



HOT TOPICS
EM PNEUMOLOGIA

BRONCOLOGIA NA SARCOIDOSE

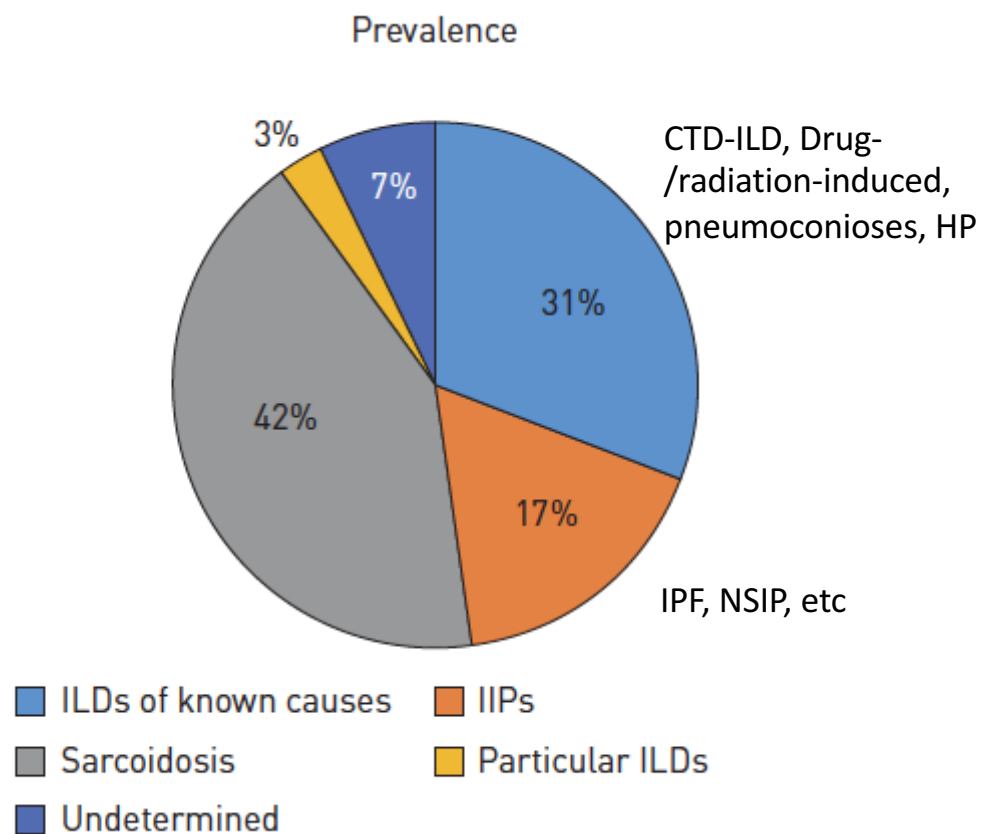
www.heldernovaisbastos.pt
hnovaisbastos@med.up.pt

23rd October 2020

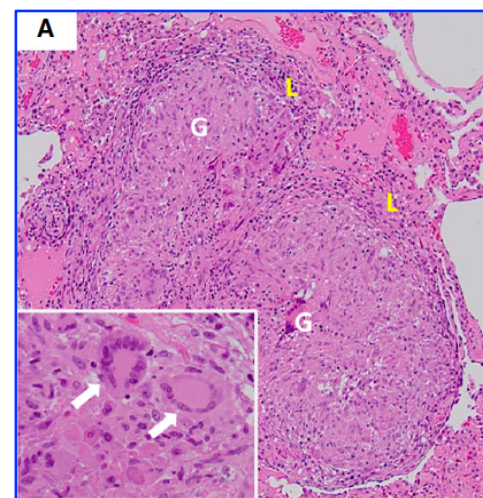


Sarcoidosis

- The most common interstitial lung disease



- Diagnosis based on 3 major criteria:
 - Compatible clinical presentation
 - **Finding of non-necrotizing granulomatous inflammation in ≥ 1 tissue samples** (not always required)
 - Exclusion of alternative causes of granulomatous disease (TB, Lymphoma, etc)



Duchemann et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J 2017; 50: 1602419

Crouser et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51

Analysis of sarcoidosis in the Oporto region (Portugal)



A.V. Cardoso^{a,*}, P.C. Mota^{b,c}, N. Melo^b, S. Guimarães^d, C. Souto Moura^d, J.M. Jesus^e,
R. Cunha^e, A. Morais^{b,c}



N=409

Anos 2000-2014

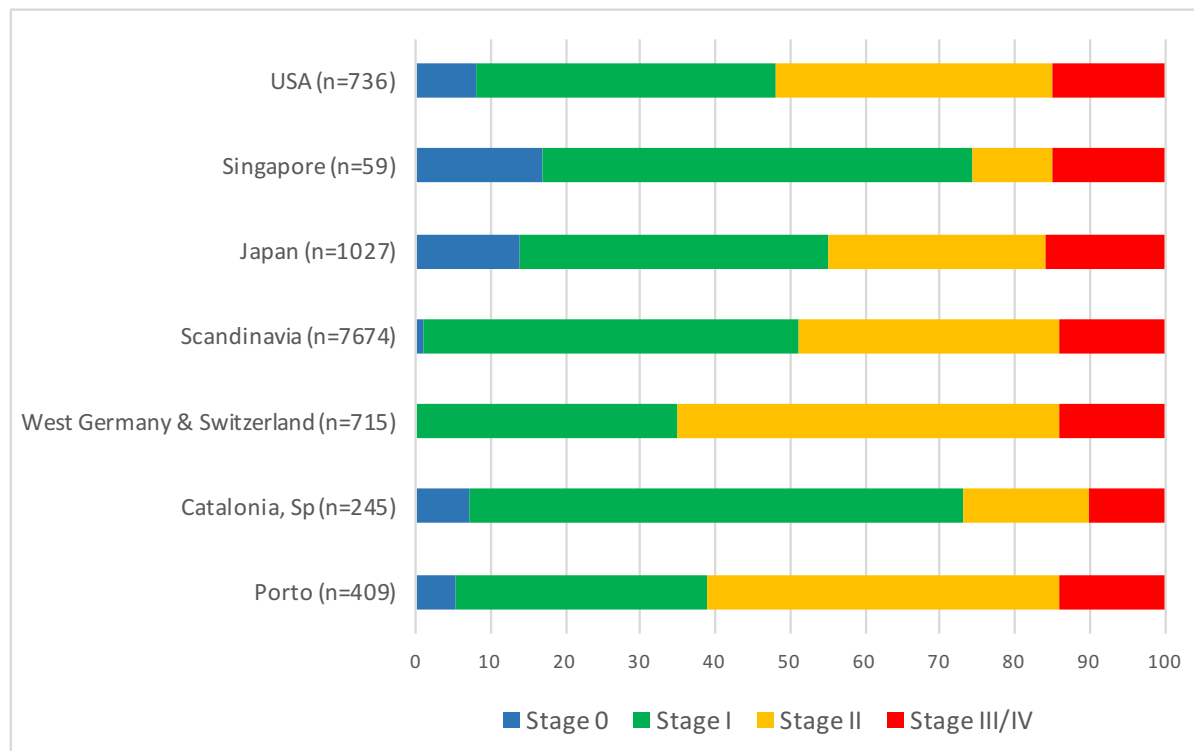
Table 3 Laboratory work-up results.

Characteristics	Mean \pm SD or %
BAL results	
Lymphocytes (%)	42.8 \pm 18.9
Lymphocytes > 15%	90.2
CD4/CD8 ratio	5.6 \pm 4.7
CD4/CD8 > 3.5	60.9
Neutrophils (%)	2.8 \pm 6.6
Eosinophils (%)	0.89 \pm 1.5
Elevated ACE (>70 UI/L)	54.3
Histological specimens	64.1
Bronchial biopsy	12.2
Skin biopsy	9.8
Transbronchial lung biopsy	7.6
Peripheral lymph node biopsy	7.6
Open lung biopsy	7.1
EBUS-TBNA	6.4
Transbronchial needle aspiration	3.2
Mediastinoscopy	3.2
Transsthoracic biopsy	2.7
Liver biopsy	2.4
Others	4.4

BAL, bronchoalveolar lavage; ACE, angiotensin-converting enzyme; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Table 2 Clinical presentations of sarcoidosis (respiratory and constitutional symptoms) and thoracic and extrathoracic involvement.

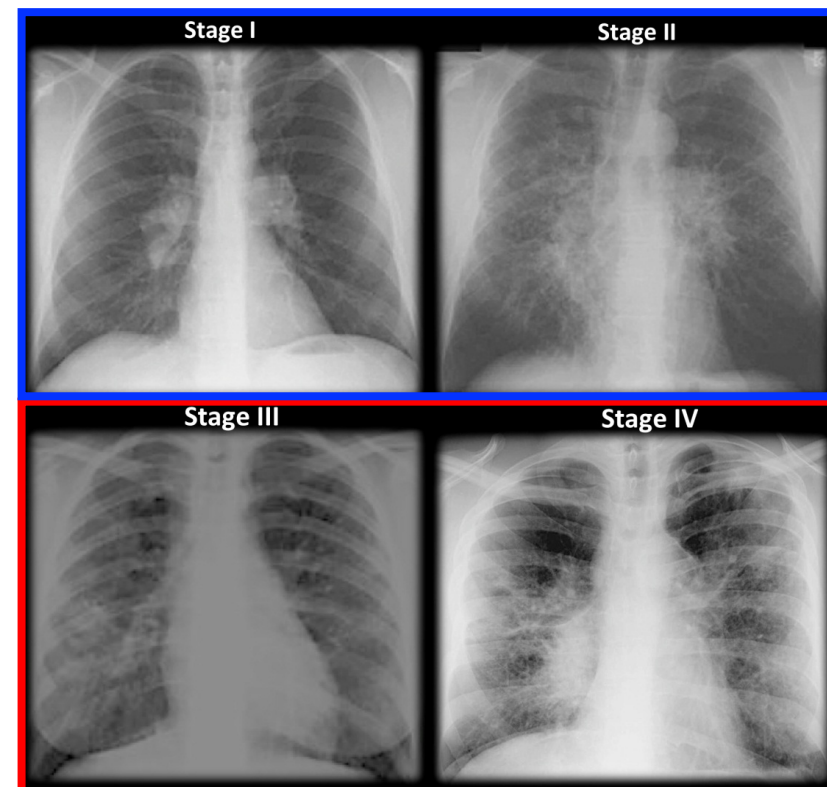
	n/total	%
Respiratory symptoms	242/396	59.2
Exertion dyspnea	175/396	44.2
Cough	173/396	43.7
Chest pain	46/396	11.6
Sputum	38/396	9.6
Wheezing	36/396	9.1
Hemoptysis	4/396	1.0
Constitutional symptoms	165/391	42.2
Asthenia	135/391	34.5
Arthralgia	94/391	24.0
Weight loss	73/391	18.7
Fever	53/391	13.6
Myalgias	31/391	7.9
Löfgren syndrome	89/391	22.8
Asymptomatic	40/396	10.1
Thoracic involvement	388/409	94.8
Stage I	138/409	33.7
Stage II	192/409	47.0
Stage III	34/409	8.4
Stage IV	23/409	5.7
Extrathoracic involvement	196/388	50.5
Skin	60/388	15.5
Nonthoracic lymph node	55/388	14.2
Eyes	53/388	13.7
Liver	26/388	6.7
Spleen	23/388	5.9
Hypercalcemia/hypercalciuria	15/388	3.9
Neurological	12/388	3.1
Cardiac	10/388	2.6
Bone	8/388	2.1
Renal	4/388	1.0



Adaptado de Rev Port Pneumol. 2017;23(5):251-258

EBUS-TBNA/cTBNA
(+ BAL, \pm TBLB, \pm EBB)

70-80%



10-15%

TBLB/TBLC
(+ BAL, \pm EBB)




Journal of
Clinical Medicine



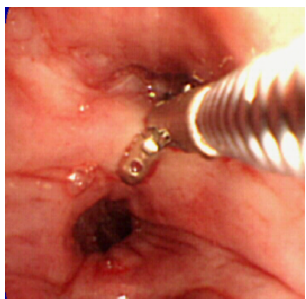
Review

Role of Bronchoscopic Techniques in the Diagnosis of Thoracic Sarcoidosis

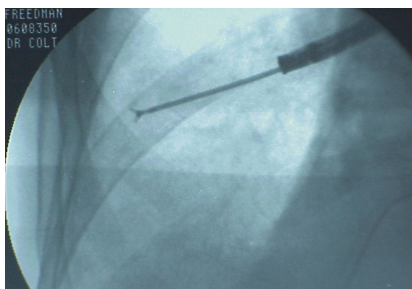
Cecília Pedro ^{1,*}, Natália Melo ², Hélder Novais e Bastos ^{1,2,3}, Adriana Magalhães ²,
Gabriela Fernandes ^{1,2}, Natália Martins ^{1,2,3} , António Morais ^{1,2} and Patrícia Caetano Mota ^{1,2}

J. Clin. Med. 2019, 8, 1327; doi:10.3390/jcm8091327

Conventional methods



endobronchial biopsy
EBB 20–61%

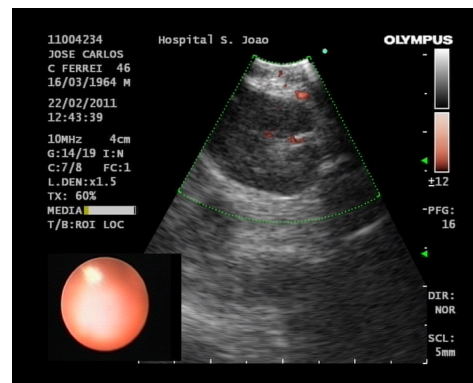


transbronchial lung biopsy
TBLB 37–90%

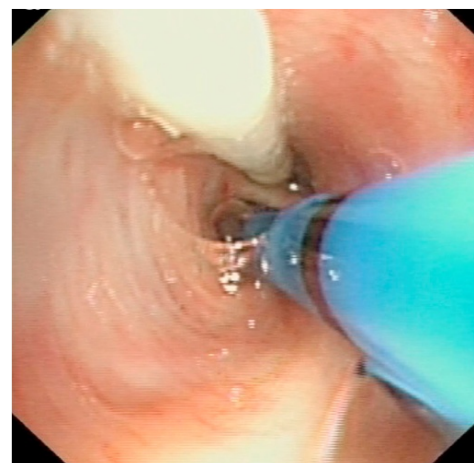


conventional transbronchial
needle aspiration
cTBNA 6–90%

Novel methods



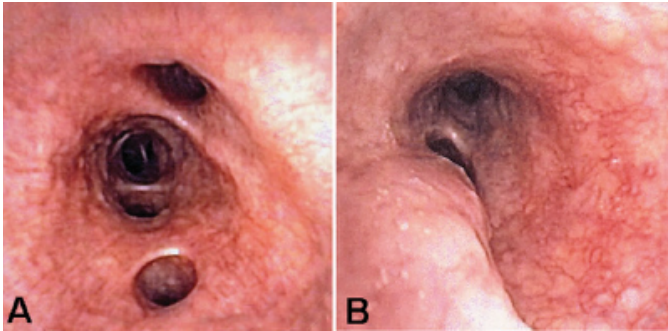
EBUS-TBNA 80–94%
EUS-FNA 77–94%
EUS-B-FNA 86%



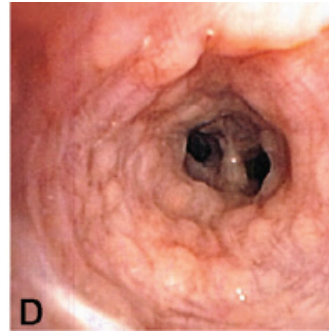
TBLC 66.7-92.6%

EBUS-TBNA, endobronchialultrasound-guided transbronchial needle aspiration;
EUS-FNA, endoscopic ultrasound-guided fine needle aspiration;
EUS-B-FNA, transesophageal ultrasound-guided needle aspiration with the use of an echo bronchoscope;
TBLC, transbronchial lung cryobiopsy

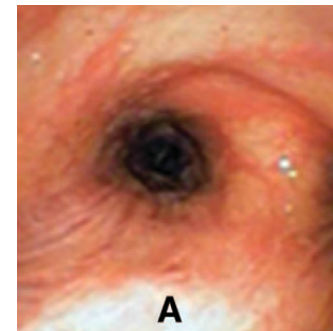
Bronchoscopic features of airway involvement in sarcoidosis



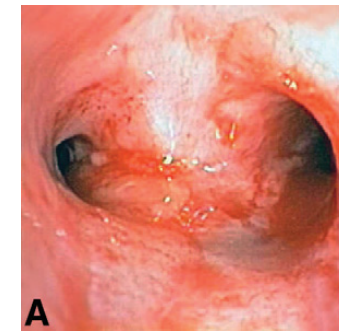
mucosal erythema, edema, capillary proliferation and granularity



Cobblestone mucosa:
typical mucosal nodules (3-4 mm) in segmental bronchus



mucosal edema and whitish plaques over the RUL bronchus carina



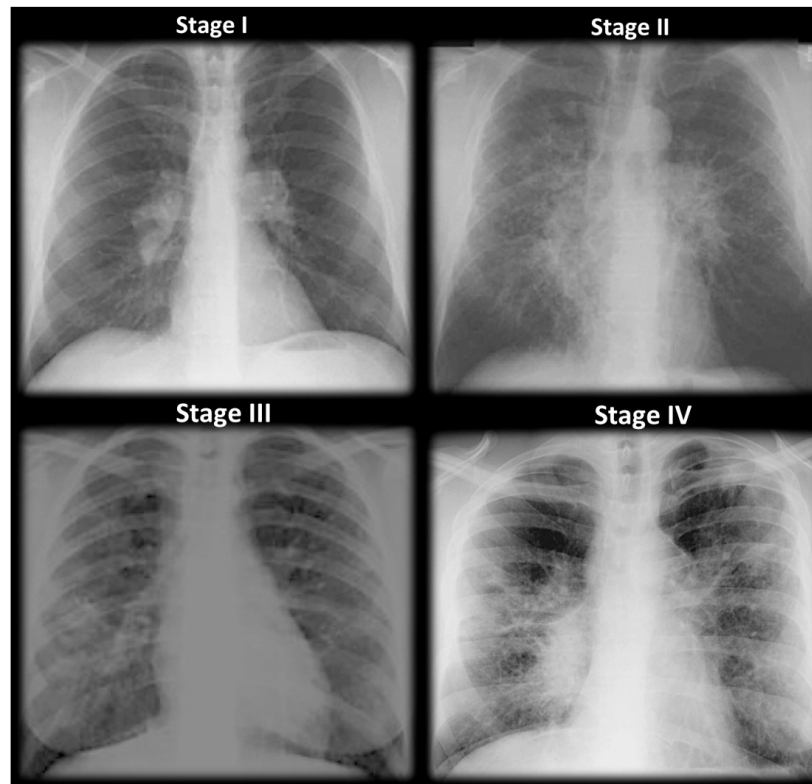
main carina with friable mucosa and mucosal pallor, and luminal narrowing

Sampling method	Normal mucosa	Abnormal mucosa
TBLB	66.1 %	79.3 %
EBB	41.7 %	75.8 %
Conventional TBNA	21.3 %	26.7 %

Sampling method	Normal mucosa	Abnormal mucosa
TBLB + EBB	77.8 %	92.8 %
TBLB + TBNA	72 %	80 %
EBB + TBNA	60.3 %	71.4 %
TBLB + EBB + TBNA	85.7 %	90 %

Diagnostic yield varies with Scadding staging

TBLB 63.1%
EBB 46.1%
cTBNA 28.6%



TBLB 75.5%
EBB 54.5%
cTBNA 36.6%

TBLB 100%
EBB 75%

TBLB 100%

Bronchoalveolar Lavage Fluid (BALF)

- Routinely recommended as an additional procedure to EBB and TBLB
- BALF lymphocytosis and a CD4/CD8 ratio ≥ 3.5 support the diagnosis of sarcoidosis in patients with a typical clinical picture (~50% cases)
 - high specificity of 93–96%
 - Low to moderate sensitivity of 52–59%

Advantages:

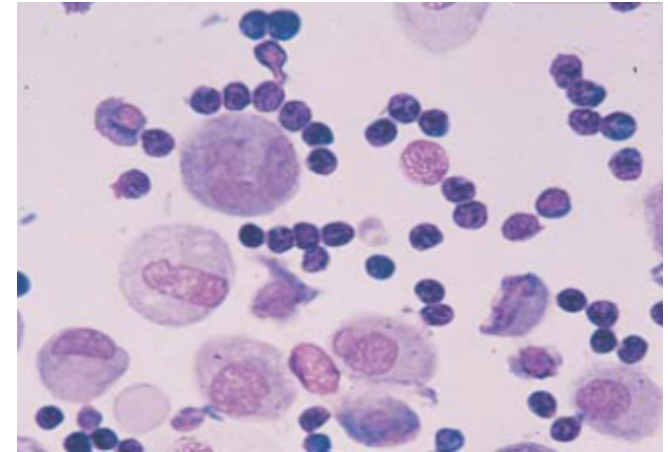
- The simplest and least invasive bronchoscopic procedure
- Differential diagnosis with granulomatous infections (fungal or mycobacterial), malignancy and lymphoproliferative disorders

Disadvantages:

- Lymphocytosis and CD4/CD8 ratio are highly variable
- 10% to 15% of cases have a normal cell count
- 12% may have an inverted ratio below 1.0 (predominance of CD8⁺ cells)

Pedro et al. J. Clin. Med. 2019, 8, 1327

Kantrow et al. European Respiratory Journal 1997 10: 2716-2721

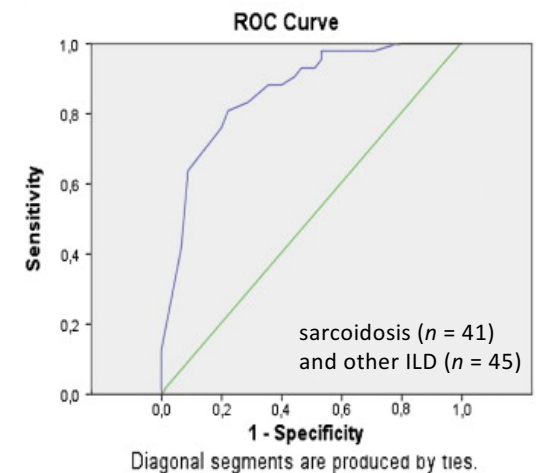


Bonella et al. Eur Respir Mon, 2010, 48, 59–72

CD103⁺CD4⁺/CD4⁺ ratio

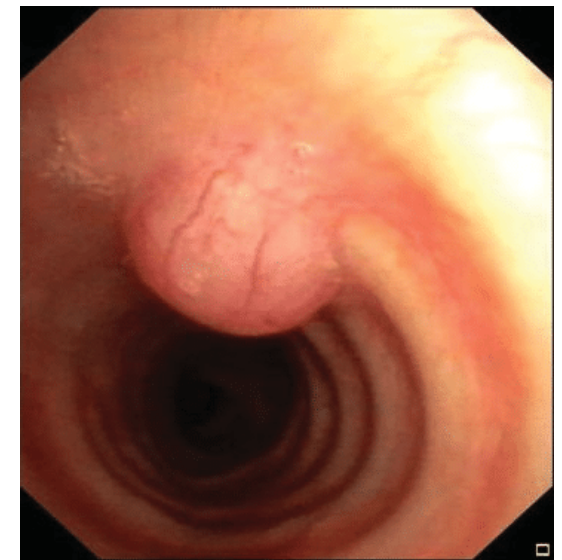
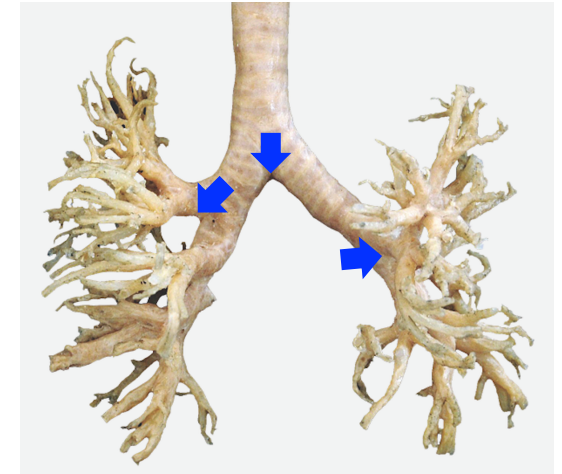
- Cutoff point of 0.45
- AUC 0.86 (95% CI): 0.78–0.94
- Sensitivity: 81%; specificity: 78%
- Better diagnostic performance for sarcoidosis even for those with a CD4⁺/CD8⁺ ratio < 3.5

Mota P et al. Respir. Med. 2012, 106, 1014–1020



Endobronchial Biopsy (EBB)

- EBB has a lower diagnostic yield than TBLB
- **≥3 samples from different sites**, such as main carina, subsegmental carina and/ or endobronchial nodules
- Should be taken, even in the absence of typical sarcoidosis characteristics
- A very low risk procedure
 - Potential complications: extensive cough, intolerance and minor bleeding

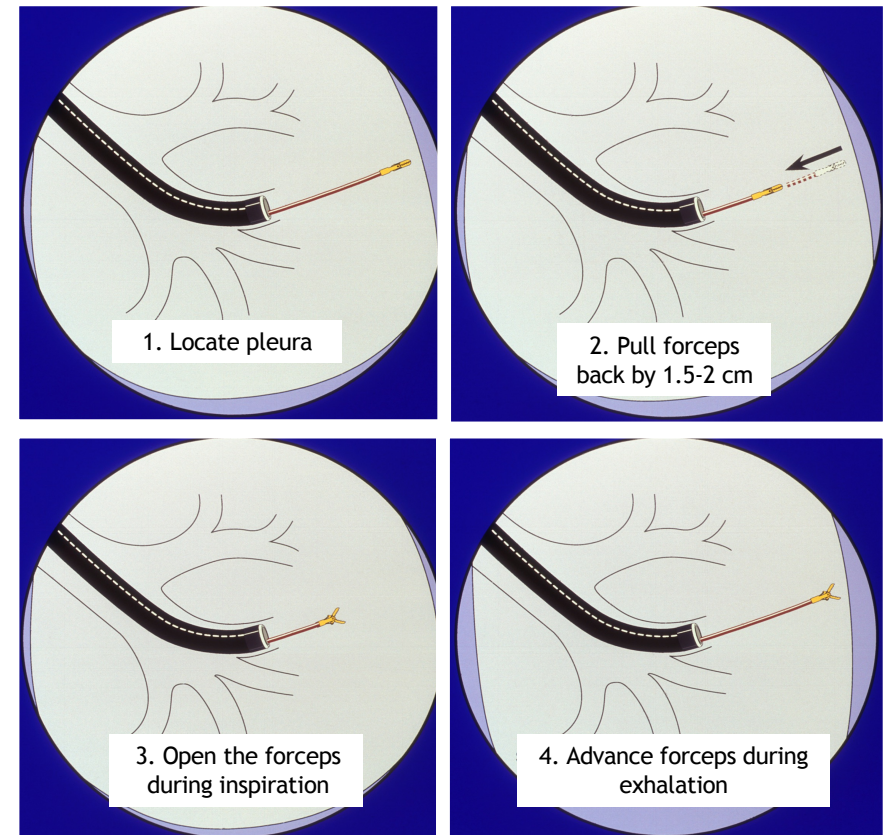


51-year-old Caucasian woman, diagnosed with sarcoidosis
Isolated endobronchial granuloma

Bonifazi et al. Seminars in Respiratory and Critical Care Medicine 2017

Transbronchial Lung Biopsy (TBLB)

- Diagnostic yield varies according:
 - to the operator's experience
 - radiological Scadding stages –
stage I: 66%;
stage II: 80%;
stage III: 83%
 - normal (66%) vs **abnormal mucosa (79%)**
 - combination with other techniques –
TBLB 69%;
TBLB + EBB 81% ;
TBLB + EBB + cTBNA 87%
- **≥4 samples from different segments**



Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

Von Bartheld et al. JAMA. 2013;309(23):2457-2464

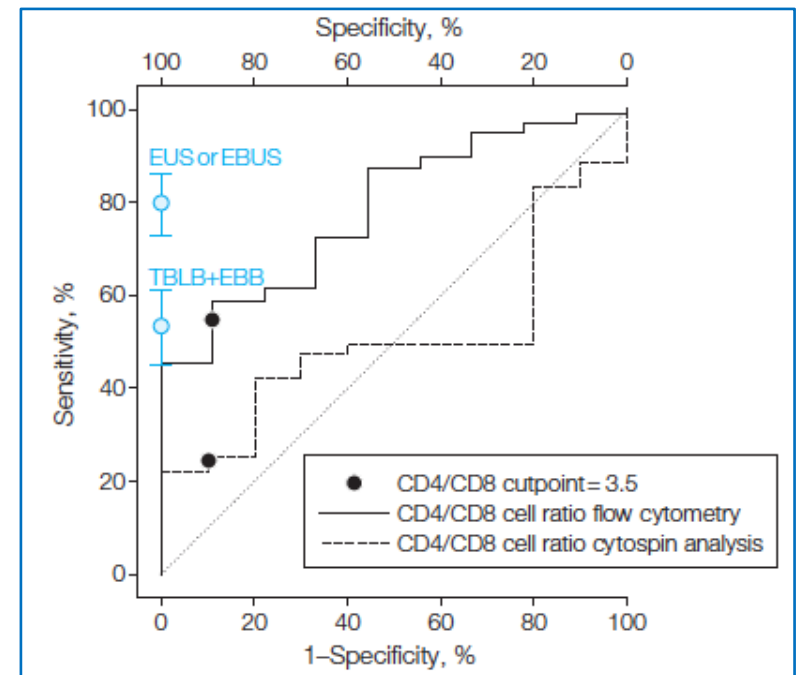
- Randomized clinical multicenter trial (14 centers in 6 countries)
- 304 consecutive patients with suspected pulmonary sarcoidosis (stage I/II)

Table 3. Granuloma Detection and Diagnostic Yield for Sarcoidosis and the Final Diagnoses by Group

	No. (%)	
	Bronchoscopy (n = 149)	Endosonography (n = 154)
Detection of granulomas, consistent with the diagnosis of sarcoidosis	72 (48)	114 (74)
Diagnostic yield of granuloma detection in patients with sarcoidosis	72/136 (53)	114/142 (80)
Final diagnosis Sarcoidosis	136 (91)	142 (92)

Table 2. Characteristics of Endoscopy

	No. (%)			
	Bronchoscopy (n = 149)		Endosonography (n = 154)	
	TBLB	EBB	EUS-FNA	EBUS-TBNA
Procedure performed	143/149 (96) ^{a,b}	138/149 (93) ^a	102/154 (66) ^c	56/154 (36) ^c
No. of biopsies, mean (SD)	5.24 (1.53)	4.10 (1.03)	5.21 (1.40)	5.75 (2.01)
Patients with ≥4 biopsy specimens collected	139/149 (93)	121/149 (81)	64/68 (94) ^d	42/43 (98) ^d
Representative material ^e	138/149 (93)	132/149 (89)	97/103 (94)	51/56 (91)



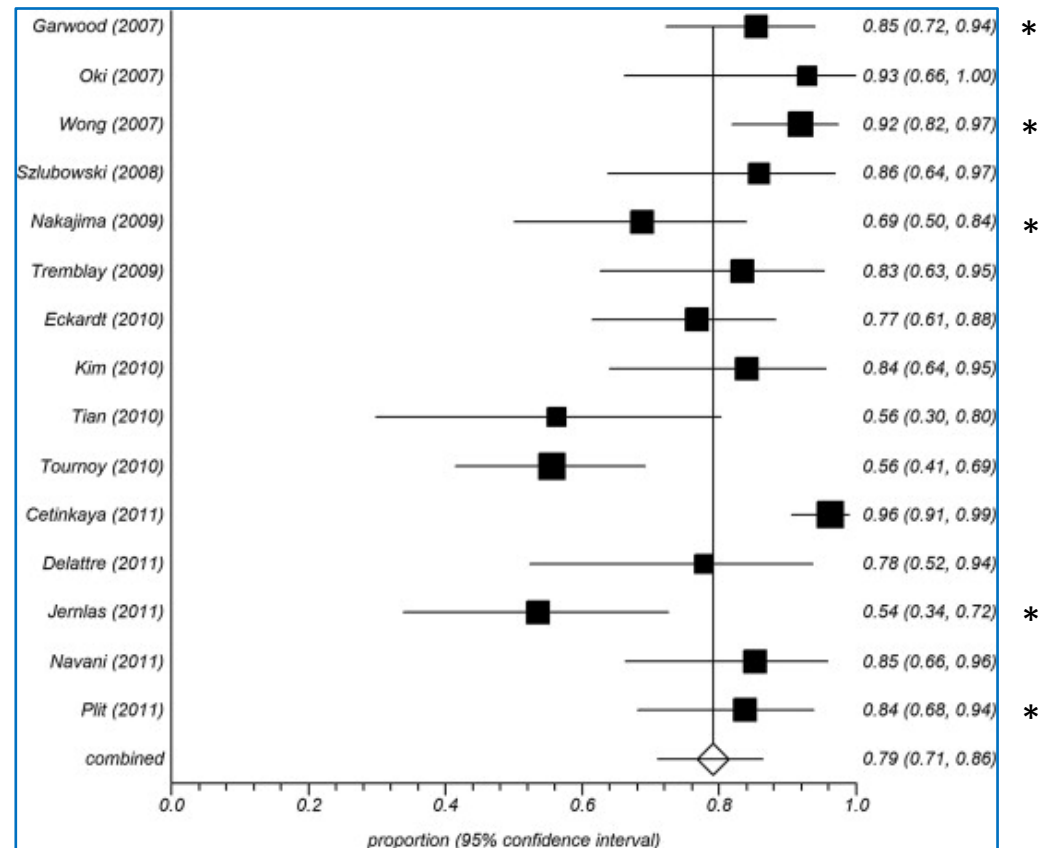
cTBNA vs EBUS-TBNA in sarcoidosis

Study/Year	Study Design	No. Pts	Study Protocol	Main results
Oki et al. Respirology 2007	Prospective study Stage I and II	15	EBUS-TBNA (22G) followed by cTBNA (19G) at same site of EBUS	<ul style="list-style-type: none"> • EBUS-TBNA: 13/14 (93%); • cTBNA: 13/14 (93%); • both: 14/14 (100%)
Tremblay et al. Chest 2009	Prospective RCT study Stage I and II	50	cTBNA (19G) vs EBUS-TBNA (22G); 50% underwent EBB and 38-40% TBLB	<ul style="list-style-type: none"> • EBUS-TBNA: 4 LN groups; DY 20/24 (83%); Sens 83% • cTBNA: 2 LN groups; DY 14/26 (54%); Sens 61% • EBUS-TBNA procedure time, 10 min longer.
Gupta et al. Chest 2014	Prospective RCT study Stage I and II	130	cTBNA (21G) vs EBUS-TBNA (21G); 93-94% underwent EBB and 92-94% TBLB	<ul style="list-style-type: none"> • EBUS-TBNA: 41/55 (74.5%) • EBUS-TBNA + EBB + TBLB: 92.7% • cTBNA: 30/62 (48%) • cTBNA + EBB + TBLB: 85.5%

Efficacy and safety of EBUS-TBNA in sarcoidosis

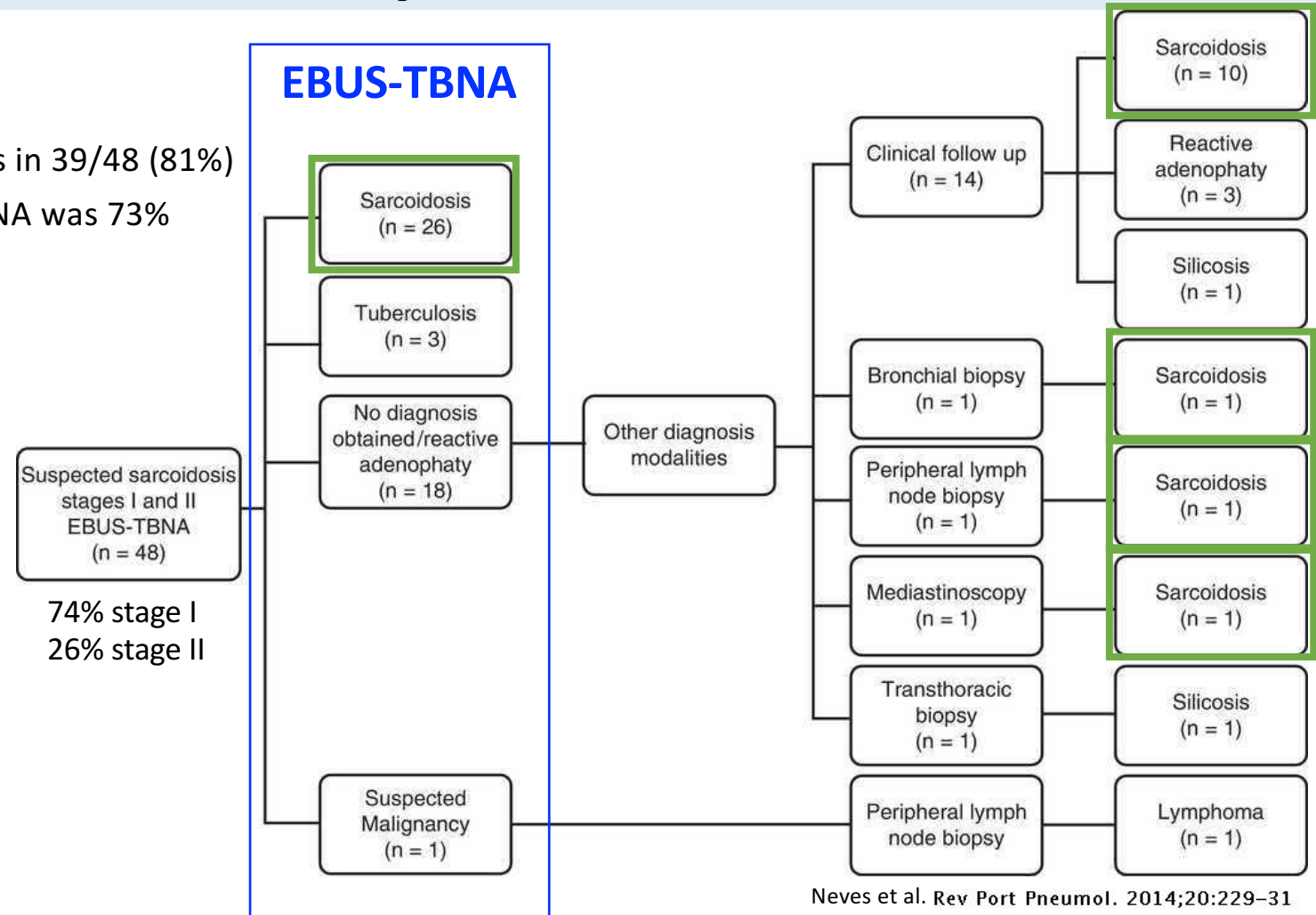
A systematic review and meta-analysis:

- 15 studies (553 patients of sarcoidosis)
- Diagnostic yield ranged from 54 to 93%
- **Pooled diagnostic 79% (95% CI, 71-86%)**
- **Only five minor complications reported**
 - Airway edema/hypoxemia (n=2)
 - Minimal pneumothorax
 - Minor bleeding
 - Prolonged cough



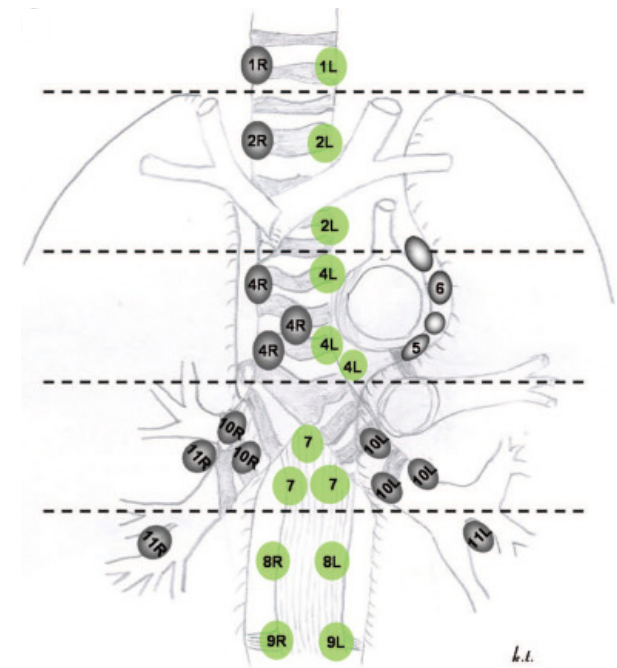
Our experience

- Final diagnosis of sarcoidosis in 39/48 (81%)
- Diagnostic yield of EBUS-TBNA was 73%
- Sensitivity 67%
- Specificity 100%
- NPV 41%



EUS in sarcoidosis

Study/Year	No. Pts	Sensitivity
Annema et al. ERJ 2005	51	EUS-FNA: 82%
Iwashita et al. Endoscopy 2008	41	EUS-FNA: 78%
Von Bartherld et al. Endoscopy 2010	101	EUS-FNA: 87% (cytology + cell-block) (stage I, 92% ; stage II, 77%)
Kocoń et al. Pol Arch Intern Med 2017	100	EUS-FNA: 75% EUS-b-FNA: 62% EBB + TBLB + cTBNA: 64%
Filarecka et al. Pol Arch Intern Med 2020	50	EBUS-TBNA: 77% EUS-b-FNA: 70% EBUS-TBNA (≥2) + EUS-b-FNA (≥2): 92%



Tournoy et al. JTO 2009

ISA trial

RCT (4 continents, 9 countries, 13 hospitals)

EBUS vs EUS-B for diagnosing sarcoidosis

Standard 22G vs ProCore 25G

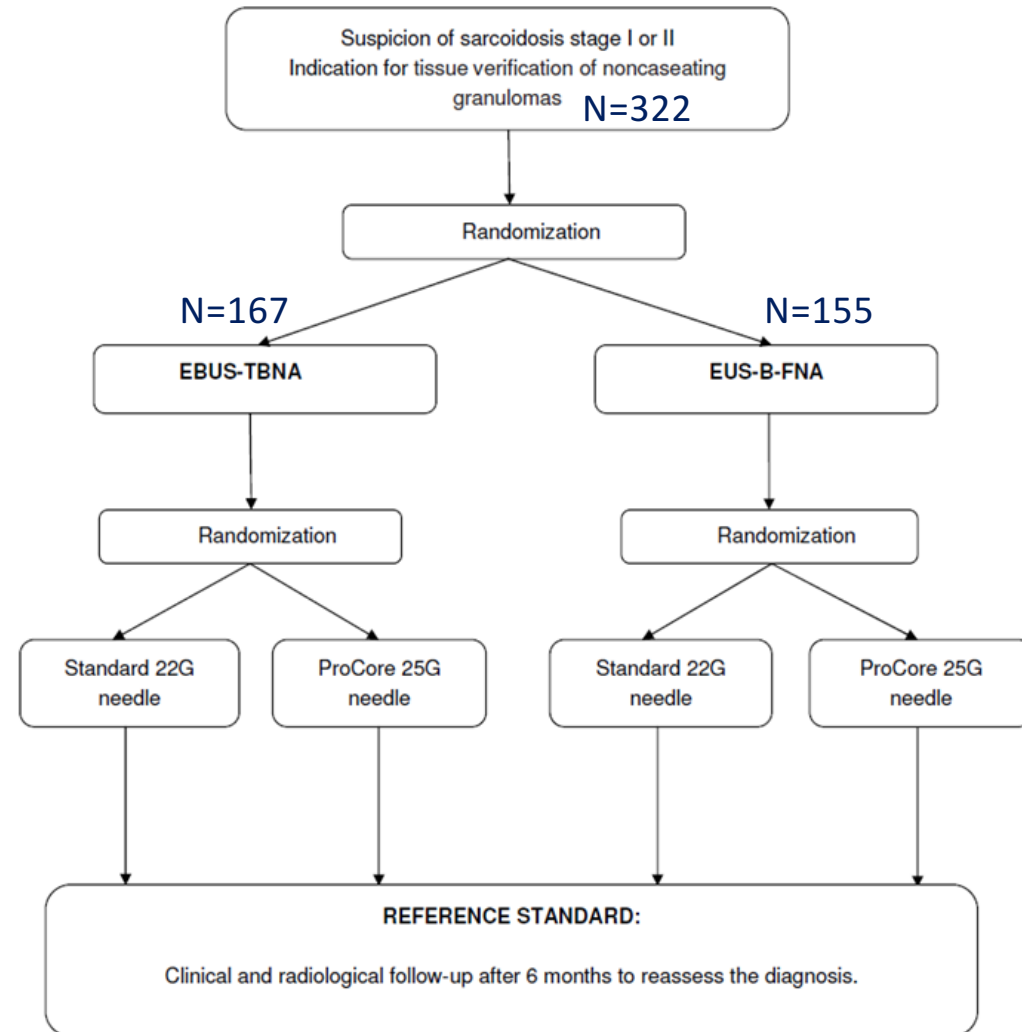


Kalverda et al. ERS Congress 2018

- 85% confirmed sarcoidosis
- Granuloma detection rate was 73% overall*
 - 75% EBUS-TBNA vs 70.3% EUS-b-FNA (NS)

*independent of needle type

- Overall sensitivity 85%
 - 84% EBUS-TBNA vs 87% EUS-b-FNA (NS)
- No major complications



Infectious complications with EUS-FNA

Table 2. Overview of SAE following EUS-FNA (n = 6,042) and EBUS-TBNA (n = 9,119) for mediastinal analysis (n = 23)

	EUS (n = 18)	EBUS (n = 5)
Infectious complications (n = 12)	10	2
Mediastinitis	5	0
Mediastinal abscess/abscess formation	2	1
Sepsis	1	1
Pleuropericarditis	1	0
Aspiration pneumonia	1	0
Perforations (n = 4)	4	0
Esophageal perforation/rupture	3	
Sinus piriformis perforation	1	
Pneumothorax (n = 2)	0	2
Hemorrhagic complications (n = 2)	2	0
Mediastinal hematoma	1	
Periesophageal bleeding	1	
Respiratory complications (n = 3)	2	1
Hypoxemia due to airway edema	■	■
Apnea under propofol	■	■
Required reversal medication	1	0

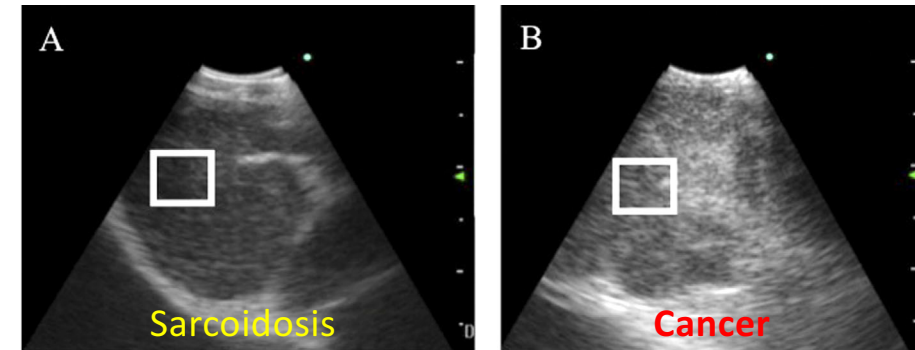


- Retrospective report of 5 cases with sarcoidosis (stage I/II) who developed mediastinal abscesses after EUS-FNA of subcarinal lymph nodes
- Use of prophylactic antibiotic treatment?

Echoic Findings of lymph nodes with Sarcoidosis

		Sarcoidosis	Lung cancer	P-value
Shape	Round	64%	86%	0.089
	Oval	36%	14%	
Margin	Distinct	71%	56%	0.113
	Indistinct	29%	44%	
Echogenicity	Homogeneous	88%	32%	<0.001
	Heterogeneous	12%	68%	
Germinal center structure	Present	71%	27%	<0.001
	Absent	29%	73%	

Imai et al. N Intern Med 2013

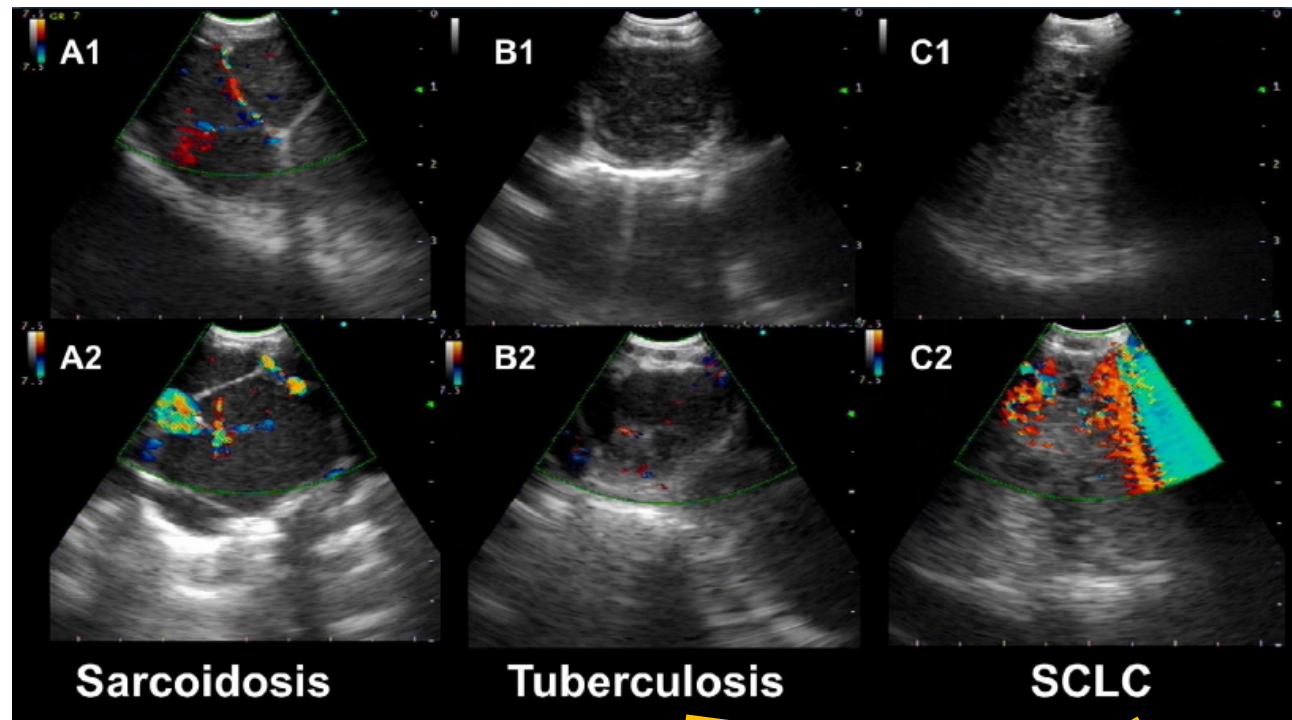


	Cancer (n=19)	TB (n=15)	Sarcoidosis (n=56)	P-value
Mediastinal LN size	3.96 cm	2.61 cm	2.44 cm	0.004
Hilar LN size	1.48 cm	1.81 cm	2.39 cm	0.001
Oval shape	89.5 %	86.7 %	67.9 %	0.09
Conglomeration	5.3 %	60 %	94.6 %	<0.001
Septal vessel	15.8 %	13.3 %	55.4 %	0.002
Distinct margin	47.4 %	13.3 %	73.2 %	<0.001
Heterogeneous	100 %	93.3 %	50 %	<0.001
Calcification	0	40 %	7.1%	<0.001
Central hilar sign	21.1 %	40 %	50 %	0.08
Coagulation necrosis sign	31.6 %	93.3 %	8.9 %	<0.001

LN ≥20 mm usually are diagnostic

Cheng et al. J Ultrasound Med 2020

Echoic Findings of lymph nodes with Sarcoidosis



	Sensitivity, %	Specificity, %
Conglomeration sign	94.6 (85.1–98.9)	70.5 (52.5–84.9)
Septal vessel sign	60.8 (46.1–74.2)	84.4 (67.2–94.7)

Absence of the conglomeration sign and the septal vessel sign and **presence of coagulation necrosis sign**

Tecnhical aspects

Does needle size matters?

	Granuloma detection rate	Ref.
Conventional 22G needle ProCore 25G biopsy needle	119/162 (73%) 117/160 (73%)	Kalverda et al. ERS Congress 2018
21G needle 22G needle	57/74 (77%) 54/69 (78.3%)	Muthu V, Gupta N, et al. <i>Chest</i> 2016
19G needle* *under investigation, no large comparative studies	14/15 (93.3%) 13/14 (93.3%)	Balwan A. J Bronchol Interv Pulmonol 2018 Tyan et al. Respiration 2017

Number of needle passes

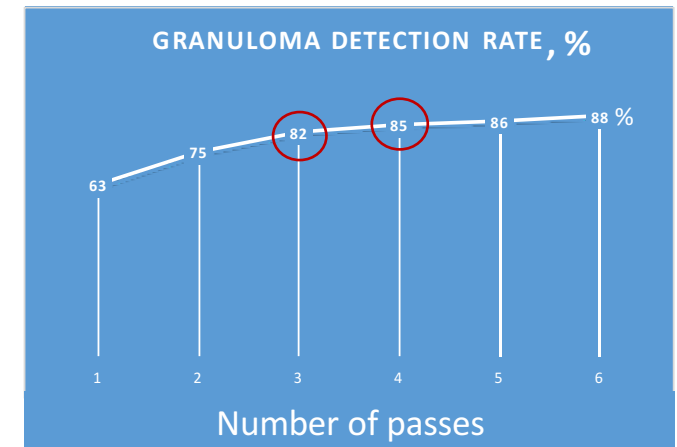
Oki et al. Respiration 2018

- EBUS-TBNA identified granulomas in 81/92 (88%) patients
- The cumulative yields of 2 passes per lesion for 2 lesions (total of 4 passes) was 86%, and of 4 passes for single lesions was 84%
- **If ROSE is not available, at least 4 passes per patient for either single or multiple lesions is recommended**

Rapid On-Site Evaluation (ROSE)

	Granuloma detection rate
cTBNA without ROSE	68%
cTBNA with ROSE	89%
EBUS-TBNA without ROSE	84%
EBUS-TBNA with ROSE	83%

Madan et al. J Bronchol Intervent Pulmonol 2017





ORIGINAL ARTICLE

The value of rapid on-site evaluation during EBUS-TBNA



A.V. Cardoso^{a,*}, I. Neves^a, A. Magalhães^a, M. Sucena^a, H. Barroca^b, G. Fernandes^{a,c}

10 patients with sarcoidosis

Table 2 Adequacy of cytological samples.

Patients	Adequate sampling		p-Value
	ROSE group	Non-ROSE group	
Total of patients, n/total (%)	38/41 (93)	32/40 (80)	0.10
Investigation of mediastinal/hilar lesions etiology, n/total (%)	27/29 (93)	24/32 (75)	0.06
Lung cancer staging, n/total (%)	11/12 (92)	8/8 (100)	1.00

Table 4 Diagnostic performance of EBUS-TBNA with and without ROSE.

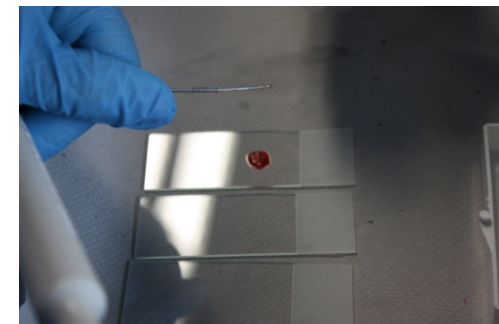
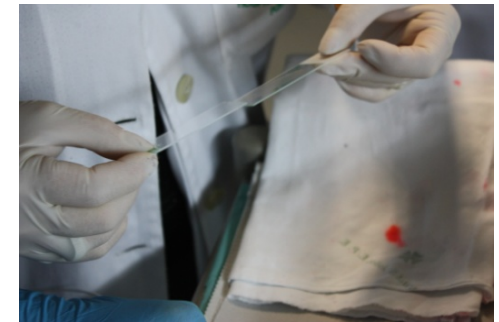
	ROSE (n = 41)	Non-ROSE (n = 40)
<i>Nondiagnostic cases</i>	17 (n = 7)	20 (n = 8)
Mediastinal/hilar lesions investigation	21 (n = 6)	25 (n = 8)
Lung cancer staging	8 (n = 1)	0 (n = 0)
<i>Sensitivity (nondiagnostic included)</i>	89 (71)	74 (52)
Mediastinal/hilar lesions investigation	85 (65)	69 (46)
Lung cancer staging	100 (88)	100 (100)
<i>Specificity</i>	100	100
<i>PPV</i>	100	100
<i>NPV (nondiagnostic included)</i>	70 (41)	69 (46)
Mediastinal/hilar lesions investigation	50 (25)	46 (29)
Lung cancer staging	100 (80)	100
<i>Accuracy (nondiagnostic included)^a</i>	91 (76)	83 (66)
Mediastinal/hilar lesions investigation ^b	87 (69)	77 (57)
Lung cancer staging ^c	100 (92)	100 (100)

Data are presented as %.

^a p-Value = 0.08 (0.20).

^b p-Value = 0.10 (0.21).

^c p-Value = NA (0.13).



Determining Factors in Diagnosing Pulmonary Sarcoidosis by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Ann Thorac Surg 2015

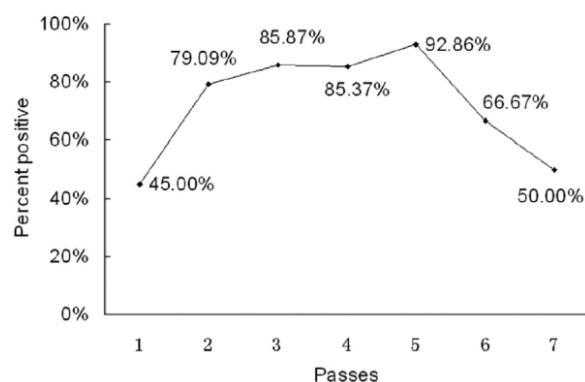


Fig 2. Yield per pass with endobronchial ultrasound-guided transbronchial needle aspiration per lymph node in patients with sarcoidosis.

in stage I than stage II. To obtain a higher diagnostic yield of EBUS-TBNA in pulmonary sarcoidosis without ROSE, operators should select the largest mediastinal or hilar lymph node accessible and puncture with preferably 3 but up to 5 passes.

The role of EBUS-TBNA and standard bronchoscopic modalities in the diagnosis of sarcoidosis

Dariusz Adam Dziedzic, Adam Peryt and Tadeusz Orlowski

Department of Thoracic Surgery, National Research Institute of Chest Disease, Warsaw, Poland

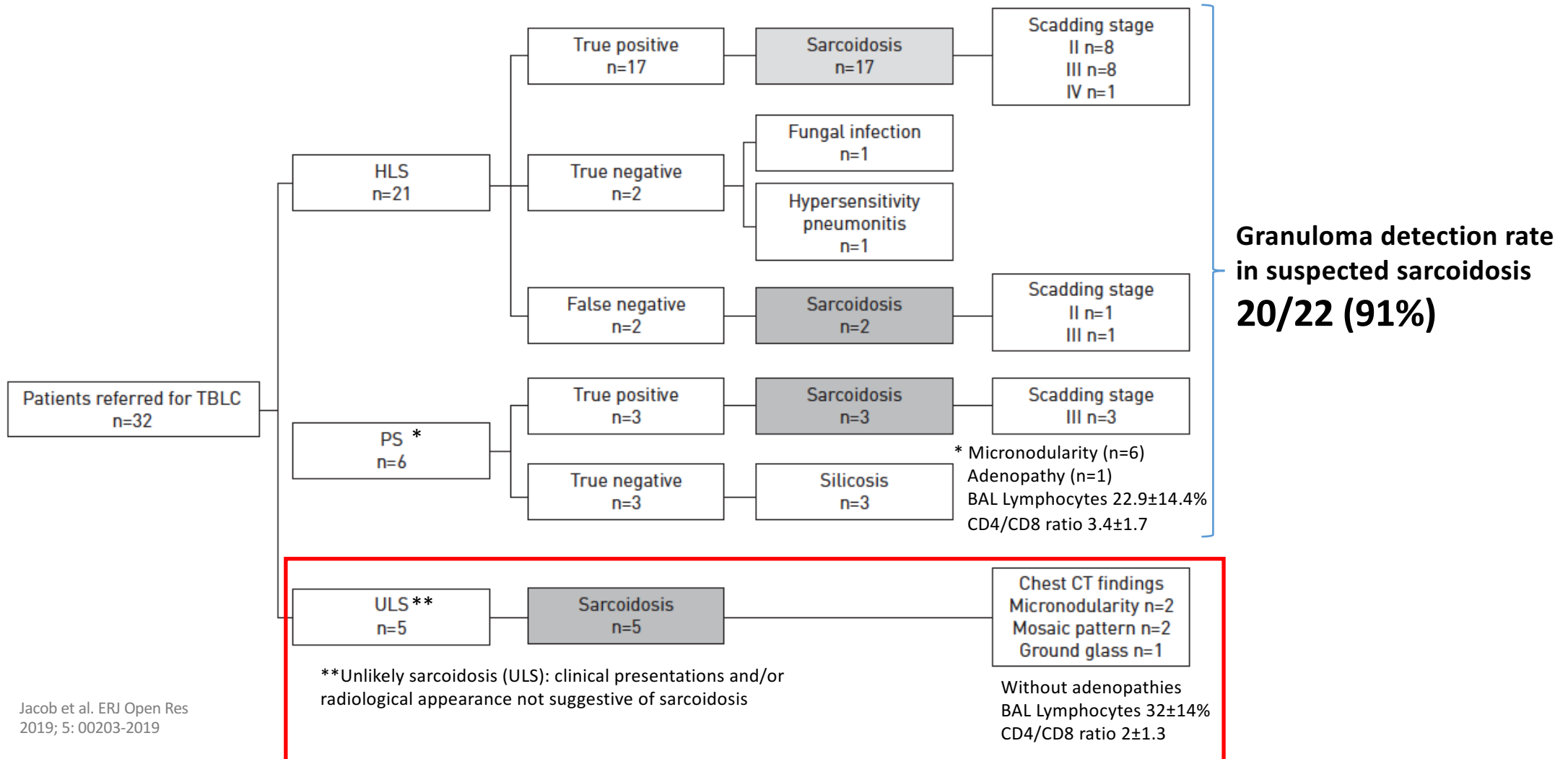
Clin Respir J 2015

Table 1. LN station biopsied

LN stations	No. of LN biopsied	No. of positive LNs
2R	18	10 (56%)
2L	12	8 (67%)
4R	323	230 (71%)
4L	195	98 (50%)
7	432	301 (70%)
11R1	47	32 (68%)
11L	18	11 (61%)

LN, lymph node.

Transbronchial lung cryobiopsy (TBLC)



Transbronchial lung cryobiopsy (TBLC)

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Total cases	2	13	14	3	2
Sarcoidosis cases	1	7	6	2	2
Number (%) EBUS-FNA positive	0/1 (0%)	5/7 (71.4%)	6/6 (100%)	0/2 (0%)	1/2 (50%)
Number (%) TBLC positive	1/1 (100%)	4/7 (57.1%)	4/6 (66.7%)	2/3 (66.7%)	1/2 (50%)

**Diagnostic yield for EBUS-FNA
and TBLC was 100%**

Aragaki-Nakahodo et al. Respir Med. 2017 Oct;131:65-69

- Particularly helpful in cases without significant adenopathy with/without parenchymal abnormalities
- Avoids surgical lung biopsies in atypical cases
- TBLC should be restricted to patients with suspected sarcoidosis and inconclusive TBLB, in whom an alternative diagnosis is likely

TBLB *versus* TBLC

	TBLB	TBLC
Diagnostic yield	80-83%	67-91%
Features	Minimal sedation Flexible bronchoscope	General anaesthesia Rigid bronchoscope
Limitations	Crush artifacts (do not represent the lung architecture) Small size	Costly May require hospitalization
Complications	Bleeding 1.3-4% Pneumothorax 2-5.5% Mortality 0.2%	Bleeding 3.1-15.6% Pneumothorax 11-15.6% Mortality 3%

MAIN TAKE HOME MESSAGES

BALF lymphocytosis and a CD4/CD8 ratio ≥ 3.5 support the diagnosis of sarcoidosis in patients with a typical clinical picture

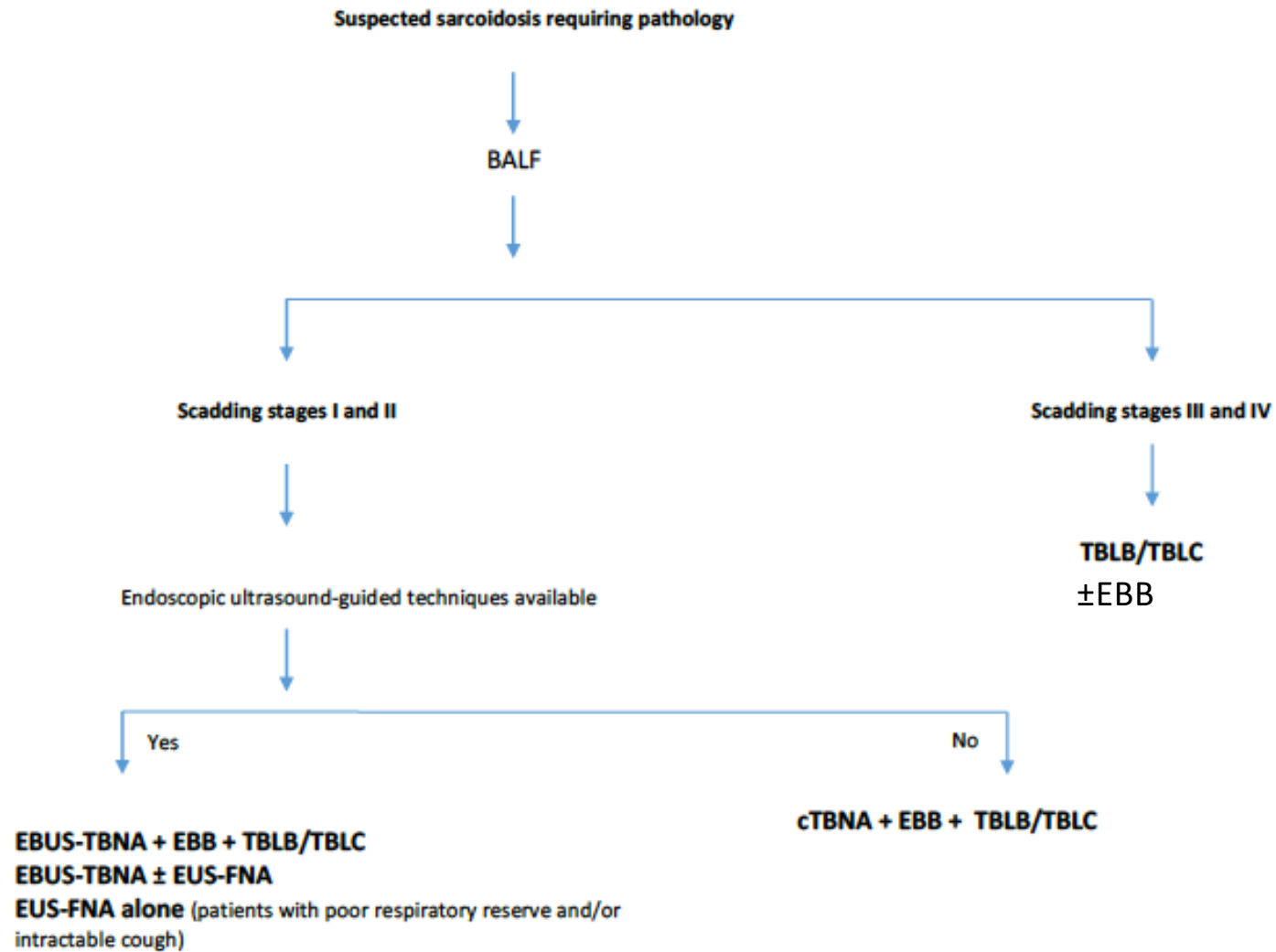
TBLB + EBB has high diagnostic yield in sarcoidosis patients with abnormal mucosa

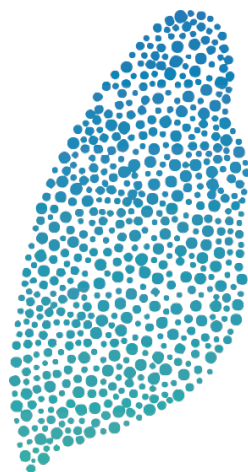
EBUS allows the selection of the best possible areas for sampling avoiding regions with increased vascularity and extensive calcification

EBUS/EUS-B-FNA is the first-line diagnostic tool in sarcoidosis stages I and II

- High yield (80-90%, better in stage I and when different techniques are combined)
- ≥ 4 needle passes per patient if no ROSE
- Safe (more complications with EUS-FNA, or when combined with EBB and TBLB)

TBLC should be restricted to patients with suspected sarcoidosis and inconclusive TBLB





XXVII
 CONGRESSO DE
 PNEUMOLOGIA
 DO NORTE
 XXXIII JORNADAS
 GALAICO DURIENSES
 5 A 7 DE MARÇO DE 2020
 SHERATON PORTO HOTEL

Obrigado pela atenção

