



Introduction

- Lung cancer remains the n°1 cancer killer in Europe and United States
- Survival is directly related to stage at diagnosis
- Patients with early-stage lung cancer have recurrence rates about 30%-40%, with a 5-year survival ranging dramatically from 50% to 90%, in part due to occult disease and inadequate nodal staging

Pathologic nodal stage is the strongest predictor of long-term survival in surgical NSCLC

Lymph node staging pathways

Imaging → CT scan and PET FDG

CT lymph node enlargement and/or
PET FDG pathological uptake

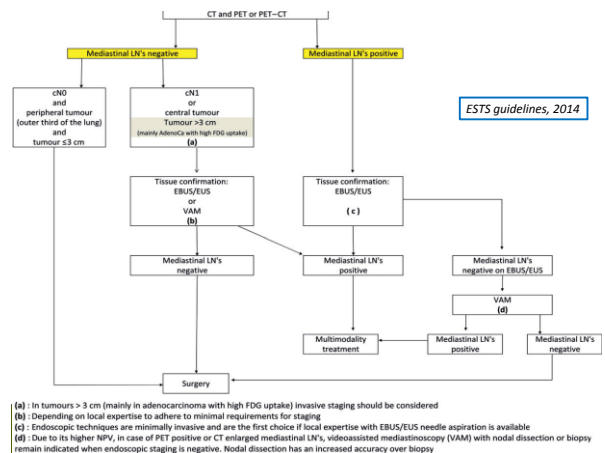


Invasive mediastinal staging

Endoscopic biopsy → EBUS-TBNA / EUS

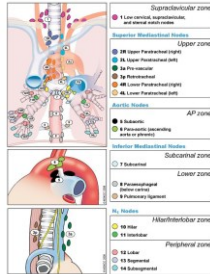
Surgical biopsy → mediastinoscopy / VATS

*Diagnosis and Management of Lung Cancer,
ACCP guidelines 3rd ed 2013*



Mediastinal Staging

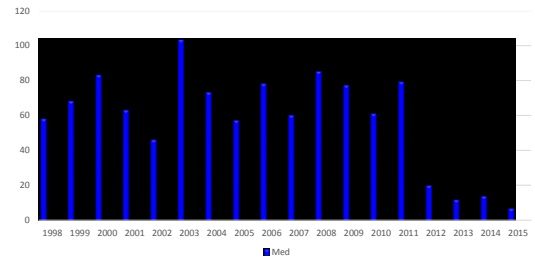
Staging modality	Lymph node access	%		
		Sensitivity*	Specificity*	NPV*
Noninvasive				
CT chest	All	55	81	83
PET	All	80	88	91
PET-CT	All	82	90	90
Invasive				
Mediastinoscopy [†]	2R, 2L, 4R, 4L, 7	78	100 [†]	91
EBUS [†]	2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, 11L	89	100 [†]	91
EUS	4L, 7, 5, 8, 9	89	100 [†]	86
Combined	2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, 11L, 5, 8, 9	91	100 [†]	96



ESTS guidelines, 2014

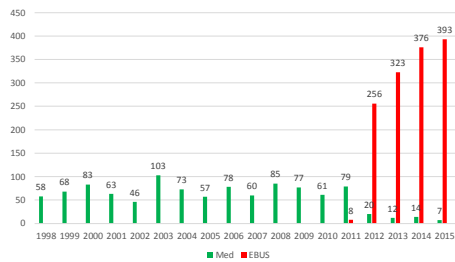
Mediastinal Staging

Mediastinoscopy at European Institute of oncology



Mediastinal Staging

MED vs EBUS



EBUS - Technique

- Outpatient setting
- Moderate sedation
- Extended hilar stations
- «All in ONE» procedure
- No complications
- High diagnostic rate



*First choice for
invasive
mediastinal
staging!*

Endobronchial Ultrasound

Table 1: Real-Time Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Systematic Mediastinal Staging of Non-Small Cell Lung Cancer

First Author	Year	N	cStage	Sedation	Site Selection	Sites Sampled	Technique	ROSE	Complications	Sensitivity (%)
Yasufuku (35)	2005	105	cN1-3	Moderate	>5 mm SA	1.6	Up to 5 passes	Yes	None	95% ^{1,3}
Szlobowski (41)	2009	226	cN0-3	Moderate	>5 mm SA	1.4	3-5 Passes	No	None	92% ¹
Lee (84)	2012	73	cN0-3	GA	All accessible	2.6 ¹	Minimum 1 pass	No	Atrial fibrillation	95% ^{1,3}
Blauwers (42)	2008	106	cN1-3	Moderate	All accessible	1.8	NR	No	Pneumothorax	95% ^{1,3}
Memoli (37)	2011	100	cN1-3	Moderate	All visible	2.3	Up to 3 passes	Yes	None	97% ¹
Yasufuku (44)	2011	153	cN0-3	GA	>5 mm SA	2.8	Up to 5 passes	Yes	None	81% ^{1,3}
Wallace (63)	2008	138	cN2-3	Moderate	Visible LNs	1.4	Minimum 3 passes	No	None	69% ^{1,3,5}
Yasufuku (28)	2006	102	cN0-3	Moderate	>5 mm SA	2.0	Up to 5 passes	Yes	None	92% ^{1,3}
Herth (32)	2006	100	cN0	Moderate	>5 mm SA	1.2	4 Passes**	No	None	92% ^{1,3}
Nakajima (40)	2010	49	cN1-3	Moderate	>5 mm SA	2.6	Up to 5 passes**	Yes	None	94% ^{1,3}
Herth (27)	2008	97	cN0	GA	>5 mm SA	1.6	2 Passes	No	None	89% ^{1,3}

Clinical Review. Kinsey et al, AJRCCM 2014

Endobronchial Ultrasound

A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer

Kazuhiro Yasufuku, MD, PhD,^a Andrew Pierre, MD, MSc,^a Gail Darling, MD,^a Marc de Perrot, MD, MSc,^a Thomas Waddell, MD, PhD,^a Michael Johnston, MD,^a Gilda da Cunha Santos, MD, PhD,^b William Geddie, MD,^b Scott Boerner, MD,^b Lisa W. Le, MSc,^c and Shaf Keshavjee, MD, MSc^a

ificity and positive predictive value for both techniques were 100%. The sensitivity, negative predictive value, and diagnostic accuracy for mediastinal lymph node staging for EBUS-TBNA and mediastinoscopy were 81%, 91%, 93%, and 79%, 90%, 93%, respectively. No significant differences were found between EBUS-TBNA and mediastinoscopy in determining the true pathologic N stage (McNemar's test, $P = .78$). There were no complications from EBUS-TBNA. Minor complications from mediastinoscopy were observed in 4 patients (2.6%).

The Journal of Thoracic and Cardiovascular Surgery 2011

European Institute of Oncology Experience

1407

EBUS-TBNA From 2011 to 2015

OVERALL			
	HISTO neg	HISTO pos	Total
EBUS neg	314	36	350
EBUS pos	0	1017	1017
Total	314	1053	1367
Inadequate EBUS N=40			
Sensitivity	= 1017/1053 = 96.6% 95% CI: 95.3% to 97.6%		
Specificity	= 314/ 314 = 100% 95% CI: 98.8% to 100 %		
PPV	= 1017/1017 = 100% 95% CI: 98.6% to 100 %		
NPV	= 314/ 350 = 89.7% 95% CI: 86.1% to 92.7%		
Accuracy	= 1331/1367 = 97.4% 95% CI: 96.4% to 98.2% (OR total correct classification)		

European Institute of Oncology Experience

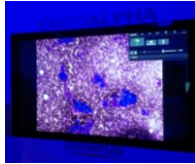
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EBUS for mediastinal staging

	HISTO neg	HISTO pos	Total
EBUS neg	144	15	159
EBUS pos	0	421	421
Total	144	436	580
Inadequate EBUS N=19			
Sensitivity	= 421/436 = 96.6% 95% CI: 94.4% to 98.1%		
Specificity	= 144/144 = 100 % 95% CI: 97.5% to 100 %		
PPV	= 421/421 = 100 % 95% CI: 99.1% to 100 %		
NPV	= 144/159 = 90.6% 95% CI: 84.9% to 94.8%		
Accuracy	= 565/580 = 97.4% 95% CI: 95.8% to 98.6% (OR total correct classification)		

EBUS

Is not just a technique but a philosophy of mediastinal staging!



EBUS - key points

- **Adequate «high» number of procedures**
 - Optimize expertise of single operators
 - Expertise of pathologists
 - Expertise for specimen handling
- **Sedation**
 - Moderate/deep sedation
 - Patients comfort and quality for operator
- **ROSE: Rapid on Site Evaluation**
 - Specimen adequacy evaluation
 - CELL BLOCKER (histological evaluation, immunohistochemistry, mutational analysis)
- **Specimen handling**

Diagnosis of Pulmonary Nodules

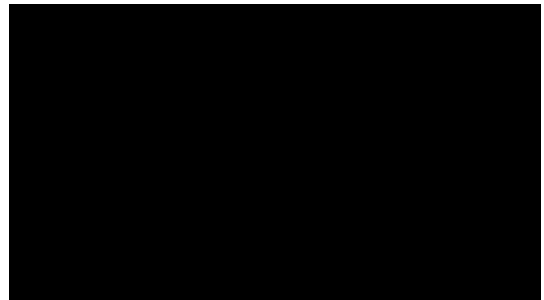
Current guidelines in the management of pulmonary nodules recommend bronchoscopy was the diagnostic procedure with more favorable profile

Newer navigation techniques: EBUS Radial Probe/ENB

- improved sensitivity for PPNS
- Very low rate of pneumothorax
- False negative rate

Diagnosis and Management of Lung Cancer,
ACCP guidelines 3rd ed 2013

EBUS-RB with Guide Sheath Technique



Diagnostic Yield of TBBs using EBUS - Guide Sheath

158 patients
Diagnostic yield: **67%**

Factors affecting yield

→ Lesion diameter

→ Position of EBUS Probe

Yamada N. et al; CHEST 2007

Table 2—Features Associated With Diagnostic Yield of TBB Using EBUS-GS

Variables	Lesions Diagnosed by EBUS, No./Total Lesions, No. (%)	p Value*
Underlying disease		
Benign	16/30 (53)	0.075
Malignant	99/128 (78)	
Lesion diameter, mm		
≤ 15	16/40 (40)	
> 15 and ≤ 20	20/54 (37)	< 0.001
> 20 and ≤ 25	26/36 (72)	
> 25 and ≤ 30	29/49 (59)	
> 30	29/49 (59)	
Location		
Right upper lobe	24/40 (60)	0.66
Right middle lobe	5/12 (42)	
Right lower lobe	30/43 (70)	
Left upper lobe	26/36 (72)	
Left lower lobe	15/23 (65)	0.211
CT bronchus sign		
Positive	34/49 (71)	
Negative	5/11 (45)	
Operator		
A	9/12 (75)	0.41
B	19/29 (66)	
C	11/19 (58)	
D	12/21 (57)	
E	19/24 (79)	< 0.001
F	24/39 (61)	
Position of the probe		
Within	90/96 (94)	
Adjacent to	22/36 (61)	0.84
Outside	1/23 (4)	
EBUS probe		
1.4-mm probe	99/128 (77)	0.84
1.7-mm probe	29/39 (74)	

*Odds ratio analyzed using the Pearson χ^2 test; Pearson χ^2 test with Yates continuity correction.

EBUS-RP

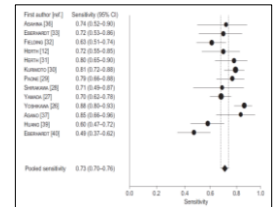
Literature review and meta-analysis:
16 articles /1420 subjects

Overall Sensitivity EBUS-RB
Ranges from 49 to 88%

Factors affecting sensitivity:
→ prevalence of malignancy
→ lesion size

5% of pneumothorax

Conclusion: EBUS is safe and relatively accurate for the diagnosis of pulmonary nodules



Steinfert et al, ERJ 2011



EBUS-RB: Key points

TABLE 1. YIELD BY LESION SIZE IN STUDIES OF ENDOBRONCHIAL ULTRASOUND-GUIDED DIAGNOSIS OF PULMONARY LESIONS

Series	Technique	n	Size (mm)	Diagnostic Yield (%)
Herth and colleagues (3)	EBUS—transbronchial forceps biopsy	21	All	80
		21	< 30	80
		29	> 30	79
Kurimoto and colleagues (4)	EBUS with guide sheath and fluoroscopy ± curette—forceps biopsy/brush	150	All	77.3
		81	< 20	72.8
		43	20–30	72.8
Kikuchi and colleagues (5)	EBUS with guide sheath and fluoroscopy ± curette—forceps biopsy/brush	26	> 30	92.3
		24	< 30	58.3
		15	< 20	53.3
Yang and colleagues (6)	EBUS—transbronchial forceps biopsy	9	20–30	66.7
		122	All	65.6
		11	< 20	54.5
Asahina and colleagues (7)	EBUS with guide sheath, virtual bronchoscopy navigation and fluoroscopy ± curette—forceps biopsy/brush	103	> 30	66.0
		18	< 20	44.4
		12	20–30	58.3
Faone and colleagues (8)	EBUS—transbronchial forceps biopsy	87	All	78.7
		25	< 20	71
		47	< 30	75
Herth and colleagues (9)	EBUS—transbronchial forceps biopsy	40	> 30	82.8
		54	Fluoroscopically invisible, mean 22 ± 0.7	70.3

Definition of abbreviation: EBUS = endobronchial ultrasound.

Eberhardt et al; AJRCCM 2007

EBUS-RB: Key points

EBUS-RB:
Small pulmonary nodules

N=212 patients
Overall diagnostic yield:
67.5%

Key points:
→ Location of the lesion
→ RB within or adjacent

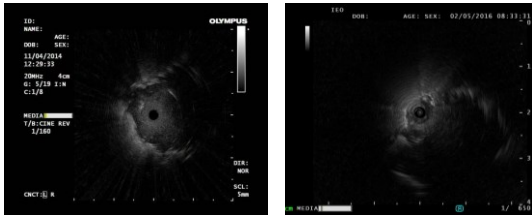
Table 1. Factors affecting diagnostic yield of EBUS-GS TBB for small pulmonary nodules (≤ 10 mm)

Characteristics	Sensitivity analysis	P value	Multivariate analysis
Age (years)			
< 70	16/30 (53)	0.883	
≥ 70	84/108 (78)		
Sex			
Male	60/107 (56)	0.899	
Female	62/96 (65)		
EBUS probe (mm)			
1.4	81/108 (75)	0.116	
1.7	29/39 (74)		
CT scan characteristics			
Solid	16/17 (94)	1.000	
Subsolid	68/95 (72)		
Location			
Subcarinal	16/19 (84)	0.883	
Mediastinal	16/19 (84)		
Location			
Subcarinal	46/107 (43)	0.001	2.89 (1.59-5.25)
Peribronchovascular	16/19 (84)		
EBUS probe			
1.4-mm probe	80/100 (80)	0.001	2.78 (1.48-5.25)
1.7-mm probe	29/39 (74)		
Adjunctive techniques			
None	30/39 (77)	0.493	
Large	40/84 (48)		
Small	40/124 (32)		

EBUS-GS, endobronchial ultrasound with a guide sheath; TBB, transbronchial biopsy; CT, computed tomography; SD, standard deviation; SE, guide sheath.

Chavez et al; JTD 2015

EBUS-RB: Key points



EBUS-RB within
Diagnostic yield **84%**

$p=0,001$

EBUS-RB tangential
Diagnostic yield **48%**

Chen A. et al; Ann Am Thor Soc 2014

European Institute of Oncology Experience

EBUS RP / GS

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From 2012 to 2015

Overall sensitivity 84,62%
Negative predicted value 60,8%
Accuracy 88%

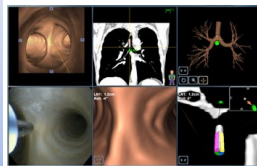
(Statistical analysis performed in a group of 161 pts)

ENB: Navigation Bronchoscopy

New technology for the
diagnosis of PPNs

Diagnostic yield:
59.9% to 87.5%

Additional techniques:
→ Fluoroscopy
→ EBUS - RB



ENB: Navigation Bronchoscopy

Table 1—Yield, Registration/Navigation Accuracy, Procedure Duration, and Pneumothorax Incidence in Studies of ENB Diagnosis of Peripheral Lung Lesions*

Study	Technique	No.	Size, mm	Diagnostic Yield, %	Error, mm	Duration, min	Pneumothorax
Becker et al ³	ENB and fluoroscopy- forceps biopsy and brush	29	All	69	Registration, 6.1 ± 1.7	Registration, 2 (1-3.3); navigation, 7.3 (1.3-14.1)	1 patient treated with chest tube
Schwarz et al ⁴	ENB and fluoroscopy- forceps biopsy and brush	13	All	69	Navigation, 5.8 ± 3.7 Navigation, 10.4 ± 7.8 Navigation, 5.7		
Gildea et al ⁵	ENB and fluoroscopy- forceps biopsy and brush	54	All	71	Registration, 6.6 ± 2.1; navigation, 9.0 ± 5.0	Registration, 3 ± 2; navigation, 7 ± 6; total, 51 ± 13	2 patients treated with chest tubes
			< 30	74			
			> 30	74			
			< 30	72			
			> 30	82			

*Values are given as the mean ± or No. (range), unless otherwise indicated.

Eberhardt R. et al; CHEST 2007

ENB: Navigation Bronchoscopy

ENB alone in peripheral lung lesions

Without fluoroscopy

N=89
Diagnostic yield: 67%
Not influenced by lesion size
↓
Small fluoroscopy invisible nodules

Mean time: 26.9 min (+/-6.5 min)
2% pneumothorax

Variables	Patients, No.	All Lesions
Baseline characteristics		
Lesions biopsied, No.	92	92
Female gender, %	89	44
Age, yr	69	67 ± 12
Size, mm	92	24 ± 6
Stage specimens, No.	81	3 ± 1
Foreign lesions	22	22 (24)
Malignant lesions	70	70 (76)
Diagnostic yield		
Overall positive diagnostic yield	92	62 (67)
Positive diagnostic yield by lesion size		
≤ 20 mm	35	22 (63)
> 20 mm	57	40 (70)
≤ 30 mm	64	36 (57)
> 30 mm	6	6 (75)
Procedure details		
Registration points	83	8 ± 1
Registration error, mm	89	4.8 ± 1.5
Navigation error, mm	86	9 ± 6
Registration time, min	82	3.2 ± 2.3
Navigation time, min	82	4.5 ± 3.4
Total time, min	82	26.9 ± 6.5

*Values are given as the mean ± SD or No. (%), unless otherwise indicated. χ^2 test.
Fisher's exact test, $P = 0.02$.
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Eberhardt R. et al; CHEST 2007

Multimodality Bronchoscopic Diagnosis of Peripheral Lung Lesions A Randomized Controlled Trial

Ralf Eberhardt¹, Devanand Ananthan², Amin Emu³, David Feller-Kopman⁴, and Felix Hirth⁵

TABLE 5. DIAGNOSTIC YIELDS BY SIZE, LOCATION, AND DISEASE TYPE, AND PNEUMOTHORAX RATE

	EBUS, n (%)	ENB, n (%)	EBUS and ENB, n (%)	p
Overall diagnostic yield	27/39 (69)	23/39 (59)	35/40 (88)	0.02*
Yield by lesion size				
≤ 20 mm	7/9 (78)	3/4 (75)	9/10 (90)	0.02*
20–30 mm	16/23 (70)	11/22 (50)	21/24 (88)	p = 0.99
> 30 mm	4/7 (57)	9/13 (69)	5/6 (83)	
Yield by lobar location				
Bilateral upper lobes	16/27 (59)	17/22 (77)	17/20 (85)	0.01*
Right middle lobe	3/3 (100)	2/3 (67)	2/2 (100)	
Bilateral lower lobes	8/9 (89)	4/11 (29)	16/18 (89)	p = 0.99
Yield for malignant disease				
Sensitivity	23/32 (72)	16/29 (55)	28/31 (90)	0.009*
Specificity	7/7 (100)	10/10 (100)	9/9 (100)	—
Positive predictive value	23/23 (100)	16/16 (100)	28/28 (100)	—
Negative predictive value	7/16 (44)	10/23 (44)	9/12 (75)	0.16
Yield for benign disease				
Sensitivity	4/7 (57)	7/10 (70)	7/9 (78)	0.79
Specificity	32/32 (100)	29/29 (100)	31/31 (100)	—
Positive predictive value	4/4 (100)	7/7 (100)	7/7 (100)	—
Negative predictive value	32/35 (91)	29/32 (91)	31/33 (94)	0.90
Pneumothorax rate	2/39 (5)	2/39 (5)	3/40 (8)	0.99

For definition of abbreviations, see Table 3.

*p < 0.05.

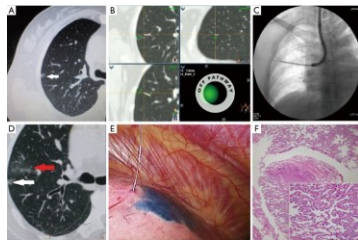
AJRCCM 2007

ENB: placement of fiducial markers

Multimodality safety
placement of fiducial
markers with EBUS – GS
and ENB

→ Radiotherapy in low
performance
patients

→ Minimally invasive
surgery after tissue
sampling



Steinfurt D. et al; Journal of Thorac Oncology 2015
Sun J; Journal of Thoracic Diseases 2015

ENB: Navigation Bronchoscopy

ENB remains....

- High cost procedure
- Useful for fluoroscopy INVISIBLE nodules?
- An alternative to be used with EBUS-GS when EBUS + fluoro fails to identify the lesion?
- Placement of fiducial markers for minimally invasive surgery

CONCLUSION

BEST PATIENT CARE



LESS PROCEDURES with MORE RESULTS

"ALL IN ONE"
PROCEDURE

- DIAGNOSIS
- STAGING
- Placement fiducial markers

