XXVII CONGRESSO DE PNEUMOLOGIA DO NORTE

XXXIII JORNADAS GALAICO DURIENSES

5 A 7 DE MARÇO DE 2020
SHERATON PORTO HOTEL

Papel do EBUS/EUS no diagnóstico de sarcoidose e linfoma

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18th October 2020

SÃO JOÃO HOSPITAL

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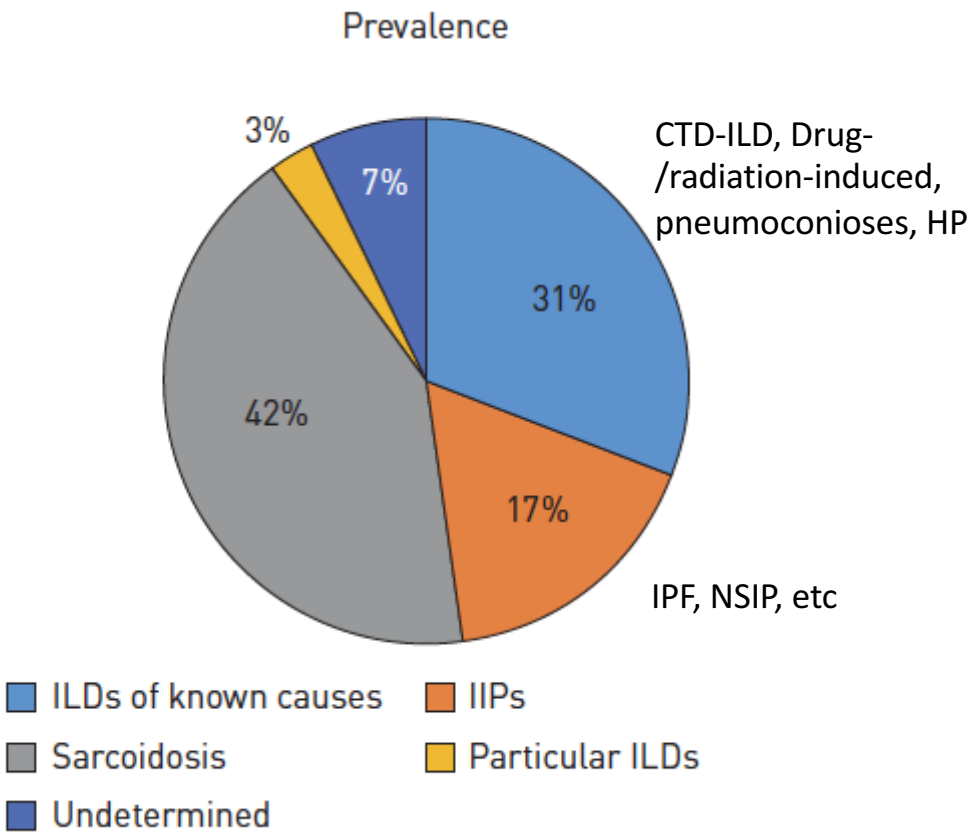
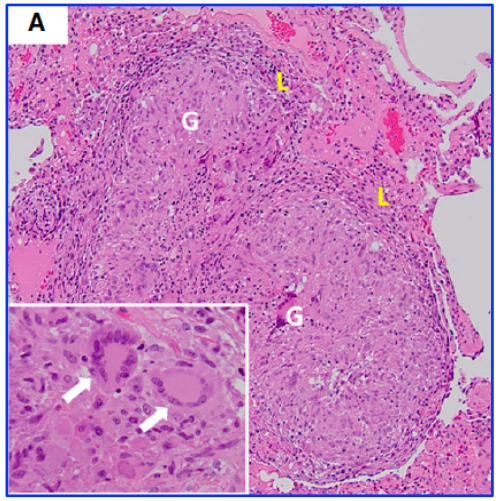
Sarcoidosis

- The most common interstitial lung disease



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

- 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)

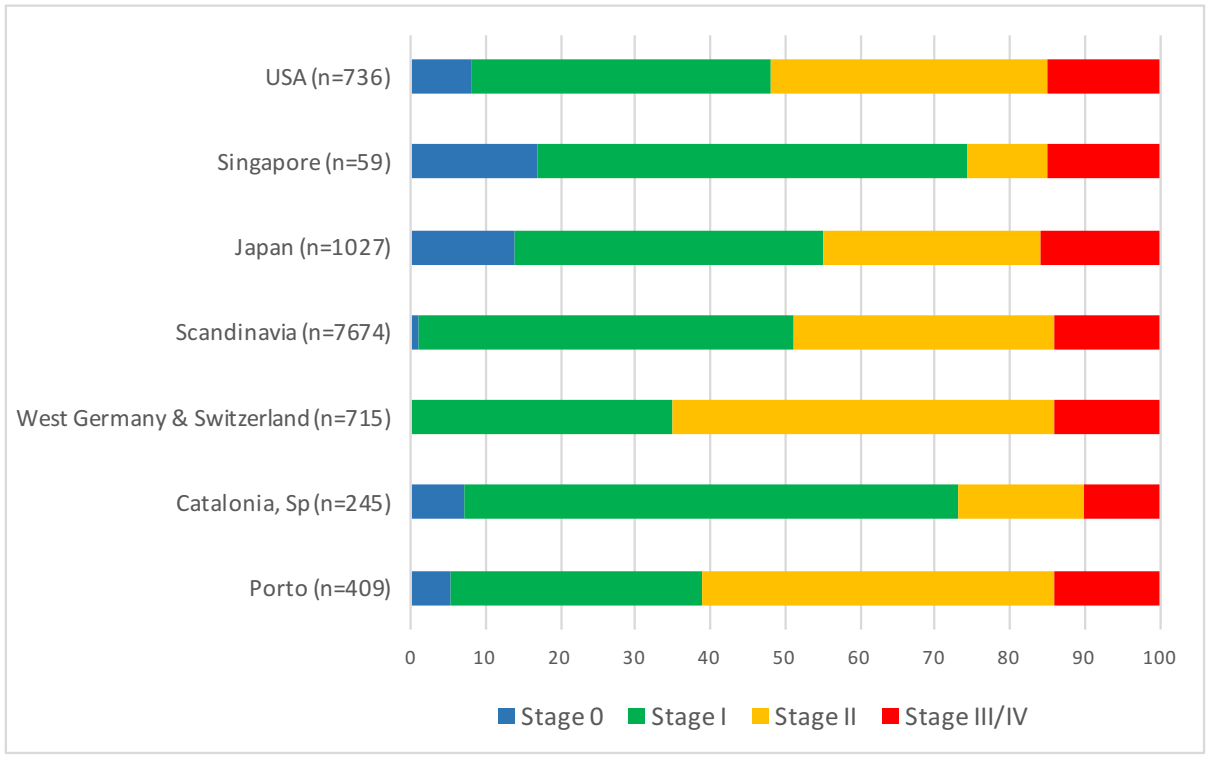


Crouser et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51

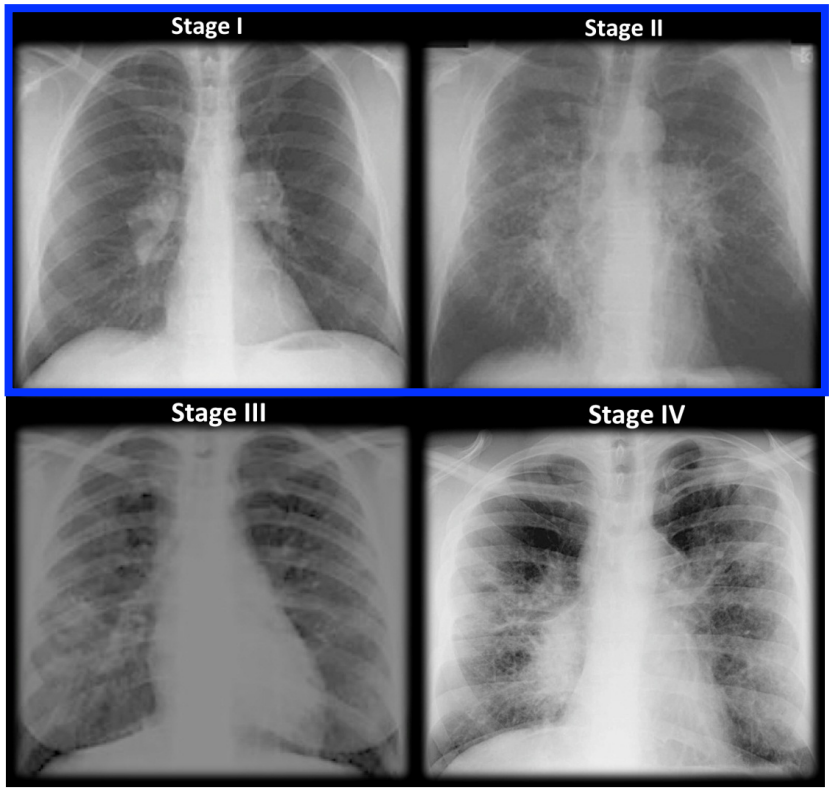
EBUS-TBNA

(vs conventional TBNA; ± BAL, ±TBLB, ±EBB)

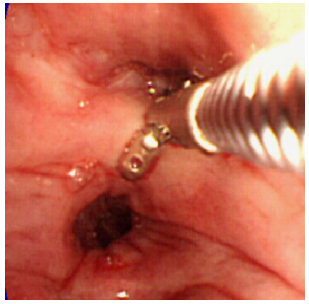
70-80%



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

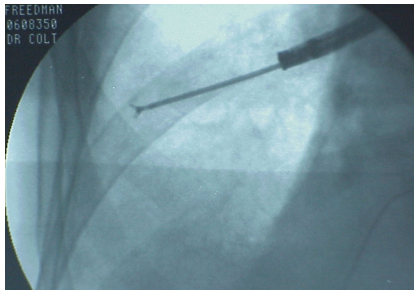


Conventional methods



endobronchial biopsy

EBB 20–61%



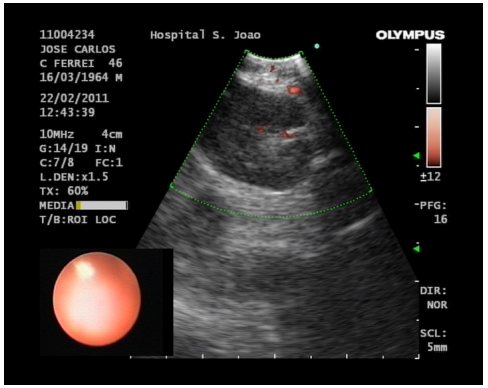
transbronchial lung biopsy

TBLB 37–90%

conventional transbronchial needle aspiration

cTBNA 6–90%

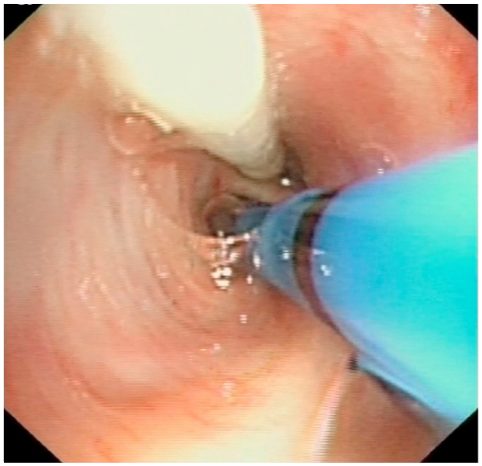
Novel methods



EBUS-TBNA 80–94%

EUS-FNA 77–94%

EUS-B-FNA 86%

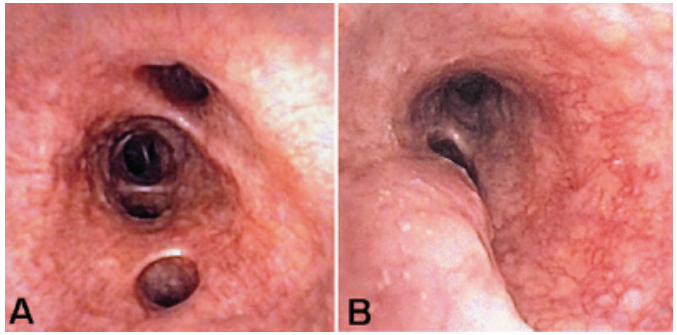


TBLC 66.7-92.6%

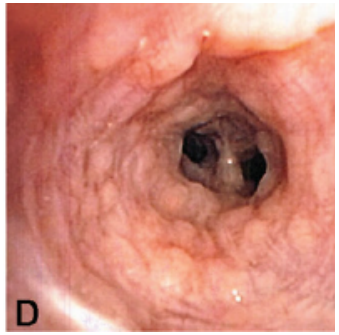
EBUS-TBNA, endobronchialultrasound-guided transbronchial needle aspiration;
EUS-FNA, endoscopic ultrasound-guided fine needle aspiration;
EUS-B-FNA, transesophageal ultrasound-guided needle aspiration with the use of an echo bronchoscope;
TBLC, transbronchial lung cryobiopsy

Images source: https://bronchoscopy.org/art-of-bronchoscopy | *Data source:* Pedro et al. J. Clin. Med. 2019, 8, 1327; Jacob et al. ERJ Open Res. 2019 Oct; 5(4): 00203-2019

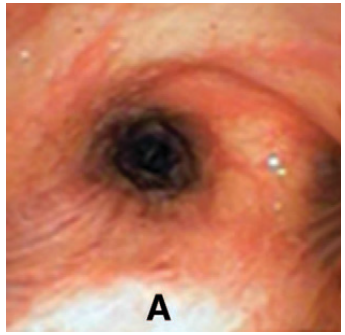
Bronchoscopic features of airway involvement in sarcoidosis



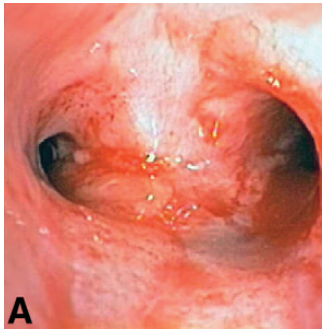
mucosal erythema, edema, capillary proliferation and granularity



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

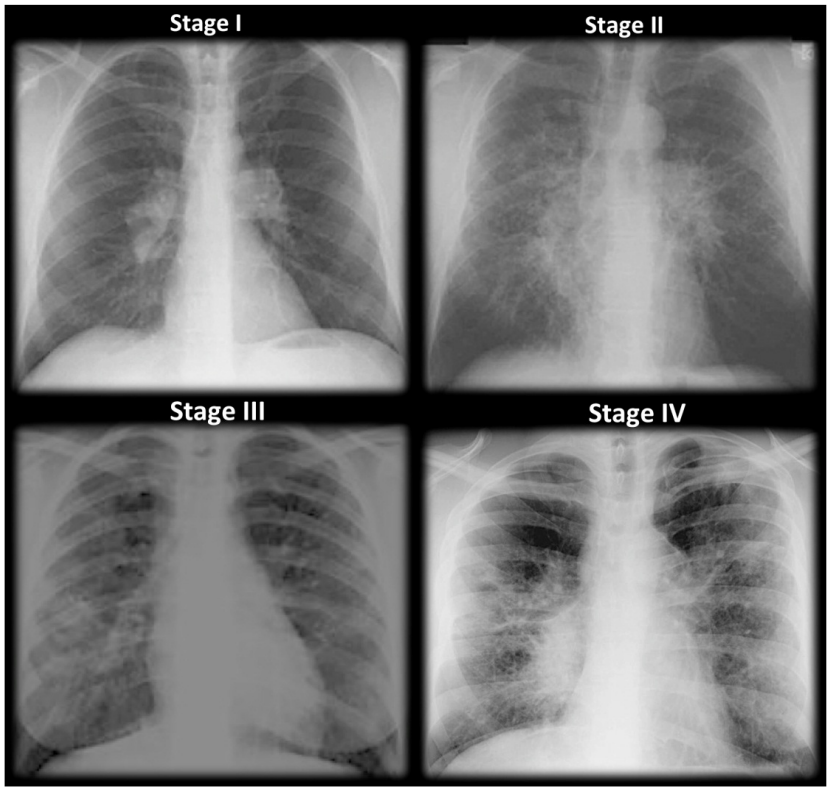
Sampling method	Normal mucosa	Abnormal mucosa
TBLB	66.1 %	79.3 %
EBB	41.7 %	75.8 %
Conventional TBNA	21.3 %	26.7 %

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 %**

Polychronopoulos & Prakash. Chest 2009; 136:1371–1380 | Goyal et al. J Bronchol Intervent Pulmonol 2014;21:220–226

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%

Goyal et al. J Bronchol Intervent Pulmonol 2014;21:220–226

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

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

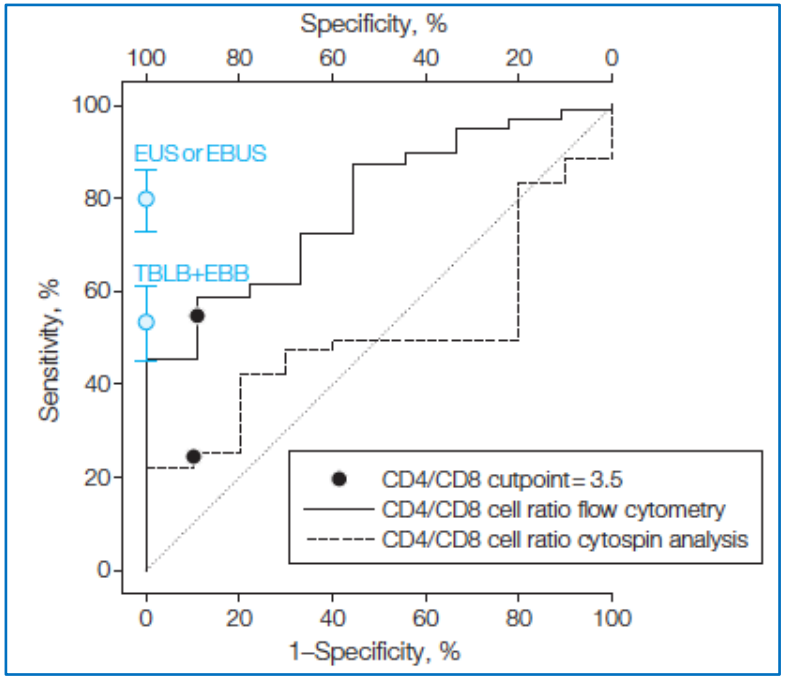
- Randomized clinical multicenter trial (14 centers in 6 countries)
- 304 consecutive patients with suspected pulmonary sarcoidosis (stage I/II)

Table 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)

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)



cTBNA vs EBUS-TBNA in sarcoidosis

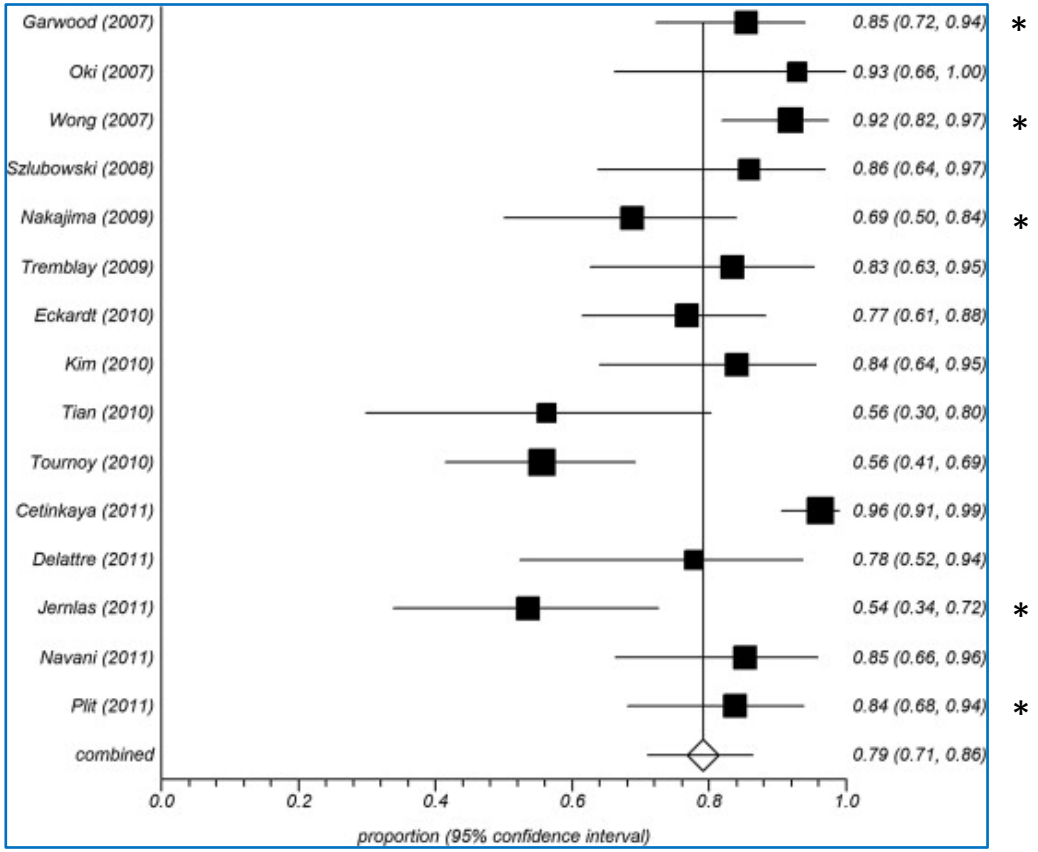
Study/Year	Study Design	No. Pts	Study Protocol	Main results
Oki et al. Respirology 2007	Prospective study Stage I and II	15	EBUS-TBNA (22G) followed by cTBNA (19G) at same site of EBUS	• **EBUS-TBNA**: 13/14 (**93%**); • cTBNA: 13/14 (93%); • both: 14/14 (100%)
Tremblay et al. Chest 2009	Prospective RCT study Stage I and II	50	cTBNA (19G) vs EBUS-TBNA (22G); 50% underwent EBB and 38-40% TBLB	• **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	• **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

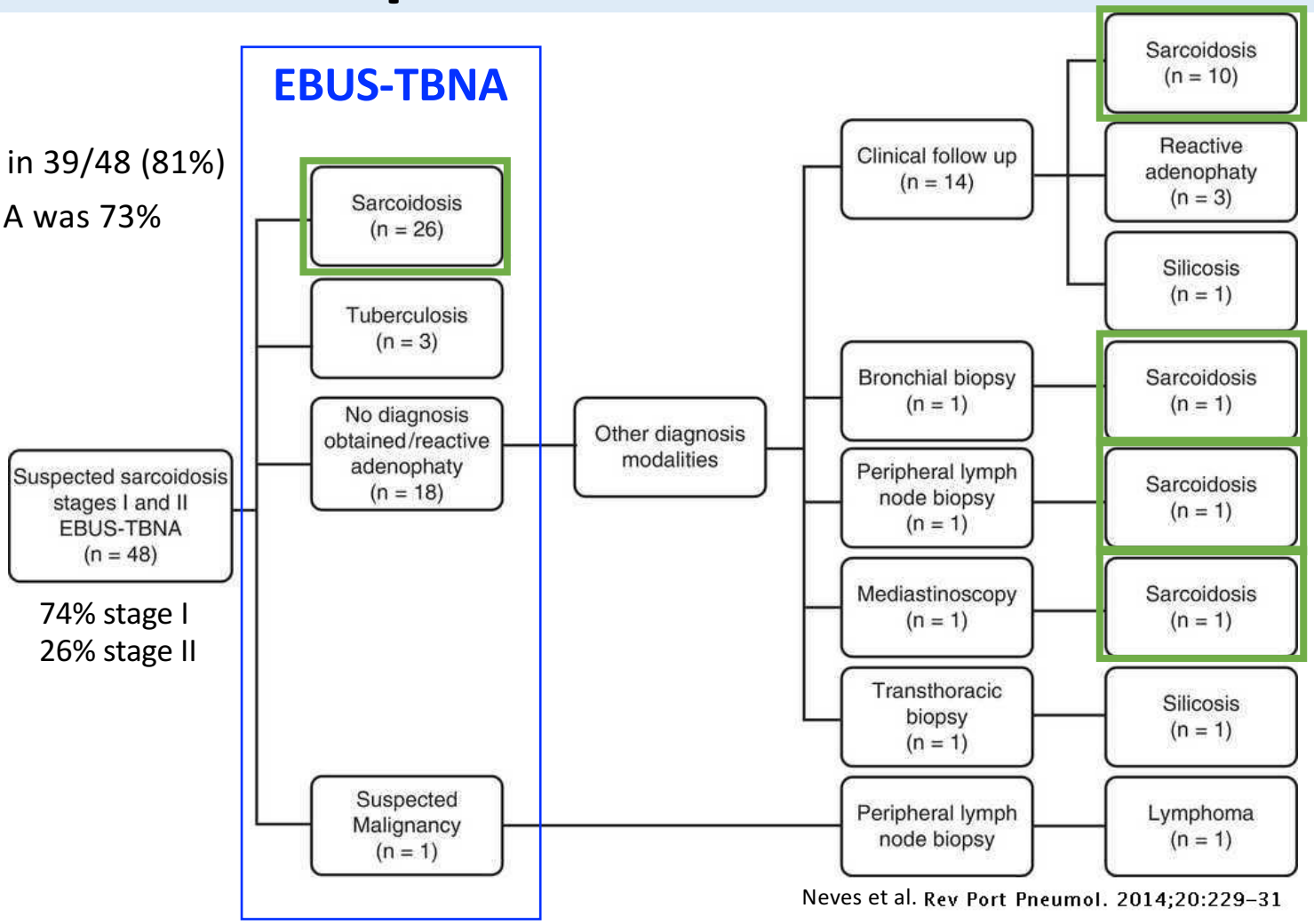


Agarwal et al. Respir Med 2012;106:883-892

ROSE*

Our experience

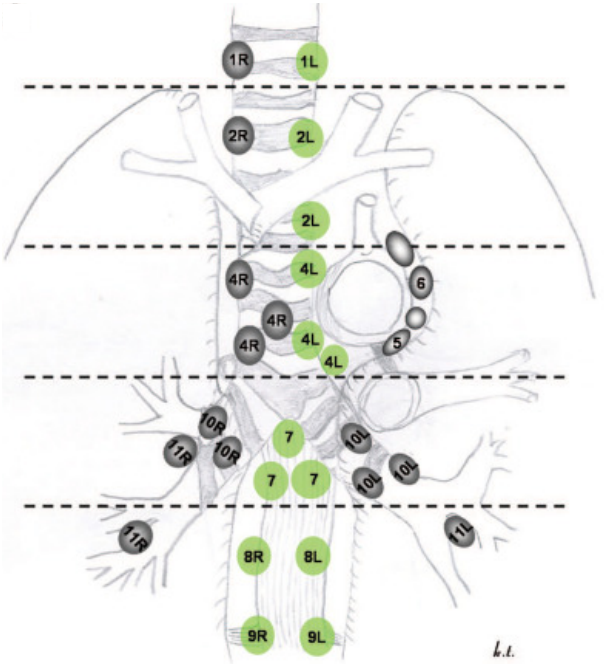
- Final diagnosis of sarcoidosis in 39/48 (81%)
- Diagnostic yield of EBUS-TBNA was 73%
- Sensitivity 67%
- Specificity 100%
- NPV 41%



Neves et al. Rev Port Pneumol. 2014;20:229–31

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

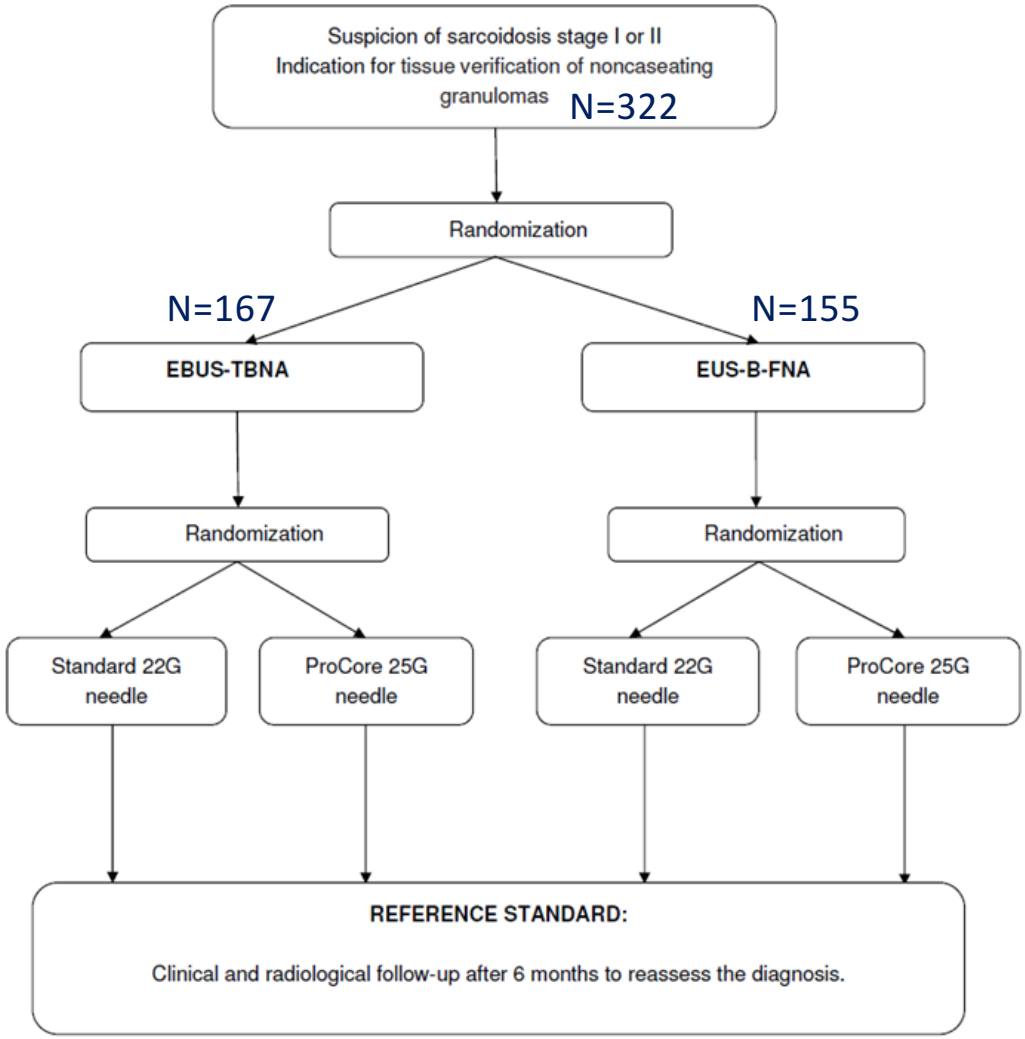
Standard 22G vs ProCore 25G

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)

*independet of needle type

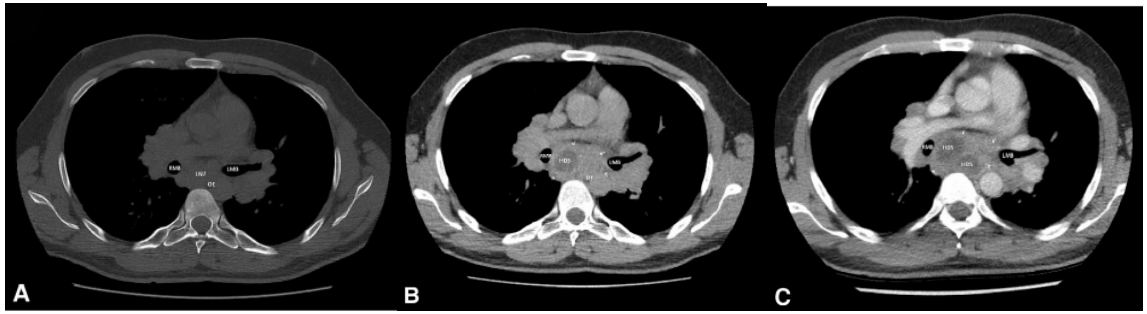
- Overall sensitivity 85%
  - 84% EBUS-TBNA vs 87% EUS-b-FNA (NS)
- No major complications



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



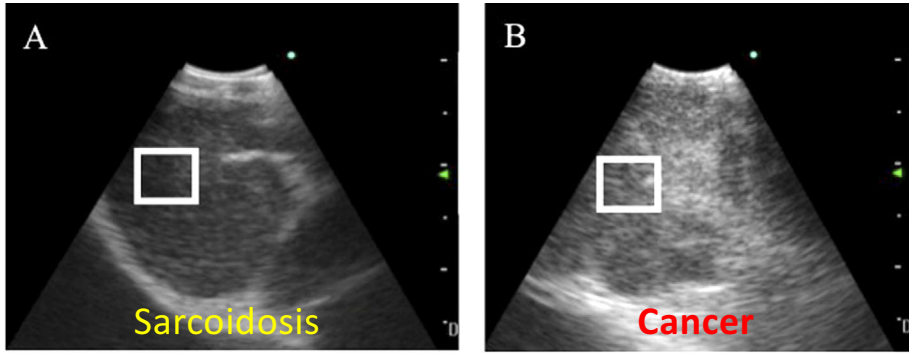
- Retrospective report of 5 cases with sarcoidosis (stage I/II) who developed mediastinal abscesses after EUS-FNA of subcarinal lymph nodes
- Use of prophylactic antibiotic treatment?

von Bartheld et al. Respiration 2014 | von Bartheld et al. Gastrointestinal Endoscopy 2012

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%	

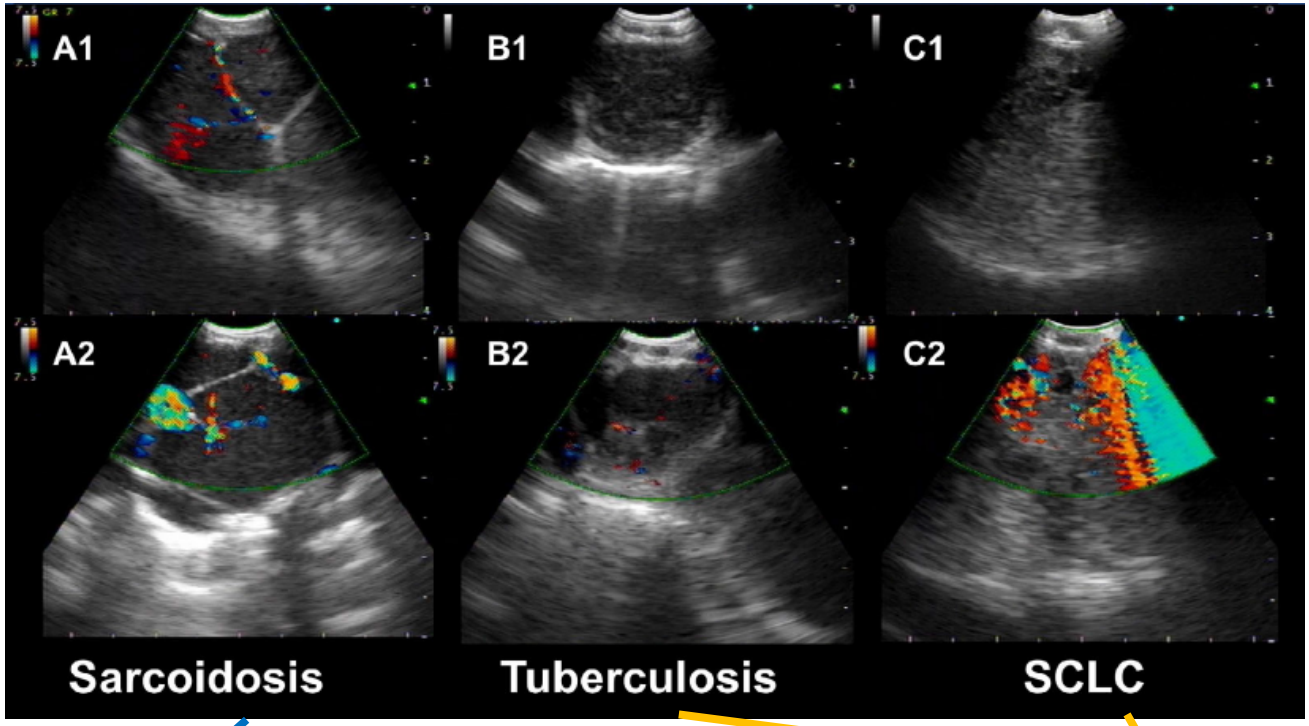
Imai et al. N Intern Med 2013



	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

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**

Cheng et al. J Ultrasound Med 2020

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. *Chest* 2016
19G needle* *under investigation, no large comparative studies	14/15 (93.3%)	Balwan A. J Bronchol Interv Pulmonol 2018

Rapid On-Site Evaluation (ROSE)

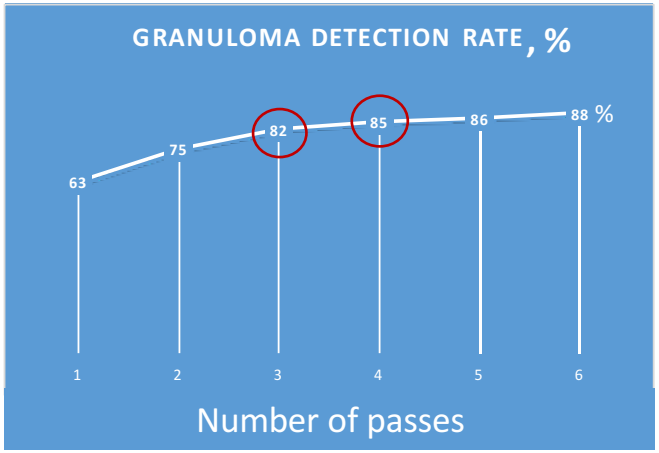
	Granuloma detection rate
cTBNA without ROSE	68%
cTBNA with ROSE	89%
EBUS-TBNA without ROSE	84%
EBUS-TBNA with ROSE	83%

Madan et al. J Bronchol Intervent Pulmonol 2017

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**



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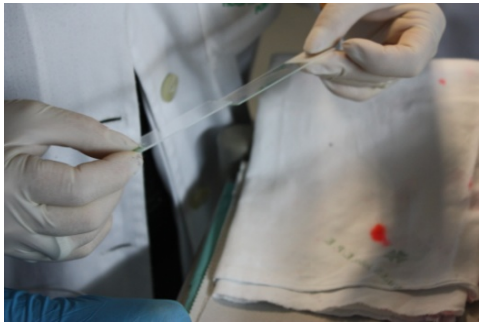
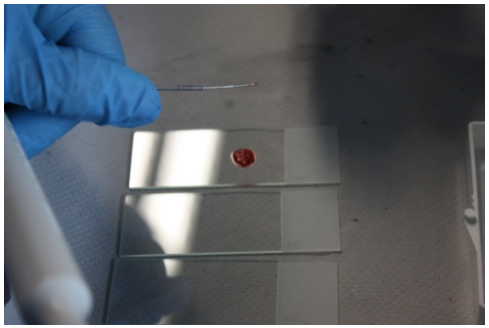
ORIGINAL ARTICLE

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





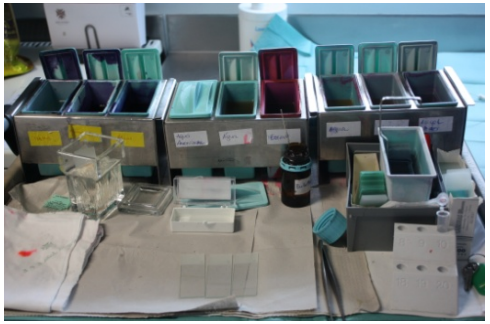


Table 2 Adequacy of cytological samples.

Patients	Adequate sampling		
	ROSE group	Non-ROSE group	*p*-Value
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)
Nondiagnostic cases	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)
Sensitivity (nondiagnostic included)	89 (71)	74 (52)
Mediastinal/hilar lesions investigation	85 (65)	69 (46)
Lung cancer staging	100 (88)	100 (100)
Specificity	100	100
PPV	100	100
NPV (nondiagnostic included)	70 (41)	69 (46)
Mediastinal/hilar lesions investigation	50 (25)	46 (29)
Lung cancer staging	100 (80)	100
Accuracy (nondiagnostic included)[a]	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;99:441–6)

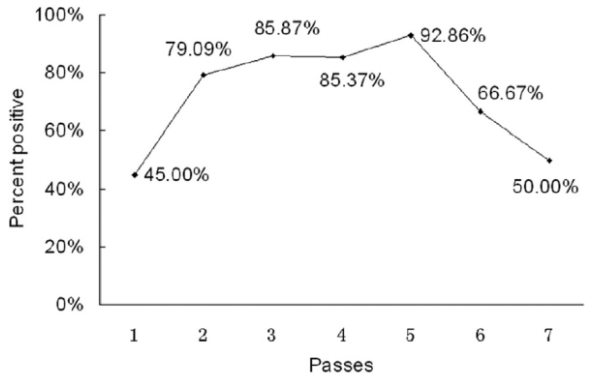


Fig 2. Yield per pass with endobronchial ultrasound-guided transbronchial needle aspiration per lymph node in patients with sarcoidosis.

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.

Lymphoma is a rare indication for EBUS

- 92 out of 4803 EBUS procedures **(1.9%)** had either suspected or proven lymphoma

Dhooria et al. J Bronchol Intervent Pulmonol 2018

Higher diagnostic yield for recurrent lymphoma

- **Only 24.2%** subjects with new-onset lymphoma could be appropriately subtyped
- Among the suspected cases of recurrence, EBUS-TBNA (±EUS-B) was sufficient for management in 81.8%

Dhooria et al. J Bronchol Intervent Pulmonol 2018

TABLE 2. Final Diagnosis

Final Diagnosis	n = 49
Malignant lymphoma [n (%)]	33 (67)
Lymphoma subclassification	
Hodgkin lymphoma	9
Non Hodgkin lymphoma	21
Follicle center lymphoma	2
Chronic lymphocytic leukemia	3
Large B-cell lymphoma	11
Mantle cell lymphoma	1
Nodal marginal zone B-cell lymphoma	2
Angioimmunoblastic T-cell lymphoma	1
T-cell lymphoma, NOS	1
Lymphoma, NOS	3

	Sensitivity, %	NPV, %
Primary lymphoma	55	57
Reccurrent lymphoma	88	90

Talebian-Yazdi et al. J Bronchol Intervent Pulmonol 2014

Diagnostic accuracy of EBUS in Lymphoma: meta-analysis

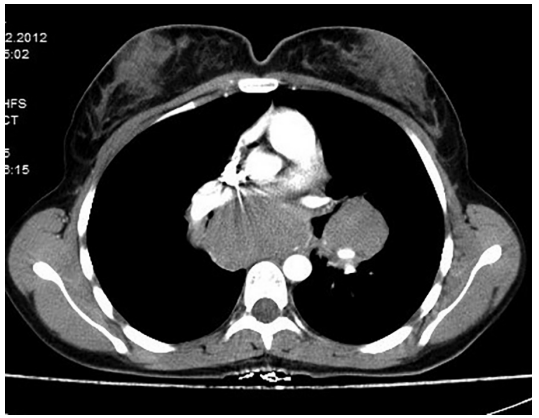
- 425 cases of lymphoma
  - 227 cases were new diagnoses, and 177 were recurrent
- EBUS-TBNA was performed using 21G and 22 G needles
- Average number of passes ranged between 3 to 5.1

	Pooled sensitivity
Overall	66.2% (95%CI, 55-75.8%)
ROSE – Yes	66.7% (95%CI, 53.2-78%)
No	63.3% (95%CI, 36.6-83.7%)
Needle – 21 G	48.9% (95%CI, 29.2-69%)
22 G	72.8% (95%CI, 60-82.9%)

Ability to Subtype Lymphoma

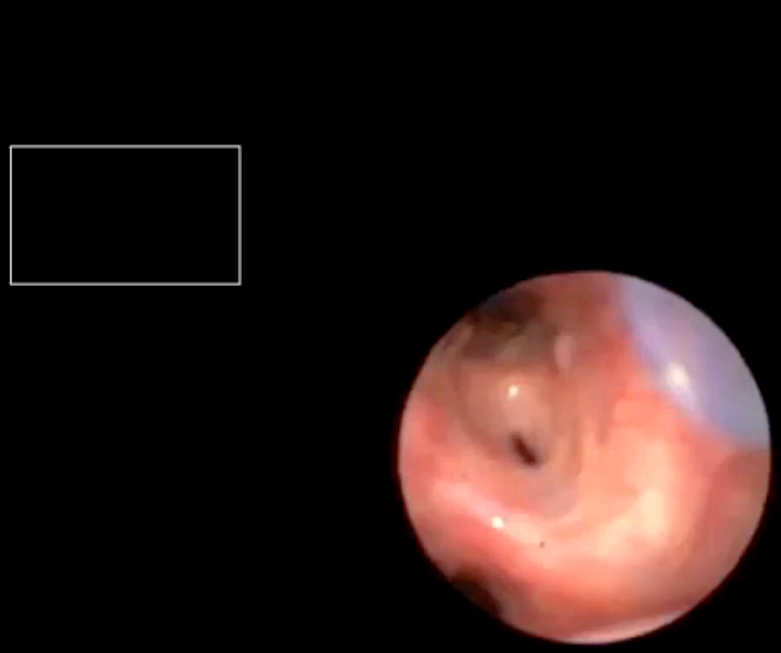
- Sufficient samples ranged between 27% to 97%
- Pooled analysis showed that **63.9%** of samples achieved by EBUS-TBNA were sufficient for ancillary testing

No significant complications



Labarca et al. Ann Am Thorac Soc. 2019 | Erer et al. Endosc Ultrasound 2017

EBUS-guided cautery-assisted transbronchial nodal forceps biopsy



Diagnostic yield for lymphoma (n = 16) was 93.8% (95% CI, 56.5%-100%) [vs EBUS-TBNA of 62.5% (95% CI, 33.6%-100%),*P* = 0.042].

Ray et al. Ann Thorac Surg 2020

TAKE HOME MESSAGES

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)

EBUS is a minimally invasive, safe and sensitive method for the assessment of recurrent mediastinal malignant lymphoma

EBUS-guided cautery-assisted transbronchial nodal forceps biopsy has the potential to increase the histological yield of lymphoma

XXVII CONGRESSO DE PNEUMOLOGIA DO NORTE

XXXIII JORNADAS GALAICO DURIENSES

5 A 7 DE MARÇO DE 2020
SHERATON PORTO HOTEL

Obrigado pela atenção