Role of EBUS in mediastinal staging of lung cancer

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Overview of the seminar

- Introduction
- Endosonography to stage the mediastinum
- Technical aspects of EBUS-TBNA for mediastinal staging
- Comparison of staging methods
- Suitability of EBUS-TBNA for sub typing of NSCLC
- Adequacy for multiple tumor genotyping
- Staging algorithm

Introduction

- Treatment of choice for patients with localized non small cell lung cancer (NSCLC) who have no evidence of mediastinal nodal metastasis- Pulmonary resection
- Patients with contra lateral mediastinal lymph node metastases (N3)- should not be operated
- Treatment of patients with NSCLC metastases restricted to the ipsilateral mediastinal (N2) lymph nodes: controversial

- -(1)Definitive concomitant chemoradiotherapy
  - (2) Neoadjuvant therapy followed by surgery if mediastinal lymph nodes become free of tumor (nodal downstaging)
- In the absence of extrathoracic, contralateral lung, or pleural cavity metastasis, assessment of the mediastinum becomes crucial for operable patients with resectable NSCLC

CG121 Lung Cancer. NICE guidelines

Role of CT

- Lymph nodes with a short axis diameter of less than 10 mm in axial CT scans –more likely to be benign than are enlarged nodes
- Roughly 40% of all nodes deemed to be malignant by CT are benign and 20% of nodes deemed to be benign by CT are malignant
- CT has moderate test characteristics, with a sensitivity of 51% (95% CI 47–54) and a specificity of 86% (95% CI 84–88)

Silvestri GA et al.Noninvasive staging of NSCLC.CHEST 2007

Role of PET

- FDG PET assessment of mediastinal lymph nodes in NSCLC has a sensitivity of 74% (69–79) and a specificity of 85% (82–88)
- Combination of node size and metabolic characteristics provided by integrated FDG PET CT -improved accuracy of staging by better anatomic localization of FDG hotspots
- For most patients, integrated FDG PET CT does not eliminate the need for invasive testing

Gould et al. Ann Intern Med 2003

- In patients with small peripheral tumors without enlarged or FDG-avid hilar or mediastinal lymph nodes- <6% mediastinal nodal metastasis
- Most clinicians use these criteria to rule out mediastinal involvement and proceed with thoracotomy

Detterbeck FC et al. Chest 2007

Which patients with resectable lung cancer require sampling of mediastinal nodes?

- **1)Abnormal mediastinum by imaging**: Mediastinal lymph nodes suspected of containing metastases on the basis of either size (short axis ≥10 mm) or FDG uptake. Nodal metastasis in this group ranges from 50% to 80%
- **2)Normal mediastinum by imaging**:small mediastinal lymph nodes without increased FDG uptake-still has a 6–30% prevalence of mediastinal metastases-in the presence of a centrally located primary tumor, enlarged or FDG-avid hilar lymph nodes, or a primary tumor and lymph nodes that are not FDG avid

Hishida T et al. Thorax 2008

Thoroughness of mediastinal staging

- Detterbeck and coworkers have classified 3 levels:
- Level A staging (complete sampling) is defined as sampling of each visible lymph node in each station (1, 2R, 2L, 3, 4R, 4L, and 7) using at least three passes per node or rapid on-site cytologic examination (ROSE)

Detterbeck F et al,CHEST;2010

- Level B staging (systematic assessment) requires sampling nodes in each station using at least three passes per node or ROSE at stations 2R, 2L, 4R, 4L, and 7
- Both complete (Level A) and systematic (Level B) staging require sampling stations 5 and 6 if a left upper lobe tumor is present
- Invasive staging of stations 5 and 6 may require transthoracic needle aspiration or a surgical approach

- Level C staging (selective assessment) is defined by aspiration of at least one abnormal lymph node (>1 cm by CT or ultrasound) or fewer than three passes and no ROSE
- Systematic surgical mediastinal staging has a superior accuracy when compared with selective approaches, although the effect on overall survival is less clear

Detterbeck FC et al. Sem Th Ca Vas Sur;2007

Surgical staging of the mediastinum

- Most accurate method to establish the clinical N stage
- For more than 50 years, this procedure has been done by cervical mediastinoscopy
- Ideally 5(at least 3) mediastinal nodal stations—paratracheal left (stations 2L and 4L),paratracheal right (stations 2R and 4R), and subcarinal (station 7)—should be examined, with at least one node biopsy sample taken from each station unless none are present after dissection

- A 2007 systematic review of surgical mediastinoscopy in more than 6500 patients with NSCLC reported a sensitivity of 78% (76–79) and a negative predictive value of 88% (86–88)
- If CT or FDG PET suggest enlarged or FDG-avid lymph nodes outside the range of a cervical mediastinoscopy—targeted surgical staging with video-assisted thoracoscopy or parasternal mediastinotomy (Chamberlain procedure) can be used

Detterbeck FC et al:Chest 2007

Endosonography to stage the mediastinum

- Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUS-TBNA) enable accurate and systematic assessment of mediastinal lymph nodes
- In a meta-analysis by Micames and colleagues,which included 18 studies and 1201 patients, EUS-FNA had a pooled sensitivity of 83% (95% CI 78–87) and a specificity of 97% (96–98)

- Eight studies restricted to patients who had enlarged mediastinal nodes according to CT had a pooled sensitivity of 90% (84–94).
- In patients without enlarged mediastinal lymph nodes (four studies) sensitivity was 58% (39–75)

Micames CG et al. CHEST 2007

- In a metaanalysis by Gu and colleagues, including 11 studies and 1299 patients, EBUS-TBNA had a sensitivity of 93% (91–94) and a specificity of 100% (99–100)
- The sensitivity in patients selected on the basis of positive CT or PET results was 94% (93–96), which was better than that in the subgroup without any selection, who have a sensitivity of 76% (65–85)

Gu P et al. Eur J Cancer 2009

- A meta-analysis by Adams and colleagues, which included ten studies of EBUS-TBNA, reported a sensitivity of 88% (79–94)
- One study including 20 patients was also used in the meta-analysis of Gu and colleagues

Adams K et al. Thorax 2009

Noninvasive and invasive staging modalities prior to thoracotomy

Modality	Sensitivity, %[a]	Upper Mediastinal Stations (2, 4, 7)	Lower Mediastinal Stations (8, 9)	AP Zone Mediastinal Stations (5, 6)	Hilar Stations (10)	Interlobar Stations (11)
CT scan	55	+	+	+	+	+
PET scan	80	+	+	+	+	+
EBUS	89	+	–	–	+	+
EUS[b]	89	+	+	±	–	–
MED	81	+[c]	–	+[d]	±	–
VAM	89	+[c]	–	+[d]	±	–
EBUS + EUS	91	+	+	±	+	+
EBUS + EUS + MED	94	+	+	±	+	+
VATS[e]	99	+	+	+[f]	+	+

AP = aortopulmonary; EBUS = endobronchial ultrasound; ECM = extended cervical mediastinoscopy; EUS = esophageal ultrasound; MED = mediastinoscopy; – = not accessible; + = Accessible; ± = occasional access, depending on lymph node size and operator technique; VAM = video-assisted mediastinoscopy; VATS = video-assisted thoracic surgery.

[a]Refers to the overall sensitivity for detecting metastasis in the mediastinal lymph nodes but results are not specific for individual lymph node stations.

[b]EUS has access mainly to left-sided lymph nodes.

[c]Access to anterior but not posterior subcarinal (station 7) nodes; MED also has access to stations 1 and 3.

[d]Only accessible by ECM, not by traditional cervical MED.

[e]Only for the lymph nodes on the side of the VATS.

[f]Specific results of VATS for these stations have not been reported.

CHEST 2015;147(5):1401-12

Diagnostic yield of EBUS-TBNA for systematic mediastinal staging

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*,†,‡,§
Szlubowski (41)	2009	226	cN0-3	Moderate	>5 mm SA	1.4	3-5 Passes	No	None	89*,‖
Lee (84)	2012	73	cN0-3	GA	All accessible	2.6¶	Minimum 1 pass	No	Atrial fibrillation	95†,‡,§
Bauwens (42)	2008	106	cN1-3	Moderate	All accessible	1.8	NR	No	Pneumothorax	95†,‡,§
Memoli (37)	2011	100	cN1-3	Moderate	All visible	2.3	Up to 3 passes	Yes	None	87†,‡
Yasufuku (44)	2011	153	cN0-3	GA	>5 mm SA	2.8	Up to 5 passes	Yes	None	81‡,§
Wallace (63)	2008	138	cN2-3	Moderate	Visible LNs	1.4	Minimum 3 passes	No	None	69*,†,‡,§
Yasufuku (28)	2006	102	cN0-3	Moderate	>5 mm SA	2.0	Up to 5 passes	Yes	None	92*,†,‡
Herth (32)	2006	100	cN0	Moderate	>5 mm SA	1.2	4 Passes**	No	None	92‡,§
Nakajima (40)	2010	49	cN1-3	Moderate	>5 mm SA	2.6	Up to 5 passes**	Yes	None	94†,††
Herth (27)	2008	97	cN0	GA	>5 mm SA	1.6	2 Passes	No	None	89‡,§

Definition of abbreviations: cStage = clinical stage before procedure; EBUS-TBNA endobronchial ultrasound–guided transbronchial needle aspiration; GA = general anesthesia (not differentiated from deep sedation); LN = lymph node; NR = not reported; SA = short axis.

Sensitivity presented is per patient.

*Sensitivity includes metastases to sites not accessible by EBUS-TBNA.

†If EBUS-TBNA negative, sensitivity is compared to clinical follow up ⩾ 6 months.

‡If EBUS-TBNA negative, sensitivity is compared to LN dissection at resection.

§If EBUS-TBNA negative, sensitivity is compared to mediastinoscopy.

‖If EBUS-TBNA negative, sensitivity is compared to transcervical extended mediastinal lymphadenectomy.

¶Sites sampled during staging of possible surgical disease.

Technique of EBUS-TBNA

- Lymph node to be aspirated is visualized under ultrasound, generally using a 7.5 MHz transducer
- A saline-filled balloon may be used to enhance the ultrasound image
- Images may be frozen and measurement of a lymph node performed
- Verification of the presence of vasculature within the ultrasound field may be confirmed using Doppler mode

- The sheath is advanced under visualization. The needle may then be safely inserted into the lymph node (accounting for the 30-degree angle between the needle and transducer)
- The stylet is used to remove bronchial epithelial cells. Suction may be applied
- Aspirated material is then smeared onto glass slides for fixation and evaluation. Additionally, material for creation of cell block, microbiologic evaluation, and flow cytometry may be collected and may be helpful when evaluating for alternative or concurrent diagnoses

EBUS-TBNA technical aspects

Parameter	Description	Rationale	Comments
F: frequency	Fast 1-2 downstroke movements of the needle per s	Cut the nodal tissue	Cells are conducted into the needle by capillary force[a]
		Allows capillary action	
A: amplitude	Move the needle from capsule to capsule	Assure sampling of all intranodal regions (subcapsular, hilar)	In adenocarcinoma, subcapsular nodal involvement may be the only site of malignant cells[15]
	Avoid inadvertent removal or distal capsule penetration		
S: suction	No suction technique	Suction may not increase the yield and may result in bloodier specimens[16]	When nonsuction technique fails to yield an adequate sample (as in fibrotic nodes), the conventional aspiration with suction may be used and vice versa[17]
	A syringe filled with air can still be connected to the needle, but no negative pressure is applied	Bloody aspirates compromise specimen purity relevant for molecular testing	
T: time	Spend little time (<6 s) inside the node	FNAs from thyroid/breast suggest that the less time spent in the node, the better the specimen purity[17]	For hypervascular and densely fibrotic nodes, smaller needles (25-gauge) may perform better[17]
E: edge	Keep the needle inside the node at all times during the aspiration	Rarely, complications can occur: pericarditis, mediastinitis, pneumothorax, pneumomediastinum, bleeding[18]	Aspiration of extra nodal tissues will also likely result in a nondiagnostic specimen
	Avoid inadvertent through-and-through penetration of the node		
R: route	Change the direction of the needle inside the node by flexing or extending the lever of the bronchoscope handle	Cut into previously nontraumatized lymph node tissue	Easier to perform with the 25-gauge than with the 21- or 22-gauge needles
		Potentially increase the quantity and quality of the aspirated material	This element remains to be further studied

Where to start lymph node sampling?

- Sample the highest station lymph nodes first:N3→N2→N1
- Each station should be considered for possible needle aspiration, regardless of PET avidity
- Herth and colleagues identified previously unsuspected malignancy in 9 of 97 patients by sampling lymph nodes <1 cm in short axis on CT and without FDG uptake in patients of NSCLC

Herth et al,CHEST 2008

Single needle or different needles?

- A single EBUS-TBNA needle may be used to perform the staging procedure if the N3 nodes are sampled first, followed by the N2 lymph node stations and the N1 lymph node stations
- Alternatively, a different needle may be used for each station, although this approach increases the cost of the procedure

Herth FJF,Sem Res Cr Cr Med;2011
Yusufuku K,CHEST;2006

USG characteristics of malignant nodes

- -Round shape
- -Distinct margin
- -Heterogeneous echogenicity
- -Coagulation necrosis sign
- -Increasing vascularity in specific patterns (beyond a few main vessels running toward the center of the lymph node)
- - The absence of a central nodal vessel on ultrasound may also be predictive of malignant involvement

Fujiwara T et al,Chest 2010

21-g or 22-g?

- A multicenter retrospective comparison of yield by needle size did not report significant differences, although use of the 21-gauge needle was associated with fewer passes when ROSE was used
- In a well designed prospective analysis, the two different needles were each used to sample the same lymph nodes from 33 patients. There were no differences in diagnostic yield; however, the 21-gauge needle resulted in better preservation of histologic structure.

Yarmus LB,Chest ;2013
Nakajima T et al,Respirology;2011

Comparison of staging techniques

Methods

- Patients were included if they had known or suspected lung cancer on the basis of a lung or mediastinal abnormality on CT and if they had no pathologically proven extrathoracic metastases
- Consecutive patients who met the study criteria were included
- First patient was enrolled on November 18, 2004, and the last on October 30, 2006

- CT and PET were performed separately in all patients before invasive staging
- Lymph nodes were considered enlarged if the short-axis diameter was 1 cm or greater as measured by CT
- PET activity was classified by the standard uptake value and considered positive if the value was 2 or greater

TBNA, EBUS-FNA, and EUS-FNA Staging

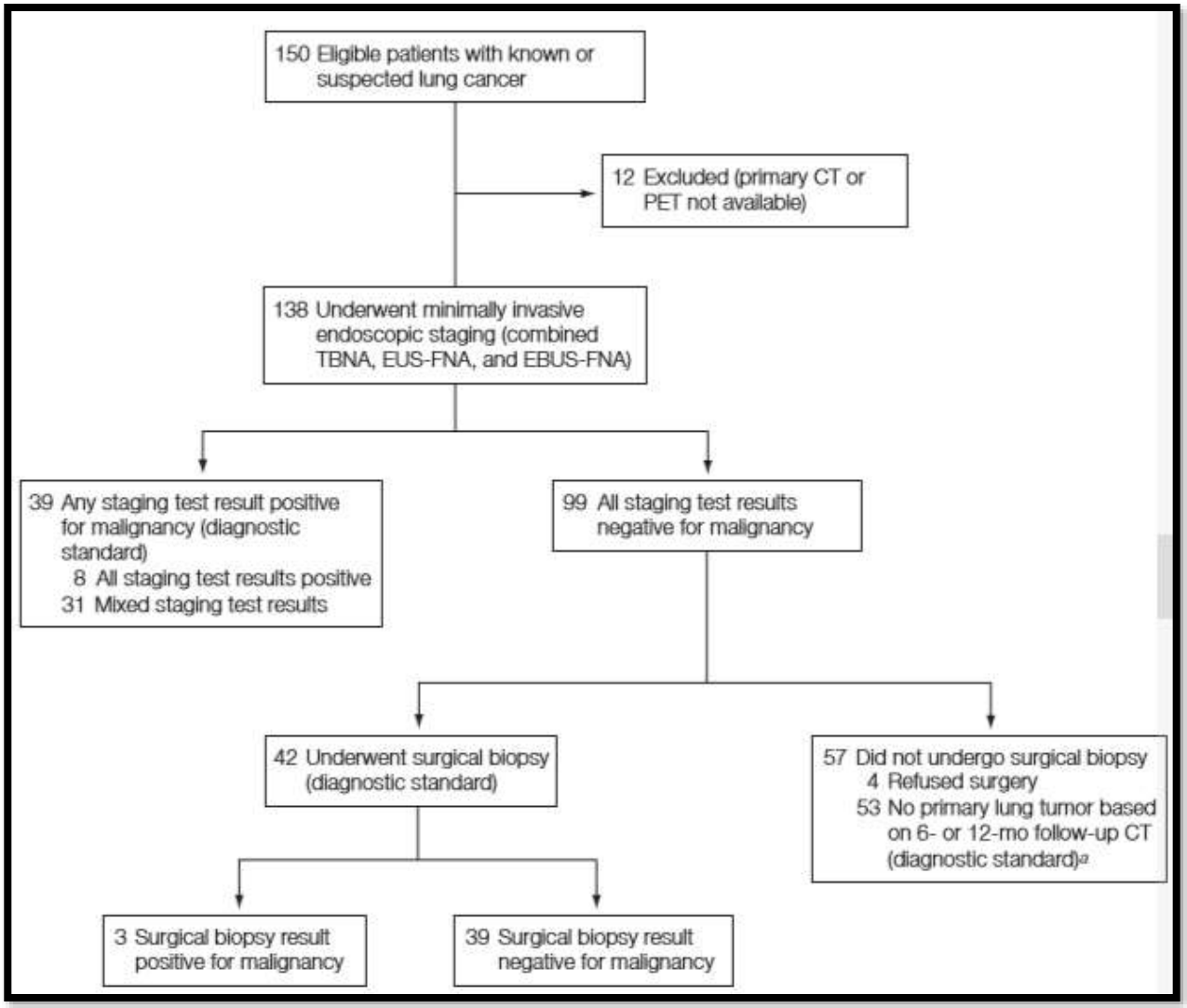
- TBNA, EBUS-FNA, and EUS-FNA were performed as a single combined procedure with the patient under conscious sedation
- Bronchoscopic TBNA was performed first, followed immediately by EBUS-FNA
- EUS FNA was performed immediately after TBNA and EBUS-FNA
- All procedures were performed blinded to the results of the other

- Performed with topical oropharyngeal anesthetic and appropriate sedation
- TBNA, with at least 3 fine needle aspiration (FNA) passes, was performed at regions with enlarged lymph nodes on chest CT
- In EBUS, visible lymph nodes, regardless of size, were sampled using FNA. If more than 1 lymph node was present in a specific location, the largest lymph node was sampled
- ROSE was not available

Demographic characteristics of study participants(N=138)

Age at bronchoscopy, median (IQR), y	69 (60-76)
Men, No. (%)	66 (48)
Location of primary tumor, No. (%)	
Lung	
Right upper lobe	32 (23)
Right middle lobe	4 (3)
Right lower lobe	15 (11)
Left upper lobe	12 (9)
Left lower lobe	7 (5)
Right hilar	1 (1)
Mediastinal only	65 (47)
Unknown	2 (1)
Procedure duration, median (IQR), min	
TBNA	15 (9-20)
EUS-FNA	21 (15-30)
EBUS-FNA	26 (20-32)
Procedure results, No. (%)[a]	
Positive	42 (30)
Negative	92 (67)
Unknown[b]	4 (3)

Flow of patients through the study



Final Histological results

Histological Classification	Patients, No. (%) (N = 138)
Benign	51 (37)
Adenocarcinoma	38 (28)
Squamous cell carcinoma	16 (12)
Non–small cell lung cancer	13 (9)
Small cell lung cancer	7 (5)
Sarcoidosis	6 (4)
Lymphoma	4 (3)
Bronchioalveolar cell carcinoma	1 (1)
Carcinoid	1 (1)
Metastatic breast cancer	1 (1)

Estimated sensitivities and NPVs

Procedure	Fraction (%) [95% CI][a]	
	Sensitivity	NPV
TBNA	15/42 (36) [22-52]	96/123 (78) [70-85]
EUS-FNA	29/42 (69) [53-82]	96/109 (88) [80-93]
EBUS-FNA	29/42 (69) [53-82]	96/109 (88) [80-93]
EUS-FNA + TBNA	33/42 (79) [63-90]	96/105 (91) [84-96]
EBUS-FNA + TBNA	32/42 (76) [61-88]	96/106 (91) [83-95]
EUS-FNA + EBUS-FNA	39/42 (93) [81-99]	96/99 (97) [91-99]

Abbreviations: CI, confidence interval; EBUS-FNA, endobronchial ultrasound-guided fine-needle aspiration; EUS-FNA, transesophageal endoscopic ultrasound-guided fine-needle aspiration; TBNA, transbronchial needle aspiration.

[a] For sensitivity, fraction indicates No. of positive cases detected by test/No. positive by diagnostic standard. For NPV, fraction indicates No. of true-negative results/No. of true-negative plus false-negative results by the procedure.

Selected comparisons of sensitivities

Comparison	Sensitivity Difference, Fraction (%) [95% CI][a]	*P* Value[b]
EBUS vs TBNA	14/42 (33) [14-51]	.003
EUS + EBUS vs EUS + TBNA	6/42 (14) [5-28]	.03
EUS + EBUS vs EUS	10/42 (24) [12-39]	NA
EUS + EBUS vs EBUS	10/42 (24) [12-39]	NA
EUS + TBNA vs EUS	4/42 (10) [3-23]	NA
EUS + TBNA vs TBNA	18/42 (43) [30-59]	NA

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound-guided fine-needle aspiration; EUS, transesophageal endoscopic ultrasound-guided fine-needle aspiration; NA, not applicable because 1 test is a subset of another; TBNA, transbronchial needle aspiration.

[a] Fraction indicates No. of additional cases detected by 1 test (the first of each pair) compared with the other test/No. positive by diagnostic standard.

[b] By exact McNemar test.

Locations of malignant lymph nodes detected by each procedure in patients with NSCLC(n=68)

AJCC Station	No. of Lymph Nodes Detected, by Procedure[b]			
	TBNA	EUS	EBUS	Surgery
1	1	0	1	0
2	2	1	3	0
3	2	0	10	0
4	1	0	3	0
5	0	9	2	1
6	0	4	1	2
7	6	13	11	1
8	0	0	0	0
9	0	0	0	1

Abbreviations: AJCC, American Joint Committee on Cancer; EBUS, endobronchial ultrasound-guided fine-needle aspiration; EUS, transesophageal endoscopic ultrasound-guided fine-needle aspiration; TBNA, transbronchial needle aspiration.

[a] Also includes patients with adenocarcinoma, squamous cell carcinoma, and bronchioalveolar cell carcinoma.

[b] Some patients had multiple malignant lymph nodes.

Subgroup analysis

- Four nonmutually exclusive subgroups were predefined to determine whether a single procedure would be adequate for diagnosis in certain patients, as defined by the location of the abnormal lymph nodes
- Subgroup 1 (“EUS suited”) was defined as patients who presented with a PET-positive subcarinal node or in whom CT showed an enlarged lymph node in a subaortic, subcarinal, paraesophageal ,or pulmonary ligament location

- In this subgroup of 54 patients, EUS-FNA was not significantly more sensitive than EBUS-FNA (estimated sensitivities,75% [15/20] vs. 70% [14/20], respectively)
- The combination of EUS-FNA plus EBUS-FNA had a sensitivity of 100%
- The NPVs of EUS FNA, EBUS-FNA, and EUS plus EBUS were 87% (34/39), 85% (34/40), and 100% (34/34), respectively

- Subgroup2(“EBUS suited”) was defined as patients who presented with a PET-positive subcarinal node or with an enlarged lymph node in an upper paratracheal , lower paratracheal, or subcarinal location
- In this subgroup of 74 patients, EBUS-FNA was more sensitive than EUS-FNA (estimated sensitivities, 76% [22/29] vs. 69% [20/29], respectively)
- Both were less sensitive than the combination (100% [29/ 29])
- NPVs of EUS-FNA, EBUS-FNA, and EUS plus EBUS were 83% (45/54), 87% (45/52), and 100% (45/ 45), respectively

- Subgroup 3(“bronchoscopy suited”) was defined as patients who presented with a PET-positive subcarinal node or an enlarged lymph node in the subcarinal location
- In this subgroup of 50 patients, the estimated sensitivity of TBNA (47% [9/19]) was lower than those of EUS-FNA (74% [14/19]), EBUS-FNA (68% [13/19]), and EUS plus EBUS (100%)
- NPVs were 76%(31/41) for TBNA, 86%(31/36) for EUS-FNA, 84% (31/37) for EBUS-FNA, and 100% (31/ 31) for EUS plus EBUS

- Subgroup 4 (“CT- and PET-negative mediastinum”) was defined as patients who had negative results by CT and PET; 60 study participants met this criterion
- In this subgroup, TBNA had low estimated sensitivity(17%[2/12]),whereas the estimated sensitivities of EUS-FNA, EBUS-FNA, and EUS plus EBUS were 67% (8/12), 50% (6/12), and 75% (9/ 12), respectively
- NPVs were 83% (48/58) for TBNA, 92%(48/52) for EUS FNA, 89% (48/54) for EBUS-FNA, and 94% (48/51) for EUS plus EBUS

Comparison of EBUS-TBNA with mediastinoscopy

GENERAL THORACIC SURGERY

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

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- Prospective, controlled trial in patients with confirmed or suspected NSCLC who required a mediastinoscopy as part of their staging investigations to determine suitability for resection
- All patients underwent CECT chest+upper abdomen
- PET was available for patients who were eligible to undergo PET scan

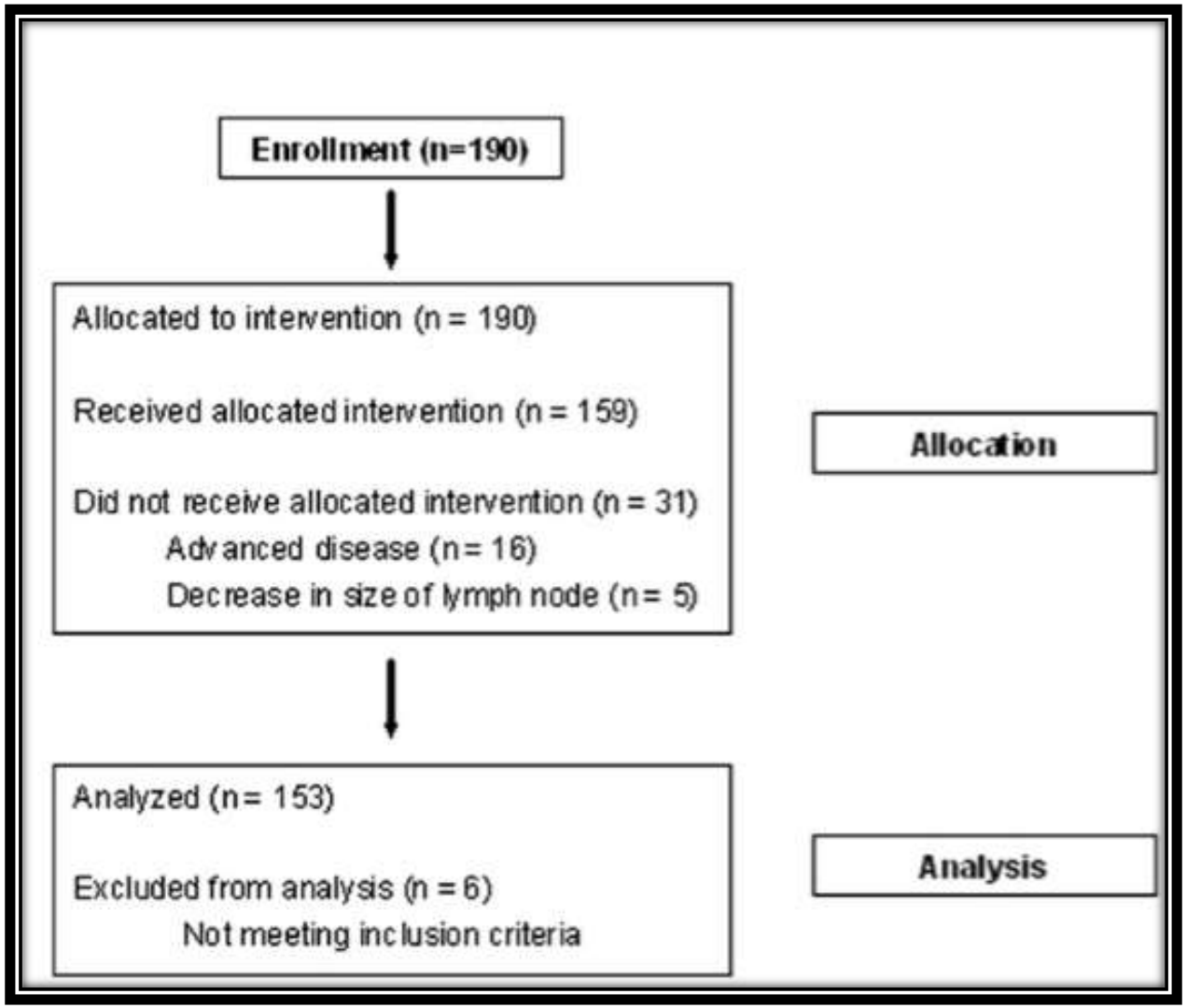
- Under GA, all patients underwent EBUS-TBNA followed by standard cervical mediastinoscopy in same setting
- Each patient served as his/her own control
- Surgeon was blinded for pathologic findings of EBUS-TBNA
- Both EBUS-TBNA and mediastinoscopy were performed in all patients even if EBUS-TBNA yielded N2 or N3 disease

- If there was no evidence of N2 or N3 disease on EBUS-TBNA or mediastinoscopy samples, patients underwent thoracotomy, pulmonary resection, and mediastinal lymphadenectomy at the same setting or at a different time
- **EBUS-TBNA:** Convex probe EBUS was used to perform EBUS-TBNA.CP-EBUS was integrated with a convex transducer(7.5 MHz) that scans parallel to the insertion direction of the bronchoscope

- A dedicated 22-gauge needle was used to perform all EBUS-TBNA procedures
- Smears were air dried and fixed in modified Carnoy's solution. The air dried smears were stained with a modified Field's stain and evaluated by an on-site cytopathologist to confirm "adequate" cell material
- Adequate cell material was defined as sufficient material for a specific diagnosis or the presence of lymphocytes on the specimen

- If adequate tissue was not identified by rapid on-site evaluation(ROSE) after 5 passes, the biopsy of that site was terminated
- Contralateral lymph nodes were sampled first followed by midline or ipsilateral lymph nodes
- Where multiple nodes were seen, most suspicious node in each group was targeted
- Suspicious nodes were defined as round, well demarcated and echo poor

- Different needles were used for different lymph node station to prevent cross contamination
- Localization of lymph nodes was described according to the 7th TNM classification of lung cancer
- EBUS-TBNA was performed for all lymph nodes greater than 5 mm in CT short-axis diameter or suspicious lymph nodes on EBUS


Enrollment (n=190)
Allocated to intervention (n = 190)
Received allocated intervention (n = 159)
Did not receive allocated intervention (n = 31)
Advanced disease (n = 16)
Decrease in size of lymph node (n = 5)
Allocation
Analyzed (n = 153)
Excluded from analysis (n = 6)
Not meeting inclusion criteria
Analysis

Patient characteristics

Patient characteristics	n = 153
Age, mean (SD), y	66.8 (9.5)
Gender, no. (%)	
Male	84 (55)
Female	69 (45)
Histology of lung cancer, no. (%)	
Adenocarcinoma	90 (59)
Squamous cell carcinoma	39 (25)
Adenosquamous	2 (1)
Large cell carcinoma	6 (4)
Other types of NSCLC	12 (8)
SCLC	4 (3)
Location of primary tumor, no. (%)	
Right upper lobe	60 (39)
Right middle lobe	7 (5)
Right lower lobe	27 (18)
Left upper lobe	34 (22)
Left lower lobe	25 (16)

Clinical stage, no. (%)	
IA	47 (31)
IB	26 (17)
IIA	3 (2)
IIB	10 (7)
IIIA	59 (39)
IIIB	5 (3)
IV	3 (2)
Nodal stage by CT or PET, no. (%)	
0	90 (59)
1	7 (5)
2	51 (33)
3	5 (3)
Short axis of LN biopsied, mean (SD), mm	
All	6.9 (2.9)
2R	6.7 (2.7)
4R	7.0 (2.9)
2L	3.3 (1.2)
4L	5.6 (2.0)
7	8.1 (3.3)
EBUS time, mean (SD), min	20.2 (8.1)

LN stations biopsied by EBUS-TBNA and mediastinoscopy

LN station	Total	Malignant	Benign	Inadequate
LN stations biopsied by EBUS-TBNA				
2R	30	12	12	6
4R	137	25	74 (5)	38
2L	2	1	0	1
4L	108	15	39 (1)	54
7	149	25	101 (2)	23
Total	426	78	226 (8)	122
LN stations biopsied by mediastinoscopy				
2R	115	16	97 (2)	2
4R	151	26	124 (4)	1
2L	26	1	23	2
4L	132	12	118 (4)	2
7	149	24	122 (4)	3
Total	573	79	484 (14)	10

Number of false-negative LN stations in parentheses. *LN*, Lymph node; *EBUS-TBNA*, endobronchial ultrasound-guided transbronchial needle aspiration.

Lymph node staging based on different modalities

N Stage	CT	EBUS-TBNA	Mediastinoscopy	Final pathology
0	90 (59%)	107 (70%)	109 (71%)	90 (59%)
1	7 (5%)	3 (2%)	N/A	10 (7%)
2	51 (33%)	33 (22%)	35 (23%)	42 (27%)
3	5 (3%)	10 (7%)	9 (6%)	11 (7%)

CT, Computed tomography; *EBUS-TBNA*, endobronchial ultrasound-guided transbronchial needle aspiration.

Agreement in mediastinal LN staging between EBUS-TBNA and mediastinoscopy

	Mediastinoscopy		
EBUS N stage	**N stage**	**Final N stage**	**No. of cases**
Staged correctly by both EBUS and mediastinoscopy			
0 or 1	0 or 1	0 or 1	100
2	2	2	28
3	3	3	8
Staged incorrectly			
0 or 1	0 or 1	2	4
2	0	2	5
3	2	3	2
0	2	2	5
0	3	3	1

The specificity and positive predictive value of both tests were 100%. The sensitivity, negative predictive value, and diagnostic accuracy rate of EBUS-TBNA and mediastinoscopy were 81%, 91%, 93%, and 79%, 90%, 93%, respectively. *EBUS*, Endobronchial ultrasound.

- Both EBUS-TBNA and mediastinoscopy were incorrect in 4 patients
- 1 patient had metastasis located in station 4R and 3 patients had metastasis in station 5 or 6,which were out of reach of both EBUS-TBNA and mediastinoscopy
- Mediastinoscopy incorrectly staged the mediastinum in 7 patients and EBUS-TBNA correctly diagnosed these patients with N2(n=5) or N3(n=2) disease

- On the other hand, EBUS-TBNA incorrectly staged 6 patients and mediastinoscopy correctly staged these patients with N2(n=5) or N3(n=1) disease
- 6 patients understaged by EBUS-TBNA included metastases in lymph node stations not sampled by EBUS-TBNA(station 2 R) in 2 patients and micro metastases in 4 patients(stations 4R,4L,7)

- Majority of patients had clinical N0 disease on chest CT or PET scan (n=90, 59%), with a normal mediastinum by CT imaging criteria
- This contributes to the sensitivity of 81% in assessing the mediastinum by EBUS-TBNA ,because sensitivity is related to the underlying prevalence of N2/N3 disease
- Majority of instances of inadequate sampling by EBUS-TBNA were in lymph nodes less than 5 mm in short axis. None of these inadequate samplings had metastases on final pathology

Study limitations

- EBUS-TBNA performed under GA through an ET tube in majority of cases. This might contribute to the high diagnostic yield . However, stations 2R and 2 L were sometimes difficult to assess because of the presence of ET tube
- A cytopathologist was always present for ROSE for EBUS-TBNA. Because not all centers have the resources to perform ROSE, the results may not be generalizable to all settings

- Present study shows that EBUS-TBNA can replace mediastinoscopy for accurate staging of mediastinum in potentially resectable lung cancer
- EBUS-TBNA avoids an incision, is more comfortable for the patient and enables mediastinal reassessment

ORIGINAL ARTICLE

Comparison of Endobronchial Ultrasound and/or Endoesophageal Ultrasound with Transcervical Extended Mediastinal Lymphadenectomy for Staging and Restaging of Non–Small-Cell Lung Cancer

Marcin Zielinski, MD, PhD, Artur Szlubowski, MD, PhD,† Marcin Kołodziej, MD,‡ Stanislaw Orzechowski, MD,‡ Ewa Laczynska, MD,‡ Juliusz Pankowski, MD, PhD,§ Magdalena Jakubiak, BS,§ and Anna Obrochta, BS§*

J Thorac Oncol. 2013;8: 630–636

- All consecutive patients considered candidates for surgical treatment of NSCLC, who had undergone either primary staging or restaging after neodjuvant chemo- or chemo-radiotherapy with EBUS, EUS, or combined EBUS with EUS (CUS) with FNA and cytological study of the aspirated specimen at a Poland hospital from January 1, 2007 to December 31, 2010, were included

Primary staging

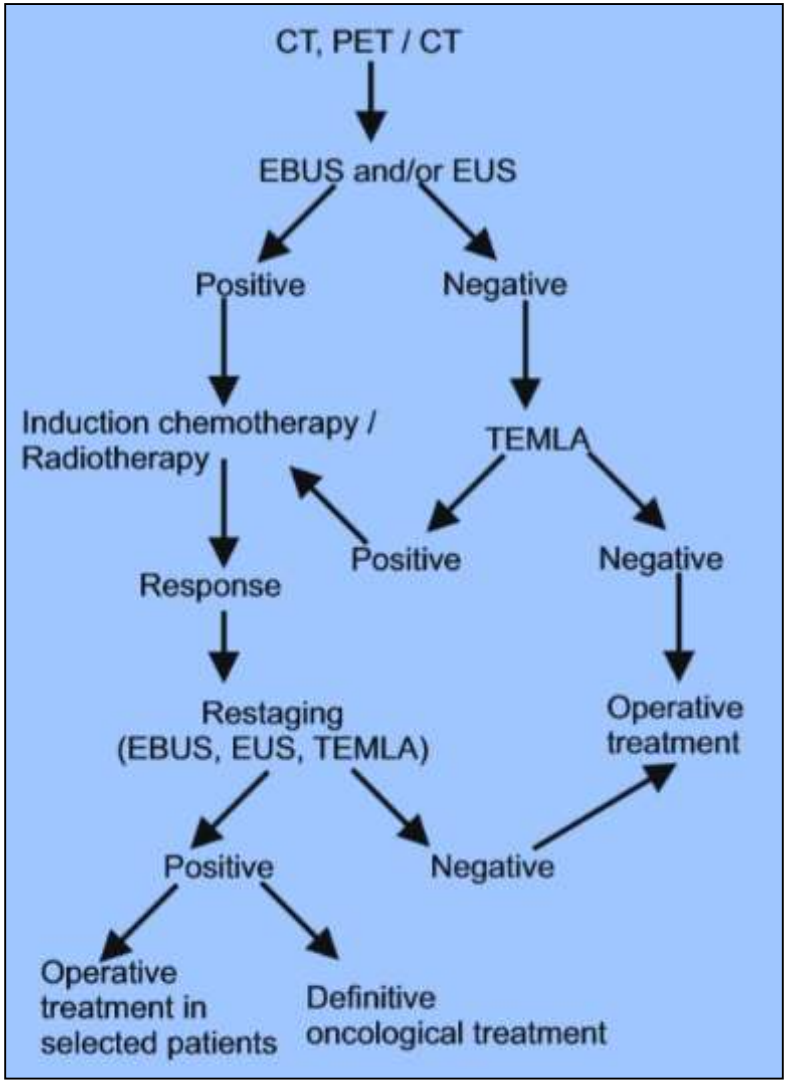
- Always started with CT (and PET/ CT on selective patients)
- Patients with M1 disease discovered on CT or PET/CT were excluded from further staging
- CT or PET/CT was followed by EBUS, EUS, or CUS. The choice of the particular endoscopic procedure was decided by the endoscopist, based on the localization of the suspected nodes

- In case of positive results (discovery of metastatic mediastinal nodes), the patients were referred for neoadjuvant chemo- or chemo-radiotherapy, depending on the opinion of the oncologist
- In case of negative results, the patients underwent TEMLA
- All patients with negative TEMLA underwent thoracotomy for lung resection and intraoperative systematic exploration for any residual mediastinal lymph nodes

- Thoracotomy with pulmonary resection and systematic nodal dissection supplementing the previous TEMLA was the final test for the mediastinal nodal staging
- In case of positive results (discovery of metastatic mediastinal nodes) the patients were referred for neoadjuvant chemo- or chemoradiotherapy, depending on the opinion of the oncologist

- In patients with partial or complete response after neoadjuvant therapy, restaging with the imaging studies and EBUS/EUS was performed
- Patients who were considered operable and had no evidence of persistent N2/N3 nodes underwent pulmonary resection and systematic nodal dissection

Primary staging of patients with NSCLC



- Number of nodes biopsied with EBUS, EUS, and CUS, and the number of nodes removed on TEMLA for the primary staging and restaging were calculated
- Diagnostic results of EBUS/EUS were compared with the results of TEMLA for primary staging and for restaging

Results

- PET/CT was performed on 78 patients. Distant metastases were discovered in nine patients (11.5%)
- Sensitivity of PET/CT was 54%, specificity 78%, positive predictive value (PPV) 37%, and negative predictive value (NPV) 87%
- The endoscopic ultrasound staging was performed on 623 patients: EBUS in 351, EUS in 72, and CUS in 200 patients. There was no mortality or morbidity after EBUS and EUS

- Mean number of nodes biopsied in the staging group -2.1 (range, 1–3) during EBUS, 2.4 (range, 1–4) during EUS, and 3.7 (range, 2–5) during CUS
- TEMLA preceded by negative EBUS/EUS- performed on 276 patients
- Mean number of nodes removed during TEMLA for the primary staging - 32.8 (range, 8–77)
- One patient died after TEMLA (30-day in-hospital mortality 0.4%) from myocardial infarction
- Morbidity after TEMLA- 7.2%

- TEMLA led to the discovery of metastatic nodes in 50 patients, including 43 patients with N2 involvement and seven patients with N3 metastases
- There were 31 patients with single-level involvement (29 patients with N2 and 2 patients with N3) and 19 patients with multilevel metastatic involvement (14 with N2 and 5 with N3)

- 226 patients were considered candidates for primary surgery. 30 were not operated for various reasons
- 189 pulmonary resections with systematic lymphadenectomy and seven exploratory thoracotomies (3.6%) in the primary staging group (operability 196 of 226, 86.7%; resectability 189 of 196, 96.4%)
- 2 patients died after resection(mortality 2 of 196,1%)

- After thoracotomy, residual N2 nodes omitted during previous TEMLA were found in two patients (single station 8 node in 1 patient, single station 5 nodes in the other)
- There were 88 patients in the restaging endoscopy group, including 32 patients who underwent EBUS, six patients who underwent EUS, and 50 patients who underwent CUS

- Mean number of nodes biopsied in the restaging group was 2.1 (range, 1–3) during EBUS, 2.4 (range, 1–4) during EUS, and 3.7 (range, 2–5) during CUS
- TEMLA was performed for restaging in 78 patients
- Mean number of nodes removed during TEMLA in the restaging group was 27.9 (range, 10–46)

- There were 14 patients with N2 involvement and one with N3 disease
- Patients with no mediastinal nodal involvement were regarded as candidates for surgery

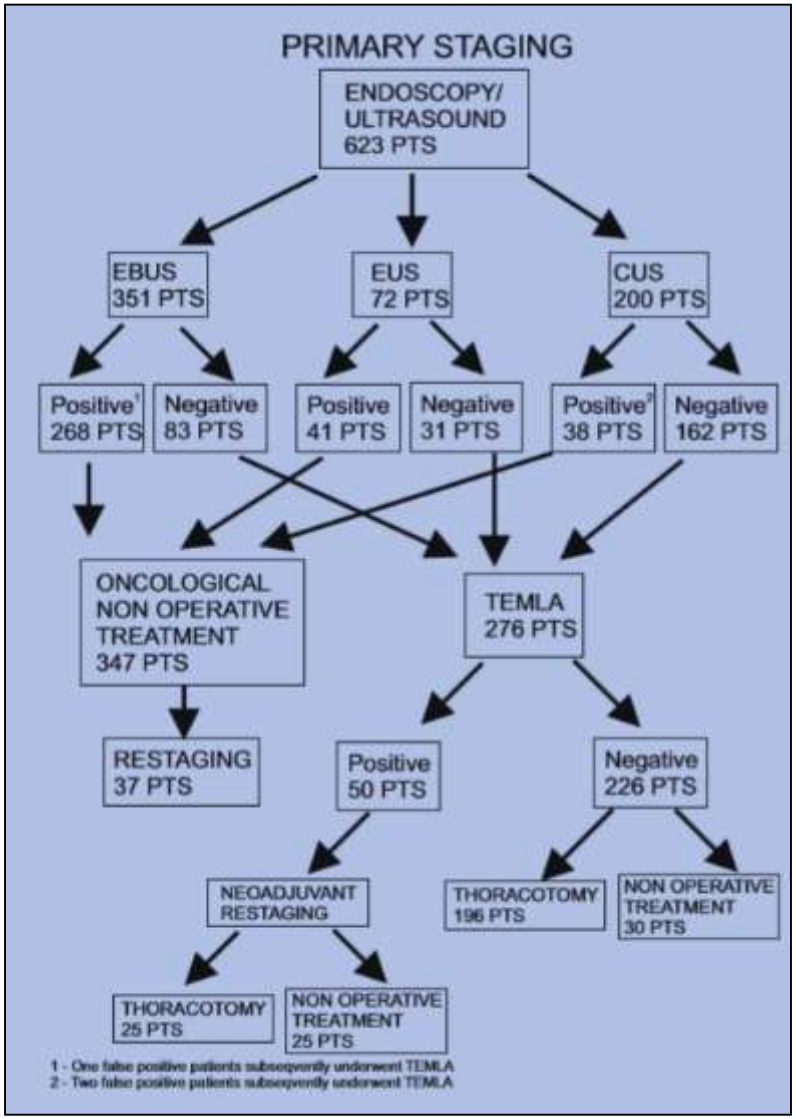
Comparison of diagnostic yield of EBUS/EUS and TEMLA for Primary Staging of NSCLC

Comparison of Diagnostic Yield of EBUS/EUS and TEMLA for Primary Staging of NSCLC

Diagnostic Parameter	Primary Staging EBUS/EUS 623 Patients (%)	Primary Staging TEMLA 276 Patients (%)	Difference (p)
Sensitivity	87.8	96.2	< 0.01
Specificity	98.7	100	$= 0.03$
NPV	82.5	99.6	< 0.01
PPV	99.1	100	$= 0.07$
Prevalence	63.1	18.4	< 0.01

EBUS/EUS, endobronchial ultrasound/endoesophageal ultrasound; TEMLA, transcervical extended mediastinal lymphadenectomy; NSCLC, non–small-cell lung cancer; NPV, negative predictive value; PPV, positive predictive value.

Restaging of NSCLC after neoadjuvant treatment



Comparison of Diagnostic Yields of EBUS/EUS and TEMLA for Restaging of NSCLC after Neoadjuvant Treatment

Diagnostic Parameter	Restaging EBUS/EUS 105 Patients (%)	Restaging TEMLA 78 Patients (%)	Difference (p)
Sensitivity	64.3	96.6	< 0.01
Specificity	100	100	$= 1.00$
NPV	82.1	98.5	< 0.01
PPV	100	100	$= 1.00$
Prevalence	40.0	19.2	< 0.01

- The results of TEMLA were significantly better than those of EBUS and EUS, despite significantly lower prevalence of metastatic nodes in TEMLA groups, both for primary staging and restaging
- Prevalence of the metastatic mediastinal nodes in the TEMLA group for primary staging and restaging were 18.4% and 19.2%, respectively, which indicated the number of metastatic nodes omitted during previous EBUS/EUS

- Mean number of biopsied nodes on EBUS, EUS, and CUS were 2.1, 2.4, and 3.7, respectively in comparison with 32.8 and 27.9 mean number of nodes removed with the surrounding mediastinal fatty tissue during TEMLA at staging and restaging, respectively

[Original Research **Pulmonary Procedures**]

CHEST

Endosonographic Mediastinal Lymph Node Staging of Lung Cancer

Moishe Liberman, MD, PhD; John Sampalis, PhD; André Duranceau, MD; Vicky Thiffault, RN; Rachid Hadjeres, MD; and Pasquale Ferraro, MD

CHEST 2014; 146(2):389-3 97

Study design

- This single-center prospective study was conducted in patients with potentially resectable NSCLC
- All subjects underwent EBUS, EUS, and SMS as well as a CT scan of the chest and upper abdomen and PET-CT scan prior to enrollment

Inclusion and Exclusion Criteria

Criteria
Inclusion criteria
Lung lesion (<1 cm) with mediastinal lymphadenopathy[a] and/or positive PET-CT scan in the mediastinum
Lung lesion (≥1 cm) without mediastinal lymphadenopathy[a] or positive PET-CT scan in the mediastinum
Exclusion criteria
Age < 18 y
CT scan and/or PET-CT scan positivity in an extrathoracic site (adrenal gland, liver, brain, bone)
Indeterminate pulmonary nodule <1 cm in diameter without mediastinal lymphadenopathy[a] on CT scan and a negative PET-CT scan
History of previous mediastinoscopy
Biopsy specimen-proven positive mediastinal LNs
Inability to consent for the study
Cervical or thoracic anatomy precluding mediastinoscopy
Inability to tolerate general anesthesia
Preoperative plan for carinal resection or carinal pneumonectomy (CM contraindicated prior to operative procedure due to additional difficulty secondary to scarring at time of resection)
Active pulmonary infection (bronchitis, pneumonia)
Active cutaneous infection overlying proposed surgical sites

CM = cervical mediastinoscopy; LN = lymph node.
[a]Lymphadenopathy was defined as short-axis lymph node diameter of >10 mm on CT scan.

Study interventions

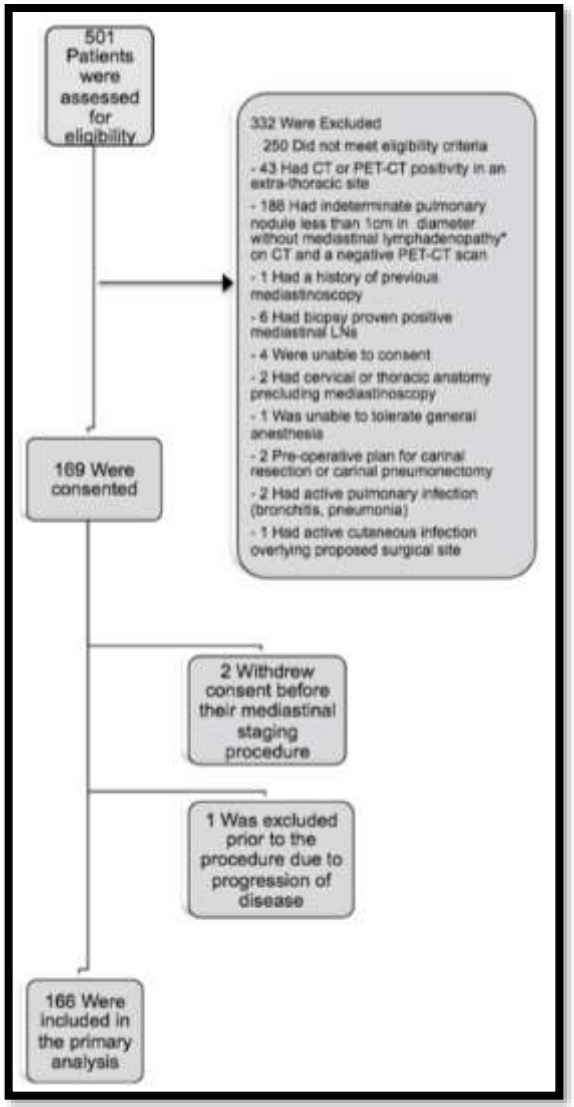
- All procedures took place in the operating room under general anesthesia
- Through a LMA, flexible videobronchoscopy was used to survey the airway. EBUS was then performed with a linear puncture echoendobronchoscope (BF-UC180F; Olympus America, Inc)
- All accessible LN stations were examined, and standard SMS LN stations were biopsied by fine-needle aspiration with a 22-gauge needle under real-time EBUS guidance
- Other suspicious LN stations based on CT scan, PET-CT scan, or EBUS were also biopsied

- LMA was removed, and patients underwent orotracheal intubation with a single-lumen endotracheal tube
- EUS was then performed with the same technique used for EBUS (EUS linear scope GF-UC140P-AL5 [Olympus America, Inc] and EUS 22-gauge needle
- In addition to mediastinal LN stations, the celiac axis LNs, liver, and bilateral adrenal glands were evaluated and biopsied if found to be abnormal
- A minimum of two needle passes was performed into each LN station

- Rapid-on-site cytologic examination of EBUS/EUS specimens was not performed
- EBUS and EUS were immediately followed by CM. An attempt to biopsy stations 4R, 4L, and 7 was made in all patients. Stations 1, 2R, and 2L were biopsied selectively based on clinical suspicion (CT scan, PET-CT scan, and surgical evaluation)
- Patients with isolated mediastinal adenopathy in the level 5 or 6 position underwent CM followed by left-sided AM (Chamberlain procedure)

- Order of LN biopsy for EBUS, EUS, and mediastinoscopy was from the highest-level station to the lowest-level station to avoid cross-contamination of lower-level stations and avoid upstaging
- All medically acceptable patients with negative mediastinal staging underwent anatomic pulmonary resection performed during a separate operation
- Systematic mediastinal LN sampling or dissection was performed at the time of pulmonary resection

Flow of study participant selection



Interprocedural agreement between Endosonographic and surgical staging

Modality	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	Cohen κ Coefficient (95% CI)
EBUS	0.72 (0.58-0.83)	1.0 (0.97-1.0)	1.0 (0.91-1.0)	0.88 (0.81-0.93)	0.91 (0.85-0.95)	0.77 (0.66-0.88)
EUS	0.62 (0.48-0.75)	1.0 (0.97-1.0)	1.0 (0.89-1.0)	0.85 (0.78-0.91)	0.88 (0.82-0.92)	0.69 (0.56-0.82)
Combined EBUS/EUS	0.91 (0.79-0.97)	1.0 (0.97-1.0)	1.0 (0.93-1.0)	0.96 (0.90-0.99)	0.97 (0.93-0.99)	0.93 (0.87-0.99)

NPV = negative predictive value; PPV = positive predictive value. See Table 3 legend for expansion of other abbreviations.

- EBUS, EUS, combined EBUS/EUS, and SMS sampled a mean of 2.2, 1.7, 3.9, and 3.1 LN stations, respectively
- Prevalence of N2/N3 disease was 32% (53 of 166 patients)
- There were 5 patients in whom the SMS procedure yielded positive results for N2 disease and the endosonographic mediastinal staging procedure findings were negative

Secondary outcomes

	EBUS	EUS	Combined EBUS/EUS	SMS
Negative predictive value	90% (95% CI, 0.83-0.95)	90% (0.83-0.95)	92% (0.85-0.96)	89% (0.82-0.94)
Diagnostic accuracy	90% (0.83-0.95)	89% (0.82-0.94)	91% (0.84-0.96)	89% (0.82-0.94)

Adverse events

- Major adverse events occurring during SMS were tracheal injury requiring muscle flap coverage (n=1), external jugular vein injury requiring vessel ligation (n=1), left sided recurrent nerve injury resulting in vocal cord paralysis (n=1), and left -sided vocal cord paresis that recovered after 4 months (n=1)
- Major adverse events occurring during EBUS were left sided mainstem bronchus laceration requiring surgical repair (n=1) and massive hemoptysis controlled with endoscopic interventions (n=1)
- Major adverse events occurring during EBUS were left sided mainstem bronchus laceration requiring surgical repair (n=1) and massive hemoptysis controlled with endoscopic interventions (n = 1). There were no major adverse events during EUS

Conclusions from the trial

- In patients with potentially resectable NSCLC, the combined EBUS/EUS procedure is sensitive and accurate
- Endosonography leads to improved staging compared with SMS because it allows for the biopsy of LNs and metastases not attainable with SMS techniques
- The combined EBUS/EUS procedure can replace SMS in patients with potentially resectable NSCLC
- Negative results of a combined EBUS/EUS procedure in the preoperative evaluation of potentially resectable lung cancer do not require confirmation with surgical staging

ORIGINAL ARTICLE

Endobronchial Ultrasound versus Mediastinoscopy for Mediastinal Nodal Staging of Non–Small-Cell Lung Cancer

Sang-Won Um, MD, PhD, Hong Kwan Kim, MD, PhD,† Sin-Ho Jung, PhD,‡ Joungho Han, MD, PhD,§ Kyung Jong Lee, MD,* Hye Yun Park, MD, PhD,* Yong Soo Choi, MD, PhD,† Young Mog Shim, MD, PhD,† Myung-Ju Ahn, MD, PhD,‖ Keunchil Park, MD, PhD,‖ Yong Chan Ahn, MD, PhD,¶ Joon Young Choi, MD, PhD,# Kyung Soo Lee, MD, PhD,** Gee Young Suh, MD, PhD,* Man Pyo Chung, MD, PhD,* O Jung Kwon, MD, PhD,* Jhingook Kim, MD, PhD,* and Hojoong Kim, MD, PhD**

J Thorac Oncol. 2015;10: 331–337

Inclusion criteria

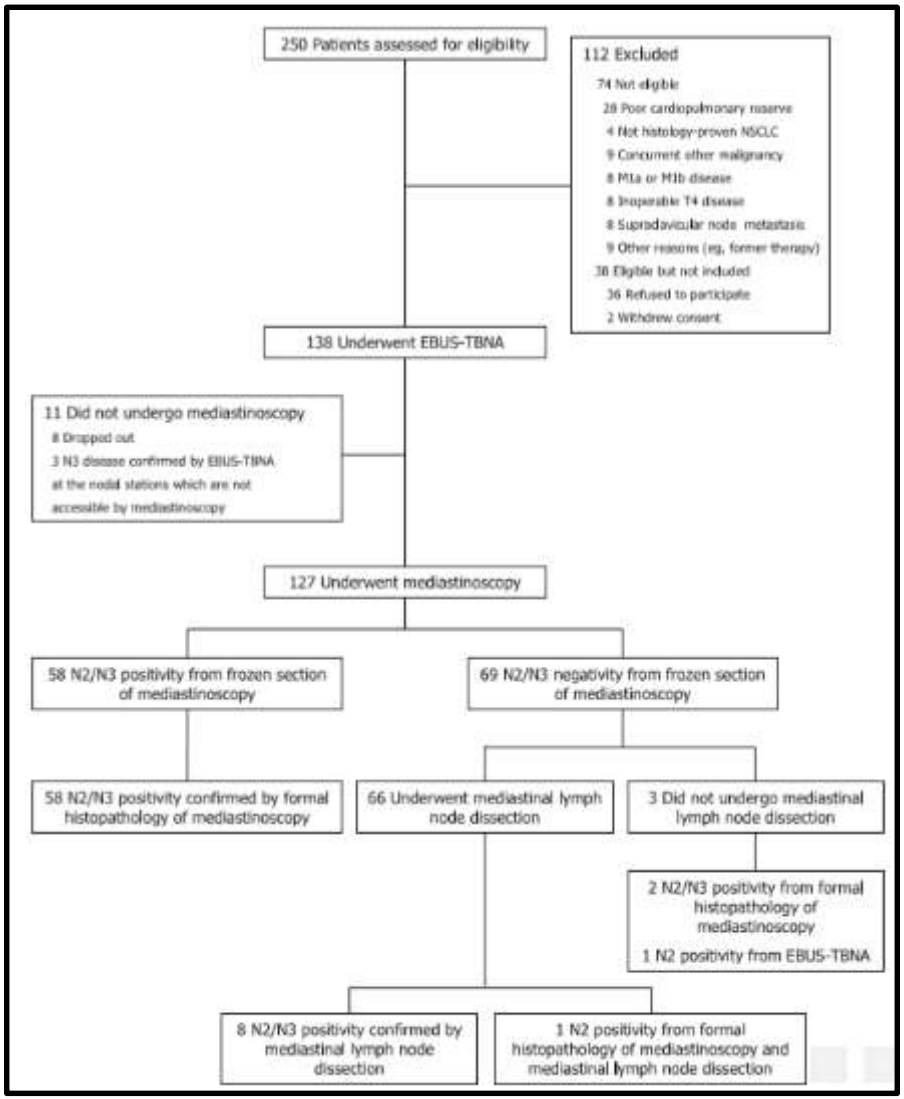
- (1) Histologically proven NSCLC
- (2) a suspicion of N2 or N3 lymph node metastasis on chest CT or PET/CT scans [at least one of three criteria had to be met, and these were: (a) enlarged (short-axis diameter 1 cm or more) mediastinal node(s), (b) FDG uptake by mediastinal node(s), and/or (c) FDG uptake by N1 node(s)]
- (3) the subject was a candidate for curative surgery.

Study design

- Each patient underwent EBUS-TBNA followed by mediastinoscopy. Thoracic surgeons and pathologists were blinded to the EBUS-TBNA data
- However, if N3 disease was confirmed by EBUS-TBNA at any nodal station examined that was inaccessible by mediastinoscopy, the latter procedure was cancelled and the EBUS-TBNA results were reported because performance of mediastinoscopy was not ethically justifiable
- Mediastinoscopy was performed within 3 weeks of EBUS-TBNA

- EBUS-TBNA and biopsies were conducted using a convex probe-EBUS bronchoscope (BF-UC260F-OL8; Olympus, Tokyo, Japan) and a 22-gauge needle
- Interventions were conducted with local anesthesia through nebulization with lidocaine and conscious sedation using midazolam
- Each visible station was sampled systematically. If a station had multiple lymph nodes on EBUS, lymph nodes were chosen based on the size and FDG uptake
- ROSE was not available

Enrollment of patients



Clinical characteristics of the patients(n=138)

Nodal stage by PET/CT	138 (100)
N1	20 (14.5)
N2	94 (68.1)
N3	24 (17.4)
Final histopathology	138 (100)
Squamous cell carcinoma	75 (54.3)
Adenocarcinoma	55 (39.9)
NSCLC NOS	6 (4.3)
LCNEC	1 (0.7)
Pleomorphic carcinoma	1 (0.7)
Number of nodal stations examined	
EBUS-TBNA (n = 138)	3 (1–6)
Mediastinoscopy (n = 127)	3 (1–6)
Mediastinal lymph node dissection (n = 64)	3 (1–6)
Time interval between EBUS-TBNA and mediastinoscopy, days (n = 127)	6 (0–19)
Number of passes per each nodal station during EBUS-TBNA	2 (1–5)
Type of mediastinoscopy	127 (100)
Traditional	42 (33.1)
Video-assisted	85 (66.9)
Lung resection surgery	55 (100)
Lobectomy	47 (85.5)
Bilobectomy	8 (14.5)
Pneumonectomy	9 (16.4)
Wedge resection	1 (1.8)

Mediastinal nodal stations in 127 patients who underwent both EBUS-TBNA and mediastinoscopy

	EBUS-TBNA	Mediastinoscopy	Lymph Node Dissection[a]	Subtotal
1R	3	2	1	5
2L	5	9	0	12
2R	43	48	16	67
3A	0	0	11	11
3P	0	0	1	1
4L	89	98	14	111
4R	114	121	38	125
5	0	0	20	21
6	0	0	6	6
7	122	120	56	126
8	0	0	4	4
9L	0	0	13	14
9R	0	0	21	21
Total	376	398	201	524
Short-axis diameter of the largest lymph node in each nodal station (mm)	9 (3–30)	10 (3–30)	10 (3–28)	9 (3–30)

[a]Mediastinal lymph node dissection was conducted in 64 patients.
EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Diagnostic Performance of EBUS-TBNA and Mediastinoscopy on a Per-Person Basis ($n = 127$)

	EBUS-TBNA	Mediastinoscopy	*p* Value
Sensitivity	66/75 (88.0) [80.6–95.4]	61/75 (81.3) [72.5–90.2]	0.0039
Specificity	52/52 (100) [100–100]	52/52 (100) [100–100]	NA
Accuracy	118/127 (92.9) [88.5–97.4]	113/127 (89.0) [83.5–94.4]	0.0001
PPV	66/66 (100) [100–100]	61/61 (100) [100–100]	NA
NPV	52/61 (85.2) [76.3–94.1]	52/66 (78.8) [68.9–88.7]	0.0018

Data are presented as numbers/total numbers (%) [with 95% confidence intervals].
EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

Diagnostic Sensitivities of EBUS-TBNA and Mediastinoscopy on an Individual Lymph Nodal Station Basis

	EBUS-TBNA	Mediastinoscopy	*p* Value
2R ($n = 67$)	10/18 (55.6) [32.6–78.5]	11/18 (61.1) [38.6–83.6]	0.8243
2L ($n = 12$)	0/3 (0) [0–0]	3/3 (100) [100–100]	0.0833
4R ($n = 125$)	34/41 (82.9) [71.4–94.4]	33/41 (80.5) [68.4–92.6]	0.1668
4L ($n = 111$)	17/21 (81.0) [64.2–97.7]	11/21 (52.4) [31.0–73.7]	0.0270
7 ($n = 126$)	33/40 (82.5) [70.7–94.3]	30/40 (75.0) [61.6–88.4]	0.0614

Suitability of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration Specimens for Subtyping and Genotyping of Non–Small Cell Lung Cancer

A Multicenter Study of 774 Patients

Neal Navani[1,2,3], James M. Brown[1,2], Matthew Nankivell[3], Ian Woolhouse[4], Richard N. Harrison[5], Vandana Jeebun[5], Mohammed Munavvar[6], Benjamin J. Ng[7], Doris M. Rassl[8], Mary Falzon[9], Gabrijela Kocjan[9], Robert C. Rintoul[7], Andrew G. Nicholson[10], and Sam M. Janes[1,2]

Am J Respir Crit Care Med Vol 185, Iss. 12, pp 1316–1322, 2012

Methods

- Consecutive patients with suspected NSCLC underwent EBUS-TBNA between January 2009 and March 2011 across five centers in the United Kingdom
- Interpretation of the EBUS-TBNA specimens was performed by the local pathologist
- Classification of NSCLC was based on morphological appearances (H&E stain), and immunostaining was performed if clinically indicated and if the sample was sufficient

- EGFR mutations were detected using DNA sequencing techniques, and patients were considered to be positive for EGFR mutation if 1 of 29 EGFR mutations was detected by polymerase chain reaction–based assays
- Primary endpoint was the proportion of patients with NSCLC undergoing EBUS-TBNA in whom it was possible to subtype the lung cancer
- Coprimary endpoint was the proportion of samples that was suitable for EGFR testing as determined by the local testing center

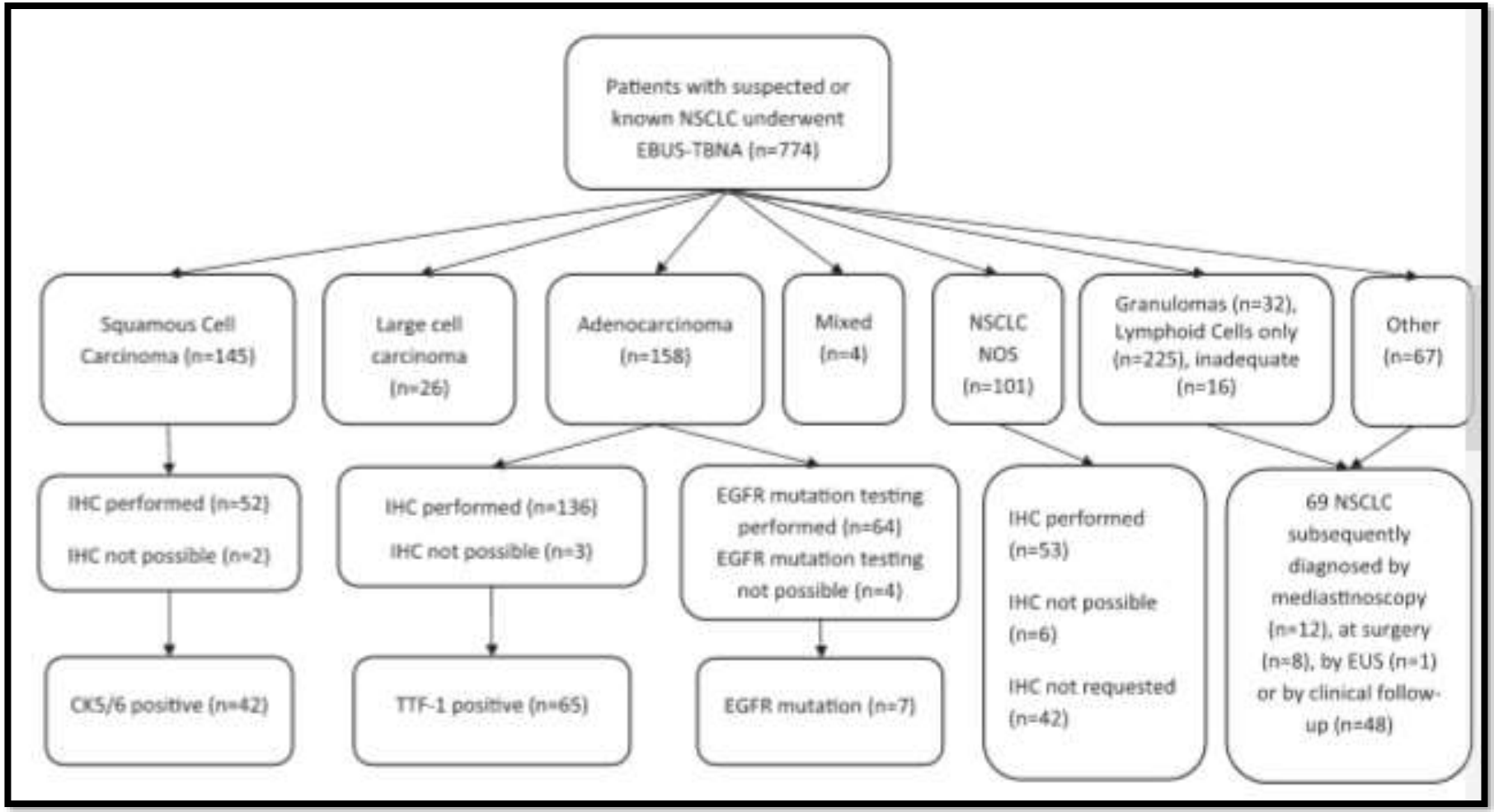
Baseline characteristics of patients

Patient Characteristics	Number
Gender	
Male	455 (59%)
Female	319 (41%)
Age, yr	
<50	43 (5%)
50–75	540 (70%)
>75	191 (25%)
Ethnicity	
Caucasian	683 (88%)
South Asian	21 (3%)
East Asian	5 (1%)
African	3 (<1%)
Caribbean	2 (<1%)
Other	1 (<1%)
Unknown	59 (8%)
Total	774

Yield according to lymph node stations

Lymph Node Station	Number of Nodes Sampled	Mean Size of Lymph Node (*mm*)	Prevalence of NSCLC	Sensitivity	Negative Predictive Value	Diagnostic Accuracy
2R	13	17	60%	83%	80%	90%
2L	3	15	33%	100%	100%	100%
3P	3	25	33%	100%	100%	100%
4R	282	21	84%	90%	65%	92%
4L	113	18	73%	80%	64%	85%
7	436	23	74%	90%	77%	92%
10R	104	18	76%	87%	71%	90%
10L	46	18	81%	90%	71%	93%
11R	41	16	82%	93%	75%	94%
11L	6	13	100%	50%	0%	50%
Overall	1047	21	77%	88%	72%	91%

Flowchart of patients



Factors to predict NSCLC-NOS

Covariate	Unadjusted OR of NSCLC-NOS (95% CI)	Univariate *P* Value	Adjusted OR of NSCLC-NOS (95% CI)	Multivariate* *P* Value
Age	0.99 (0.97–1.01)	0.53		
Lymph node location (mediastinal vs. hilar)	0.64 (0.34–1.19)	0.159		
Lymph node size	1.0 (0.96–1.05)	0.92		
Pathological differentiation	1.66 (0.92–3.00)	0.09	1.44 (0.79–2.62)	0.24
Immunohistochemistry performed	0.47 (0.27–0.82)	0.008	0.50 (0.28–0.88)	0.016

Definition of abbreviations: CI = confidence interval; NSCLC-NOS = non-small cell lung cancer not otherwise specified; OR = odds ratio.

* On the basis of univariate results, only pathological differentiation and performance of immunohistochemistry were included in the multivariate model. Performing immunohistochemistry significantly reduced the odds of obtaining a diagnosis of NSCLC-NOS.

BRIEF REPORT

Adequacy of Lymph Node Transbronchial Needle Aspirates Using Convex Probe Endobronchial Ultrasound for Multiple Tumor Genotyping Techniques in Non–Small-Cell Lung Cancer

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J Thorac Oncol. 2013;8: 1438–1444

Patient selection

- Patients with a diagnosis of lung cancer and whose tumors were genotyped for at least EGFR mutations were retrospectively identified through an ongoing Institutional Review Board–approved protocol at Beth Israel Deaconess Medical Center
- Patients and tumor pairs were excluded if genotyping of at least EGFR mutation, KRAS mutation, and ALK translocations were not performed
- There were 207 patient-tumor specimens that were submitted for these multiple tumor genotype techniques between 2007 and 2012

EBUS Technique and Tumor Collection with TBNA

- The CP-EBUS bronchoscope used for tissue acquisition was a 7.5 MHz Olympus fitted with color Doppler ultrasound capability
- A 21-gauge needle was used to obtain TBNA samples. Two to eight passes (usually 3 passes) per lymph node were obtained
- Out of 207 patient-tumor pairs that were included in the cohort, 42 samples(20.2%) were obtained from EBUS-TBNA

Baseline patient and tumor characteristics

	All Patients (N = 207)	CP-EBUS-TBNA Lymph Node Cohort (*n* = 42)
Age in years at the time of biopsy, median (range)	65 (29–89)	61.5 (39–84)
Women, *n* (%)	129 (62.3)	28 (66.7)
Race, *n* (%)		
White	161 (77.8)	34 (81.0)
Asian	19 (9.18)	2 (4.76)
Black	17 (8.21)	2 (4.76)
Others	10 (4.83)	4 (9.52)
Smoking status, *n* (%)		
Current smoker	42 (20.3)	10 (23.8)
Former smoker	110 (53.1)	23 (54.8)
Never smoker	55 (26.6)	9 (21.4)
Stage, *n* (%)		
I	14 (6.76)	0 (0)
II	13 (6.28)	1 (2.38)
III	27 (13.0)	7 (16.7)
IV	153 (73.9)	34 (81.0)
Histology, *n* (%)		
Adenocarcinoma	174 (84.1)	36 (85.7)
Squamous cell carcinoma	9 (4.35)	0 (0)
NSCLC (NOS)	22 (10.6)	6 (14.3)
Others	2 (0.97)	0 (0)
Anatomic site of biopsy, *n* (%)		
Bone	13 (6.28)	0 (0)
Brain	17 (8.21)	0 (0)
Liver	3 (1.45)	0 (0)
Lung	98 (47.3)	0 (0)
Lymph node	51 (24.6)	42 (100)
Pleura	23 (11.1)	0 (0)
Others	2 (0.97)	0 (0)

Type of biopsy, *n* (%)		
Core-needle biopsy	39 (18.8)	0 (0)
Surgical biopsy	95 (45.9)	0 (0)
Cell block from FNA	61 (29.5)	42 (100)
Cell block from fluid	12 (5.80)	0 (0)
EGFR mutation analysis		
Success, *n* (%, [95% CI])	191 (92.3 [87.5–95.4])	40 (95.2 [82.6–99.2])
Positive/mutated	32 (15.5)	5 (11.9)
Negative/wild-type	159 (76.8)	35 (83.3)
Failure	16 (7.73)	2 (4.8)
KRAS mutation analysis		
Success, *n* (%, [95% CI])	190 (91.8 [87.0–95.0])	38 (90.5 [76.5–96.9])
Positive/mutated	65 (31.4)	18 (42.9)
Negative/wild-type	125 (60.4)	20 (47.6)
Failure	17 (8.21)	4 (9.5)
ALK FISH analysis		
Success, *n* (%, [95% CI])	186 (89.9 [84.7–93.5])	38 (90.5 [76.5–96.9])
Positive	11 (5.31)	1 (2.4)
Negative	175 (84.5)	37 (88.1)
Failure	21 (10.1)	4 (9.5)

Success and failure rates of genotype tests

	CP-EBUS–Derived Node Cell Blocks	All Other Methods of Tissue Acquisition	Mediastinal/Hilar Nodes from Surgical Biopsies	Lung Core Biopsies (Bronchoscopy)	Lung Core-Needle Biopsies (Image-Guided)
EGFR mutation analysis					
Success, *n* (%)	40 (95.2)	151 (91.5)	8 (100)	12 (86)	6 (55)
Failure, *n* (%)	2 (4.8)	14 (8.5)	0 (0)	2 (14)	5 (45)
Total	42	165	8	14	11
p value	Ref	0.54	1	0.26	0.003
ALK FISH analysis					
Success, *n* (%)	38 (90.5)	148 (89.7)	8 (100)	12 (86)	6 (55)
Failure, *n* (%)	4 (9.5)	17 (10.3)	0 (0)	2 (14)	5 (45)
Total	42	165	8	14	11
p value	Ref	1	1	0.63	0.01
KRAS mutation analysis					
Success, *n* (%)	38 (90.5)	152 (92.1)	8 (100)	13 (93)	8 (73)
Failure, *n* (%)	4 (9.5)	13 (7.9)	0 (0)	1 (7)	3 (27)
Total	42	165	8	14	11
p value	Ref	0.75	1	1	0.15

CP-EBUS, convex probe endobronchial ultrasound; *EGFR*, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; *KRAS*, Kirsten rat sarcoma viral oncogene homolog.

Failed Specimens Using CP-EBUS–Derived Nodal Tissue

- Insufficient tumor cells in the cell block specimen
- In CP-EBUS–derived nodal tissues that were successful 17 of 19 (89.4%) had 100 cells or more whereas in failure cases only two of five (40%) had 100 cells or more ($p = 0.042$)
- Other possible characteristics- the size of the nodal tissue biopsied, the location of the node, the number of passes per lymph node, use of touch preparation for rapid on-site evaluation, presence of extensive desmoplastic stromal response, and number of slides cut from the paraffin block used for immunohistochemical and ancillary studies-were not significantly different

TAKE HOME MESSAGE