EBUS Guided Mediastinal Lymph node Sampling

The Future of Lymph node Sampling

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Objectives

- Endobronchial Ultrasound in Lung Cancer Diagnosis
- EBUS scopes
- EBUS in the Era of Molecular Testing and NGS
- Future of Lymph node Sampling
“Everything we see hides another thing; we always want to see what is hidden by what we see. There is an interest in that which is hidden and which the visible doesn’t show us”

The Need to Develop Endobronchial Ultrasound

- 1980 - CT was the standard for Pre-operative staging
- Primary Tumors and Metastasis - ✓
- Lymph nodes and Airway Involvement - ❌
- The view of Bronchoscopist in the airways was limited
  ✓ Discoloration
  ✓ Displacement
  ✓ Destruction
- Demand for a new pre-operative staging modality
How EBUS was in the air

- Ultrasound in Medicine - 1970
- Late 80s – Transesophageal Ultrasound and RP EBUS
- The GI EUS – GIF-UM 3 -1989
- Mediastinum - still in question!
  - Large size of the GI scopes
  - Access to all lymph node stations

This led to transfer of application to endobronchial space
EBUS Development (1990-1994)

- UM 1-W/ Olympus
- Market 1990
- GI application - small ducts
- 7.5 MHz, 360 degree / OD - 3.4
- Rigid Bronchoscopy application

- Thomas Hurther - Aachen
- Miniature probe - blood vessels
- Boston sc sonocath probes

- First to publish - First Pioneer 1992 paper / 100 patients' data
EBUS Development (1994 -1999) - Radial Probes
M. Krasnik - request for integrated EBUS Scope
EBUS Development (1999) - Prototype EBUS Scopes

- 1999 - First prototype - BUMP - XBF-UM30P

![Prototype EBUS Scopes](image-url)
EBUS Development (2002) - Prototype EBUS Scopes

- 2002 - BF Convex
Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions

M Krasnik, P Vilmann, S S Larsen, G K Jacobsen

Table 1  Demographic data of 11 patients describing the clinical problem, location of lesions targeted by EBUS-FNA, and treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location of lesion targeted</th>
<th>Cytology results</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown hilar lesion, suspicion of recurrent renal cancer</td>
<td>10L</td>
<td>Clear cell carcinoma</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Unknown mediastinal mass</td>
<td>10L</td>
<td>Squamous cell carcinoma</td>
<td>Exploratory surgery</td>
</tr>
<tr>
<td>Right sided lung cancer</td>
<td>10R</td>
<td>NSCLC</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Right sided lung cancer</td>
<td>10R</td>
<td>Benign</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Right sided lung cancer</td>
<td>4L</td>
<td>NSCLC</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Recurrent lung cancer</td>
<td>10L</td>
<td>NSCLC</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Unknown right sided mediastinal lesion</td>
<td>4R</td>
<td>Carcinoma</td>
<td>Pneumonectomy</td>
</tr>
<tr>
<td>Right sided lung cancer</td>
<td>10R</td>
<td>NSCLC</td>
<td>Chemotherapy</td>
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<td>Left sided lung cancer</td>
<td>10L</td>
<td>Benign</td>
<td>Mastectomy</td>
</tr>
<tr>
<td>Left sided lung cancer</td>
<td>4R</td>
<td>SCLC</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Caro superior syndrome (unknown nature)</td>
<td>2R</td>
<td>Adenocarcinoma</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Left sided lung cancer</td>
<td>1R</td>
<td>Carcinoma</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

- 11 patients
- 15 Lesions
- 13 Malignant
- 02 Benign
- No complications
Conclusions

In patients with extensive mediastinal infiltration, invasive staging is not needed. In patients with discrete node enlargement, staging by CT or positron emission tomography (PET) scanning is not sufficiently accurate. The sensitivity of various techniques is similar in this setting, although the false-negative (FN) rate of needle techniques is higher than that for mediastinoscopy. In patients with a stage II or a central tumor, invasive staging of the mediastinal nodes is necessary. Mediastinoscopy is generally preferable because of the higher FN rates of needle techniques in the setting of normal-sized lymph nodes. Patients with a peripheral clinical stage I NSCLC do not usually need invasive confirmation of mediastinal nodes unless a PET scan finding is positive in the nodes. The staging of patients with left upper lobe tumors should include an assessment of the aortopulmonary window lymph nodes.
Methods for Staging Non-small Cell Lung Cancer

Diagnosis and Management of Lung Cancer,
3rd ed: American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines

Conclusions: Since the last iteration of the staging guidelines, PET scanning has assumed a more prominent role both in its use prior to surgery and when evaluating for metastatic disease. Minimally invasive needle techniques to stage the mediastinum have become increasingly accepted and are the tests of first choice to confirm mediastinal disease in accessible lymph node stations. If negative, these needle techniques should be followed by surgical biopsy. All abnormal scans should be confirmed by tissue biopsy (by whatever method is available) to ensure accurate staging. Evidence suggests that more complete staging improves patient outcomes.

CHEST 2013; 143(5)(Suppl):e211S–e250S
EBUS Scopes

- BF-UC 180 F
- BF-UC 190 F with 20 forward oblique view
- Processors: EU-ME1, EU-ME2, EU-ME3

- Angle of view - 35° Forward oblique / 20° Forward oblique
- Scan Direction - Longitudinal
- Insertion Tube Diameter - 6.2mm / OD 6.9 mm
- Instrument Channel Diameter - 2.2mm
- Angulation Up/down - 120/90
EBUS Scopes

- **EB-1970UK, EB19-J10U**
- Hitachi ultrasound systems with thoracic probes

- Angle of view - *45° Forward oblique*
- Scan Direction - *Longitudinal*
- Insertion Tube Diameter – *6.3mm*
- Instrument Channel Diameter – *2/2.2mm*
- Angulation Up/down – *120/90*
EBUS Scopes

- EB-530US
- SU-8000 ultrasound processor

- Angle of view - 10° Forward oblique
- Scan Direction - Longitudinal
- Insertion Tube Diameter – 6.3mm
- Instrument Channel Diameter – 2mm
- Angulation Up/down – 130/90
Established EBUS Scopes

<table>
<thead>
<tr>
<th>Model</th>
<th>Diameter (mm)</th>
<th>Working channel (mm)</th>
<th>Working length (mm)</th>
<th>Field of view</th>
<th>Depth penetration (mm)</th>
<th>Frequency (MHz)</th>
<th>Scan modus</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB19-J10U Video EBUS-scope (Pentax)</td>
<td>7.3</td>
<td>2.2</td>
<td>600</td>
<td>100° / 45° Oblique optic</td>
<td>2-50</td>
<td>5.0-13.0</td>
<td>Electronic 75° curved linear array</td>
<td>Compatible with Hitachi Hi-Vision Scanner</td>
</tr>
<tr>
<td>BF-UC190F Video-EBUS-scope (Olympus)</td>
<td>6.6</td>
<td>2.2</td>
<td>600</td>
<td>80° / 20° Oblique optic</td>
<td>2-50</td>
<td>5.0-12.0</td>
<td>Electronic 65° curved linear array</td>
<td>Compatible with EU-ME2, Hitachi Aloka ProSound F75</td>
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<tr>
<td>EB-530US Video-EBUS-scope (Fujifilm)</td>
<td>6.7</td>
<td>2.0</td>
<td>610</td>
<td>120° / 10° Oblique optic</td>
<td>3-100</td>
<td>5.0-12.0</td>
<td>Electronic 60° curved linear array</td>
<td>Compatible with SU-1-S/H Compatible with Hitachi Aloka ProSound F75</td>
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</tbody>
</table>
Endobronchial Ultrasound - Clinical Applications

- **Lymph node staging of Lung Cancer**
  - Pre-operative staging
  - Post-operative evaluation
  - Restaging

- **Diagnosis of centrally located intra-pulmonary pathologies**

- **Mediastinal and Hilar adenopathy - Benign and Malignant**
  - Sarcoidosis (overall yield of 90-92%)
  - Lymphoma (sensitivity 57-91%)
Endobronchial Ultrasound - Anesthesia

GA vs Moderate sedation for EBUS TBNA - RCT

<table>
<thead>
<tr>
<th></th>
<th>General Anesthesia (n=75)</th>
<th>Moderate Sedation (n=74)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>LNs sampled/pt</td>
<td>3.2±1.9</td>
<td>2.8±1.5</td>
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<tr>
<td>Dx Yield</td>
<td>70.7%</td>
<td>68.9%</td>
<td>0.816</td>
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<tr>
<td>Sensitivity</td>
<td>98.2%</td>
<td>98.1%</td>
<td>0.979</td>
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<tr>
<td>Completion Rate</td>
<td>100%</td>
<td>93.3%</td>
<td>0.028</td>
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<tr>
<td>Major Complication</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Minor Complication</td>
<td>5.3%</td>
<td>29.6%</td>
<td>&lt; 0.001</td>
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</table>

Standard EBUS Image Classification

Malignant Predictors

✓ Size > 1cm
✓ Round Shape
✓ Distinct Margins
✓ Heterogenous Echo signal
✓ Absence of CHS
✓ High color power doppler index
✓ Absent CNS
EBUS Imaging - Vascular Patterns

(A) Grade 0

(B) Grade I

(C) Grade II

(D) Grade III

(E) BA inflow sign

Grade

0

I

II

III

BA inflow sign

negative

positive

Number of lymph nodes

non-metastatic

metastatic

(A) Grade 0

(B) Grade I

(C) Grade II

(D) Grade III

(E) BA inflow sign
Combination of ROSE + Elastography
Beginners

❖ Forward Oblique view
❖ Reaching 4R, 10R and 4L
❖ Bronchoscopy image
❖ Use of second bronchoscope
❖ Financial implications
EBUS - Procedural Aspects

EBUS 6 LANDMARKS

SEARCH FOR THE LANDMARKS IN THIS ORDER:
4L → 7 → 10L → 10R → AZYGOS → 4R

4L
AZ
10R

4R
AZYGOS VEIN
10R

4L
AZYGOS VEIN
10L

7

PFC 2015
EBUS - Procedural Aspects - Sampling Order

M1b – N3 – N2 – N1
EBUS - Procedural Aspects

**EUS 6 LANDMARKS**

Search for the landmarks in this order:
1. LIVER → ABDOMINAL AORTA →
2. LEFT ADRENAL GLAND →
3. 7 ↔ 4L ↔ 4R

**EUS-B-FNA in lung cancer work up**
EBUS + EUS b - Complimentary
# EBUS - Procedural Aspects

<table>
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<tr>
<th>First Author</th>
<th>Year</th>
<th>Stage</th>
<th>Thoro</th>
<th>Prev</th>
<th>Sens</th>
<th>Spec</th>
<th>Sens*</th>
<th>PPV</th>
<th>NPV</th>
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<td>95</td>
<td>85</td>
<td>100</td>
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</table>

**Median Cn0-3**
- Sens: 85%
- Spec: 95%
- Sens*: 85%
- PPV: 100%
- NPV: 100%

**Median Cn0**
- Sens: 75%
- Spec: 95%
- Sens*: 75%
- PPV: 100%
- NPV: 100%

**Median Cn0**
- Sens: 85%
- Spec: 95%
- Sens*: 85%
- PPV: 100%
- NPV: 100%

**Summary TM: median 9267**
- Cn0-2: 33
- Sens*: 85%
- Spec: 95%
- PPV: 100%
- NPV: 100%

**Summary VAM: median 9955**
- Cn0-2: 33
- Sens*: 85%
- Spec: 95%
- PPV: 100%
- NPV: 100%

**Summary ALL: median 5,609**
- Cn0-2: 33
- Sens*: 85%
- Spec: 95%
- PPV: 100%
- NPV: 100%
EBUS in the Era of Molecular analysis and NGS

**Table 1. Common Molecular Abnormalities in Lung Adenocarcinoma**

<table>
<thead>
<tr>
<th>Molecular Abnormality</th>
<th>Frequency</th>
<th>Possible Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>25%</td>
<td>No targeted agent*</td>
</tr>
<tr>
<td>EGFR</td>
<td>23%</td>
<td>Erlotinib, afatinib, gefitinib, osimertinib</td>
</tr>
<tr>
<td>ALK</td>
<td>6%</td>
<td>Alectinib, ceritinib, crizotinib</td>
</tr>
<tr>
<td>TP53</td>
<td>4%</td>
<td>No targeted agent*</td>
</tr>
<tr>
<td>BRAF</td>
<td>3%</td>
<td>Dabrafenib/trametinib</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>3%</td>
<td>No targeted agent*</td>
</tr>
<tr>
<td>MET</td>
<td>2%</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>ROS1</td>
<td>1.5%</td>
<td>Crizotinib, ceritinib</td>
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<tr>
<td>HER2</td>
<td>1%</td>
<td>Ado-trastuzumab emtansine</td>
</tr>
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<td>RET</td>
<td>1%</td>
<td>Cabozantinib, vandetanib</td>
</tr>
<tr>
<td>MEK1</td>
<td>0.4%</td>
<td>No targeted agent*</td>
</tr>
<tr>
<td>NRAS</td>
<td>0.2%</td>
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<td>β-catenin</td>
<td>0.2%</td>
<td>No targeted agent*</td>
</tr>
<tr>
<td>IDH1</td>
<td>0.1%</td>
<td>No targeted agent*</td>
</tr>
<tr>
<td>No identified abnormality</td>
<td>33%</td>
<td>No targeted agent*</td>
</tr>
</tbody>
</table>

*These patients may be candidates for pembrolizumab if their tumors exhibit high programmed death ligand 1 expression.

NSCLC = non-small-cell lung cancer; PD-L1 = programmed death ligand 1.
EBUS in the Era of Molecular analysis and NGS

• Molecular classification - essential part of routine lung cancer care

• Growing number of targetable molecular alterations

• 30% of the patients diagnosed with NSCLC, tumor cellularity is < 40%

• In approximately 23% of patients, the tissue is not adequate for molecular analyses due to the difficulty of reaching tumor sites with non-invasive methods

• Moreover, in some cases, tumor necrotic cells decrease cellular density, resulting in low-quality sequencing.
EBUS in the Era of Molecular analysis and NGS

EBUS - Techniques

- Size - 19G / 25G
- Shape - Procore/Acquire

- Slow Pull
- Fanning
- IFB
The need for new Techniques of Tissue Acquisition

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</tr>
<tr>
<td>MET</td>
<td>2%</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>ROS1</td>
<td>15%</td>
<td>Crizotinib, cetinib</td>
</tr>
<tr>
<td>HER2</td>
<td>1%</td>
<td>Ado-trastuzumab emtansine</td>
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<tr>
<td>RET</td>
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<td>Cabozantinib, vandetanib</td>
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<tr>
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<td>0.4%</td>
<td>No targeted agent&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>0.2%</td>
<td>No targeted agent&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>β-catenin</td>
<td>0.2%</td>
<td>No targeted agent&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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EBUS in the Era of Molecular analysis and NGS

IntraNodal Forceps Biopsy

EBUS in the Era of Molecular analysis and NGS

IntraNodal Forceps Biopsy

<table>
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<tr>
<th>Modality</th>
<th>Diagnostic yield</th>
<th>Numbers</th>
<th>Significance</th>
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<tbody>
<tr>
<td>EBUS-TBNA</td>
<td>81%</td>
<td>60/74</td>
<td>p=0.09</td>
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<tr>
<td>EBUS-MFB</td>
<td>91%</td>
<td>67/74</td>
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</tr>
<tr>
<td>TBNA+MFB</td>
<td>97%</td>
<td>72/74</td>
<td>p&lt;0.001</td>
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Endobronchial ultrasound-guided transbronchial cryo-nodal biopsy: a novel approach for mediastinal lymph node sampling

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⁴Department of Pulmonary, Critical Care and Sleep Medicine, Medipulse Hospital, Jodhpur, India.
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Figure 1: Case 1 – (A) Non-contrast CT thorax showing sub-carninal and hilar nodes, (B) Non caseating epithelioid granuloma with giant cells and fibrosis. H&E 40x, CD4 cells (C) are is more evident than CD 8 cells (D) while few B lymphocytes are highlighted with CD 20 (E); Case 2 – (F) Contrast CT thorax showing left hilar mass with paratracheal lymphnodes, (G) Adenocarcinoma cells,H&E ,10x (H) with positivity for ROS1(D4D6) , 10x; Case 3 – (I) Contrast CT showing left interlobar node, (J) Metastatic Carcinoma from breast,H&E,10x, Tumour cells are positive for Her2 (K) ,ER (L) and GATA3 (M); Case 4 – (N) Non-contrast CT showing right parahilar lesion with sub-carinal lymphnode, (O) Necrotising Granuloma,H&E,40x (P) Ziehl-Neelsen stain highlights few pink rod shaped bacilli (red arrow), CD8 cells (Q) are more evident than CD 4 cells (R) while few B lymphocytes are highlighted with CD 20 (S)
EBUS in the Era of Molecular analysis and NGS
EBUS - Mediastinal Cryobiopsy
No needle Technique

Dr. Hari Kishan Gonuguntla MD.DM
Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial

Jing Zheng, Jie-Rui Guo, Zai-Sheng Huang, Wei-Lai Fu, Xian-Li Wu, Na Wu, Wolfgang M. Kuebler, Felix J.F. Herth, Ye Fan
European Respiratory Journal 2021 58; 2100055; DOI: 10.1183/13993003.00055-2021
Results

Definitive Diagnosis - 181/197 patients (93.3%)
152 patients - Both TBNA and cryobiopsy - yield diagnosis

26 additional cases where TBNA failed - Cryobiopsy established the diagnosis

   6 - NSCLC
   6- Lymphoma
   1 - Seminoma
   8 - Tuberculosis
   5 - Sarcoidosis

Conversely - 3 NSCLC patients - diagnosis was established only by TBNA

Overall diagnostic yield for TBNA - 79.9% and for Cryo 91.8%

Sub group analysis - no difference in diagnostic yield in common lung cancer (94.1% for TBNA vs 95.6% for cryobiopsy)

The diagnostic yield of mediastinal cryobiopsy was significantly higher in Uncommon tumors (91.7% versus 25.0%)

Benign lesions - 80.9% versus 53.2%
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Anesthesia</th>
<th>Airway</th>
<th>Targeted LN</th>
<th>Needle size / passes</th>
<th>ROSE</th>
<th>Cryo size</th>
<th>Track creation</th>
<th># MCB pass</th>
<th>Freezing time</th>
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<tr>
<td>Zhang(28)</td>
<td>2021</td>
<td>CS</td>
<td>transoral</td>
<td>2R/L to 12R/L</td>
<td>7G x 4</td>
<td>no</td>
<td>1.1</td>
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<td>transoral</td>
<td>2R/L to 13R/L</td>
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<td>Ariza-Prota(30)</td>
<td>2023</td>
<td>CS</td>
<td>transoral</td>
<td>7, 4R mostly</td>
<td>22G x 3-5</td>
<td>no</td>
<td>1.1</td>
<td>TBNA</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Gershman(31)</td>
<td>2022</td>
<td>CS/DS</td>
<td>LMA</td>
<td>7, 4L</td>
<td>19G x 3</td>
<td>no</td>
<td>1.1 / 1.7</td>
<td>TBNA / Nd YAG / track dilation</td>
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<td>Oikonomidou(50)</td>
<td>2022</td>
<td>CS/DS</td>
<td>LMA / ETT + jet vent</td>
<td>N/A</td>
<td>19/21 / 22G x 4</td>
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<td>3</td>
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<td>Maturu(32)</td>
<td>2023</td>
<td>GA</td>
<td>LMA</td>
<td>7,4R,11L,11R</td>
<td>19G</td>
<td>yes</td>
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<td>TBNA</td>
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<td>Genova(33)</td>
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<td>TBNA</td>
<td>2</td>
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<tr>
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<td>2022</td>
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<td>7, retrotach mass</td>
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<td>no</td>
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<td>TBNA</td>
<td>1-2</td>
<td>8</td>
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<tr>
<td>Zhang(27)</td>
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<td>10L</td>
<td>22G x 4</td>
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<td>7</td>
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<td>Ishiguro(52)</td>
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<td>?</td>
<td>TBNA</td>
<td>2</td>
<td>?</td>
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<tr>
<td>Kho(38)</td>
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<td>TIVA</td>
<td>RB</td>
<td>7</td>
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<td>TBNA</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Tamburrini(34)</td>
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<td>GA</td>
<td>RB</td>
<td>7</td>
<td>21G</td>
<td>no</td>
<td>1.1</td>
<td>TBNA + forceps</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Zhang(35)</td>
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<td>CS</td>
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<td>7</td>
<td>21G x 4</td>
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<td>TBNA + sheath</td>
<td>1</td>
<td>7</td>
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<tr>
<td>Hetze(53)</td>
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<td>?</td>
<td>transoral</td>
<td>4L</td>
<td>7G x 4</td>
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<td>1.1</td>
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<td>Schwick(41)</td>
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<td>GA</td>
<td>ETT</td>
<td>7</td>
<td>19G x 2-3</td>
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<td>1.1</td>
<td>TBNA + sheath</td>
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<td>5-7</td>
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<td>Takenura(54)</td>
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<td>?</td>
<td>?</td>
<td>11s</td>
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<td>Zhang(55)</td>
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<td>11L</td>
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<td>no</td>
<td>1.1</td>
<td>EC knife</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

LMA, laryngeal mask airway; ETT, endotracheal tube; RB, rigid bronchoscopy; LN, lymph node; G, gauge; EC, electrocautery; Nd YAG, neodymium-doped yttrium aluminum garnet.
Take Home Message

- EBUS - Diagnostic procedure of choice in Lung Cancer Staging
- EBUS + EUSb – Complete Mediastinal Staging
- In the Era of Molecular Analysis - More tissue acquisition
- Mediastinal Cryo biopsy - safe and feasible
- Mediastinal Cryobiopsy - Improves the Diagnostic yield in all pathologies
- Training aspects - Simulator Training is essential
Email: harikishang@gmail.com
Teşekkür Ederim