NEWER TECHNIQUES FOR INCREASING YEILD OF EBUS

(19G/ EBUS-IFB/ EBUS-TBNC)

DM seminar

Dr. Pratibha jha

INTRODUCTION

- EBUS-TBNA has revolutionized the diagnosis of mediastinal lesions
- It is the current standard for sampling hilar and mediastinal LN given its minimally invasive nature and high sensitivity especially in lung cancer
- However, limited sample and lack of tissue architecture restricts its diagnostic yield in cases of lymphoma and sarcoidosis, which frequently require histopathological assessment rather than cytological evaluation

Diagnostic yield of EBUS-TBNA : Malignancy

- EBUS TBNA is current standard for staging lung cancer recommended by ACCP guidelines over mediastinoscopy
- The sensitivity of EBUS TBNA is 90-92% for detecting malignancy
- However, advances in molecular, genetic, and PD-L1 testing have increased demands for tissue sample which might not be met by sample retrieved by EBUS-TBNA
- Furthermore, PD-L1 testing on EBUS-TBNA samples has not been validated and EBUS-TBNA samples PD-L1 status may be discordant to that of the surgical resected specimen

Kuijvenhoven J.C, et al. Respiration 2020;99:441–450
sakata KK, et al. Chest 2018;154:827-37

Diagnostic yield of EBUS-TBNA : sarcoidosis

- Diagnostic yield of EBUS-TBNA for sarcoidosis is lower than that for carcinoma ranging from 54% to 93%, with a pooled diagnostic accuracy of 79%
- Diagnostic yield can be enhanced with transbronchial and endobronchial lung biopsy, but with increased risk of bleeding and pneumothorax

Agarwal R et al, Respiratory Medicine (2012) 106, 883e892

Diagnostic yield of EBUS-TBNA : lymphoma

- Diagnostic yield is lower than that for either carcinoma or sarcoidosis, approximately 66% and as low as 38% especially for denovo lymphoma than relapsed lymphoma
- Non_x0002_Hodgkin’s and Hodgkin’s lymphoma treatment depend on specific subtyping and histologic grade, cell morphology, immunophenotype and tissue architecture which requires a larger tissue sample

Erer OF, et al. Endosc Ultrasound 2017;6:317-22.

Needle size : does it matter ?

- Several needle sizes are commercially available, including 25, 22, 21 and 19G
- ACCP guidelines 2016 recommend use of either 21 G or 22 G for EBUS TBNA
- Acquisition of sufficient tissue samples with 22G needle (ID-0.41 mm) remains a concern. Hence, flexible 19G (Flex 19 G) needle (ID-0.69 mm) was developed
- 19G needle is suggested to increase diagnostic yield, tissue size, which may improve histologic evaluation and advanced molecular testing
- However 19 G needle may lead to a higher degree of tissue trauma or a larger amount of aspirated blood, which can alter the diagnostic yield and cellularity of the sample.

Comparison of Sample Adequacy and Diagnostic Yield of 19- and 22-G EBUS-TBNA Needles

Chaddha, Udit MD*; Ronaghi, Reza MD*; Elatre, Waafa MD†; Chang, Ching-Fei MD*; Mahdavi, Ramyar MD*

- Prospective observational study, 27 patients recruited
- For EBUS, 19- and 22-G needles were used in an alternating manner at each lymph node station
- Sample adequacy: at least 40 lymphocytes/ HPF, tangible body macrophages, or anthracotic pigment-laden macrophages. Samples were considered to be “bloody” based on subjective assessment
- Sample adequacy and hemorrhage were determined on ROSE, while diagnosis was done by pathologist

Journal of Bronchology & Interventional Pulmonology 25(4):p 264-268, October 2018

Results:

Fifty-six lymph nodes were analyzed. Diagnoses included cancer (36%, including 1 lymphoma), reactive lymphoid tissue (53%), and sarcoidosis (11%). One hundred sixty-two and 163 passes were made with the 22- and 19-G needle, respectively. Sample adequacy was 73% and 46% with the 22 and 19-G needle, respectively ($P<0.001$). Significantly fewer passes were bloody with the 22-G compared with the 19-G needle (19% vs. 59%; $P<0.001$). Diagnostic yield was not different between the 22- and 19-G needles (95% vs. 93%; $P=0.62$).

TABLE 1. 27 Patients, 56 Lymph Nodes

	22-G Needle [n/N (%)]				19-G Needle [n/N (%)]			
Lymph Node Station	**Adequate**	**Bloody**	**Diagnostic**	**Paucicellular**	**Adequate**	**Bloody**	**Diagnostic**	**Paucicellular**
4R (n=7)	12/17 (71)	3/17 (29)	7/7 (100)	0/7 (0)	9/18 (50)	10/18 (56)	6/7 (86)	1/7 (14)
4L (n=1)	2/2 (100)	0/2 (0)	0/1 (0)	1/1 (100)	0/2 (0)	1/2 (50)	1/1 (100)	0/1 (0)
7 (n=23)	54/73 (74)	11/73 (15)	21/23 (91)	2/23 (9)	36/73 (49)	41/73 (56)	21/23 (91)	2/23 (9)
11R (n=13)	27/36 (75)	6/36 (17)	13/13 (100)	0/13 (0)	15/38 (42)	21/36 (58)	12/13 (92)	1/13 (8)
11L (n=11)	21/32 (64)	9/32 (28)	11/11 (100)	0/11 (0)	14/32 (44)	22/32 (69)	11/11 (100)	0/11 (0)
12R (n=1)	2/2 (100)	0/2 (0)	1/1 (100)	0/1 (0)	1/2 (50)	1/2 (50)	0/1 (0)	1/1 (100)
Overall	118/162 (73)	30/162 (19)	53/56 (95)	3/56 (5)	75/163 (46)	96/163 (59)	52/56 (93)	4/56 (7)

Use of an Additional 19-G EBUS-TBNA Needle Increases the Diagnostic Yield of EBUS-TBNA

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- Repeated aspirations with the 22-G needle were performed until diagnostic material was obtained, two passes with lymphocytes were obtained, or a total of 5 passes for ROSE were performed
- Following this, if there was diagnostic uncertainty (eg. non diagnostic, probable lymphoma), or need for larger tissue for NSCLC for molecular testing, or inclusion into research protocol was felt, then 3 passes with 19 G was taken
- Adequacy for PD-L1 testing: presence of 100 tumor cells and is consistent with
- Adequacy for molecular genomic testing: 10% of the sample being tumor

Results:

A 19-G EBUS-TBNA needle was utilized following standard sampling with a 22-G needle in 48 patients (50 sites) during the same procedure. Although the diagnostic yield between the needles was equivalent, the concordance rate was only 83%. The 19-G determined a diagnosis in 4 additional patients (8%) and provided additional histopathologic information in 6 other cases (12%). Conversely, in 3 cases (6%) diagnostic information was provided only by the 22-G needle. Compared with 22-G EBUS-TBNA alone, sampling with both the 22- and 19-G EBUS needles resulted in an increase in diagnostic yield from 92% to 99% (*P*=0.045) and a number needed to sample of 13 patients to provide one additional diagnosis. There were no significant complications.

TABLE 2. Diagnostic Yield (Per Patient) by Endobronchial Ultrasound-guided Transbronchial Needle Aspiration Needle

		19-G Needle	
	Correct Diagnosis	**Yes**	**No**
22-G needle	Yes	41	3
	No	4	0

A Randomized Clinical Trial of Flex 19G Needles versus 22G Needles for Endobronchial Ultrasonography in Suspected Lung Cancer

Christophe Dooms[a] Sara Vander Borght[b, c] Jonas Yserbyt[a] Dries Testelmans[a]

- Aim : Evaluate **quantitative** and **qualitative** specimen characteristics of Flex 19G
- Single-center, randomized, controlled trial, 1:1 randomization to undergo EBUS using a Flex 19G or a 22-gauge (22G) needle
- **Primary end point : histological tissue core procurement**
- Secondary end points: diagnostic yield, specimen bloodiness and overall quality, tissue surface area and NGS performance, and procedure-related complications

Dooms C et al,Respiration 2018;96:275-82

- **Technique:** First 2 needle passes taken without suction (transbronchial needle capillary sampling) then 4 needle passes taken as per TBNA technique
- **Non diagnostic:** Inadequate material (predominance of blood or bronchial epithelial cells)
- **Quality:** assessed by bloodiness score and an objective Mair's scoring system
- **Bloodiness:** blood in the field (%) : mild (<33%), moderate (33–66%), severe (>66%)
- **Mair's scoring:** based on 5 objective criteria and cumulative score is categorized into "poor" (score 0–2), "good" (score 3–6), and "superior" (score 7–10) for diagnosis
- For Genomic analysis, slides were prepared from cell block and samples were rejected if the proportion of tumor cells by visual estimation was < 10%

Method for tissue surface analysis

- Slides were digitalized using the SCN400 slide scanner (Leica Biosystems,Wetzlar, Germany) at 20x magnification and delineated to indicate the area to be measured
- Then analysed using TissueIA software (Leica Biosystems, Dublin, Ireland) for tissue surface area analysis.
- Using a specific algorithm the tissue was recognized excluding the haemorrhagic areas

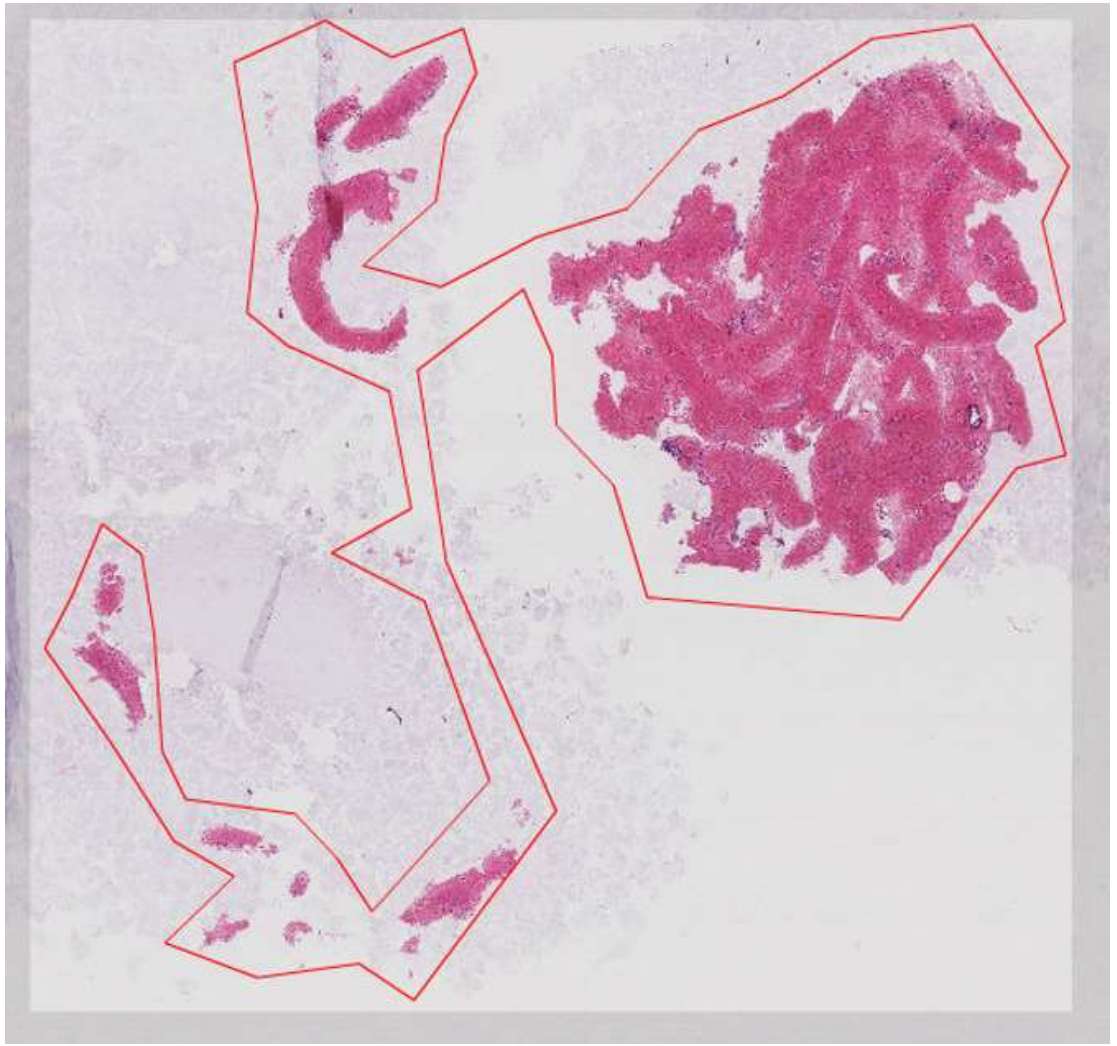


Table 2. Quantitative specimen outcomes

	19-gauge needle ($n = 39$)	22-gauge needle ($n = 39$)	p value
Tissue core present on cell block, n (%)	26 (67)	28 (72)	0.81
Median tissue surface area, mm^2 (IQR)	6.0 (3.7–11.7)	4.6 (1.9–10.3)	0.15

Table 4. Subgroup analysis of cancer specimen outcomes

Outcome measure	19-gauge needle ($n = 31$)*	22-gauge needle ($n = 36$)*	p value
Cell block selected for NGS, n/N (%)			0.57
TBNA cell block	24/31 (77)	26/36 (72)	
TBNCS cell block	6/31 (20)	9/36 (25)	
None selected	1/31 (3)	1/36 (3)	
Presence of tissue core (yes), n/N (%)	21/31 (68)	25/36 (69)	1.00
Median tissue surface area, mm^2 (IQR)	5.94 (2.54–10.52)	4.01 (2.01–8.60)	0.26
Tumor cellularity, % QNC			0.64
<10%	2	0	
11–50%	10	14	
51–100%	19	22	
Median tumor surface area, mm^2 (IQR)	4.91 (2.08–9.31)	2.35 (1.21–6.35)	0.09
Median amount of DNA extracted, ng (IQR)	1,150 (673–1,880)	818 (428–1,473)	0.09
NGS testing successful (yes), n/N (%)	29/31 (94)	35/36 (97)	0.59

Table 3. Qualitative specimen outcomes

Outcome measure	Scoring	19-gauge needle ($n = 39$)	22-gauge needle ($n = 39$)	p value
Bloodiness on TBNA, *n*				0.004
Severe	>66%	14	3	
Moderate	33–66%	22	29	
Mild	<33%	3	7	
Bloodiness on TBNCS, *n*				0.42
Severe	>66%	12	8	
Moderate	33–66%	16	15	
Mild	<33%	11	16	
Mair's background blood on TBNA				0.057
Large amount – diagnosis compromised	0	2	2	
Moderate amount – diagnosis possible	1	30	21	
Minimal amount – diagnosis easy	2	7	16	
Mair's background blood on TBNCS				0.13
Large amount – diagnosis compromised	0	8	5	
Moderate amount – diagnosis possible	1	22	19	
Minimal amount – diagnosis easy	2	9	15	
Mair's total score on TBNA				0.73
Diagnostic ease "poor"	0–2	1	0	
Diagnostic ease "good"	3–6	2	3	
Diagnostic ease "superior"	7–10	36	36	
Mair's total score on TBNCS				0.78
Diagnostic ease "poor"	0–2	7	8	
Diagnostic ease "good"	3–6	7	3	
Diagnostic ease "superior"	7–10	25	28	

A Prospective, Randomized Trial for the Comparison of 19-G and 22-G Endobronchial Ultrasound-Guided Transbronchial Aspiration Needles; Introducing a Novel End Point of Sample Weight Corrected for Blood Content

Celina Wolters,[1] Kaid Darwiche,[1] Daniel Franzen,[2] Thomas Hager,[3] Beata Bode-Lesnievska,[4] Peter J. Kneuertz,[5] Kai He,[5] Michael Koenig,[5] Lutz Freitag,[1] Lai Wei,[6] Stephan Eisenmann,[1,7] Christian Taube,[8] Gerhard Weinreich,[8] Filiz Oezkan[1,5]

Methods

- Prospective randomized study to compare 19-G & 22-G EBUS needles for **specimen tissue quality** and **procedural safety** in patients suspected to have lung ca. with mediastinal/hilar LN > 1 cm
- Technique : Rigid bronchoscopy - EBUS 19G/22G - LN >5 mm sampled - 3-5 passes and 10-15 jabbing
- ROSE was not done. Blood content of each sample was evaluated using a semiquantitative score from 0 to 2 and sample. . Each lymph node sample was weighed on a pathology slide using a precision balance and divided by the number of passes
- **The sample quality assessed according to tissue weight and corrected for blood content was the primary end point of our study**

Figure 1 Blood Content in 22-Gauge (G) and 19-G Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) Samples. The Blood Content After Endobronchial Ultrasound-Guided Needle Sampling With 19-G and 22-G Needles Is Shown (Left). Right Panel: A Color Scale Was Used to Quantify the Blood Content (0 = No Visible Blood, 1 = Light Red Shading, 2 = Red Shading, 0 = No Visible Blood, 1 = Light Red Shading, 2 = Red Shading)

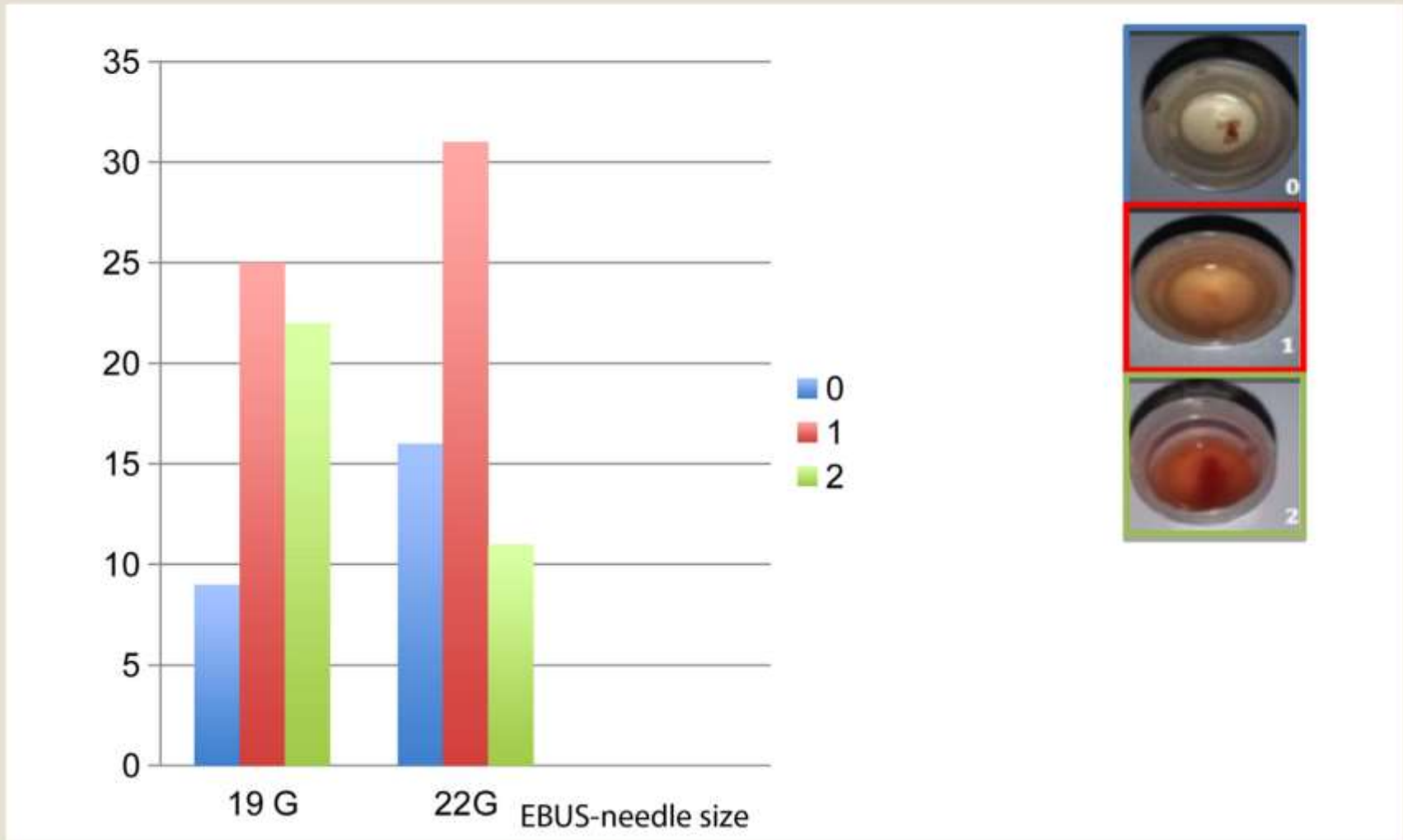


Table 2 Log10 Transformed Sample Weights Comparing 19-Gauge and 22-Gauge Samples

Needle Size	Patient n	Variable	Mean	SD	*P*
19-Gauge	54	Sample weight per needle pass	0.0200	0.0222	.0016 (log10 transformed)
		Sample weight log10	−1.899	0.424	
22-Gauge	53	Sample weight per needle pass	0.0102	0.0093	
		Sample weight log10	−2.154	0.388	

Comparison of 19-G and 22-G EBUS-TBNA Needles

Table 3 Association Between Blood Content and Needle Size

A. χ^2 Test: The Needle Size Is Significantly Associated With Increased Blood Content. Using 19-Gauge EBUS-TBNA Needles the Percentage of Blood Content Score of 2 Is Increased (41.51% vs. 18.52%) Compared With Using 22-Gauge EBUS-TBNA Needles

	Blood Content			
Needle Size	0	1	2	*P*
19-Gauge, n (%)	8 (15.09)	23 (43.40)	22 (41.51)	.029
22-Gauge, n (%)	14 (25.93)	30 (55.55)	10 (18.52)	

B. ANOVA Model Was Used to Study the Association Between Log10 Transformed Sample Weight and Blood Content. The Sample Weight Per Needle Pass Was Significantly Associated With Increased Blood Content. Larger Sample Weight Is Associated With a Higher in-Blood Content Score

Blood Content	Sample Weight log10 Mean	SE	
0	−2.253	0.086	.0021
1	−2.041	0.055	
2	−1.851	0.071	

C. The Association Between Log10 Transformed Sample Weight and the Needle Size Controlling the Confounding Factor of Blood Content Was Calculated Using the ANOVA Model. While Controlling the Effect of Blood Content, the Sample Weight Per Needle Pass Was Significantly Larger Using 19-Gauge Than 22-Gauge

Needle Size	Sample Weight log10 Estimated Mean		
19-Gauge	−1.946	0.057	.0119
22-Gauge	−2.148	0.056	

> J Bronchology Interv Pulmonol. 2019 Oct;26(4):237-244. doi: 10.1097/LBR.0000000000000562.

Tissue Acquisition During EBUS-TBNA: Comparison of Cell Blocks Obtained From a 19G Versus 21G Needle

Edward M Pickering [1], Van K Holden [1], Jonathon E Heath [2], Avelino C Verceles [1], Or Kalchiem-Dekel [1], Ashutosh Sachdeva [1]

Methods: A prospective analysis of patients undergoing EBUS-TBNA at our institutions was performed. Sampling of the same lesion(s) with both the Flex 19G and 21G needles was performed in an alternating manner. In total, 47 patients with suspected lung cancer or mediastinal/hilar lymphadenopathy were included with a total of 83 lesions biopsied. Cell block area was calculated using the Aperio ImageScope software.

Results: Mean cell area in the Flex 19G group was 7.34±12.46 mm compared with 5.23±10.73 mm in the 21G group (P=0.02). In the malignant subgroup, the average cell area was 16.16±16.30 mm in the Flex 19G group versus 11.09±15.55 mm in the 21G group (P=0.02). No significant difference was noted in the mean cell area within the nonmalignant subgroup, 1.80±3.01 mm in the 19G group versus 1.56±1.79 mm in the 21G group (P=0.60).

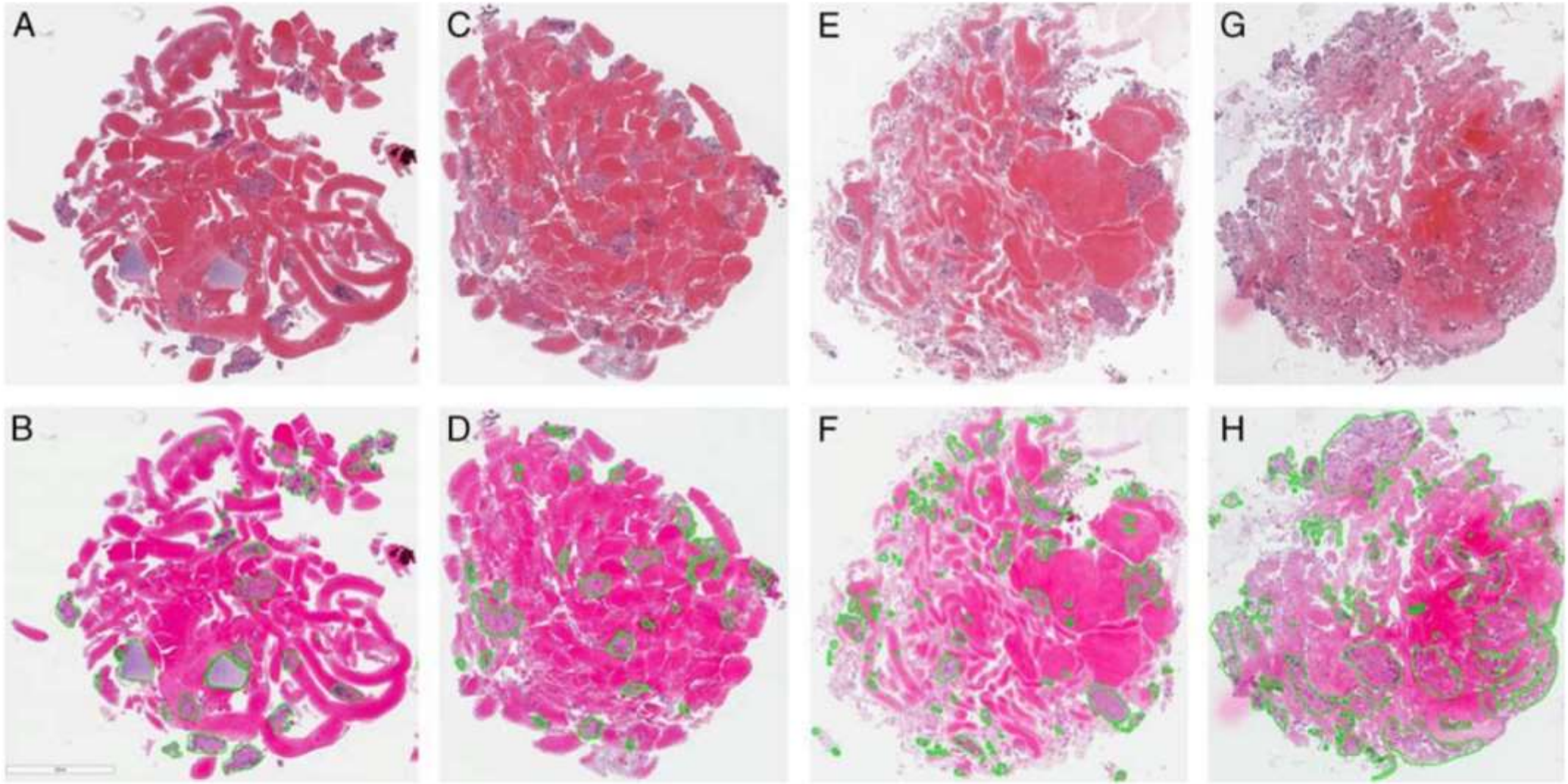


FIGURE 1. Representative H&E cell blocks at ×20 magnification. A, 21G benign lymph node. C, 19G benign lymph node. E, 21G adenocarcinoma. G, 19G adenocarcinoma. The bottom row is annotated with the Pen Tool using the Aperio ImageScope software (version 12.2.2.5015). Cell area is calculated using only that contained within the highlighted areas to exclude red blood cells, fibrin clot, and debris. B, 21G benign lymph node. D, 19G benign lymph node. F, 21G adenocarcinoma. H, 19G adenocarcinoma. H&E indicates hematoxylin and eosin.

Comparison of diagnostic performance of 19-gauge and 21-gauge needles during endobronchial ultrasound-guided transbronchial needle aspiration

Ilias Porfyridis, Frangiskos Frangopoulos, Paris Vogazianos, Panayiota Kara, Michalis Michael, Alexis Papadopoulos, Tonia Adamide, Andreas Georgiou

European Respiratory Journal 2017 50: PA823; **DOI:** 10.1183/1393003.congress-2017.PA823

Methods: 70 patients with mediastinal, hilar lymphadenopathy or lesions, without specific diagnosis after initial diagnostic bronchoscopy and conventional TBNA (19G), further investigated with EBUS-TBNA were enrolled. EBUS-TBNA bronchoscopy was performed under conscious sedation with the 21G or the 19G needles. In cases where EBUS-TBNA results were negative for malignancy, a surgical biopsy was performed where appropriate. Final diagnosis was established following the histopathological, cytological examination, surgical and clinical-radiologic findings.

Results: 21G group included 35 patients (age 66±9, 56 sampling sites) and 19G group 35 patients(age 63±13, 75 sampling sites). Malignancy was diagnosed in 17 cases in 21G and 23 in 19G group. Sample adequacy rates were 92.8%vs96% in cytology, 75%vs90.6% in histology, with diagnostic accuracy of 77.1% vs 80%(p=0.77) in cytology, 48.6% vs 68.6%(p=0.08) in histology and 79.4% vs 83%(p=0.7) combined, with AUC for the diagnosis of malignancy of 0.76(95%CI:0.6-0.9, p=0.001) and 0.85(95%CI:0.7-0.9, p<0.0001) in 21G and 19G respectively. No major complication occurred.

Endobronchial Ultrasound Transbronchial Needle Aspiration (EBUS-TBNA) versus Flexible 19G Endobronchial Ultrasound Transbronchial Needle (Flex 19G EBUS-TBNA) in the Assessment of Mediastinal and Hilar Lymphadenopathy: a Randomised Trial

Eric Daniel Tenda, Arafa M Aboelhassan, Konstantina Kontogianni, Alexandra Rice, Siobhan Crichton, Justin L Garner, Karthi Srikanthan, Andrew Nicholson, Alexander Harms, Felix Herth, Samuel V Kemp, Ralf Eberhardt, Pallav L Shah

European Respiratory Journal 2019 54: PA324; DOI: 10.1183/13993003.congress-2019.PA324

Results: A total of 500 subjects underwent an EBUS procedure. 453 lesions with a mean lymph node size of 19.2mm (+/- SD 9.97) were sampled using Flex 19G & 480 lesions with a mean lymph node size of 17.8mm (+/- 8.15) were obtained using the standard needle. The Mair score did not differ between the two needles with a mean of 4.52 (+/- 2.28) for the Flex 19G & 4.40 (+/- 2.44) for the standard needle (p= 0.468). The complication rates were: 3.2% (19G) & 3.6% (21G). The sensitivity was 77% & specificity 100% with both needles.

Comparison of the yield of 19-G eXcelon core needle to a 21-G EBUS needle during endobronchial ultrasound guided transbronchial needle aspiration of mediastinal lymph nodes for the detection of granulomas in cases of suspected sarcoidosis

Abhishek Biswas[1], John P. Wynne[2], Divya Patel[1], Michelle Weber[3], Shaleen Thakur[4], P. S. Sriram[1]

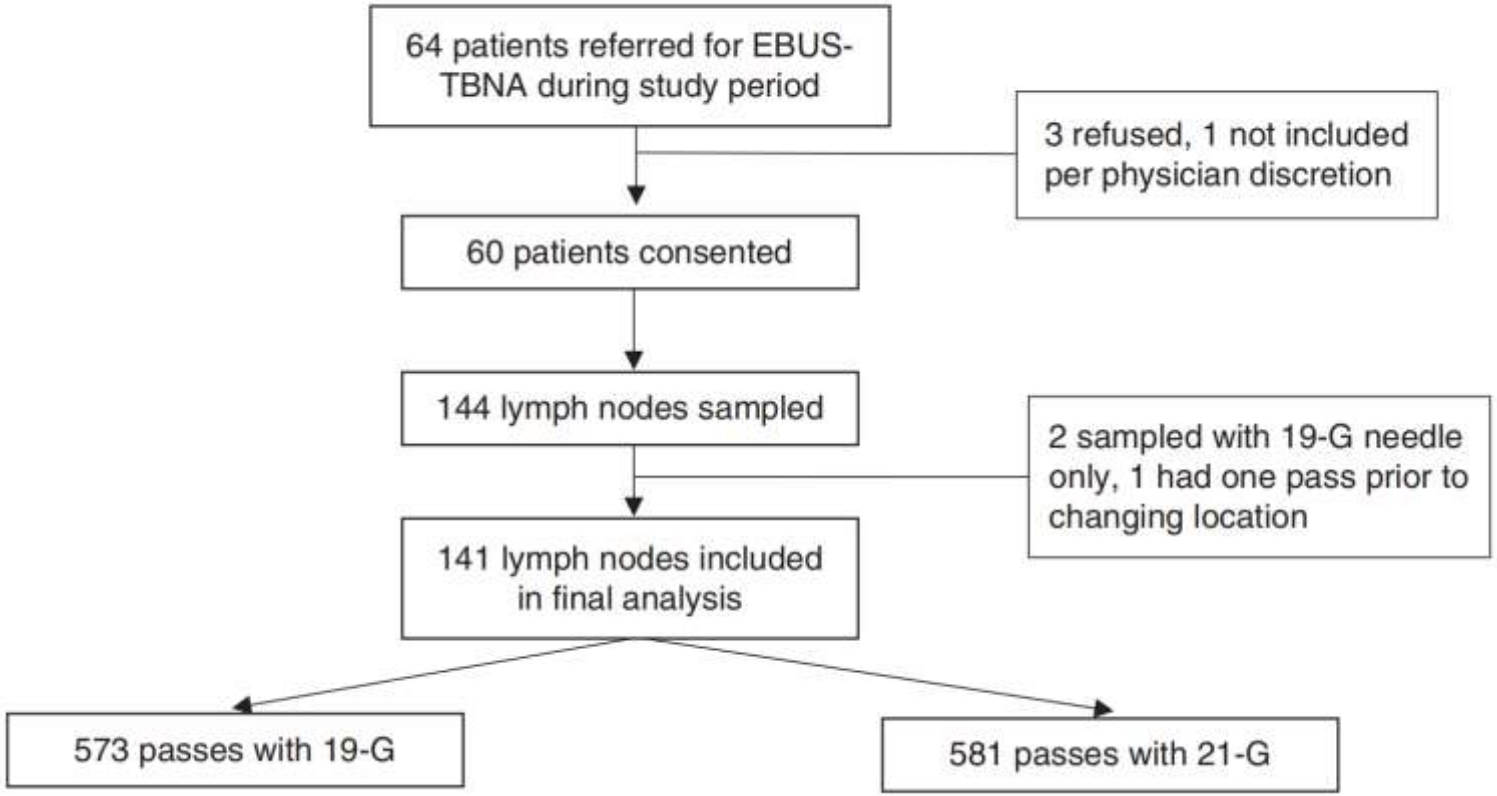
Table 1 Comparison of the yield from 21-G TBNA and 19-G core biopsy needle

Patient	TBNA	Core	Node sampled
1	Granuloma	Non-caseating granuloma	Subcarinal
2	Small granulomas	Non-caseating granuloma	Subcarinal
3	Non caseating giant cell	Poorly formed non-caseating granuloma	Subcarinal
4	Lymphoid tissue, granulomatous inflammation	Non-caseating granuloma	Subcarinal
5	Epithelioid histiocytes, granulomatous inflammation	Non-caseating granuloma	Paratracheal
6	Granulomatous inflammation	Non-caseating granuloma	Subcarinal
7	Few granulomatous areas	Non-caseating granuloma, focal necrosis	Subcarinal
8	Reactive cells	Non-caseating granuloma, anthracotic node	Subcarinal
9	Reactive lymphoid tissue	Non-caseating granuloma	Subcarinal
10	Epithelial cells and histiocytes, rare granuloma	Non-caseating granuloma	Subcarinal
11	Clusters of epithelioid histiocytes, possible granuloma	Non-caseating granuloma	Subcarinal

Evaluating Yield of 19 Versus 21 G EBUS-TBNA Needles

A Prospective Study

Firas S. Elmufdi, MBBS, Marissa K. Peterson, MS,† David Niccum, MD,* Stephen Asche, MA,‡ and Kealy Ham, MD**



J Bronchol Intervent Pulmonol 2021;28:29–33

Method

- Both 19 and 21 G needles were used at each lymph node station in alternating fashion
- Two ROSE stations were present and assigned to one of the 2 needles.
- A total of 141 lymph nodes were analyzed, with each pass through a given lymph node, the bronchoscopist alternated between 19 and 21 G
- A minimum of 3 passes with each needle was requested per lymph node
- Sample adequacy was determined by ROSE evaluation. The slides and cell blocks from both needles were assessed by a pathologist

TABLE 1. Results Summary

	19 G	21 G	*P*
Diagnostic yield			
Overall	89.4%	88.6%	0.71
Malignancy	91.3%	87.0%	0.41
NCG, sarcoidosis	63.2%	63.2%	0.99
Benign	94.7%	96.1%	0.32
ROSE adequacy			
Overall	41.1%	36.2%	0.27
Malignancy	84.8%	63.0%	0.004
NCG, sarcoidosis	21.1%	10.5%	0.41
Benign	19.7%	26.3%	0.30
Smear cellularity			
Overall	19.9% better	20.6% better	0.89
Malignancy	32.6% better	13.0% better	0.05
NCG, sarcoidosis	21.1% better	21.1% better	0.99
Benign	11.8% better	25.0% better	0.06
Cell block cellularity			
Overall	26.2% better	19.2% better	0.21
Malignancy	41.3% better	19.6% better	0.06
NCG, sarcoidosis	26.3% better	10.5% better	0.26
Benign	17.1% better	21.1% better	0.58

Prospective randomized trial to compare the safety, diagnostic yield and utility of 22-gauge and 19-gauge endobronchial ultrasound transbronchial needle aspirates and processing technique by cytology and histopathology

- 40 patients (56 lesions) undergoing EBUS TBNA lymph node evaluation were enrolled in this single-center prospective trial
- Block randomization to undergo EBUS TBNA starting with 22-gauge (22g) or 19-gauge (19g) needles.
- Specimen adequacy was defined by the ability of the pathologist to make a definitive diagnosis of normal lymphoid tissue, benign abnormality (eg, granuloma) or a specific malignant neoplasm by morphology

C.J. Manley et al. Journal of the American Society of Cytopathology (2022) 11, 114e121

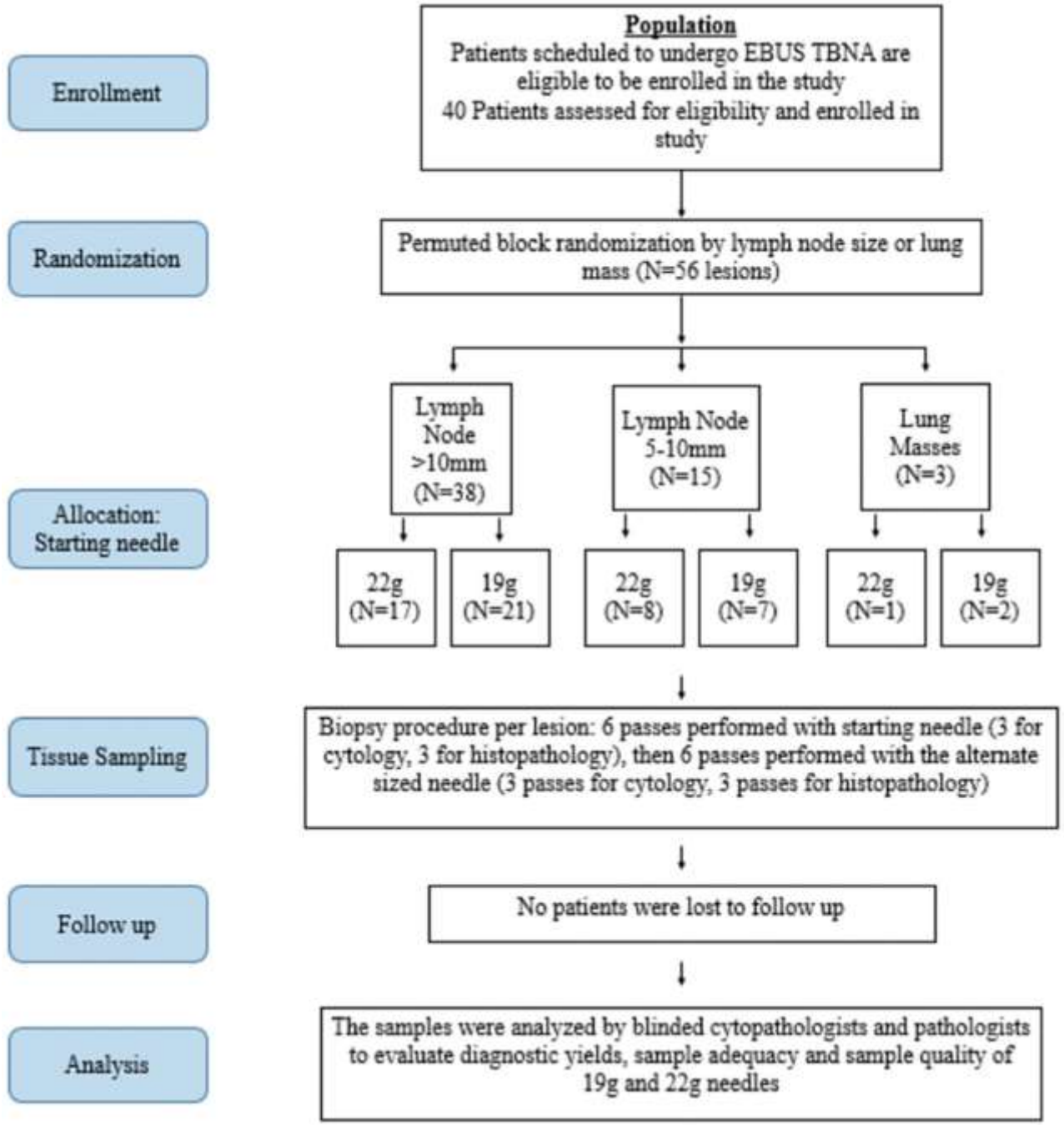

Enrollment
Population
Patients scheduled to undergo EBUS TBNA are eligible to be enrolled in the study
40 Patients assessed for eligibility and enrolled in study
Randomization
Permuted block randomization by lymph node size or lung mass (N=56 lesions)
Allocation: Starting needle
Lymph Node >10mm (N=38)
Lymph Node 5-10mm (N=15)
Lung Masses (N=3)
22g (N=17)
19g (N=21)
22g (N=8)
19g (N=7)
22g (N=1)
19g (N=2)
Tissue Sampling
Biopsy procedure per lesion: 6 passes performed with starting needle (3 for cytology, 3 for histopathology), then 6 passes performed with the alternate sized needle (3 passes for cytology, 3 passes for histopathology)
Follow up
No patients were lost to follow up
Analysis
The samples were analyzed by blinded cytopathologists and pathologists to evaluate diagnostic yields, sample adequacy and sample quality of 19g and 22g needles

Table 3 Diagnostic yield of EBUS samples processed as core biopsy and cytologic method with and without cell block.

Method	Needle size		*P* value
	19g	22g	
Core biopsy	87.5%	83.9%	0.625
Cytology smear	76.4%	76.4%	1.00
Cytology smear and cell block	89.3%	87.5%	1.00

Table 5 Molecular adequacy for 35 lesions with carcinoma or thymoma, separated by processing technique and needle gauge.

Core biopsy		Cytology with cell block	
22-gauge	19-gauge	22-gauge	19-gauge
27/35 (77%)	28/35 (80%)	27/35 (77%)	28/35 (80%)

$P = 1.00$ for the comparison of 19-gauge versus 22-gauge in both cases.

Summary

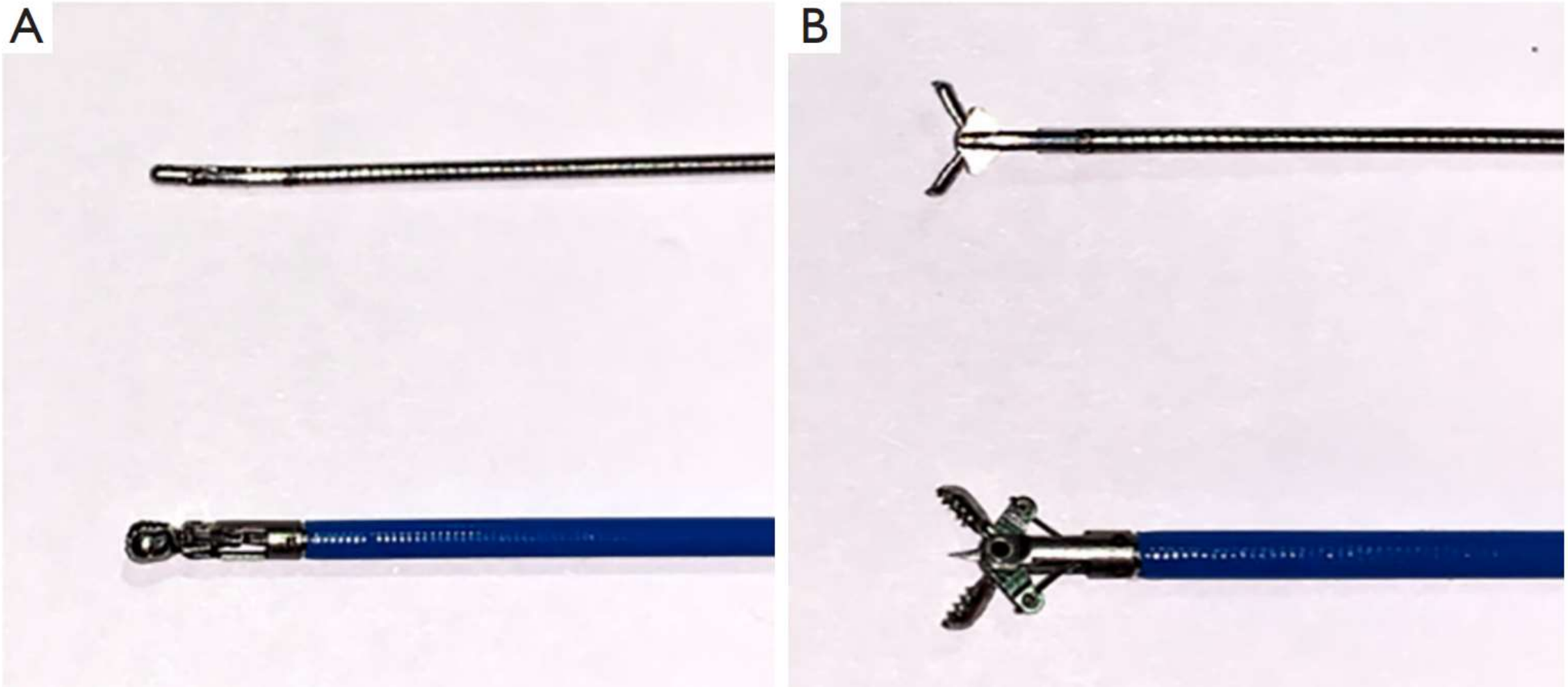
- Diagnostic yield does not improve with 19 G needle
- Few studies have shown larger tissue size, more tumour cells with 19 g which may be beneficial for molecular testing
- 19 G needle may decrease number of attempts when combined with ROSE in cases with high pretest probability of lung cancer

EBUS-IFB

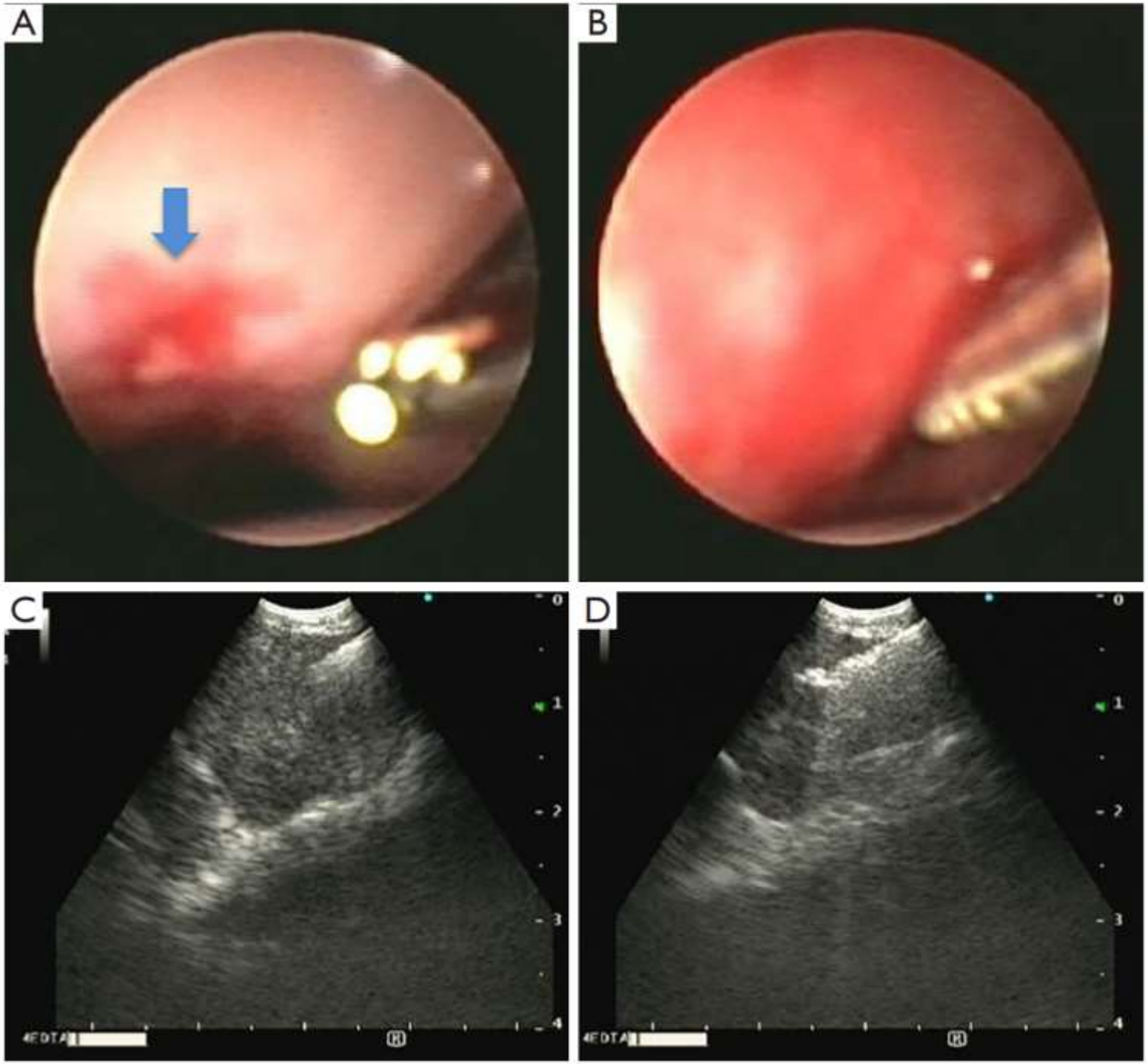
EBUS-IFB technique

- Performed with EBUS bronchoscope TBNA needle and miniforceps (1 to1.9 mm)
- The airway is punctured first with a needle (usually 22G) as part of EBUS-TBNA
- Creates defect in the airway mucosa and a tract for introduction of miniforceps
- If a 19-gauge needle is used, the needle entry alone should create a tract of sufficient size, otherwise cautery or knife can be used to create a hole
- Miniforceps are introduced through the puncture site (under sonographic guidance) into the target lymph node, once inside the lesion, the miniforceps are opened and biopsy specimens are taken under continuous EBUS surveillance

http://www.asvide.com/watch/32949



Cheng G et al, J Thorac Dis 2019;11(9):4049-4058



Cheng G et al, J Thorac Dis 2019;11(9):4049-4058

Bronchoscopic Miniforceps Biopsy for Mediastinal Nodes

Masahide Oki, MD, Hideo Saka, MD, and Chieko Sako, MD

- 22 patients were enrolled and 19 G EBUS TBNA needle was used followed by 1.15 mm forcep biopsy however forcep biopsy was successful only in 18 pts
- Location of forcep biopsy was confirmed by fluoroscopy
- A specific diagnosis was made in 12 patients, MFB helped in diagnosing 3 patients with negative results of TBNA (2 sarcoidosis, 1 small cell carcinoma)
- Forcep biopsy was found to be complementary to the TBNA technique

J Bronchol 2004;11:150–153

FIGURE 1. Ensheathed miniforceps (FB-56D-1, Olympus).

FIGURE 3. Miniforceps advanced into the subcarinal region.

TABLE 1. Results of Diagnostic Methods in the 12 Patients With Specific Diagnoses

Group	Patient	Diagnosis	MFB	TBNA, Histology	TBNA, Cytology
1	1	Squamous cell carcinoma	Diagnostic	Diagnostic	Positive
	2	Small cell carcinoma	Diagnostic	Diagnostic	Positive
	3	Small cell carcinoma	Diagnostic	Nondiagnostic	Positive
	4	Squamous cell carcinoma	Nondiagnostic	Diagnostic	Positive
	5	Large cell carcinoma	No specimen	Diagnostic	Positive
2	1	Small cell carcinoma	Diagnostic	Diagnostic	Positive
	2	Sarcoidosis	Diagnostic	Diagnostic	Negative
	3*	Tuberculosis	Diagnostic	Diagnostic	Negative
	4*	Sarcoidosis	Diagnostic	No specimen	Negative
	5	Adenocarcinoma	Diagnostic	Diagnostic	Positive
	6*	Sarcoidosis	Diagnostic	No specimen	Negative
	7	Adenocarcinoma	Diagnostic	Diagnostic	Positive

Ann Thorac Surg. 2008 Jun;85(6):1874-8. doi: 10.1016/j.athoracsur.2008.02.031.

Endobronchial ultrasound-guided miniforceps biopsy in the biopsy of subcarinal masses in patients with low likelihood of non-small cell lung cancer

Felix J F Herth [1], Ross K Morgan, Ralf Eberhardt, Armin Ernst

Methods: Patients being evaluated for subcarinal lesions exceeding 2.5 cm (short axis) and without known or suspected non-small cell lung cancer were included. Bronchoscopy was performed, and EBUS-guided BNA of the lesion was performed first with a 22-gauge needle, followed by the 19-gauge needle. The miniforceps was then passed through the airway into the lesion (three to five passes) under real-time EBUS guidance. Three biopsy specimens were obtained.

Results: The study enrolled 75 patients (41 men; mean age, 51.5 years). Specimens were acquired from each patient using the three techniques and processed separately. A specific diagnosis was made in 36% of patients with the 22-gauge needle, 49% with the 19-gauge needle, and in 88% with the miniforceps. The increase in diagnostic yield with miniforceps was most significant in patients with sarcoidosis (88% vs 36% for TBNA, p = 0.001) or lymphoma (81% vs 35%, p = 0.038). No complications occurred.

Endobronchial-Ultrasound Guided Miniforceps Biopsy of Mediastinal and Hilar Lesions

Ara Chrissian, MD, David Misselhorn, RRT, and Alexander Chen, MD

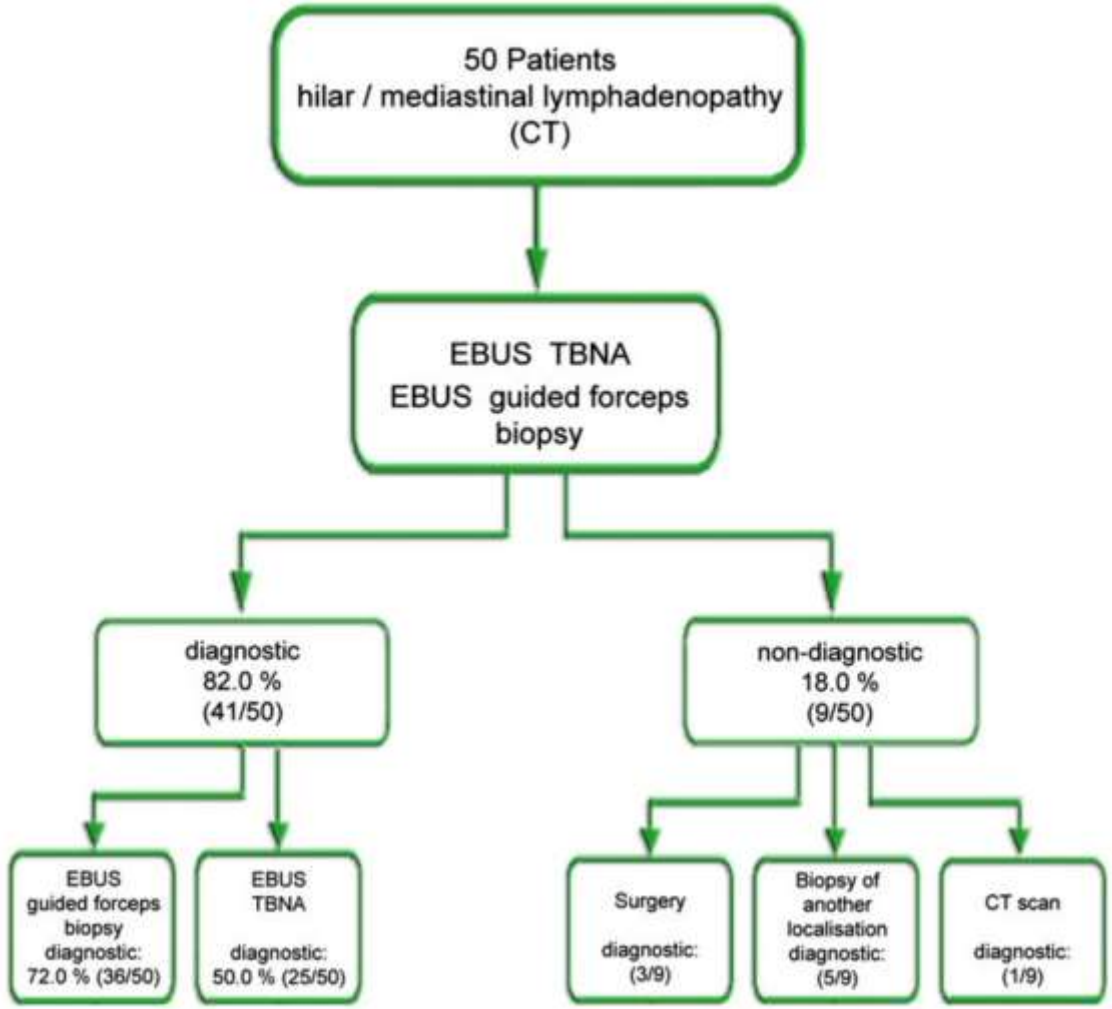
- 50 patients underwent EBUS-TBNA and EBUS-MFB of 74 lymphnode stations
- Patients with high likelihood of non small cell lung cancer were excluded
- Technique : 4-6 passes taken by 22G EBUS-TBNA needle followed by 1 mm miniforcep advanced through the puncture site and 3 biopsies taken

Ann Thorac Surg 2011;92:284 –9

Table 2. Diagnostic Yield

	EBUS-TBNA (%)	EBUS-MFB (%)	*p* Value MFB vs TBNA	Combined (%)	*p* Value Combined vs TBNA
Overall Yield	60/74 (81)	67/74 (91)	0.09	72/74 (97)	<0.001
Nonmalignant disease	43/49 (88)	43/49 (88)	ND[a]	48/49 (98)	0.025
Granulomatous disease	29/33 (88)	29/33 (88)		33/33 (100)	
Other nonmalignant	14/16 (88)	14/16 (88)		15/16 (94)	
Malignant disease	17/25 (68)	24/25 (96)	0.008	24/25 (96)	NP[b]
Non-small cell lung carcinoma	4/5 (80)	5/5 (100)		5/5 (100)	
Small cell lung carcinoma	6/8 (75)	8/8 (100)		8/8 (100)	
Breast carcinoma	4/4 (100)	4/4 (100)		4/4 (100)	
Renal cell carcinoma	1/1 (100)	1/1 (100)		1/1 (100)	
Sarcoma	0/1 (0)	0/1 (0)		0/1 (0)	
Lymphoma	0/4 (0)	4/4 (100)		4/4 (100)	
Other malignant	2/2 (100)	2/2 (100)		2/2 (100)	

The Contribution of Endobronchial Ultrasound-guided Forceps Biopsy in the Diagnostic Workup of Unexplained Mediastinal and Hilar Lymphadenopathy



Franke kJ et al. Lung (2012) 190:227–232

Table 1 Diagnostic yield of EBUS-guided forceps biopsy and EBUS–TBNA

Diagnosis	No. of patients diagnosed by EBUS-guided forceps biopsy	No. of patients diagnosed by EBUS–TBNA	No. of final diagnoses
Small-cell lung cancer	5	6	6
Non-small-cell lung cancer	3	5	6
Lymph node metastasis of extrapulmonary carcinoma	2	0	4
Sarcoma	1	1	1
Malignant lymphoma	1	0	2
Hemangioendothelioma	0	0	1
Sarcoidosis	7	4	8
Tuberculosis	2	1	2
Abscess	0	1	1
Nonspecific lymphadenitis	1	0	1
Anthracofibrosis	7	3	7
Silicosis	1	1	2
Reactive lymphadenopathy	5	3	8
Hamartochondroma	1	0	1
Lung cancer	8	11	12
Diagnoses other than lung cancer	28	14	38
Total	36 (72%)	25 (50%)	50 (100%)

Evaluation of a Novel Endobronchial Ultrasound-Guided Lymph Node Forceps in Enlarged Mediastinal Lymph Nodes

- Prospective study, 55 patients with enlarged (>10 mm) mediastinal or hilar lymph nodes
- All mediastinal and hilar lymph node stations were assessed systematically and punctured 3 times with a 22-gauge needle if their diameter exceeded 5 mm.
- A single enlarged lymph node was identified as the index lymph node for transbronchial forceps biopsy (TBFB), three specimens were obtained

Darwiche K, et al. Respiration 2013;86:229–236

Table 2. Diagnostic yield of EBUS-TBNA, EBUS-TBFB, and a combined approach

	EBUS-TBNA	EBUS-TBFB	Combined	p value[a]
Overall diagnostic accuracy	34/48 (71%)	40/48 (83%)	42/48 (88%)	n.s.
Malignant	16/20 (80%)	15/20 (75%)	16/20 (80%)	n.s.
NSCLC	13/16 (81%)	12/16 (75%)	13/16 (81%)	n.s.
SCLC	2/2 (100%)	2/2 (100%)	2/2 (100%)	n.s.
Other than NSCLC	1/2 (50%)	1/2 (50%)	1/2 (50%)	n.s.
Benign	18/28 (64%)	25/28 (89%)	26/28 (93%)	<0.05
Sarcoidosis	11/18 (61%)	16/18 (89%)	17/18 (94%)	<0.05
Anthracosilicosis	0/2	2/2	2/2	
Tuberculosis	1/1	1/1	1/1	
Bronchogenic cyst	0/1	0/1	0/1	
Reactive lymphadenopathy	6/6	6/6	6/6	

Endobronchial Ultrasound-Guided Cautery-Assisted Transbronchial Forceps Biopsies: Safety and Sensitivity Relative to Transbronchial Needle Aspiration

- Prospectively enrolled 50 unselected patients
- All lymph nodes exceeding 1 cm were sequentially biopsied under EBUS guidance using TBNA and ca-TBFB
- 3 TBNA and 2 forceps passes were taken at each station
- Safety and sensitivity were assessed at the nodal level for 111 nodes
- Results : There were no significant adverse events
- On one hand, only ca-TBFB would have missed 6 of the 31 patients with malignancy, on the other hand, only TBNA would have missed 3 of 8 patients with sarcoidosis

Bramley et al. Ann Thorac Surg 2016;101:1870–6

Conditions Positively Identified by a Consensual Gold Standard[a]		Nodes Positively Diagnosed per Biopsy Technique, No (Sensitivity in %)			
Condition	Nodes per Condition	TBNA	ca-TBFB		*p* Value[b]
Malignant					
NSCLC	33	33 (100)	24 (73)		0.002
Small cell lung cancer	14	14 (100)	13 (93)	[c]	
Lymphoma	5	5 (100)	4 (80)	[c]	
Metastatic other[d]	2	2 (100)	1 (50)	[c]	
Total malignant	54	54 (100)	42 (78)		<0.001
Nonmalignant					
Granulomatous inflammation	19	6 (32)	17 (85)	[c]	
Infection	2	1 (50)	2 (100)	[c]	
Lymphocytes only	36	33 (92)	28 (78)		0.072
Total nonmalignant	57	40 (70)	47 (82)	[c]	
Overall Total		94 (85)	89 (80)	[c]	

Bramley et al. Ann Thorac Surg 2016;101:1870–6

Table 2. Cautery-Assisted Transbronchial Forceps Biopsy[a] Rate of Nodal Penetration by Lymph Node Characteristics

Ability to Successfully Biopsy Node by Lymph Node Location and Size	Specific Diagnosis/ Lymphocytes (n = 90)	Total (n = 111)	Nodal Penetration (%)
Location			
Paratracheal[b]	24	37	64.8
Parabronchial[c]	66	74	89.2
Lymph node size, mm			
5–9.9	6	7	85.7
10–14.9	40	53	75.5
15–20	19	24	79.2
>20	25	27	92.6

Ability To Successfully Biopsy Node By Lymph Node Depth[d]	Specific Diagnosis/ Lymphocytes (n = 67)	Total (n = 81)	Nodal Penetration (%)
Lymph node depth, mm			
1–1.9	5	5	100
2–3	30	37	81.1
>3	32	39	82.1

Bramley et al. Ann Thorac Surg 2016;101:1870–6

Improved Diagnostic Yield and Specimen Quality With Endobronchial Ultrasound-Guided Forceps Biopsies: A Retrospective Analysis

- Retrospectively reviewed patients who underwent EBUS-TBNA and concomitant ca-TBFB on the same lymph nodes in a tertiary care center between 2011 and 2016
- In addition to above, patients underwent BAL, endobronchial, transbronchial biopsies, or other bronchoscopic techniques based on the radio_x0002_graphic findings
- Lymph nodes sized greater than 5 mm underwent TBNA with 20 to 30 agitations per pass using the 21- or 22-gauge needle, 3 passes per station

Amrik RS et al, Ann Thorac Surg 2020;109:894-901

Methods

- Then, LN's > 1 cm identified, incision was made by electrocautery knife in the airway wall adjacent to the node and biopsy taken by 1.9-mm spiked fenestrated alligator forceps
- Approximately 5 biopsies during each of 3 passes at each LN station
- Specimen quality was assessed by the amount of cellular material, background blood, degree of cellular degeneration and trauma and retention of normal architecture.
- Quality in each subdomain was scored on an ordinal 0 to 2 scale where higher scores reflect higher quality, resulting in an overall score ranging from 0 to 8.

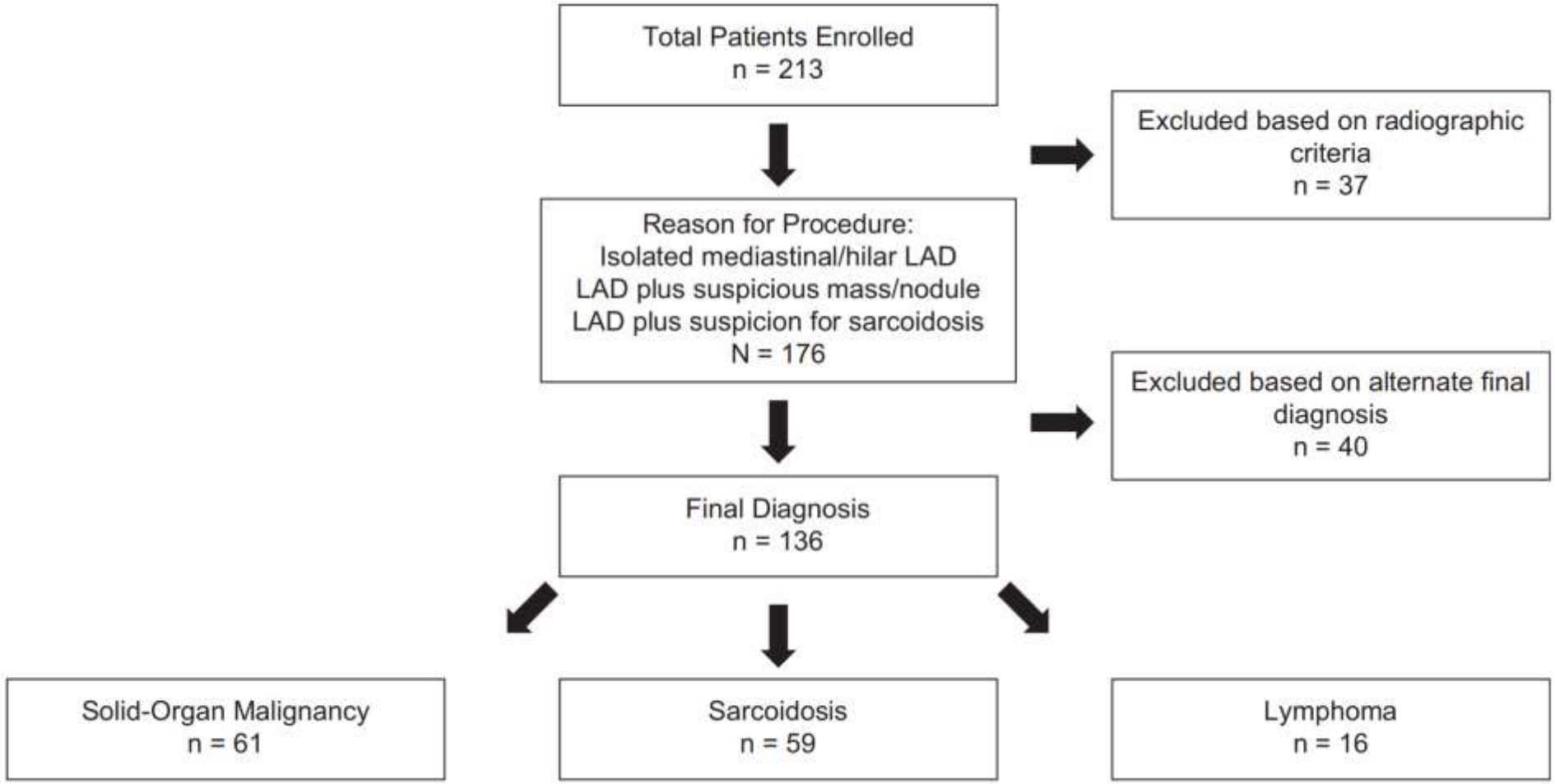
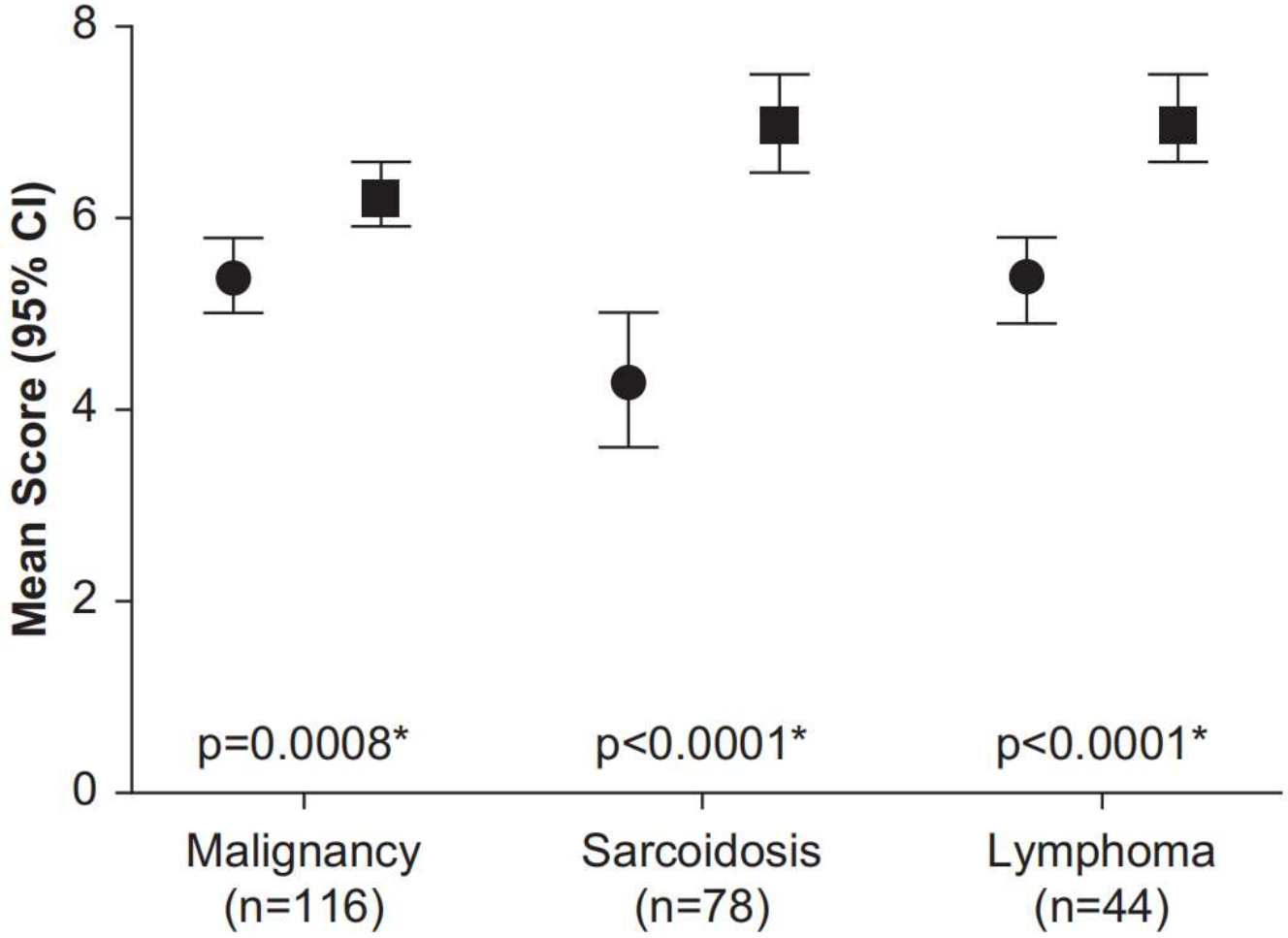


Figure 1. This study retrospectively evaluated 213 patients. We excluded patients in the final analysis who did not meet criteria for any of the 3 clinical radiographic findings: patients with isolated mediastinal lymphadenopathy (LAD), adenopathy associated with a suspicious nodule or mass, and adenopathy associated with other radiographic findings consistent with sarcoidosis. The final analysis includes patients diagnosed by bronchoscopy with solid-organ malignancy, sarcoidosis, or lymphoma.

Methods	TBNA	TBNA+TBFB
Diseases		
Malignancy (n=61)	91.8% (95% CI, 70.7%-100%)	93.4% (95% CI, 72.1%-100%; P ¼ .50).
Sarcoidosis (n=59)	62.7% (95% CI, 45.4%-86.6%)	94.9% (95% CI, 73.0%-100%; P < .001)
Lymphoma (n=16)	62.5% (95% CI, 33.6%-100%)	93.8% (95% CI, 56.5%-100%; P ¼ .042)

Quality assessment

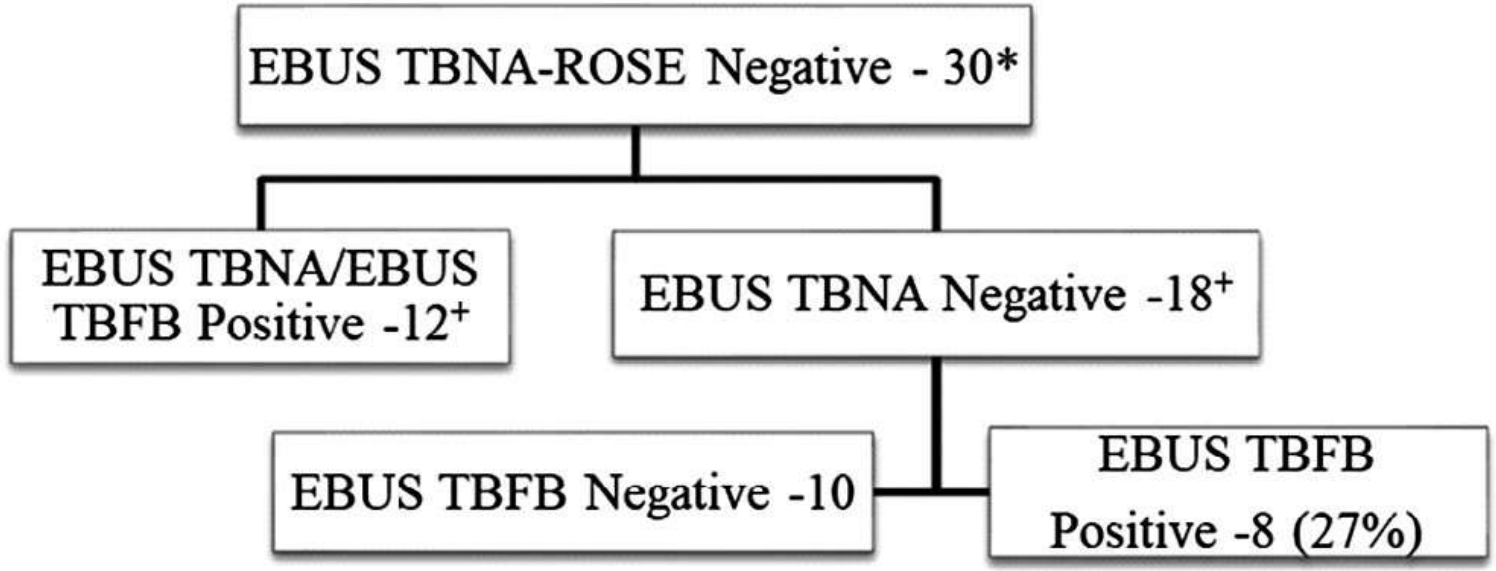


(Circles and squares indicate TBNA and ca_x0002_TBFB, respectively)

Endobronchial ultrasound-guided mediastinal lymph node forceps biopsy in patients with negative rapid-on-site-evaluation: A new step in the diagnostic algorithm

- 30 patients with enlarged LN and non diagnostic EBUS ROSE were enrolled
- Technique : TBNA - site selection - EBUS probe removed - electrocautery under conventional bronchoscope - TBFB by 1.5mm forceps under EBUS - 4 biopsy taken
- Of the 30 EBUS-TBNA patients with a non-diagnostic ROSE, 12/30 patients were subsequently found to be diagnostic on final cytopathology
- EBUS-TBFB led to positive diagnostic results in an additional 8/30 patients (27%)

Mehta RM, et al. Clin Respir J. 2020;14:314–319



Sr. No	Age (Yrs)	Gender	No. LN Station—EBUS TBNA	EBUS TBFB-Station[24]	EBUS TBFB-LN size (mms)	Diagnosis
1	25	F	3 (4R,7,4L)	7	53	Tuberculosis
2	28	F	2 (4R,7)	4R	24	Tuberculosis
3	35	M	4 (4R,7,4L,11L)	7	28	Tuberculosis
4	44	M	4 (4R,7,4L,11L)	4R	20	Hodgkin's Lymphoma
5	55	M	3 (4R,7,2R)	4R	21	Tuberculosis
6	56	F	3 (4R,7,11L)	7	17	Tuberculosis
7	61	M	2 (4R,7)	4R	28	Aspergillosis
8	66	M	4 (4R,7,11R,11L)	7	25	Tuberculosis

Combined EBUS-IFB and EBUS-TBNA vs EBUS-TBNA Alone for Intrathoracic Adenopathy: A Meta-Analysis

- The overall diagnostic yield of EBUS-IFB and EBUS-TBNA compared with EBUS-TBNA alone.
- Secondary outcome was the combined diagnostic yield of EBUS-IFB and EBUS-TBNA compared with EBUS-TBNA alone in patients with suspected sarcoidosis and lymphoma
- The other secondary outcome was the safety profile of the EBUS-IFB intervention
- One case of mild pneumomediastinum noted

TABLE 2 Summary of Included Studies

Study (First Author, y, Reference)	Study Design	Age (Mean/Range), y	Selection Criteria	Total Events (Patients/Lymph Nodes)	Overall EBUS-TBNA Yield	Overall EBUS-TBNA + IFB Yield	EBUS-TBNA Yield for Sarcoidosis	EBUS-TBNA + IFB Yield for Sarcoidosis	EBUS-TBNA Yield for Lymphoma	EBUS-TBNA + IFB Yield for Lymphoma	Gold Standard
Herth, 2008[19]	Prospective case series	53 (27-71)	Subcarinal lymph node (>25mm)	75	27/75	66/75	6/25	22/25	3/26	21/26	Surgical biopsy (mediastinoscopy or VATS)
Chrissian, 2011[20]	Prospective case series	NA	Subcarinal: 17; paratracheal: 21; hilar: 36 (mean size, 28 mm)	Patients, 50; lymph nodes, 74.	60/74	72/74	29/33	33/33	0/4	4/4	Mediastinoscopy
Franke, 2012[15]	Prospective case series	57.7 (± 13.9)	Lymph node stations (4, 7, 10, 11, 12) (mean size, 18.7 mm	50	25/50	41/50	4/8	7/8	0/2	1/2	Surgical biopsy (mediastinoscopy or VATS) or CT follow-up
Darwiche, 2012[21]	Prospective case series	54 (19-79)	Lymph node >10 mm	48	34/48	42/48	11/18	17/18	NA	NA	Surgical biopsy (mediastinoscopy or VATS) or CT follow-up
Ray, 2020[22]	Retrospective observational	Patients with malignancy, 67.5 (± 10.5) Patients with sarcoidosis,53.1 (±14.6) Patients with lymphoma, 49.2 (± 19.5)	Mediastinal or hilar lymph nodes	136	103/136	128/136	37/59	56/59	10/16	15/16	NA
Radchenko, 2019[23]	Retrospective observational	59.2 (21-87)		84	63/84	79/84	6/18	15/18	2/2	2/2	Surgical biopsy (mediastinoscopy) or CT follow-up

CT, computed tomographic; EBUS, endobronchial ultrasound; IFB, intranodal forceps biopsy; NA, not applicable, information not available; TBNA, transbronchial needle aspiration; VATS, video-assisted thoracoscopic surgery.

TABLE 3 Materials and Methods Used Across Individual Studies (Type of Transbronchial Needle Aspiration Needle, Type and Size of Intranodal Forceps Biopsy Forceps)

Study (First Author, y, Reference)	Technique and Type of TBNA	Number of TBNA Passes at Each LN Station	Type of Intranodal Forceps Used	Size of Intranodal Forceps Used (mm)	Technique of Intranodal Forceps Biopsy	Number of IFB Passes at Each LN station
Herth, 2008[19]	19- and 22-gauge Olympus TBNA needle[a]	3-4	Miniforceps (Olympus, Shinjiku, Japan)	1.15	Forceps through puncture site of EBUS-TBNA	3-5 (with the aim of obtaining 3 biopsy specimens)
Chrissian, 2011[20]	22-gauge Olympus TBNA needle	4-6	Miniforceps (Boston Scientific, Marlborough, MA)	1.0	Forceps through puncture site of EBUS-TBNA	Minimum 3 biopsy specimens
Franke, 2012[15]	22-gauge (SonoTip II EBUS; Medi-Globe, Achenmühle, Germany).	3	21-gauge biopsy forceps (outside diameter, 0.8 mm; long oval cups; Endo-Passion, Durbheim, Germany)	0.8	Forceps through puncture site of EBUS-TBNA	2
Darwiche, 2012[21]	22-gauge Olympus TBNA needle	3	Puncture biopsy forceps (MTW-Endoskopie, Wesel, Germany)	1.1	The puncture biopsy forceps uses a 19-gauge needle tip for puncture through which the forceps can be inserted	3
Ray, 2020[22]	22- or 21-gauge Olympus needle[b]	3	Spiked fenestrated alligator forceps (Olympus FB- 241K)	1.9	An electrocautery knife (Olympus KD- 31C-1) using Erbe (Tubingen, Germany) VIO 300D-40W was used to make incisions and then forceps advanced through them	3
Radchenko, 2019[23]	22-gauge Olympus needle	Mean number, 6.74 (SD 1.42)	Spybite (Boston Scientific))	1.0	Forceps through puncture site of EBUS-TBNA	6.09 (SD –1.44)

[a]We used data on the basis of the yield of the 22-gauge Olympus needle to maintain consistency across various studies; [b]Occasionally, the 19-gauge Olympus needle was used, but not reported separately. EBUS, endobronchial ultrasound; IFB, intranodal forceps biopsy; LN, lymph node; TBNA, transbronchial needle aspiration.

A

Study or Subgroup	IFB + TBNA Events	Total	TBNA Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Chrissian 2011	72	74	60	74	7.5%	8.40 [1.84, 38.43]
Darwiche 2013	42	48	34	48	14.5%	2.88 [1.00, 8.30]
Franke 2012	41	50	25	50	18.8%	4.56 [1.83, 11.32]
Herth 2008	66	75	27	75	21.4%	13.04 [5.62, 30.23]
Radchenko et al., 2019	79	84	63	84	15.2%	5.27 [1.88, 14.75]
Ray 2019	128	136	103	136	22.5%	5.13 [2.27, 11.58]
Total (95% CI)		**467**		**467**	**100.0%**	**5.87 [3.81, 9.04]**
Total events	428		312			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.85$, df = 5 (P = 0.32); $I^2 = 15\%$

Test for overall effect: Z = 8.03 (P < 0.00001)

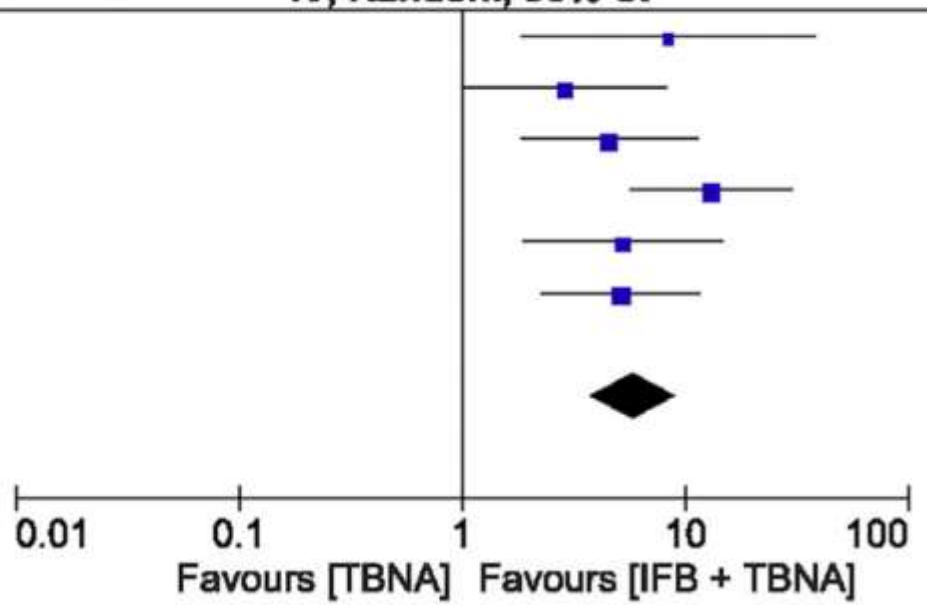


TABLE 4 Complications in Patients Undergoing Endobronchial Ultrasound–Guided Intranodal Forceps Biopsy and Endobronchial Ultrasound–Guided Transbronchial Needle Aspiration

Study (First Author, y, Reference)	Total Patients Undergoing IFB	Pneumomediastinum	Bleeding	Respiratory Failure	Pneumothorax	Other Complications
Herth, 2008[19]	75	0	0	0	0	0
Chrissian, 2011[20]	50	0	0	0	0	0
Franke, 2012[15]	50	1	3[a]	0	0	0
Darwiche, 2013[21]	48	0	0	0	0	0
Ray, 2019[22]	136	4	1 (hemoptysis within 10 days)	1	4[b]	1 (pneumonia within 10 days)
Radchenko, 2019[23]	84	0	0	2	1[#]	1 death[c]
Total	443	5 (1%)	4 (0.9%)	3 (0.7%)	5 (1%)[b]	2

[a]Bleeding treated with 1 mg of norepinephrine in puncture hole; [b]Patients in the study by Ray and colleagues and Radchenko and colleagues also underwent transbronchial lung biopsies followed by intranodal forceps biopsy. Causality could not be assigned to the complications. The pneumothorax was attributed to the transbronchial biopsy, whereas the pneumomediastinum was attributed to intranodal forceps biopsy. No interventions were needed for the pneumomediastinum, which was self-resolving; [c]Death in 1 patient was attributed to complications of critical aortic stenosis in this patient who had to undergo biopsy as part of an evaluation for valve replacement. IFB, intranodal forceps biopsy.

Discussion

- Overall diagnostic yield of combined EBUS-TBNA and EBUS-IFB was higher than that of EBUS-TBNA alone, especially for benign disorders
- The complication rates (pneumothorax, 1%; bleeding, 0.8%; pneumomediastinum, 1%) were higher than what has been reported with EBUS-TBNA alone (pneumothorax, 0.03%; bleeding, 0.68%) but lower than TBLB or mediastinoscopy
- The overall sarcoidosis- and lymphoma-specific yields for the comparison group (EBUS-TBNA) were lower than in other studies on EBUS-TBNA

Endobronchial ultrasound-guided transbronchial cryo-nodal biopsy

Introduction

- Cryobiopsy, a bronchoscopic technique based on cooling, crystallization & subsequent collection of tissue is an established biopsy technique for the diagnosis of ILD
- Provides larger samples compared to forceps, needle or brush **without crush artifacts**
- Higher quality material for molecular analysis and markers on immunohistochemistry
- A novel ultrathin cryoprobe has been developed and is available since 2019 (20402-401, Erbe Elektromedizin GmbH, Tue_x0002_bingen)

Procedure

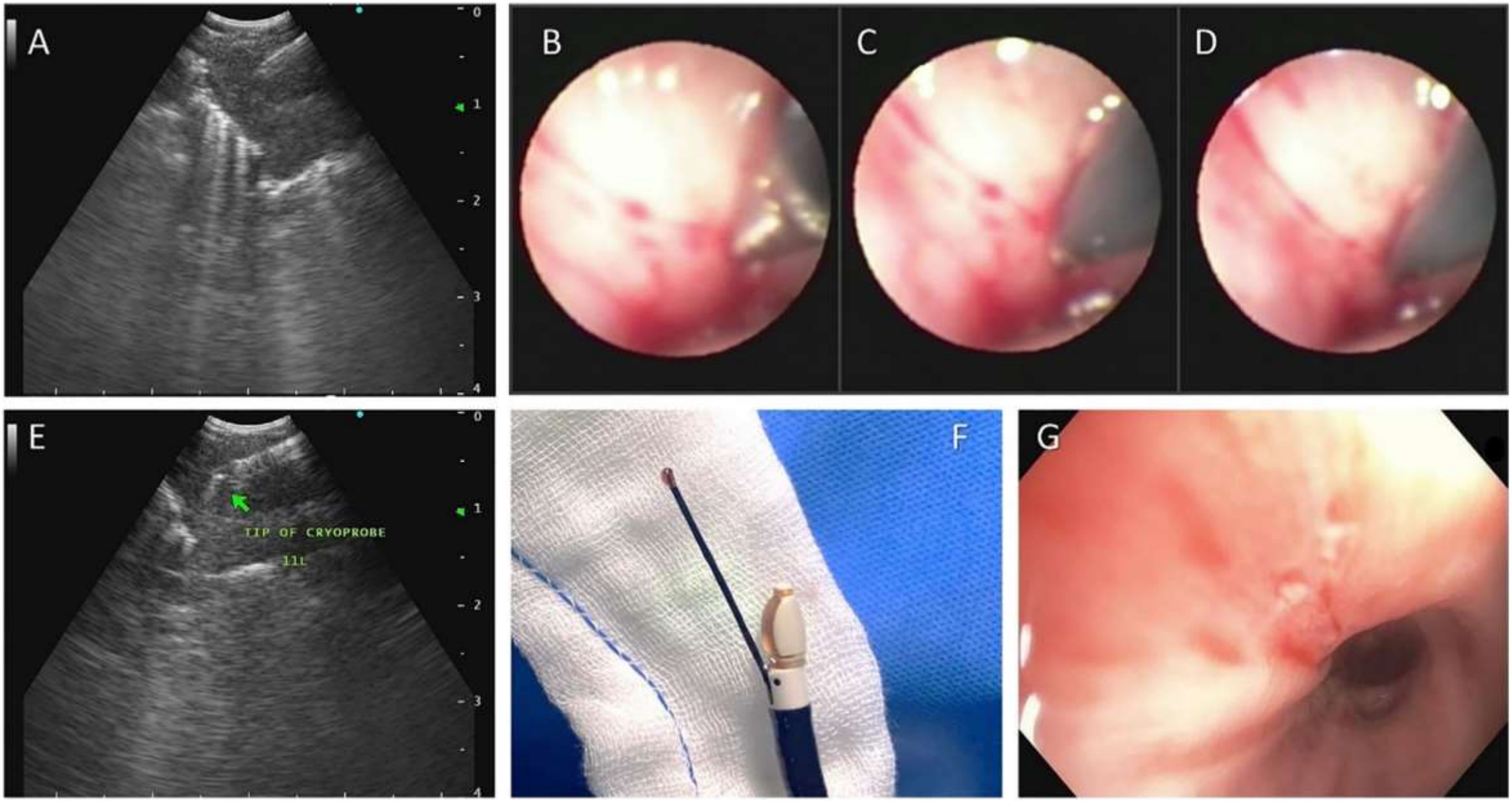
- An EBUS-TBNA is performed in a regular way
- The puncture channel through airway wall and inside the lymph node serves as a track for the ultrathin cryoprobe afterwards.
- As the TBNA-needle is thinner than the cryoprobe, same site is punctured for 2-4 times, aiming to widen airway puncture and track in the node for the cryoprobe
- EBUS-TBNA is performed in a close-to-perpendicular angle with the stylet left inserted for stabilization purposes

- The cryoprobe is then inserted into the working channel of the EBUS-bronchoscope
- Subsequently, the cryoprobe is extended from the working channel and contact with the bronchial wall is made.
- Usually, oozing from the puncture location complicates the exact identification of the entry point.
- In the suspected position of the entry point according to the sonographic image, the cryoprobe is repeatedly pushed against the bronchial wall with the right hand.
- A loss of resistance is felt when the probe passes the air_x0002_way wall and enters the lymph node. The positioning can then be verified on the sonography image

Endobronchial ultrasound-guided transbronchial cryo-nodal biopsy: a novel approach for mediastinal lymph node sampling

- Described the feasibility, technique and complications of using EBUS-TBCNB in four patients with mediastinal adenopathy
- After initial puncture with the EBUS-TBNA needle, a 1.1-mm cryo-probe was introduced into the working channel of the EBUS bronchoscope.
- A high-frequency cautery needle knife may be used to create an entry site for the cryo-probe.
- The probe was advanced slowly and pushed gently through the previous puncture site .
- Under real-time USG guidance, the cryo-probe position was confirmed within the lymph node.
- The cryo-probe was activated for 3 sec and the scope unit with the probe inside was pulled out.

Gonuguntla HK et al, Respirology Case Reports, 9 (8), 2021, e00808



Gonuguntla HK eta al, ,Respirology Case Reports, 9 (8), 2021, e00808

Table 1. Characteristics of lymph node, ROSE, and TBNCB in the four patients.

	Case 1	Case 2	Case 3	Case 4
Enlarged lymph node stations	7, 4L, 4R, 10R, 10L, 11L	7, 4L, 11L	4L, 11L	7, 4R
Size (cm)	>1	>1	>1	>1
Shape	Oval	Oval	Oval	Round
Margin	Indistinct	Distinct	Distinct	Indistinct
Echogenicity	Homogenous	Heterogenous	Homogenous	Heterogenous
Central hilar structure	No	Yes	No	No
Vascular pattern	Avascular	Avascular	Hilar	Non-hilar, central
Elastography pattern	II	III	III	II
Visual appearance of aspirate	Lymphoid	Lymphoid and bloody	Black	Lymphoid
Lymph node station from which EBUS-TBNA was done	7, 11L	7, 11L	4L, 11L	7
EBUS-TBNA needle size (G)	21	21	19	22
ROSE adequacy	Adequate	Adequate	Adequate	Adequate
ROSE diagnosis	Granulomatous inflammation	Adenocarcinoma	Atypical cells	Granulomatous inflammation with caseous necrosis
Lymph node station from which TBCNB was done	7	7	11L	7
Number of cryo-biopsies obtained	1	2	2	2
HPE diagnosis from TBCNB	Sarcoidosis	Adenocarcinoma	Metastatic adenocarcinoma	Tuberculosis
Complications	Nil	Nil	Nil	Minimal bleeding

Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial

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- Patients aged >15 yrs with mediastinal lesion of ⩾1 cm in the short axis were recruited
- Following identification of the mediastinal lesion by linear EBUS, fine-needle aspiration and cryobiopsy sequentially performed in a randomized order
- For transbronchial mediastinal cryobiopsy, a small incision in the tracheobronchial wall adjacent to the mediastinal lesion was made using a high-frequency needle-knife (Olympus KD-31C-1, Olympus)
- The probe was cooled down with liquid carbon dioxide for 7 s, and then retracted with the bronchoscope and the frozen biopsy tissue.

Methodology

- Four TBNAs and three cryobiopsies were taken at each station. ROSE was not done
- 197 patients were enrolled
- Patients were excluded in cases of mediastinal cysts or abscesses, contraindications to endoscopy or mediastinal biopsy, or potential need for additional procedures other than EBUS (such as endobronchial biopsy).
- Primary end-points: diagnostic yield : percentage of patients for whom mediastinal biopsy provided a definite diagnosis,
- Secondary end-points: sample adequacy and size, and duration of procedure

TABLE 1 Baseline characteristics

	"TBNA first" group	"Cryobiopsy first" group	p-value
Subjects n	99	98	
Age (years)	57.1±11.4	58.2±13.3	0.53
Sex			0.27
Female	44 (44.4%)	36 (36.7%)	
Male	55 (55.6%)	62 (63.3%)	
Ethnic origin			0.84
Asian	65 (65.7%)	63 (64.3%)	
Caucasian	34 (34.3%)	35 (35.7%)	
BMI ($kg \cdot m^{-2}$)	23.4±2.7	22.6±3.6	0.06
Smoking (pack-year)	18.6±20.6	18.8±21.8	0.95
Lesion size (short axis, cm)	2.3±1.2	2.2±1.1	0.81
Lesion station n			0.61
7	28	21	
12R	2	2	
11R	10	4	
10R	7	11	
4R	33	34	
2R	2	2	
12L	0	2	
11L	2	5	
10L	4	6	
4L	10	9	
2L	1	2	

Data are presented as n (%) or mean±SD, unless otherwise stated. TBNA: transbronchial needle aspiration; BMI: body mass index.

TABLE 2 Diagnostic yields of TBNA and transbronchial mediastinal cryobiopsy

	Total	TBNA	Cryobiopsy	p-value
Subjects n	194	194	194	
Diagnostic yield n (%)				0.001
No	13 (6.7%)	39 (20.1%)	16 (8.2%)	
Yes	181 (93.3%)	155 (79.9%)	178 (91.8%)	
Common tumour n				
Lung, adenocarcinoma	75	68	72	
Lung, squamous cell	24	24	23	
Lung, large cell	3	3	3	
Lung, NSCLC (NOS)	7	6	5	
Lung, small cell	26	26	26	
Total n (%)	135 (69.6%)	127 (65.5%)	129 (66.5%)	0.58
Uncommon tumour n				
Lung, carcinoid	1	0	1	
Lung, sarcomatoid	1	1	1	
Lymphoma	8	1	7	
Seminoma	1	0	1	
Thymic carcinoma	1	1	1	
Total n (%)	12 (6.2%)	3 (1.5%)	11 (5.7%)	0.001
Benign disorder n				
Sarcoidosis	15	10	15	
Tuberculosis	16	8	16	
Pneumoconiosis	7	7	7	
Total n (%)	47 (24.2%)	25 (12.9%)	38 (19.6%)	0.004

TBNA: transbronchial needle aspiration; NSCLC: non-small cell lung cancer; NOS: not otherwise specified.

- TBNCB gave additional pathological information in 4 lung cancer patients
- Two adenocarcinomas with sarcoma_x0002_ like differentiation, one squamous cell cancer with TB and one small cell cancer with large cell neuroendocrine carcinoma
- However 3 cases of NSCLC were missed by TBNCB, detected only by TBNA
- In cases of NSCLC, 93.3% of the cryobiopsy materials were suitable for gene mutation PCR testing, while this ratio was only 73.5% for TBNA
- 13 patients (6.7%) had non-definite diagnosis.
- Three of these cases underwent a cervical mediastinoscopy, one had the lesion surgically resected and one had a regular bronchoscopy, three were diagnosed with NSCLC, one with lymphoma and rest others had benign disease

TABLE 4 Procedure-related adverse events

	"TBNA first" group	"Cryobiopsy first" group	p-value
Subjects n	98	98	
Bleeding n			
Grade 2	9	9	
Grade 3	0	2	
Grade 4	0	0	
Total n (%)	83 (84.7%)	86 (87.8%)	0.53
Pneumothorax n (%)	1 (1.0%)	1 (1.0%)	1
Pneumomediastinum n (%)	0 (0%)	1 (1.0%)	1
Death n (%)	0 (0%)	0 (0%)	-

TBNA: transbronchial needle aspiration.

Transbronchial needle aspiration combined with cryobiopsy in the diagnosis of mediastinal diseases: a multicentre, open-label, randomised trial

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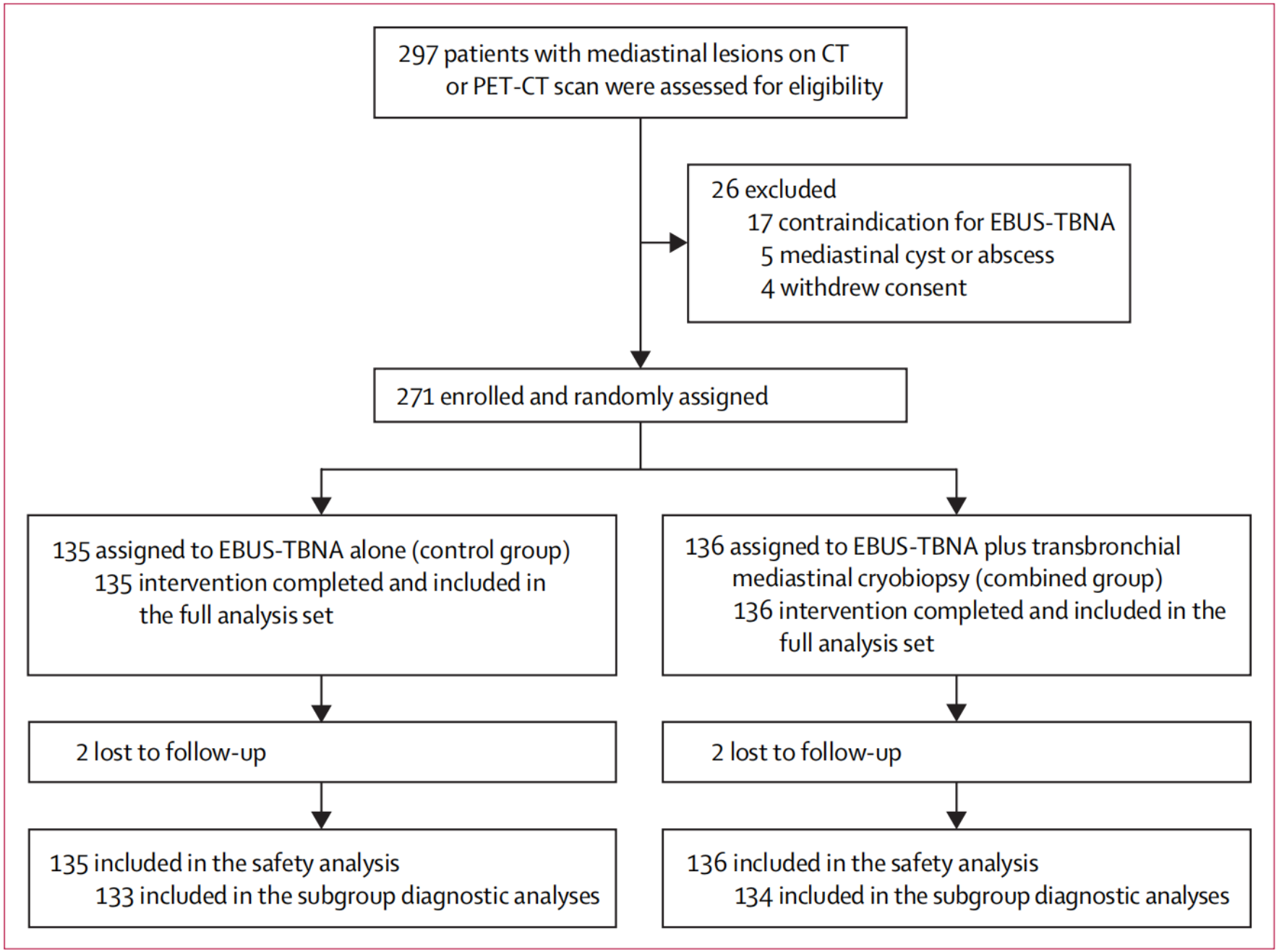
- Open-label, randomized trial comparing combined EBUS-TBNA and TBNCB (four passes of needle aspiration plus one-time cryobiopsy) or EBUS-TBNA alone (four passes).
- The coprimary outcomes were differences in procedure-related complications and diagnostic yield
- Prespecified secondary endpoints comprised the diagnostic yield of transbronchial mediastinal cryobiopsy, specimen adequacy, size, and suitability for molecular genetic assay, and duration of the bronchoscopic procedure.

- Technique : incision in the bronchial wall with a high-frequency needle-knife (Olympus KD-31C-1)---> cryoprobe through the incision into the lesion---> cooling with liquid CO2 for 7 s---> thawing in saline and fixed in formalin--->ROSE not done
- In case of no definite diagnosis, additional procedures surgical resection, mediastinoscopy, or CT-guided percutaneous needle aspiration biopsy would be considered
- Plausible benign finding, not verified pathologically, was confirmed by either surgical biopsy or 6 months of radiographical follow-up showing stability or decrease in size
- All participants received postprocedural chest radiography within 24 h, and were followed up for potential EBUS_x0002_related adverse events for 4 weeks after biopsy


297 patients with mediastinal lesions on CT or PET-CT scan were assessed for eligibility
26 excluded
17 contraindication for EBUS-TBNA
5 mediastinal cyst or abscess
4 withdrew consent
271 enrolled and randomly assigned
135 assigned to EBUS-TBNA alone (control group)
135 intervention completed and included in the full analysis set
136 assigned to EBUS-TBNA plus transbronchial mediastinal cryobiopsy (combined group)
136 intervention completed and included in the full analysis set
2 lost to follow-up
2 lost to follow-up
135 included in the safety analysis
133 included in the subgroup diagnostic analyses
136 included in the safety analysis
134 included in the subgroup diagnostic analyses

	EBUS-TBNA alone group (n=135)	Combined group (n=136)
Age, years	56·2 (12·5)	57·3 (12·5)
Sex		
Female	56 (41%)	50 (37%)
Male	79 (59%)	86 (63%)
Ethnicity		
Asian	85 (63%)	86 (63%)
White	50 (37%)	50 (37%)
BMI, kg/m²	24·1 (3·6)	23·6 (4·0)
Smoking, pack-years	13·3 (22·2)	15·2 (19·2)
Lesion short axis diameter, cm	2·1 (0·8)	2·0 (0·9)
Lesion station		
7	43 (32%)	47 (35%)
13R	1 (1%)	1 (1%)
12R	2 (1%)	2 (1%)
11R	15 (11%)	15 (11%)
10R	1 (1%)	2 (1%)
4R	23 (17%)	30 (22%)
2R	14 (10%)	4 (3%)
13L	0	1 (1%)
11L	7 (5%)	6 (4%)
10L	5 (4%)	6 (4%)
4L	8 (6%)	16 (12%)
2L	12 (9%)	6 (4%)
3A	1 (1%)	0
3P	3 (2%)	0

Data are mean (SD) or n (%). EBUS-TBNA=endobronchial ultrasound-guided transbronchial needle aspiration.

Table 1: **Baseline characteristics**

	EBUS-TBNA alone group (n=135)	Combined group (n=136)	p value
Diagnostic yield	..	..	0·0039
No definitive diagnosis	26 (19%)	10 (7%)	..
Definitive diagnosis	109 (81%)	126 (93%)	..
Procedure time, min	17·0 (8·2)	22·3 (6·4)	<0·0001
Adverse events			
Coughing	12 (9%)	19 (14%)	0·19
Dyspnoea	4 (3%)	2 (1%)	0·67
Haemoptysis	2 (1%)	3 (2%)	1·00
Bleeding	..	..	..
Grade 2	14 (10%)	16 (12%)	0·72
Grade 3	2 (1%)	3 (2%)	1·00
Grade 4	0	0	..
Pneumothorax	4 (3%)	2 (1%)	0·67
Pneumomediastinum	0	1 (1%)	1·00
Death	0	0	..

Data are n (%) or mean (SD) unless otherwise stated. EBUS-TBNA=endobronchial ultrasound-guided transbronchial needle aspiration.

Table 2: **Diagnostic yield and adverse event analyses in the full analysis set (interindividual comparisons)**

	Total (n=134)	EBUS-TBNA alone (n=134)	EBUS-TBNA plus cryobiopsy (n=134)	p value
Diagnostic yield	..	..	..	0·0026
No definitive diagnosis	..	24 (18%)	8 (6%)	..
Definitive diagnosis	..	110 (82%)	126 (94%)	..
Lung cancer	..	..	..	1·00
Any	64 (48%)	63 (47%)	63 (47%)	..
Lung, adenocarcinoma	31 (23%)	30 (22%)	30 (22%)	..
Lung, squamous cell	7 (5%)	7 (5%)	7 (5%)	..
Lung, large cell	3 (2%)	3 (2%)	3 (2%)	..
Lung, neuroendocrine	1 (1%)	1 (1%)	1 (1%)	..
Lung, small cell	22 (16%)	22 (16%)	22 (16%)	..
Other metastatic carcinoma	..	..	..	-
Any	5 (4%)	5 (4%)	5 (4%)	..
Breast cancer	2 (1%)	2 (1%)	2 (1%)	..
Oesophageal cancer	1 (1%)	1 (1%)	1 (1%)	..
Prostatic cancer	2 (1%)	2 (1%)	2 (1%)	..
Uncommon tumour	..	..	..	0·27
Any	17 (13%)	10 (7%)	13 (10%)	..
Lymphoma	10 (7%)	5 (4%)	8 (6%)	..
Neurilemmoma	1 (1%)	1 (1%)	1 (1%)	..
NUT midline carcinoma	1 (1%)	0	0	..
Seminoma	1 (1%)	1 (1%)	1 (1%)	..
Thymic carcinoma	1 (1%)	0	0	..
Thymoma	3 (2%)	3 (2%)	3 (2%)	..
Benign disorder*	..	..	..	0·0009
Any	48 (36%)	32 (24%)	45 (34%)	..
Pneumoconiosis	10 (7%)	9 (7%)	10 (7%)	..
Sarcoidosis	16 (12%)	12 (9%)	16 (12%)	..
Tuberculosis	19 (14%)	11 (8%)	19 (14%)	..

Discussion

- Mediastinal cryobiopsy is be complementary to TBNA
- Adds to diagnostic sensitivity of EBUS-TBNA especially for benign diseases
- Its not associated with severe adverse events