and in 39.6% from different sites (in the same lobe or in two different lobes), with a significant increase in diagnostic yield, specifically in patients with fibrotic lung diseases (65.5% vs 93.4%, $p < 0.0001$). The 2.4 mm or 1.9 mm probes were used, with no differences in terms of diagnostic yield. Regarding safety, pneumothorax occurred in 19.2% and was influenced by baseline lung function; in all patients Fogarty balloon has been used and severe haemorrhage occurred in 0.7% of cases. Three patients (0.4% of cases) died within 30 days after the procedure.

Conclusions: We propose some sampling strategies of cryobiopsy which seem to be associated with a higher diagnostic yield and a favorable risk/benefit ratio: sampling at least two samples in different sites, using either the 2.4 mm or the 1.9 mm probe, intubating the patients and using bronchial blockers/catheters.

Table 1 Clinical characteristics, diagnostic yield and complications in patients submitted to trans-bronchial lung cryobiopsy (TLCB)

Patient characteristic (tot 699)	No. (% or SD)
Median age (SD), y	61 (11)
Male, No. (%)	413 (59.1%)
Mean FVC percent predicted (SD)	85.4 (19.7)
Mean DLCO percent predicted (SD)	61.2 (17.5)
Pathological diagnosis, No. (%)	614 (87.8)
Multidisciplinary diagnosis, No. (%)	630 (90.1)
Pneumothorax, No. (%)	134 (19.2)
Drained Pneumothorax (among those with pneumothorax), No. (%)	94 (70.1)
Mild bleeding, No. (%)	29 (4.1)
Moderate bleeding, No. (%)	53 (7.6)
Severe bleeding, No. (%)	5 (0.7%)

Ravaglia et al. BMC Pulmonary Medicine (2019) 19:16
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Table 8 Correlation between safety profile and baseline lung function

	Pneumothorax	No pneumothorax	Mann-Whitney test
FVC	80.9% (41–137)	86,6% (38–143)	p 0,0079
DLCO	58,2% (25–109)	61,9% (14–129)	p 0,0331
	Bleeding	No bleeding	Mann-Whitney test
FVC	85.9% (44–128)	85.6% (38–143)	0,8909
DLCO	61.4% (26–99)	61.4% (18–129)	0,9469

Table 7 Safety outcome

Side effects	No. (%)
Pneumothorax	134 (19.2%) - 94 drained
Bleeding	87 (12.4%) - 29 mild bleeding - 53 moderate bleeding - 5 severe bleeding
Other side effects	9 (1.3%) - 4 transient respiratory failure - 1 empyema - 1 seizures - 1 atrial fibrillation - 1 pneumomediastinum - 1 haemoptysis
Death	3 (0.4%) - 2 for AE-IPF - 1 thrombotic neoplastic microangiopathy/ carcinomatous lymphangitis

Ravaglia et al. BMC Pulmonary Medicine (2019) 19:16
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BMC Pulmonary Medicine

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Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients

Claudia Ravaglia[1*], Athol U. Wells[2], Sara Tomassetti[1,1], Carlo Gurioli[1], Christian Gurioli[1], Alessandra Dubini[3,3], Alberto Cavazza[4], Thomas V. Colby[5], Sara Piciucchi[6], Silvia Puglisi[1], Marcello Bosi[1] and Venerino Poletti[1,7]

Conclusions: We propose some sampling strategies of cryobiopsy which seem to be associated with a higher diagnostic yield and a favorable risk/benefit ratio: sampling at least two samples in different sites, using either the 2.4 mm or the 1.9 mm probe, intubating the patients and using bronchial blockers/catheters.

Table 6 Differences in terms of safety outcome and diagnostic yield between different sampling strategies

	1 site	2 sites	Fisher's exact test
Pneumothorax	64/420 (15.2%)	66/268 (24.6%)	p 0,002
Bleeding	51/418 (12.2%)	32/266 (12.0%)	p 0,947
Pathological diagnosis	358/422 (84.8%)	247/267 (92.5%)	p 0,001
Multidisciplinary diagnosis	373/422 (88.4%)	248/267 (92.9%)	p 0,043
	1 lobe	Different lobes	Fisher's exact test
Pneumothorax	36/166 (21.7%)	30/102 (29.4%)	p 0,083
Bleeding	19/166 (11.4%)	13/100 (13%)	p 0,7112
Pathological diagnosis	155/166 (93.4%)	92/101 (91.1%)	p 0,5081
linary diagnosis	156/166 (93.9%)	92/101 (91.1%)	p 0,3967
	Upper lobes (a)	Lower lobes (a)	Fisher's exact test
Pneumothorax	4/80 (5%)	57/298 (19.1%)	p 0,00004
Bleeding	5/78 (6.4%)	42/298 (14.1%)	p 0,0270
	1.9 probe	2.4 probe	Fisher's exact test
Pneumothorax	2/73 (2.7%)	130/613 (21.2%)	p < 0,0001
Bleeding	8/73 (10.9%)	78/611 (12.8%)	p 0,6460
Pathological diagnosis	62/73 (84.9%)	541/615 (87.9%)	p 0,4936
Multidisciplinary diagnosis	62/63 (84.9%)	557/615 (90.6%)	p 0,2014

(a) Cases in which biopsies were performed in the middle lobe or lingula or when it was not possible to establish the exact site of the biopsy were excluded

Tranbronchial cryobiopsy and freezing time

Respiration

Respiration 2016;92:34–39
DOI: 10.1159/000447329

Evaluation of Transbronchial Lung Cryobiopsy Size and Freezing Time: A Prognostic Animal Study

Matthew Ing[a] Rema A. Oliver[b] Brian G.G. Oliver[c] William R. Walsh[b]
Jonathan P. Williamson[d]

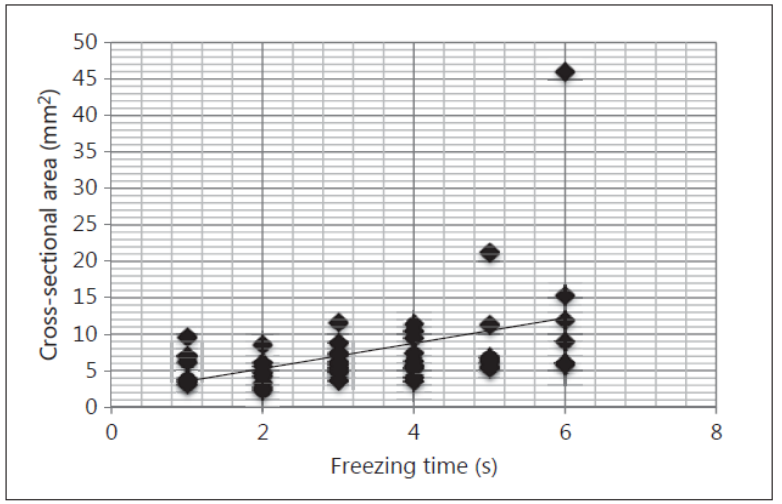

Fig. 1. Correlation between freezing time and transbronchial cryobiopsy cross-sectional area.

Table 1. Transbronchial cryobiopsy cross-sectional area

	Cryoprobe freezing time, s					
	1	2	3	4	5	6
Number of biopsies	8	8	11	9	7	6
Cross-sectional area, mm^2	5.5	4.7	6.5	7.1	9.0	15.7
Standard deviation	2.3	2.1	2.2	2.8	5.7	15.3

Table 2. Complications associated with freezing times

Complications	Freezing time, s					
	1	2	3	4	5	6
Haemorrhage						
Grade 0	4 (50)	3 (38)	2 (18)	4 (44)	2 (29)	3 (50)
Grade 1	4 (50)	5 (62)	9 (82)	5 (56)	5 (71)	2 (33)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	1 (17)
Pneumothorax	Nil	1	Nil	Nil	1	1

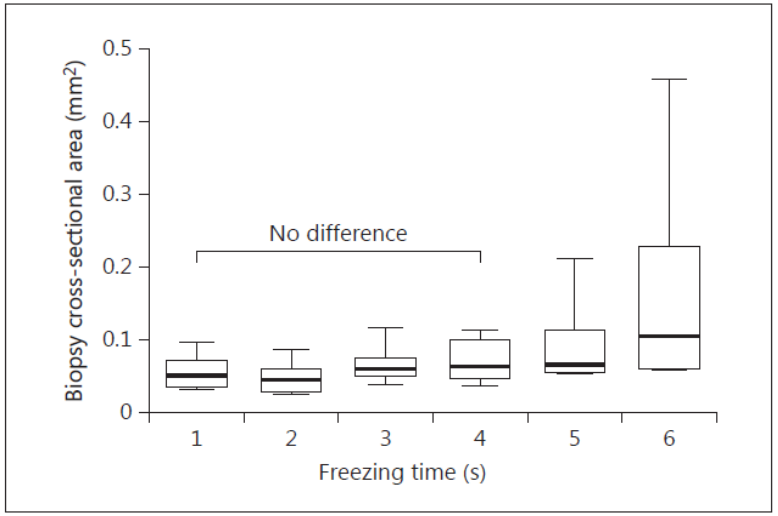

Fig. 2. Comparison of cross-sectional area of different freezing times.

Tranbronchial cryobiopsy and and bleeding

Hetzel et al. Respiratory Research (2019) 20:140
https://doi.org/10.1186/s12931-019-1091-1

Respiratory Research

RESEARCH Open Access

Bleeding risk of transbronchial cryobiopsy compared to transbronchial forceps biopsy in interstitial lung disease – a prospective, randomized, multicentre cross-over trial

Juergen Hetzel[1*], Ralf Eberhardt[2], Christoph Petermann[3], Wolfgang Gesierich[4], Kaid Darwiche[5], Lars Hagmeyer[6],

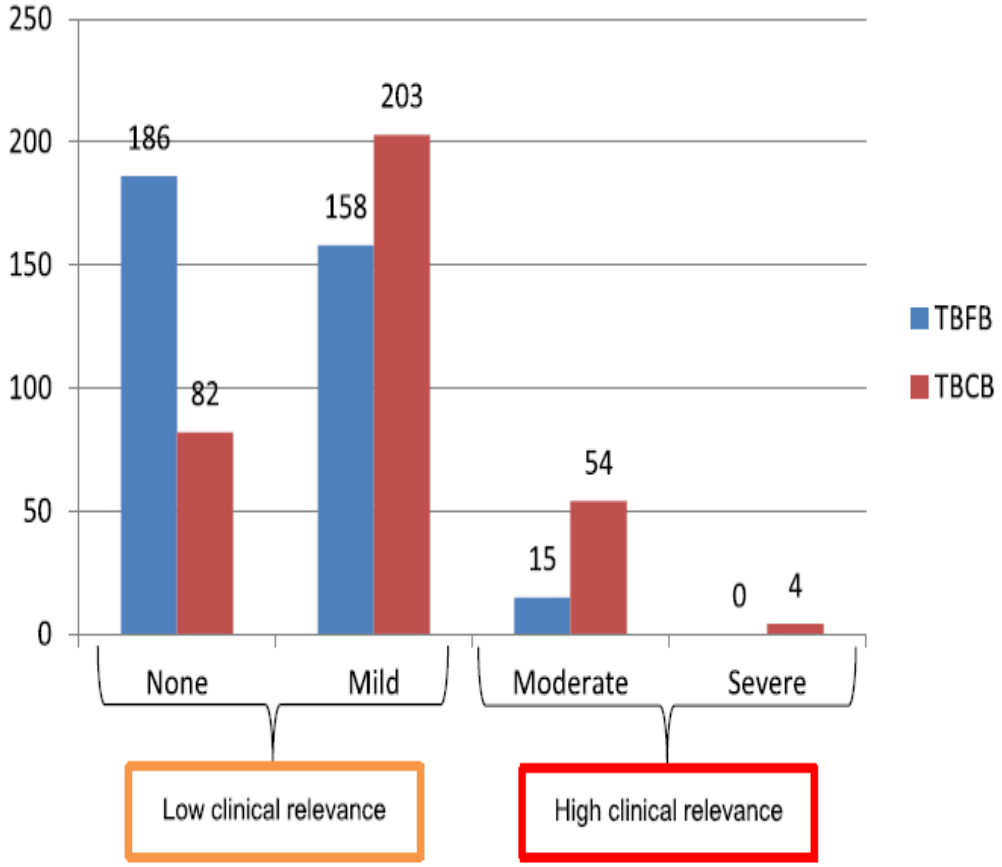

Fig. 2 Severity of biopsy-related bleeding, comparing both techniques.
(TBCB – transbronchial lung cryobiopsy; TBFB – transbronchial lung forceps biopsy)

Table 6 Influence of the size of the cryoprobe and patient's height on clinical relevance of bleeding

Relevant bleeding/Non- rel. Bleeding (%)		Patient's height	
		=< 170 cm	> 170 cm
Size of cryo probe	Small (1.9 mm)	17.2	8.3
	Large (2.4 mm)	45.3	12.3

Tranbronchial cryobiopsy and pneumothorax

Rev Port Pneumol. 2017;23(6):331–337

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portuguese journal of pulmonology
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ORIGINAL ARTICLE

Transbronchial lung cryobiopsy: Associated complications

R. Linhas[a,*], R. Marçôa[a], A. Oliveira[a,b], J. Almeida[a,b], S. Neves[a,b,c], S. Campainha[a,b,c]

Table 2 Adverse events.

Pneumothorax total [n (%)]	22 (22.4)
Pneumothorax requiring drainage [n (%)]	18 (20)
Prolonged air leak[a] [n (%)]	1 (2)
Days of drainage [median (IQR)]	1 (2)
Bleeding [n (%)]	
Grade 2	8 (8.9)
Grade 3	5 (5.6)
Grade 4	0 (0)
Transient respiratory failure [n (%)]	2 (2.2)

[a] Defined as an air leak persisting beyond the first week.[25]

Table 3 Risk factors for pneumothorax.

	Pneumothorax ($n = 22$; 22.4%)	No pneumothorax ($n = 68$; 75.6%)	p
Gender [n (%)]			
Male	9 (17)	44 (83)	0.049
Female	13 (35.1)	24 (64.9)	
Age, years [mean (SD)]	61 (15)	60 (12)	0.803
BMC, kg/m^2 [median (IQR)]	30.00 (5.42)	28.85 (7.66)	0.416
Height, cm [mean (SD)]	161 (12)	165 (9)	0.221
FVC % of predicted [median (IQR)]	78 (22)	88 (30)	0.129
DLCO % of predicted [mean (SD)]	61 (17)	65 (18)	0.333
Number of bronchopulmonary segments undergoing biopsy [n (%)]			
≥2 segments	5 (68.8)	11 (31.3)	0.527
1 segment	17 (23)	57 (77)	
Number of fragments per patient [median (IQR)]	4 (2)	4 (1)	0.607
Number of lobes undergoing biopsy [n (%)]			
≥2 lobes	3 (27.3)	8 (72.7)	1
1 lobe	19 (24.1)	60 (75.9)	
Mean size of the specimens, mm [median (IQR)]	4 (1.4)	4 (1)	0.986
Size of all specimens per patient (sum of the major diameter of each sample), mm [mean (SD)]	16 (5)	16 (5)	0.705
Presence of visceral pleura in the sample [n (%)]			
Yes	12 (60)	8 (40)	<0.001
No	10 (14.3)	60 (85.7)	
Interlobular septal thickening + honeycombing + traction bronchiectasis in HRCT [n (%)]			
Yes	2 (13.3)	13 (86.7)	0.343
No	20 (26.7)	55 (73.3)	
UIP/possible UIP histology [n (%)]			
Yes	1 (5.6)	17 (94.4)	0.062
No	21 (29.2)	51 (70.8)	
ILD associated to tobacco [n (%)][a]			
Yes	0 (0)	9 (100)	0.106
No	22 (27.2)	59 (72.8)	
Fibrotic histology [n (%)]			
Yes	2 (9.5)	19 (90.5)	0.086
No	20 (29)	49 (71)	

Tranbronchial cryobiopsy in non interstitial diseases

Respiration

Respiration 2017;94:285–292
DOI: 10.1159/000478786

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
Mycobacterium tuberculosis 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	–
Mycobacterium avium complex	1	100.0	0	0.0	1		–
Fungal	13	92.9	6	42.9	14		<0.05
Pneumocystis jirovecii	7	87.5	5	6.3	8	Immunofluorescence microscopy	–
Histoplasma capsulatum	4	100.0	1	25.0	4	Culture and microscopy	–
Aspergillus sp.	1	100.0	0	0.0	1		–
Cladophialophora sp.	1	100.0	0	0.0	1		–
Pyogenic	3	27.3	8	72.7	11		0.054
Acinetobacter baumannii	0	0.0	2	100.0	2	Culture and Vitek®2	–
Haemophilus influenzae	1	50.0	1	50.0	2		
Branhamella catarrhalis	0	0.0	1	100.0	1		–
Pseudomonas putida	0	0.0	1	100.0	1		–
Anaerobes	0	0.0	1	100.0	1		–
Pseudomonas aeruginosa	1	50.0	1	50.0	2		–
Streptococcus pneumoniae	0	0.0	1	100.0	1		–
Stenotrophomonas maltophilia	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		–
Entamoeba sp.	1	100.0	0	0.0	1	Microscopy	–
Total etiologic agents	35	72.9	20	41.7	48		<0.05

Table 2. Diagnostic yield for sample type and diagnostic group

Diagnostic group	BAL			TLCB			p value[c]
	n	total	%	n	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.

Table 4. Diagnoses of malignancy according to the sampling type

Malignant diagnostic group	BAL (n = 33)			TLCB (n = 38)			p value[a]
	n	total	%	n	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

cancers

MDPI

Article

Safety and Usefulness of Cryobiopsy and Stamp Cytology for the Diagnosis of Peripheral Pulmonary Lesions

Cancers 2019, *11*, 410; doi:10.3390/cancers11030410

Tatsuya Imabayashi, Junji Uchino *, Akihiro Yoshimura, Yusuke Chihara, Nobuyo Tamiya, Yoshiko Kaneko, Tadaaki Yamada and Koichi Takayama

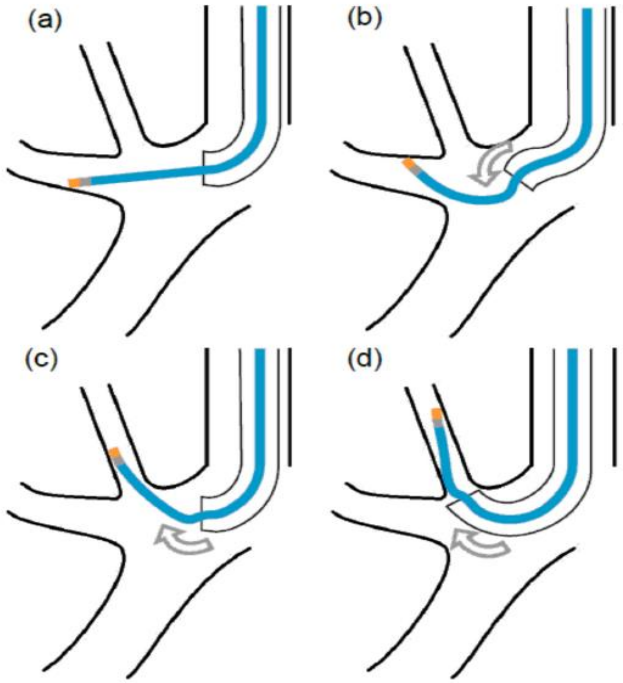


Figure 2. The cryoprobe bending method for peripheral pulmonary lesions. (**a**) When the cryoprobe has been bent as far as possible toward the lung apex, (**b**) the scope is bent in a down angle. (**c**) The shape memory property of the probe can be used to push it completely toward the lung apex. (**d**) Forward feeding of the cryoprobe instead of a guidewire, with simultaneous advancement of the scope, enables the confirmation of probe entry into the correct bronchus.

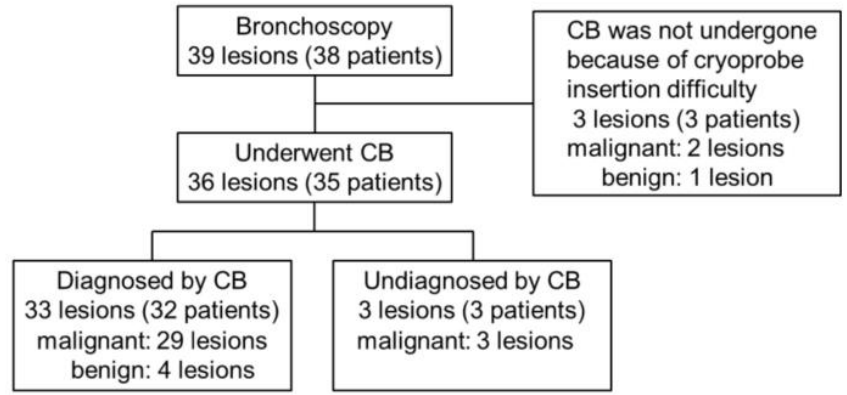


Figure 1. Flow diagram showing the results of cryobiopsy (CB) in 35 patients with peripheral pulmonary lesions.

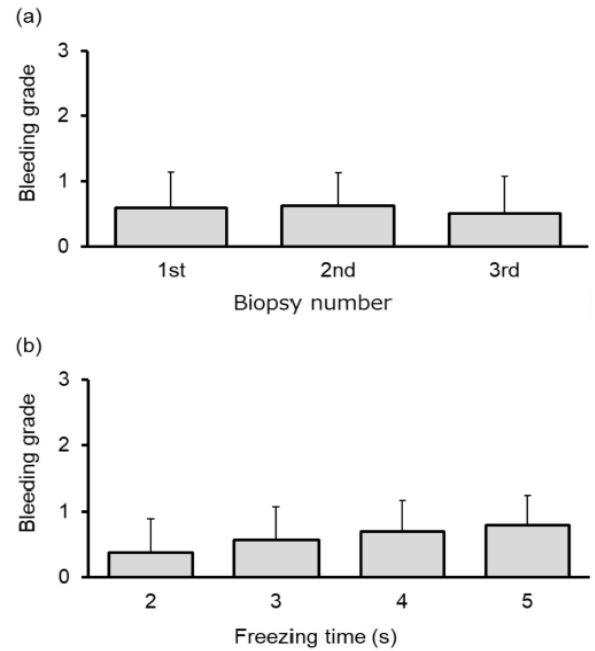


Figure 4. Severity (grade) of bleeding according to (**a**) the cryobiopsy number (first, second, third) and (**b**) the freezing time during cryobiopsy (2-, 3-, 4- and 5-s) in patients with peripheral pulmonary lesions. The severity of bleeding did not differ according to the number of biopsies ($p = 0.913$; Figure 4a) or the freezing time ($p = 0.451$; Figure 4b).

Transbronchial cryobiopsy: Future perspectives?

Review Article of Interventional Pulmonology Corner

The value of using radial endobronchial ultrasound to guide transbronchial lung cryobiopsy

Ankit Gupta[1], Houssein Youness[2], Samjot Singh Dhillon[3], Kassem Harris[4]

Transbronchial cryobiopsy: Future perspectives?

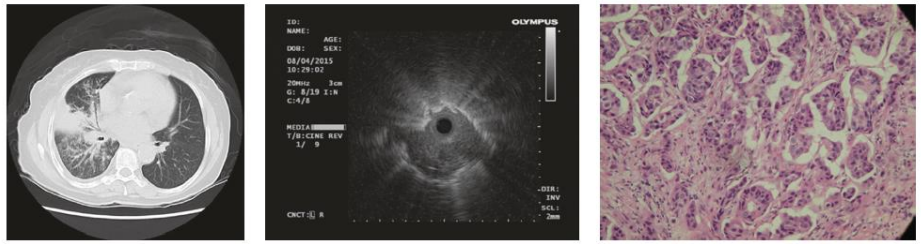
Hindawi
Canadian Respiratory Journal
Volume 2017, Article ID 7170687, 5 pages
https://doi.org/10.1155/2017/7170687

Research Article

Feasibility of Radial Endobronchial Ultrasound-Guided Bronchoscopic Cryobiopsy without Fluoroscopy for Lung Parenchymal Lesions

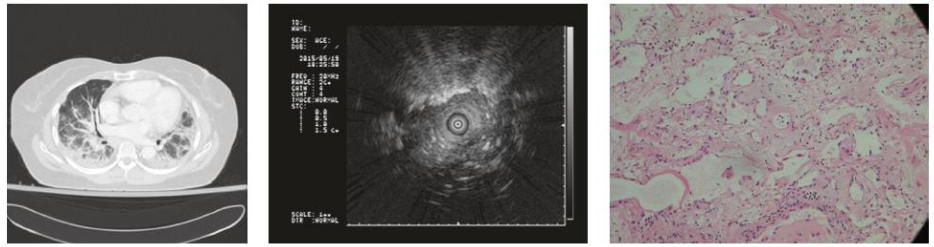
Chih-Hao Chang,[1,2] Chung-Shu Lee,[1,2] Shih-Hong Li,[1] Fu-Tsai Chung,[1] Chih-Wei Wang,[3] Yu-Hsiang Juan,[4] Han-Chung Hu,[1] Li-Fu Li,[1] Ning-Hung Chen,[1] Cheng-Ta Yang,[1] and Kuo-Chin Kao[1]

Background. Cryobiopsy is used to biopsy peripheral lung lesions through flexible bronchoscopy with fluoroscopic guidance. However, fluoroscopy is not available at some institutions. This study evaluated the feasibility of radial endobronchial ultrasound-guided bronchoscopic cryobiopsy without fluoroscopy. *Methods.* This retrospective study was conducted at Chang Gung Memorial Hospital, Linkou branch, in Taiwan. This study enrolled patients who received bronchoscopy examinations with cryotechnology between July 2014 and June 2016. The data were collected through medical chart review. *Results.* During the study period, 101 patients underwent bronchoscopy examinations with cryotechnology. Ninety patients with endobronchial tumors were excluded from this study. Eleven patients who underwent radial endobronchial ultrasound-guided bronchoscopic cryobiopsy for lung parenchymal lesions were enrolled into this study. The mean age was 61.1 ± 13.8 years. Five patients were men, and the other six were women. The number of cryobiopsies ranged from 1 to 3. In the histological biopsies, the mean specimen diameter was 0.53 ± 0.23 cm, and the mean biopsy area was 0.20 ± 0.19 cm^2. Nine of 11 patients had pathological diagnoses. No complications, including pneumothorax, respiratory failure, or major bleeding, were recorded after the procedure. *Conclusions.* Endobronchial ultrasound is used to ensure biopsy location, and endobronchial ultrasound-guided cryobiopsy is a feasible technique to biopsy peripheral lung lesions in selected cases at institutions without fluoroscopy equipment. This study provided some rationale for further studies examining the impact of fluoroscopy.



(a) (b) (c)

FIGURE 1: A 73-year-old female received cryobiopsy from right middle lobe showing correlation among the axial CT image, radial endobronchial ultrasound (EBUS) image, and histopathologic finding from biopsy. (a) Axial CT image in lung window demonstrated a right hilar mass with partial obstructive pneumonitis and numerous tiny ipsilateral lung nodules. (b) EBUS showed a heterogeneous echogenicity lesion with a continuous margin, and the probe was within the lung lesion (eccentric radial EBUS image). (c) Histologic specimen of the biopsy showed invasive nests of adenocarcinoma (hematoxylin and eosin staining, 200x).



(a) (b) (c)

FIGURE 2: A 66-year-old female received cryobiopsy from lingula showing correlation among the axial CT image, endobronchial ultrasound (EBUS) image, and histopathologic finding from biopsy. (a) Axial CT image in lung window demonstrated ground-glass opacities in peribronchial distribution and dependent atelectasis in the bilateral dependent lung. The image appearance is nonspecific with several possible differential diagnoses, including atypical pneumonia, acute interstitial pneumonitis, nonspecific interstitial pneumonitis, and/or pulmonary edema. (b) EBUS showed heterogeneous echogenicity, along with linear–discrete air bronchogram. (c) Histologic specimen of the biopsy revealed interstitial homogenous fibrosis and chronic inflammation (hematoxylin and eosin staining, 200x).

Transbronchial cryobiopsy: Future perspectives?

Respiration

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Pleural Cryobiopsy versus Flexible Forceps Biopsy in Subjects with Undiagnosed Exudative Pleural Effusions Undergoing Semirigid Thoracoscopy: A Crossover Randomized Trial (COFFEE Trial)

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Cryobiopsy: Technical notes

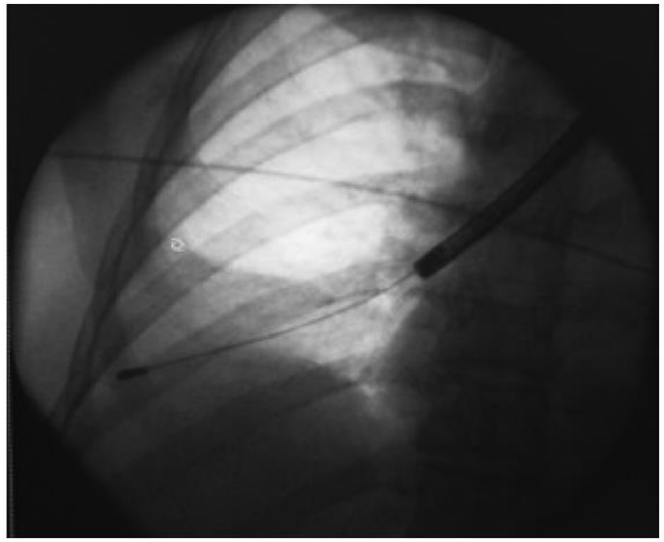

Figure 4.—Fluoroscopic view of the cryoprobe.

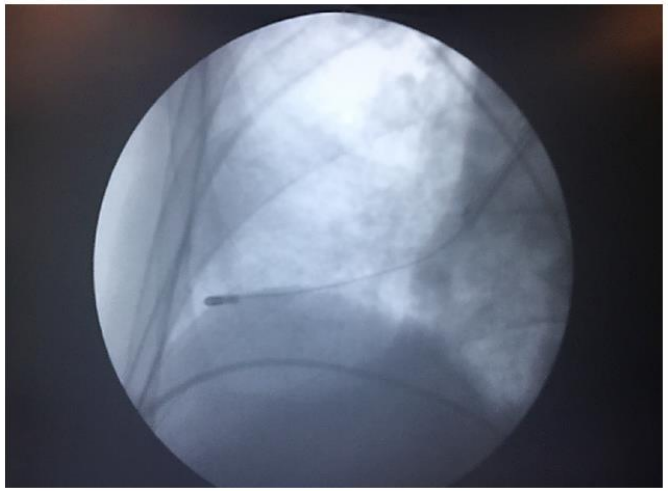

Fig. 4. The probe under fluoroscopic guidance.

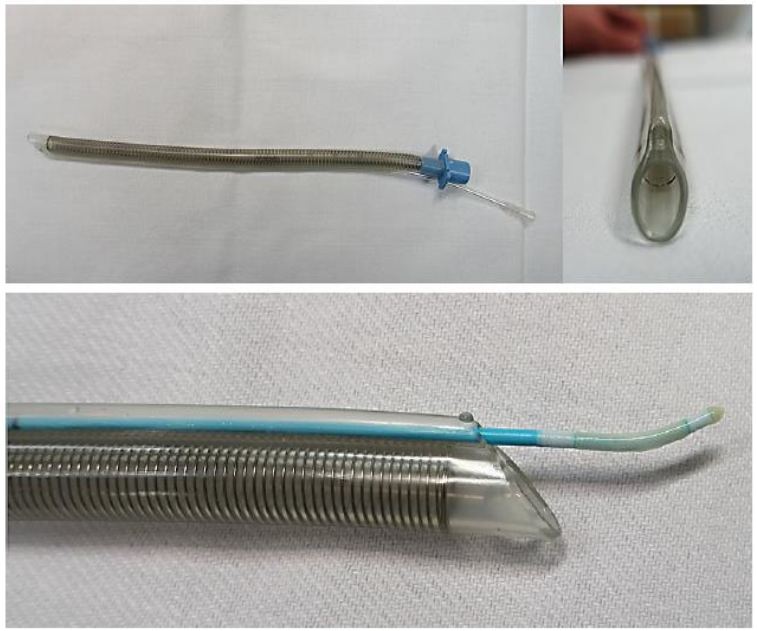

Fig. 3. Flexible tube with extra channel and angulated Fogarty balloon catheter.

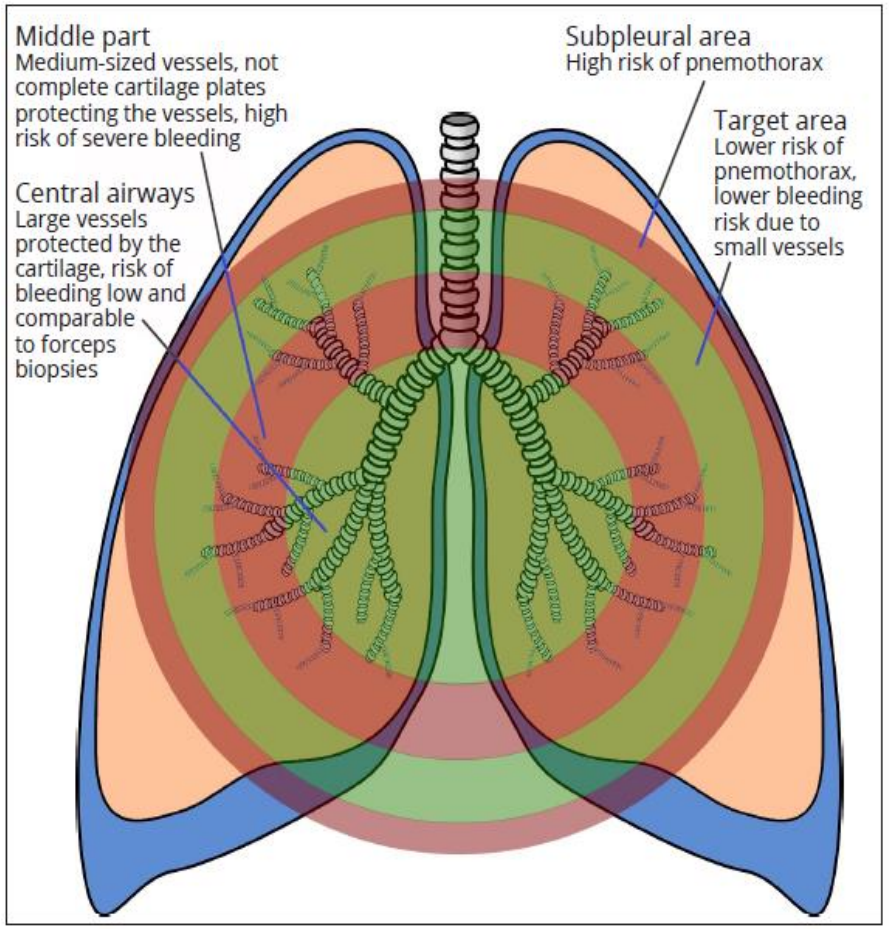

Figure 5.—The biopsies obtained in the periphery of secondary pulmonary lobule are more likely to get appropriate specimens for the histologic diagnosis of UIP. The area to perform the cryobiopsy with lower risk of pneumothorax or bleeding is the Target area. The major risk of pneumothorax is inside the Subpleural area, while the risk of severe bleeding increases if the biopsies are obtained in the middle third of lung.

Ιδανικός εξοπλισμός