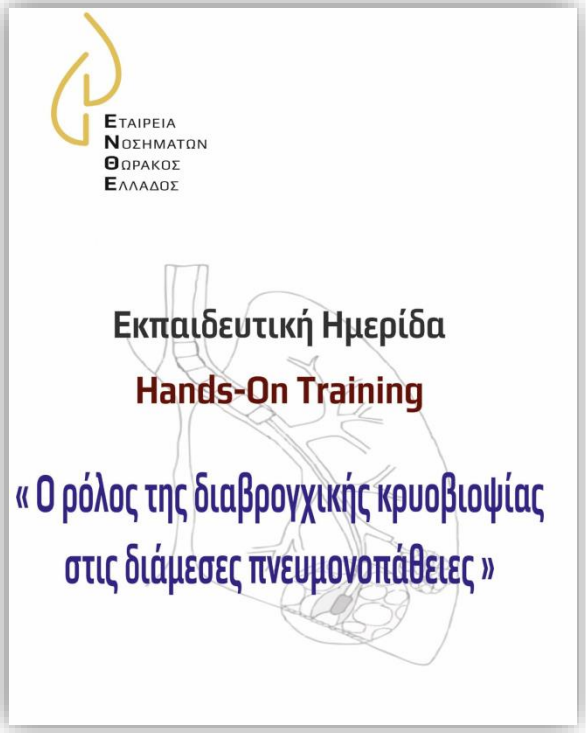

Lung cryobiopsy – Technique & results

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Conflict of Interest

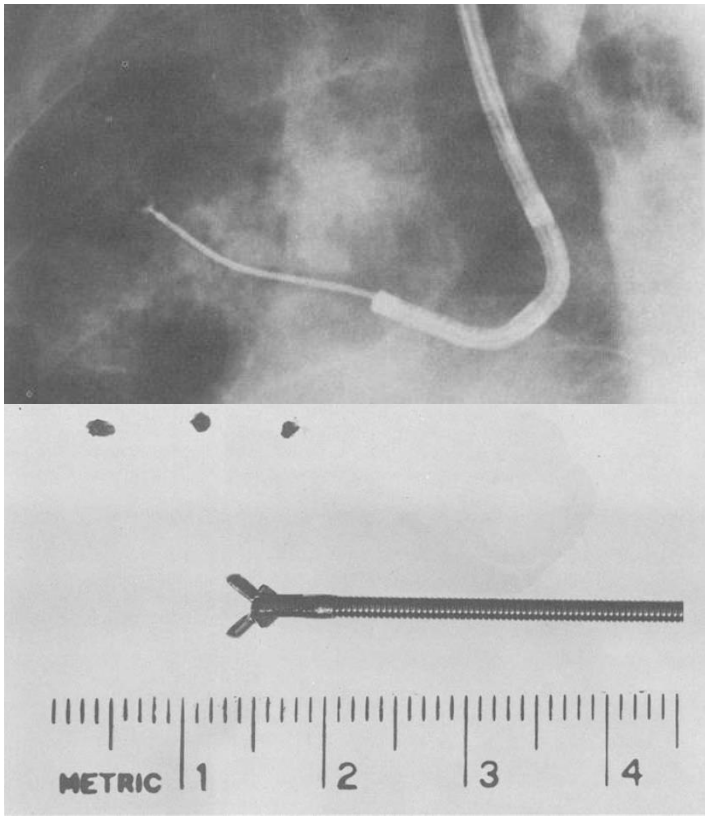
- ☑ I have **no**, real or perceived, direct or indirect conflicts of interest that relate to this presentation.
- ☐ I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation:

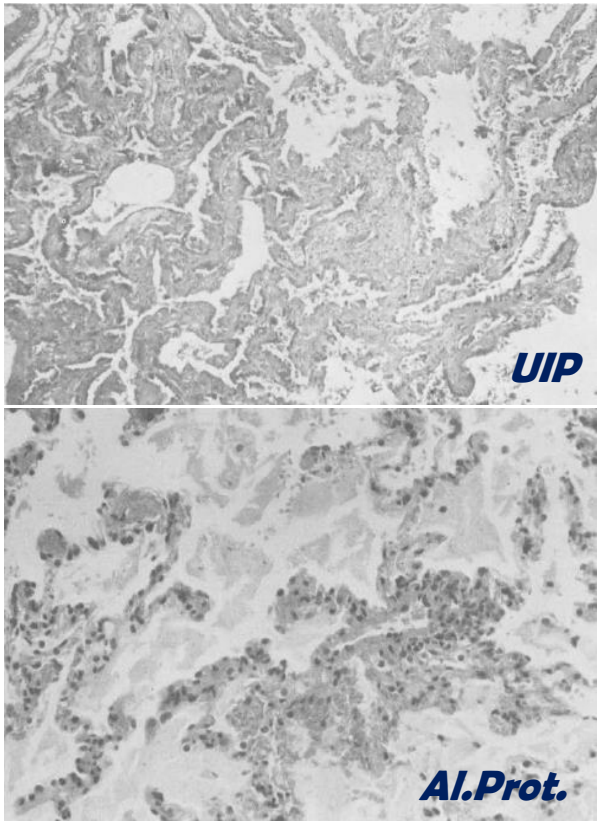
Affiliation / financial interest	Nature of conflict / commercial company name
Tobacco-industry and tobacco corporate affiliate related conflict of interest	
Grants/research support (to myself, my institution or department):	
Honoraria or consultation fees:	
Participation in a company sponsored bureau:	
Stock shareholder:	
Spouse/partner – conflict of interest (as above):	
Other support or other potential conflict of interest:	

Transbronchial Lung Biopsy Via the Fiberoptic Bronchoscope[1, 2]

AMERICAN REVIEW OF RESPIRATORY DISEASE, VOLUME 110, 1974

Of the 33 patients biopsied, 22 had diffuse lung disease and 11 had localized lung disease without endobronchial lesions. The TBB technique yielded diagnosis in 18 cases of diffuse lung disease





Comparison of Transbronchial and Open Biopsies in Chronic Infiltrative Lung Diseases[1-3]

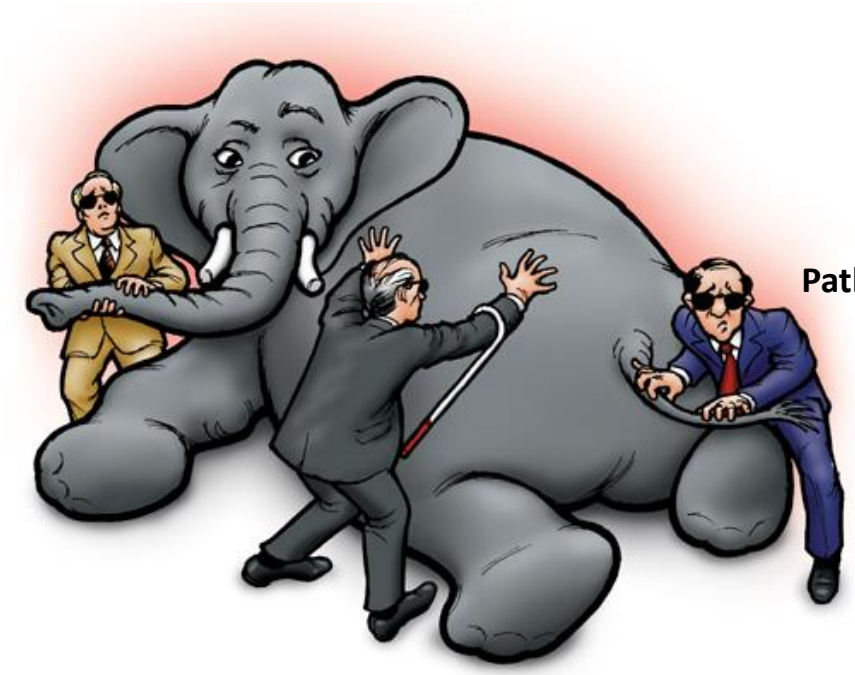
AM REV RESPIR DIS 1981; 123:280-285

- From 53 patients TBLB was diagnostic in 20 (37.7%)
- The remaining 33 patients were reported as normal lung
- Open biopsy in these 33 patients resulted in specific diagnoses in 92%

Conclusions:

1. TBLB diagnoses of interstitial pneumonia, chronic inflammation, nonspecific reaction, and fibrosis are unreliable and often entirely misleading
2. In this group, an open biopsy is required to reach a specific histologic diagnosis

Multidisciplinary assessment – MDA



Pathologist

Radiologist

Pulmonologist

High resolution CT scan

Eur Respir J 2006; 28: 1081–1084
DOI: 10.1183/09031936.06.00013106

Is bronchoscopic lung biopsy helpful in the management of patients with diffuse lung disease?

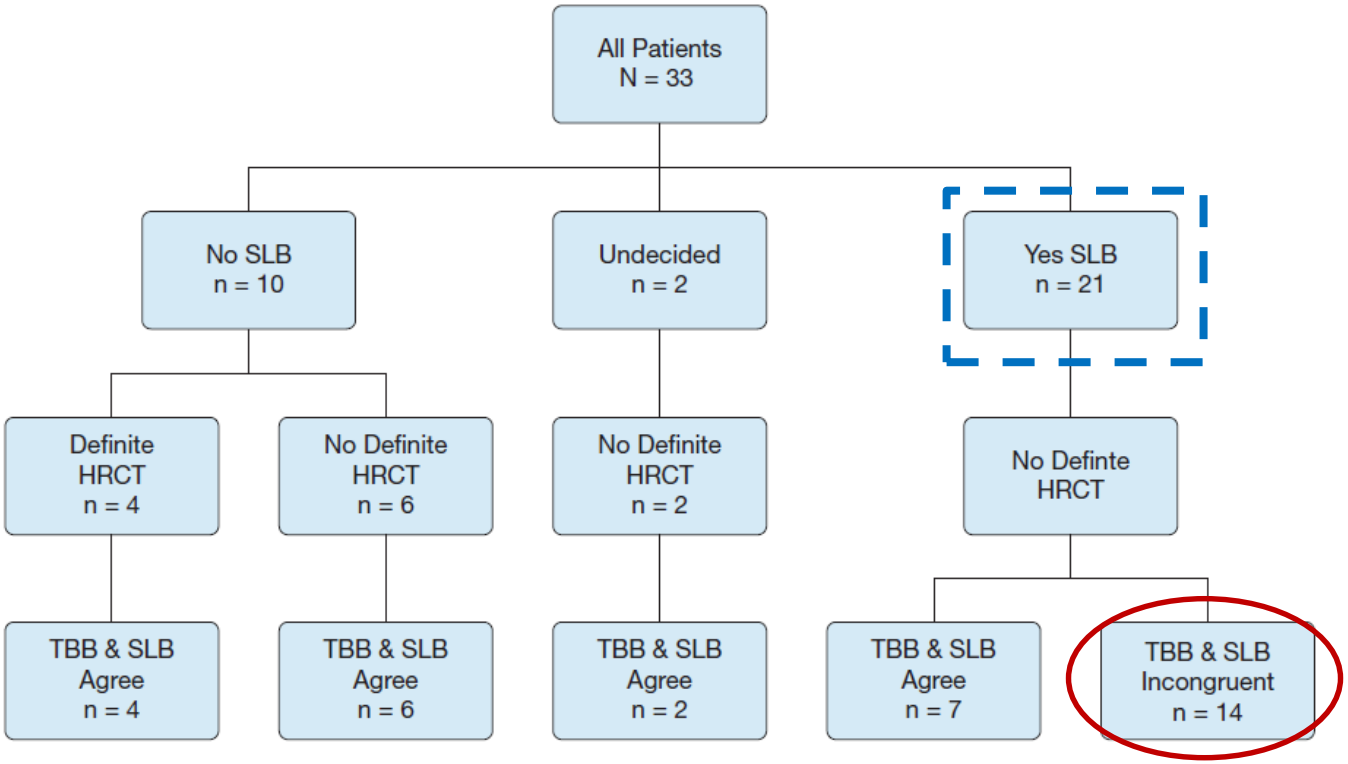
S.A. Ensminger and U.B.S. Prakash

Results:

- 603 patients underwent 651 TBLB procedures
- No specific diagnostic abnormality was identified in 107 (16.4%) of all biopsies
- Lung biopsy was clinically useful in ~75% of patients
- In the rest 25% - Failure of the procedure and inadequate sample, that could offer valuable information, was the main reason of not being useful

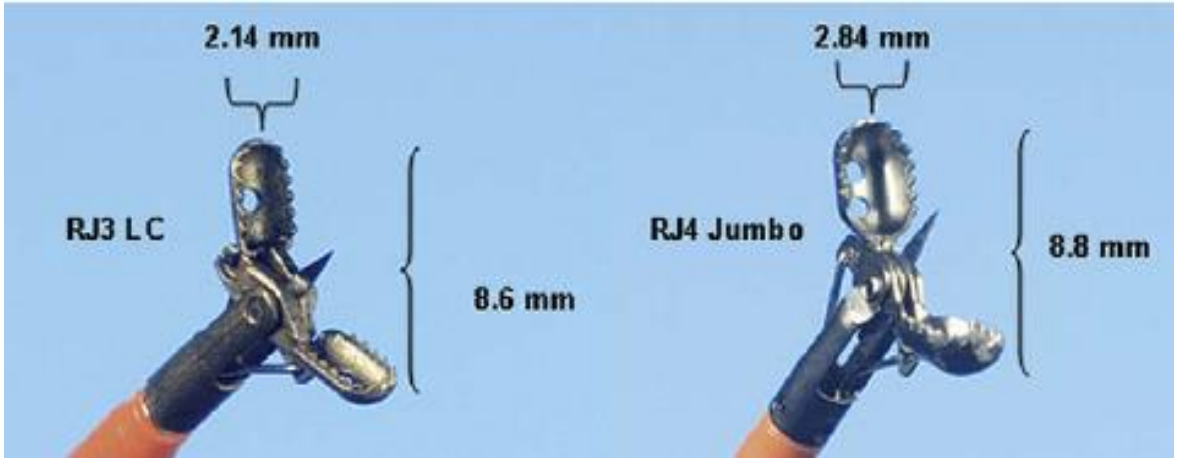
CHEST 2017; 151(2):389-399

Utility of Transbronchial vs Surgical Lung Biopsy in the Diagnosis of Suspected Fibrotic Interstitial Lung Disease



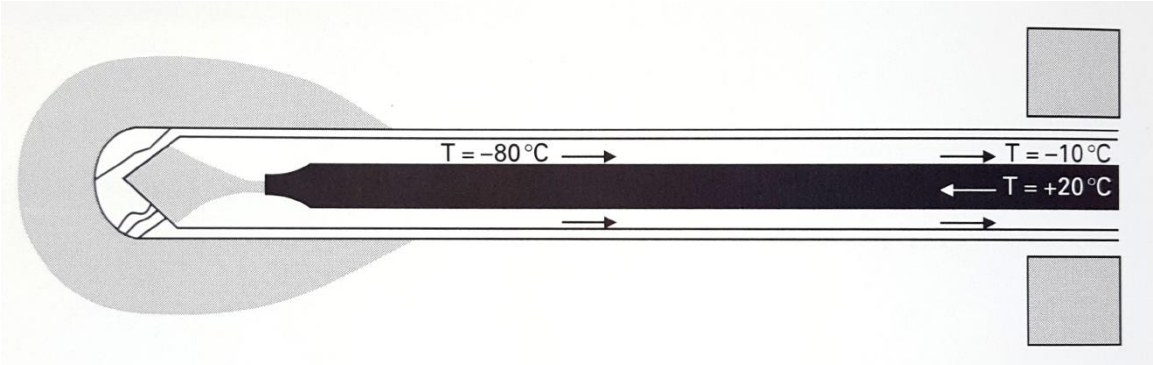
CONCLUSIONS: Information from TBB, when combined with clinical and HRCT data, may provide enough information to make a confident and accurate diagnosis in approximately 20% to 30% of patients with ILD.

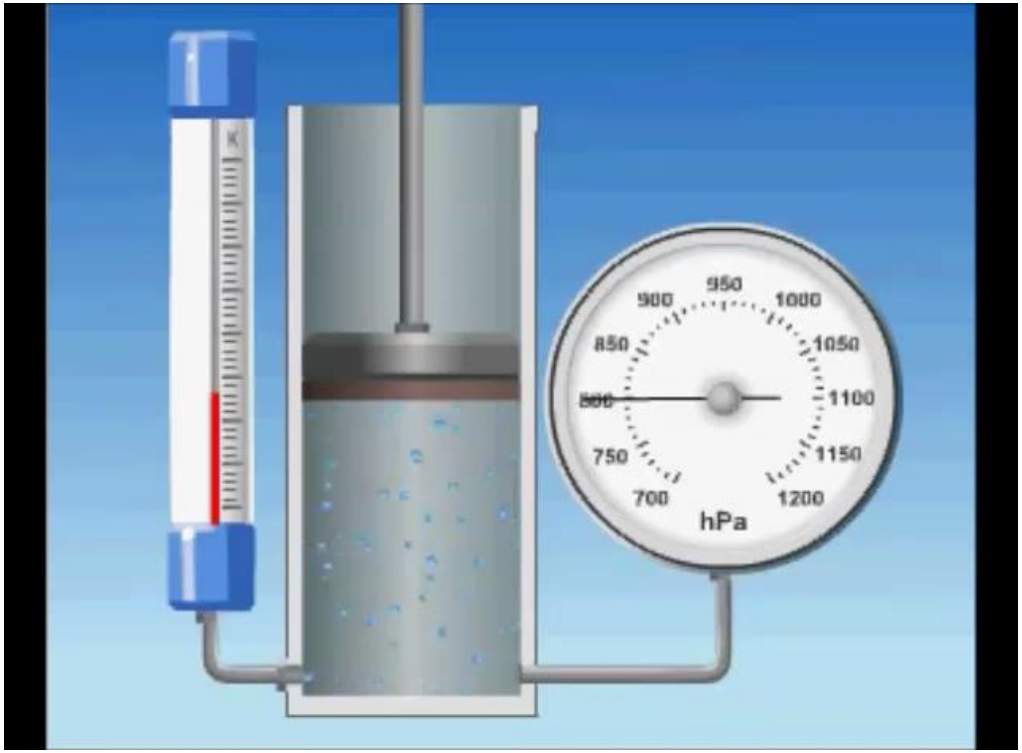
Forceps ⟶ Cryobiopsy



Cryobiopsy - Technique

<u>Principle of Joule-Thomson</u>:
Change in temperature of a fluid as it flows from a region of high pressure to a region of low pressure.





YouTube

Equipment:

1.Console and gas cylinder (CO_2, N_2O)
2.Transfer line (connects the console to the probe)
3.Cryoprobe (flexible :1.9 mm/2.4 mm and rigid: 3.0 mm)
4.Pedal

CRYOBIOPSY SETTING

Transbronchial Cryobiopsy in Diffuse Parenchymal Lung Disease: Need for Procedural Standardization

Venerino Poletti[a, b] Jürgen Hetzel[c]

Respiration 2015;90:275–278

Table 1. Transbronchial cryobiopsy for diffuse lung disease: different approaches

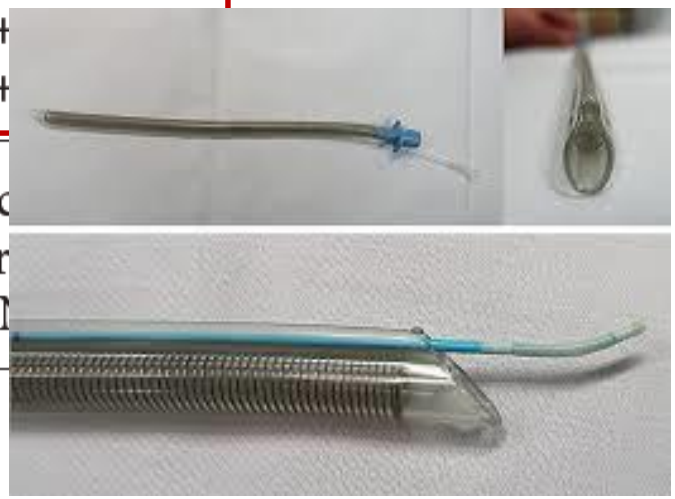
First author [Ref.]	Year	OT	RB	LM	NI	GA+JV	GA/DS	LA	Bronchial blocker	Cryoprobe size, mm	Freezing time, s
Babiak [10]	2009	x					x		N	2.4	4
Pajares [11]	2010	x					x		N	2.4	3
Griff [12]	2011		x		x		x	x			
Kropski [13]	2013	x					x			1.9	4
Yarmus [14]	2013		x (10)	x (11)		x	x		Y	1.8	3
Fruchter [15]	2013				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.

Table 2. Comparison between different transbronchial cryobiopsy modalities

	Endrotracheal tube	Rigid bronchoscopy	LMA	Moderate sedation
Need of GA/DS	Y	Y	Y	N
Control of bleeding	Y	Y	Y/N	N
Size of specimens	+++	+++	+	+
Size of OF	++	+++	+	–
Comfort for patients	+++	+		
Technical effort	++	+		

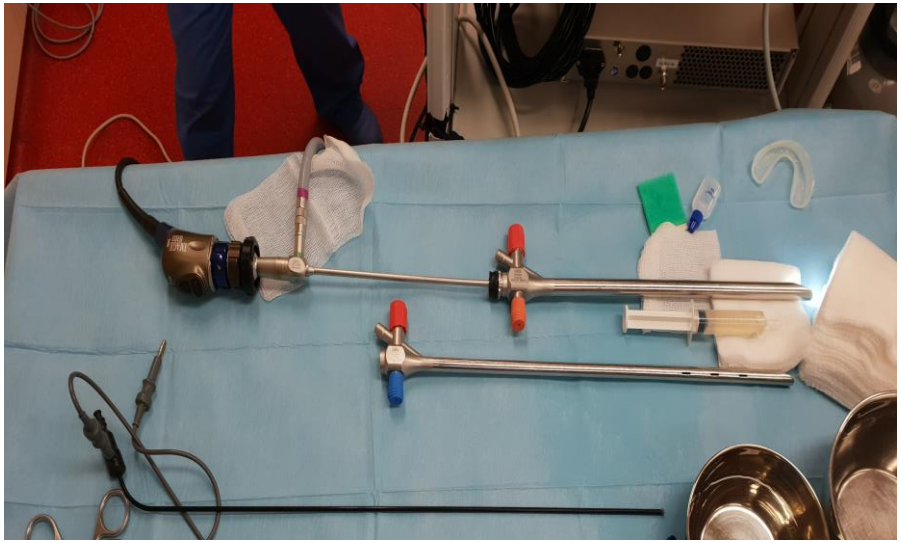
OT = Orotracheal tube; RT = rigid trac
mask; NI = no intubation; GA = gener
sedation; OF = operating field; Y = yes; N

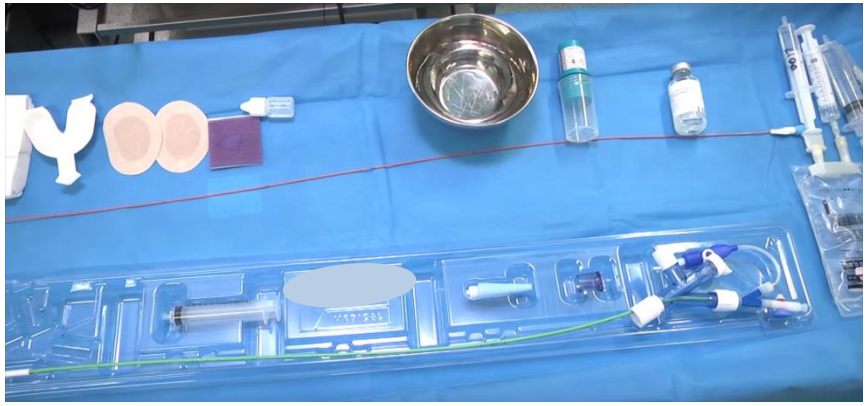


Musani et al. JOB. 2018 Ahead of print
Expert Statement. Respiration. 2018;95(3):188-200
Hetzel et al. Respiration. 2015;90:275-278

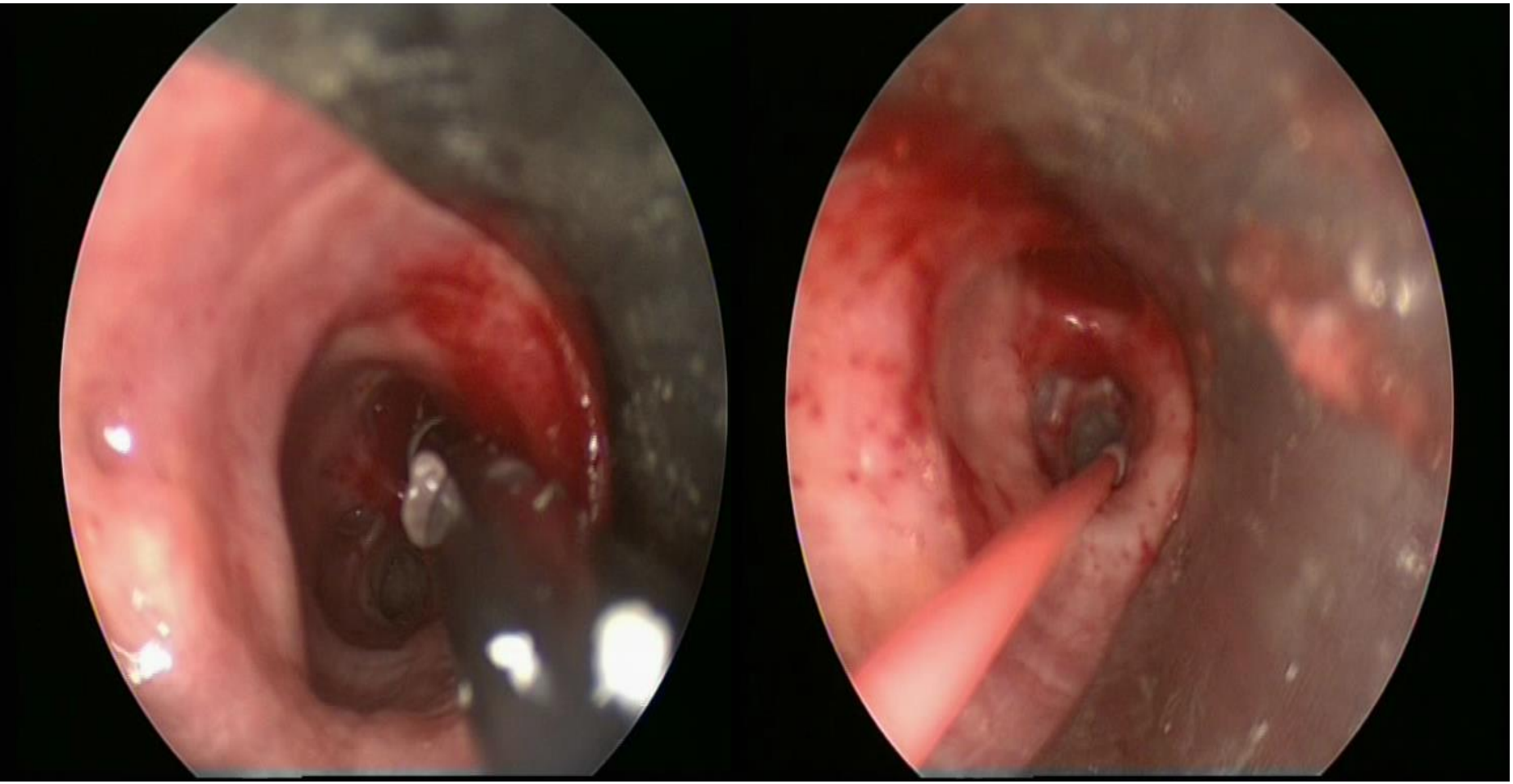
Cryobiopsy Setting :

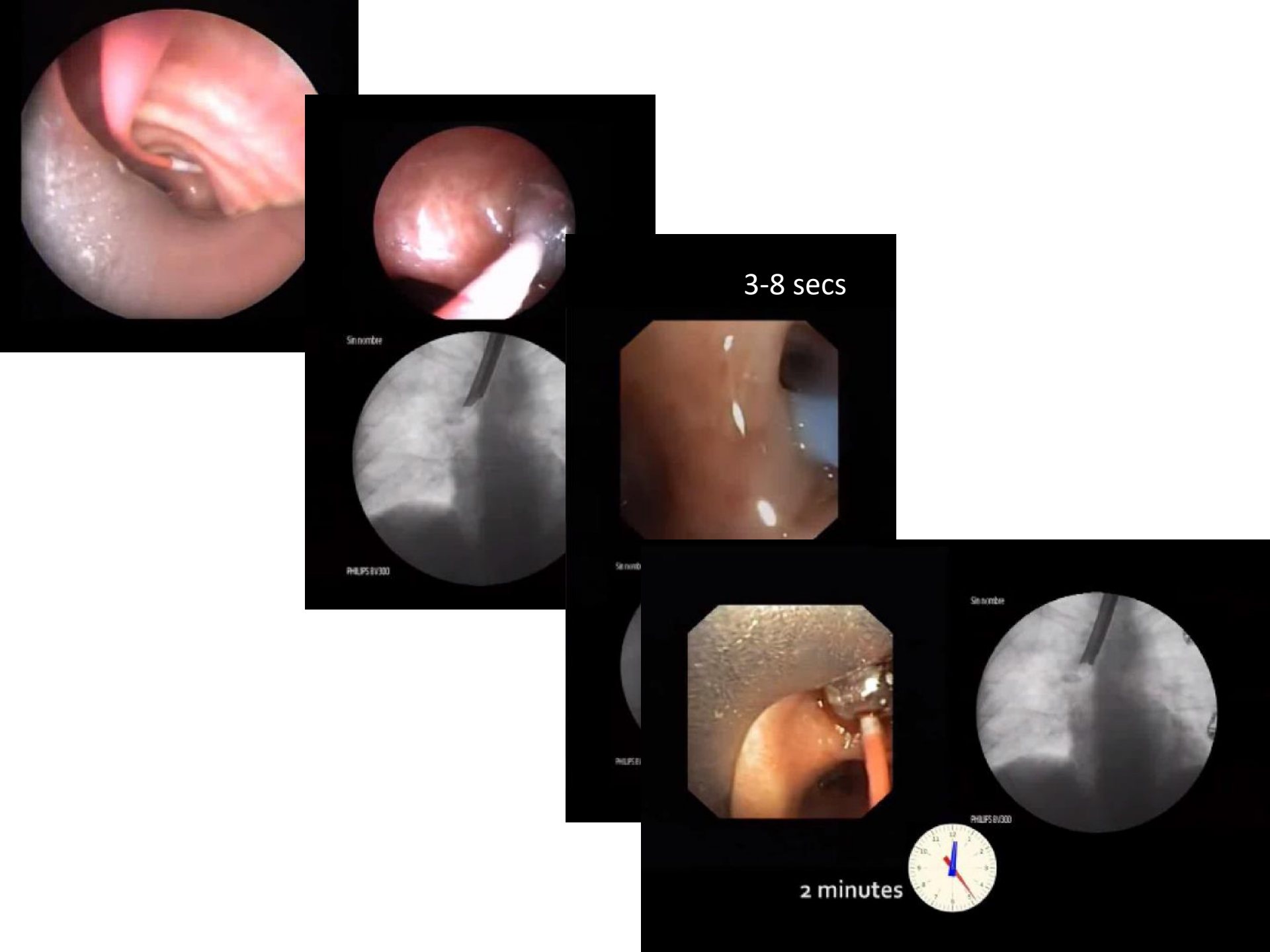
1. Rigid bronchoscopy
2. Fogarty hemostatic balloon
3. Fluoroscopy
4. Cryoprobe 1.9 / 2.4 mm





- Rigid intubation of the main bronchus with bronchoscope-ventilation through sideports.
- Hemostatic balloon placement – balloon siringe filled with diluted iodine contrast medium

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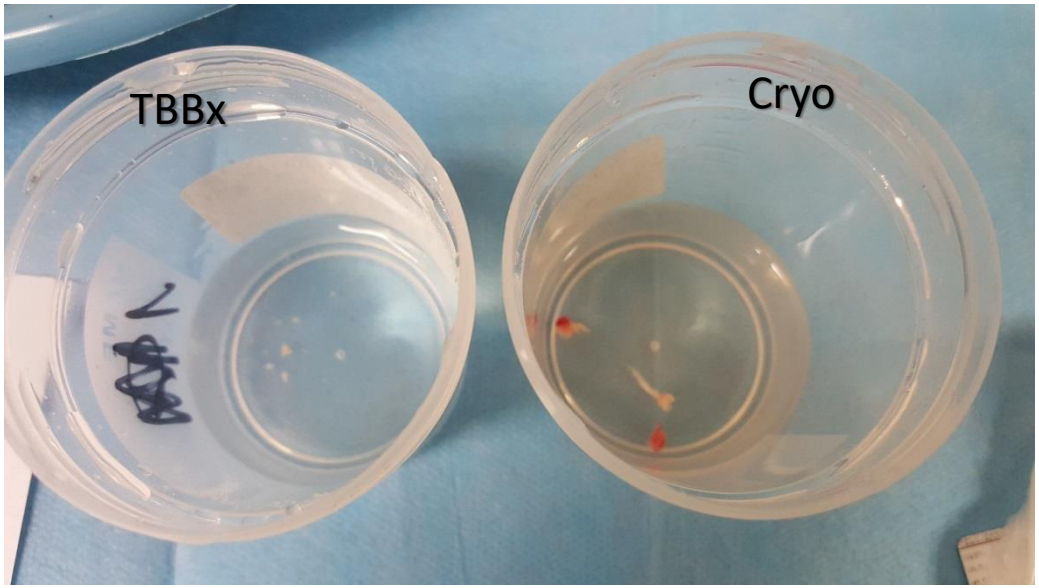
2 minutes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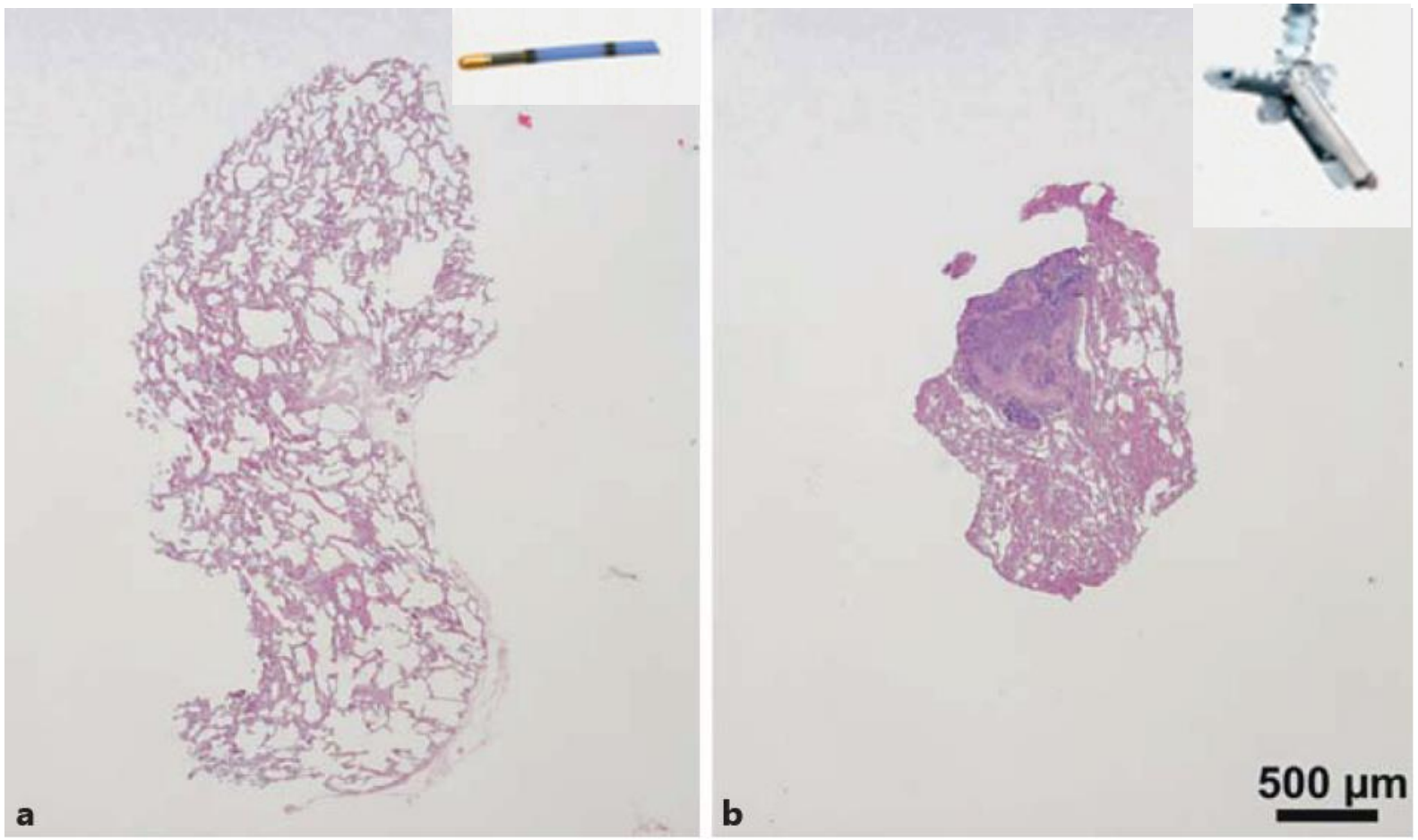
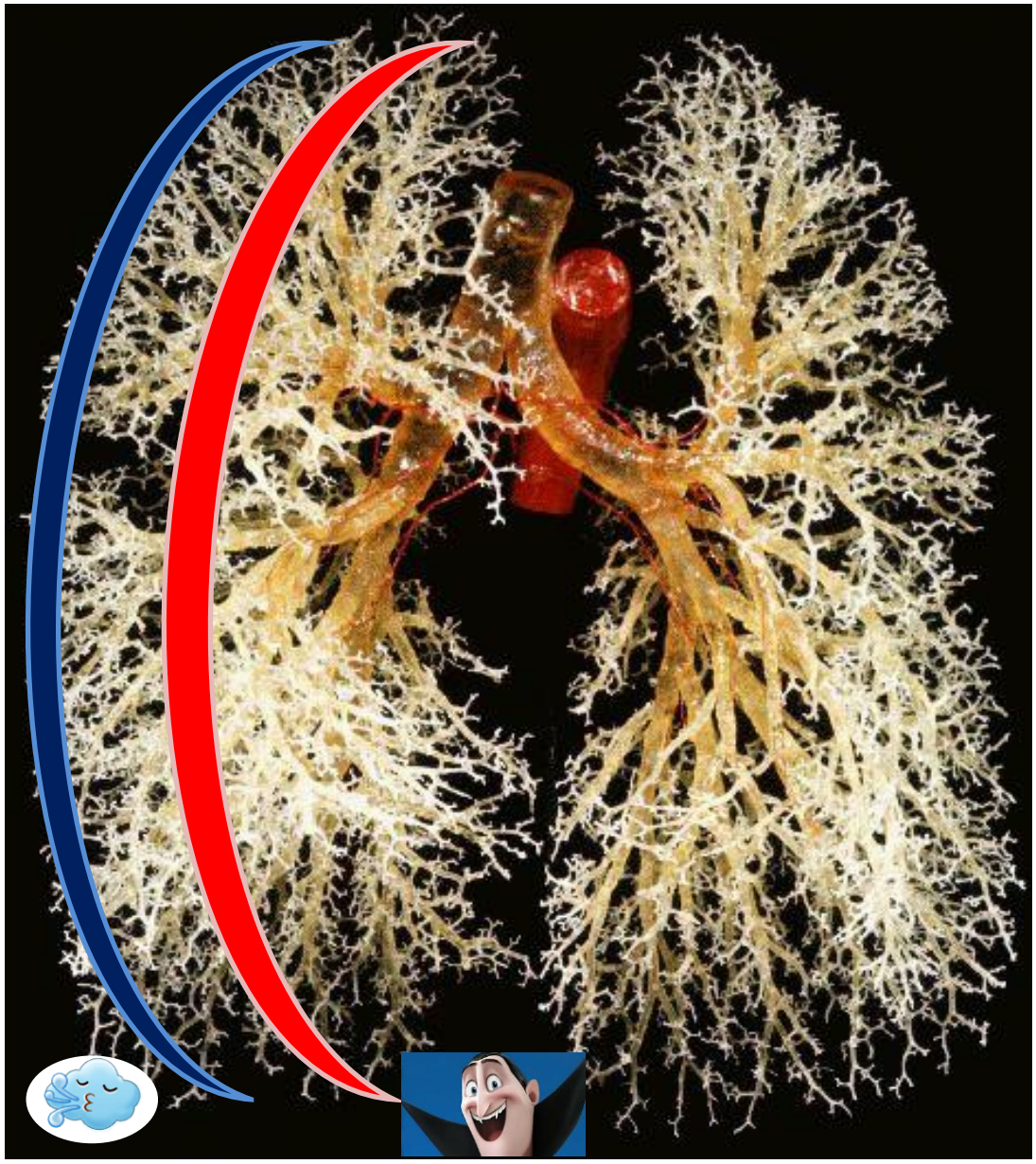


Bigger pieces
Less crash effect

Safe area for biopsy

- **At the periphery (<1cm): Pneumothorax**

- **Centrally: Bleeding**

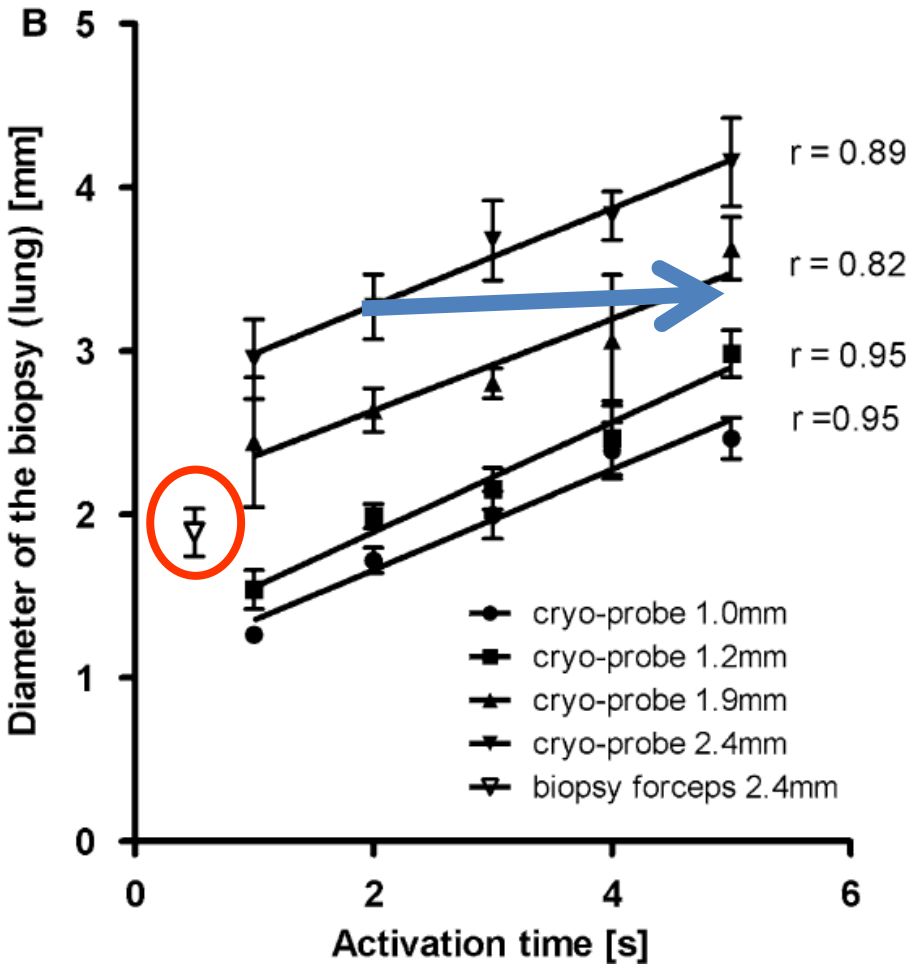


Number of biopsies

- 3-5 biopsies in a distance of >1cm from the parietal pleura wall, under fluoroscopic guidance.
- Sampling from >2 segments of the same lobe, potentially increase diagnostic yield.
- Sampling from >1 lobes? – No prospective studies available.

Tomassetti et al . Respiration 2017; 93: 285–292.
Expert Statement. Respiration. 2018;95(3):188-200
Hetzel et al. Respiration. 2015;90:275-278
Schuhmann et al. Eur Respir J 2014;43:233-239

Size of catheter - Correlation with activation time



Cryobiopsy - Results

Cryobiopsy versus conventional TBLB

Table 1 Characteristics of included studies

First author	Year	Number of subjects	Disease involved	Type of study
Babiak	2009	41—all subjects, FB and CB	ILDs	Retrospective
Schumann C.	2010	First 55—all subjects, FB and CB	Lung tumours	Randomized cohort
Aktas A.	2010	41—all subjects, CB and FB	Lung tumours	Prospective clinical trial
Griff	2011	33—15, CB; 18, FB	ILDs	Prospective clinical Trial
Hetzel J.	2012	563—282, CB; 281, FB	Lung tumours	Randomized single blinded multicentre
Schuhmann M.	2013	31—all subjects, CB and FB	Peripheral solitaryLung tumours	Randomized clinical trial
Chou C.L.	2013	75—all subjects, CB and FB	ILDs	Retrospective
Pajares	2014	77	ILDs	Randomized trial

CB, cryobiopsy; FB, forceps biopsy; ILDs, interstitial lung diseases.

Ganganah et al., Respiration 2016

Cryobiopsy versus conventional TBLB

Table 1 Characteristics of included studies

First author	Year	Number of subjects	Disease involved	Type of study	Specimen size	
					CB	FB
Babiak	2009	41—all subjects, FB and CB	ILDs	Retrospective	15.11 mm^2 (2.15–54.15 mm^2)	5.82 mm^2 (0.58–20.88 mm^2)
Schumann C.	2010	First 55—all subjects, FB and CB	Lung tumours	Randomized cohort	10.4 mm^2	5.2 mm^2
Aktas A.	2010	41—all subjects, CB and FB	Lung tumours	Prospective clinical trial	0.8 cm (0.3–4.0 cm)	0.2 cm (0.1–1.0 cm)
Griff	2011	33—15, CB; 18, FB	ILDs	Prospective clinical Trial	17.1 ± 10.7 mm^2	3.8 ± 4.0 mm^2
Hetzel J.	2012	563—282, CB; 281, FB	Lung tumours	Randomized single blinded multicentre		
Schuhmann M.	2013	31—all subjects, CB and FB	Peripheral solitaryLung tumours	Randomized clinical trial	11.17 mm^2	4.69 mm^2
Chou C.L.	2013	75—all subjects, CB and FB	ILDs	Retrospective	13.8 ± 3.8 mm	1.9 ± 0.6 mm
Pajares	2014	77	ILDs	Randomized trial	14.7 ± 11 mm^2	3.3 ± 4.1 mm^2

CB, cryobiopsy; FB, forceps biopsy; ILDs, interstitial lung diseases.

x **2-3**

Ganganah et al., Respiration 2016

Cryobiopsy versus conventional TBLB

Table 1 Characteristics of included studies

First author	Year	Number of subjects	Disease involved	Type of study	Specimen size		Diagnostic yield %	
					CB	FB	CB	FB
Babiak	2009	41—all subjects, FB and CB	ILDs	Retrospective	15.11 mm^2 (2.15–54.15 mm^2)	5.82 mm^2 (0.58–20.88 mm^2)	95.12	> 58.53
Schumann C.	2010	First 55—all subjects, FB and CB	Lung tumours	Randomized cohort	10.4 mm^2	5.2 mm^2	89.1	> 65.5
Aktas A.	2010	41—all subjects, CB and FB	Lung tumours	Prospective clinical trial	0.8 cm (0.3–4.0 cm)	0.2 cm (0.1–1.0 cm)	92.7	> 78
Griff	2011	33—15, CB; 18, FB	ILDs	Prospective clinical Trial	17.1 ± 10.7 mm^2	3.8 ± 4.0 mm^2		
Hetzel J.	2012	563—282, CB; 281, FB	Lung tumours	Randomized single blinded multicentre			95	> 85.1
Schuhmann M.	2013	31—all subjects, CB and FB	Peripheral solitaryLung tumours	Randomized clinical trial	11.17 mm^2	4.69 mm^2	61.2	> 48.4
Chou C.L.	2013	75—all subjects, CB and FB	ILDs	Retrospective	13.8 ± 3.8 mm	1.9 ± 0.6 mm	100	> 69.3
Pajares	2014	77	ILDs	Randomized trial	14.7 ± 11 mm^2	3.3 ± 4.1 mm^2	74.4	> 34.1

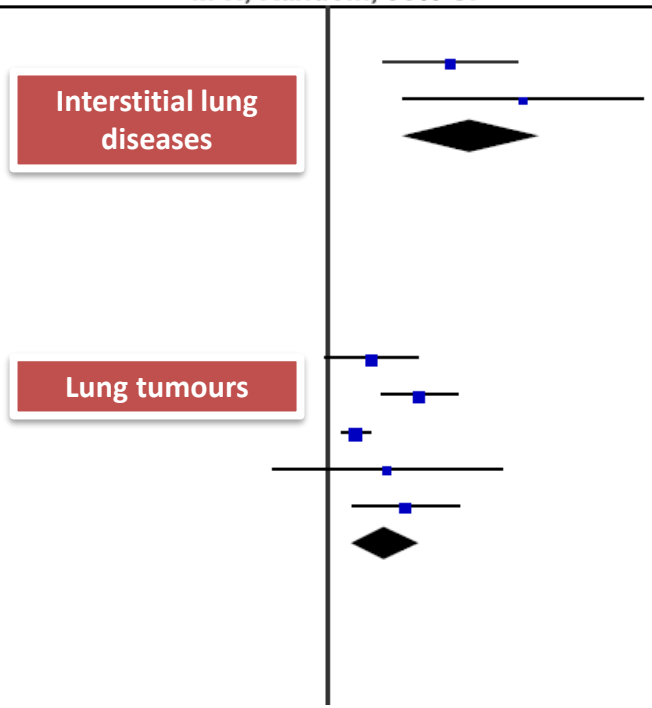
CB, cryobiopsy; FB, forceps biopsy; ILDs, interstitial lung diseases.

x **2-3**

Ganganah et al., Respiration 2016

Diagnostic yield

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)						



Ganganah et al., Respiration 2016

Cryobiopsy versus conventional TBLB

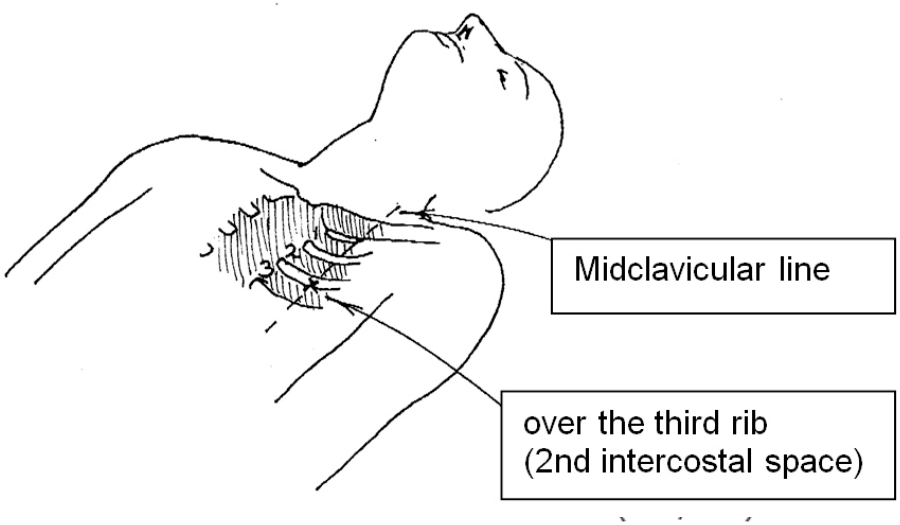
Table 1 Characteristics of included studies

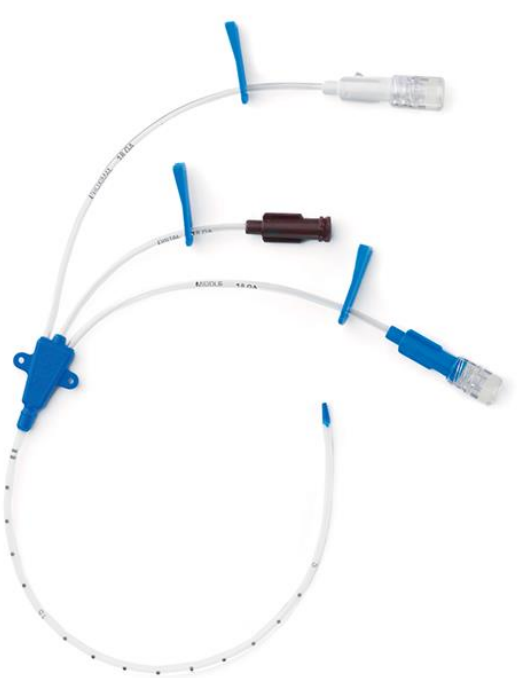
First author	Year	Number of subjects	Disease involved	Type of study	Specimen size		Diagnostic yield %		Bleeding			
					CB	FB	CB	FB		Mild	Moderate	Severe
Babiak	2009	41—all subjects, FB and CB	ILDs	Retrospective	15.11 mm^2 (2.15–54.15 mm^2)	5.82 mm^2 (0.58–20.88 mm^2)	95.12	58.53	CB FB			
Schumann C.	2010	First 55—all subjects, FB and CB	Lung tumours	Randomized cohort	10.4 mm^2	5.2 mm^2	89.1	65.5				
Aktas A.	2010	41—all subjects, CB and FB	Lung tumours	Prospective clinical trial	0.8 cm (0.3–4.0 cm)	0.2 cm (0.1–1.0 cm)	92.7	78	CB FB	19.5 21.9	4.9 0	0 0
Griff	2011	33—15, CB; 18, FB	ILDs	Prospective clinical Trial	17.1 ± 10.7 mm^2	3.8 ± 4.0 mm^2						
Hetzel J.	2012	563—282, CB; 281, FB	Lung tumours	Randomized single blinded multicentre			95	85.1	CB FB	61.8 51.55		18.2 17.8
Schuhmann M.	2013	31—all subjects, CB and FB	Peripheral solitaryLung tumours	Randomized clinical trial	11.17 mm^2	4.69 mm^2	61.2	48.4				
Chou C.L.	2013	75—all subjects, CB and FB	ILDs	Retrospective	13.8 ± 3.8 mm	1.9 ± 0.6 mm	100	69.3				
Pajares	2014	77	ILDs	Randomized trial	14.7 ± 11 mm^2	3.3 ± 4.1 mm^2	74.4	34.1	CB	30.8	56.4	0
											2	0

CB, cryob

TBCB is associated with an increased risk of bleeding which is of clinical relevance. Therefore training and additional precautions for bleeding control should be considered.

Ganganah et al., Respiration 2016





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Results:

- Total possibility: 0.06, Need for chest tube drainage insertic
- Pneumothorax more frequent when fluoroscopy was not u

Ganganah et al., Respiration 2016

Cryobiopsy *versus* VATS

Respiration 2016;91:215–227

	SLB (VATS) group (n = 150)	TBLC group (n = 297)	p value
Patients	150	297	
Age, years	59 (15–74)	60 (21–78)	0.278
Gender			
Male	85 (56.7)	172 (57.9)	0.801
Female	65 (43.3)	125 (42.1)	
Smoking			
Current smoker	21 (14.0)	40 (13.5)	
Former smoker	63 (42.0)	124 (41.8)	
Nonsmoker	65 (43.3)	133 (44.8)	0.968
FVC, % predicted	80.0 (20.0–136.0)	86.0 (37.0–137.0)	0.072
FEV_1, % predicted	83.0 (33.0–133.0)	88.0 (36.0–144.0)	0.034
DLCO, % predicted	57.0 (19.0–122.0)	58.8 (14.0–121.0)	0.078
Tiffeneau index	86 (62.0–105.0)	86 (60.0–124.0)	0.85
Histological pattern			
DIP/RB-ILD	11 (7.3)	12 (4.0)	
UIP	74 (49.3)	92 (31.0)	
NSIP	23 (15.3)	25 (8.4)	
DAD	1 (0.7)	4 (1.3)	
OP	8 (5.3)	31 (10.4)	
HP	7 (4.7)	24 (8.1)	
SAR	8 (5.3)	22 (7.4)	
Other (neoplasms, eosinophilic pneumonia, follicular bronchiolitis, alveolar proteinosis, vasculitis, AFOP, DIPNECH, or PLCH)	16 (10.7)	36 (12.1)	
Nondiagnostic pattern	2 (1.3)	51 (17.2)	*0.013*

Diagnostic yield:
98.7% vs 82.8% (p=0.013)

Table 2. Safety profile results for SLB (VATS) and TBLC

	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	4/150 (2.7)	1/297 (0.3)	*0.045*
[All deaths were caused by acute exacerbation of IPF]	4/20 (20.0)	1/66 (1.5)	*0.01*
Survival			
Alive	88 (58.7)	272 (91.6)	
Dead	43 (28.7)	13 (4.4)	
Transplantation	4 (2.7)	1 (0.3)	

Respiration 2016;91:215–227

QJM. 2017 Apr 1;110(4):207-214.

In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States

2000 to 2011

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Table 2. In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease, by Year

Year of Biopsy	Total Admissions [*Deaths (% Mortality)*]
2000	822 (7.6)
2001	962 (7.5)
2002	923 (6.9)
2003	934 (7.3)
2004	875 (7.0)
2005	876 (6.6)
2006	876 (6.6)
2007	696 (5.4)
2008	715 (5.8)
2009	709 (5.5)
2010	696 (5.7)
2011	617 (4.9)
Total	9,700 (6.4)

- 9,700 deaths associated with SLB
- Main cause of death: ILD exacerbation

Cryobiopsy *versus* VATS in IPF?

Bronchoscopic Lung Cryobiopsy Increases Diagnostic Confidence in the Multidisciplinary Diagnosis of Idiopathic Pulmonary Fibrosis

Table 3. Final Multidisciplinary Diagnosis Following BLC or SLB

	BLC	SLB	*P* Value
Cases	58 (50)	59 (50)	0.71
IPF	29 (50)	23 (39)	
iNSIP	7 (12)	5 (9)	
HP	6 (10)	9 (15)	
DIP/RB-ILD	2 (4)	4 (7)	
Other*	9 (15)	10 (17)	
No consensus	3 (5)	6 (10)	
Unclassifiable	2 (4)	2 (3)	

Definition of abbreviations: BLC = bronchoscopic lung cryobiopsy; DIP/RB-ILD = desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease; HP = hypersensitivity pneumonitis; iNSIP = idiopathic nonspecific interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; SLB = surgical lung biopsy.
Data are given as n (%).

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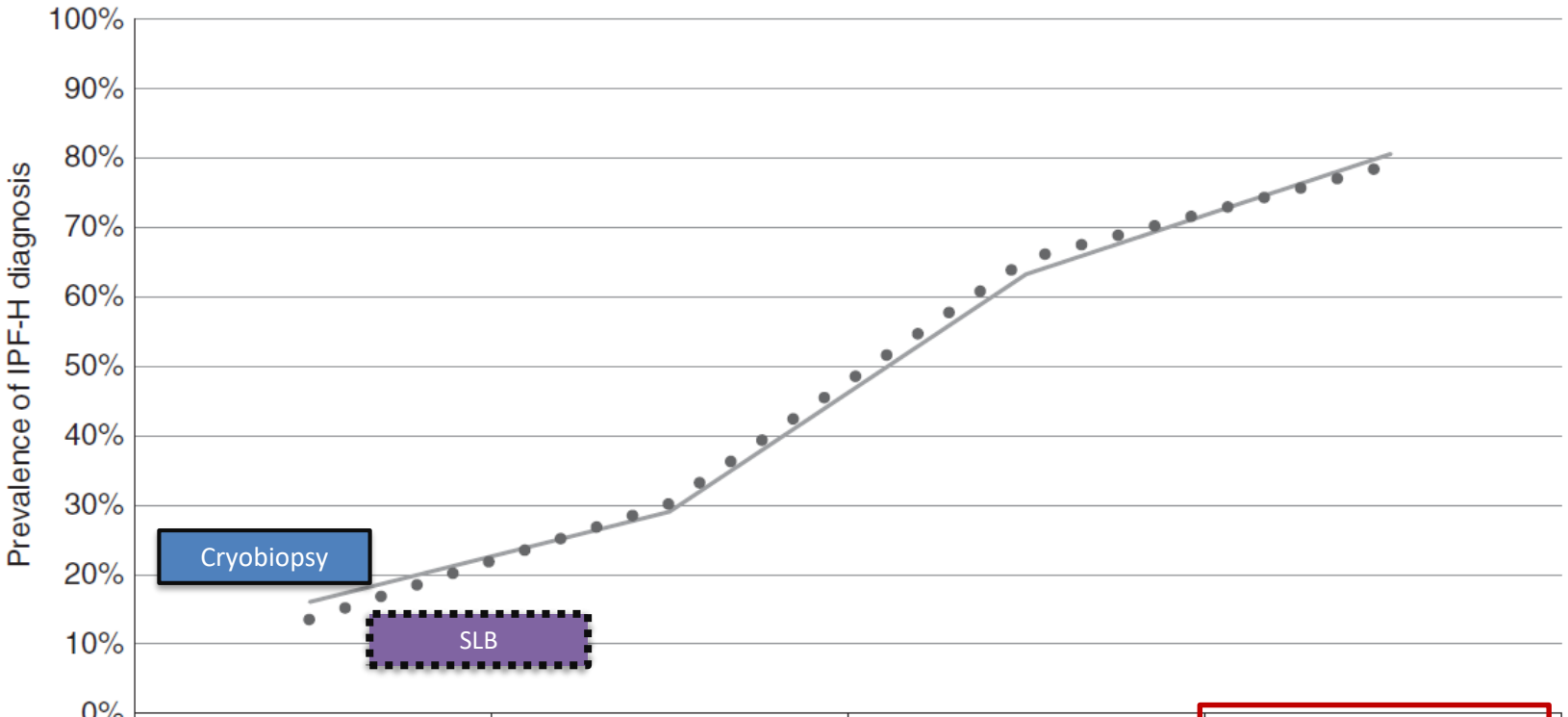

	(clinical-radiologic data)	(plus bronchoalveolar lavage)	(plus biopsy)	(plus follow-up)
BLC	16%	29%	63%	80%
SLB	14%	30%	65%	79%

BLC = bronchoscopic lung cryobiopsy

SLB = surgical lung biopsy

IPF-H = idiopathic pulmonary fibrosis diagnosis made with high confidence level;

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AMERICAN THORACIC SOCIETY DOCUMENTS

Am J Respir Crit Care Med, Sep 2018

Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

For patients with **newly detected ILD of apparently unknown cause** who are clinically suspected of having IPF and have an HRCT pattern of **probable UIP, indeterminate, or an alternative diagnosis:**

- We suggest cellular analysis of their BAL fluid *(conditional recommendation, very low quality of evidence).*
- We suggest surgical lung biopsy (SLB) *(conditional recommendation, very low quality of evidence).*
- The panel made no recommendation for or against transbronchial lung biopsy (TBBx).
- The panel made no recommendation for or against lung cryobiopsy.

ATS Journals

AJRCCM March 2019

Poor concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases

- A two-center prospective study included ILD patients with a non-definite usual interstitial pneumonia (UIP
- Twenty-one pati t the same anatomical locat
- Anonymized TBL athologist
- Pathological res ent of ILD. SLBs were more frequently concordant with the final diagnosis retained at MDA.
- TBLC would have led to a different treatment if SLB was not performed in 11/21 (52%) of cases

Cryobiopsy Compared with Surgical Lung Biopsy in ILD: Reply to Maldonado *et al.*, Froidure *et al.*, Bendstrup *et al.*, Agarwal *et al.*, Richeldi *et al.*, Rajchgot *et al.*, and Quadrelli *et al.*

To the Editor:

We are pleased with the lively discussion our study (1) has generated regarding cryobiopsy and how multidisciplinary assessment (MDA) of interstitial lung disease (ILD) should function.

Conclusions

1. Patients with ILDs without diagnosis should receive **complete clinical, laboratory and radiological (HRCT scan) examination** with MDT approach.

2. No diagnosis?...TBCB **could** be initially considered instead of SLB.

3. High likelihood of diagnosis with **BAL**: Sarcoidosis, Langerhan's Cell Histiocytosis, Alveolar proteinosis, Eosinophilic pneumonia

4. **Typical UIP** pattern in HRCT is considered adequate. In those cases that the clinical or laboratory findings need further investigation, TBCB should not be ruled out.

Thank you

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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], Rainer Muche[7], Michael Kreuter[2], Richard Lewis[8], Ahmed Ehab[1], Michael Boeckeler[1] and Maik Haentschel[1]

- 359 patients with interstitial lung disease were included.
- Both TBLB and TBCB were undertaken in each patient.
- The sequence of the procedures was randomized.
- Bleeding severity: “no bleeding”, “mild” (suction alone), “moderate” (additional intervention) or “severe” (prolonged monitoring necessary or fatal outcome)

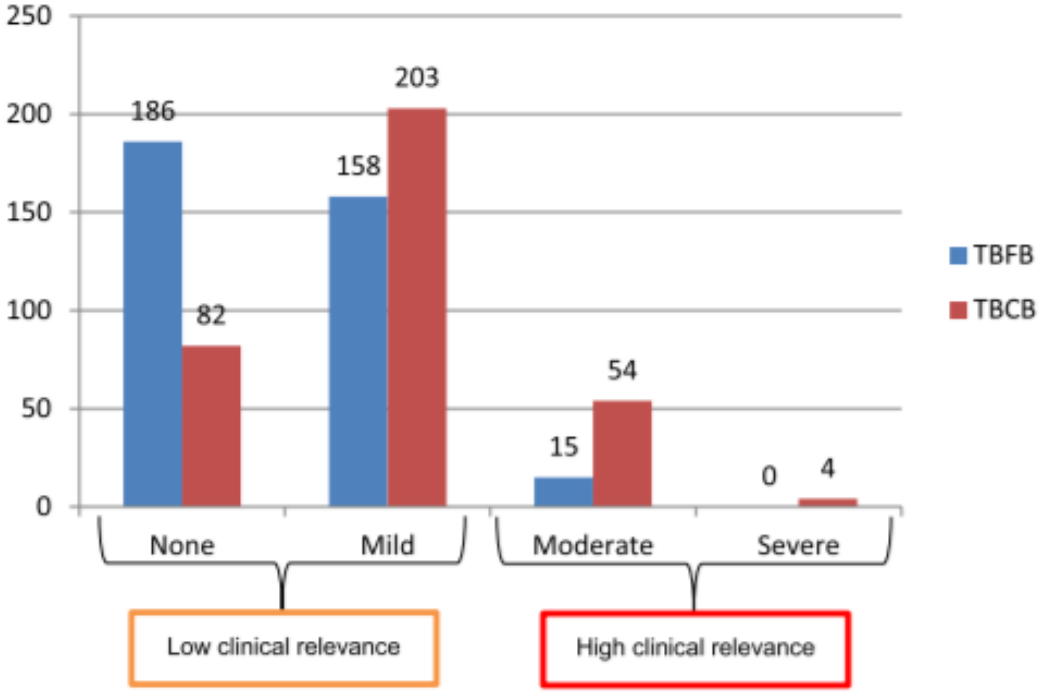

Fig. 2 Severity of biopsy-related bleeding, comparing both techniques.
(TBCB – transbronchial lung cryobiopsy; TBFB – transbronchial lung forceps biopsy)

Conclusions: TBCB was associated with an increased risk of bleeding which is of clinical relevance. Therefore training and additional precautions for bleeding control should be considered.