Utilizing EBUS (Endobronchial Ultrasound) for Diagnosis of Lung Cancer and other Pulmonary Diseases

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Objectives

- Discuss EBUS guided biopsy principles and technique.

- List and discuss conditions in which EBUS biopsy is used for.

- Discuss the role of EBUS in lung cancer staging
EBUS and TBNA

<table>
<thead>
<tr>
<th>Localization</th>
<th>Conventional TBNA</th>
<th>EBUS-Guided TBNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive Results, %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>D</td>
</tr>
<tr>
<td>2r</td>
<td>7</td>
<td>42</td>
</tr>
<tr>
<td>2l</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>4r</td>
<td>9</td>
<td>66</td>
</tr>
<tr>
<td>4l</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>APW</td>
<td>11</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>54</td>
</tr>
</tbody>
</table>

*Positive results are listed separately for specific diagnosis and positive results including lymphocyte positive aspirates. APW = aortic-pulmonary window; D = diagnostic; L = lymphocyte positive.
What is EBUS
EBUS

- EBUS is a bronchoscopic technique that uses ultrasound to visualize structures within and around the airway wall as well as the lung.

- EBUS is a minimally-invasive, safe procedure that can be performed on an outpatient basis using local anesthesia and conscious sedation.

- EBUS can access a wide range of mediastinal lymph nodes as well as N1 lymph nodes (2R, 2L, 3p, 4R, 4L, 7, 10R, 10L, 11R, 11L) and sample centrally located pulmonary lesions with high sensitivity.

- Two types of endobronchial ultrasound (EBUS) exist: radial probe EBUS (RP-EBUS) and convex probe EBUS (CP-EBUS).
Radial probe EBUS (RP-EBUS)

RP-EBUS provides high definition, 360-degree images of the airway wall and surrounding structures

RP-EBUS visualize the layers of the airway wall in greater detail

1.7mm probe inserted through the working channel of a bronchoscope

Frequency is 20Mhz

Enables the evaluation of peripheral lung nodules

RP-EBUS does not permit sampling in real-time such that sequential sampling with separate equipment is necessary
Example of RP-EBUS being used to diagnose a peripheral pulmonary lesion. Note the well demarcated outline of the lesion and the concentric nature of the image in the bottom right panel.
Convex probe EBUS (CP-EBUS)

- A curved array ultrasound transducer is built into the distal end of the EBUS.
- Has a thirty degree field of vision using white light bronchoscopy.
Types of CP-EBUS

- Olympus BF-UC180F
- Pentax EB-1970UK
- Fujinon EB-530US
Convex probe EBUS (CP-EBUS)

- The lockable sheath prevents injury to the scope during needle protrusion
- Outer diameter 6.3-6.7mm
- Instrument channel 2.0/2.2mm
- Different sizes of needles available (21, 22G)
Convex probe EBUS (CP-EBUS)

- The processor has adjustable depth and gain.
- It also has Doppler capabilities to identify blood flow in vessels, distinguishing them from lymph nodes.
- Prior to EBUS, white light bronchoscopic inspection is performed and the airways are cleared of secretions.
- Both the ultrasound image and plain-view endoscopic image are displayed on the same monitor.
- The ultrasound image can be frozen, allowing the size of lesions to be measured in two dimensions.
The Image
Getting the orientation

Caudal

cephalad
EBUS-TBNA in 15 steps

- The needle is inserted into the working channel.
- The housing is secured to the bronchoscope by sliding the hublock.
- The sheath is released by twisting the inferior screw.
- With the node visualized by US, the sheath is advanced out of the end of the scope until it slightly touches the airway wall. It is now safe to advance the needle.
- The needle lock located superiorly, is then released to a depth based on the lymph node size.
- The needle is advanced by jabbing it into the lymph node.
EBUS-TBNA in 15 steps

- 7. During this process the needle may push the airway wall away from the balloon. The transducer–wall interface might become lost and the image may show reverberation artifact. This problem is overcome by gently advancing the scope or further inflating the balloon.

- 8. The needle is visualized within the lymph node.

- 9. The stylet is moved in and out a few times to dislodge bronchial epithelium or cellular debris that may have entered the needle.

- 10. The stylet is then withdrawn from the scope.
EBUS-TBNA in 15 steps

11. The syringe is attached to the needle and suction is applied.

12. The needle is moved back and forth within the node approximately 10-15 times under ultrasound visualization.

13. Suction is released by removing the syringe from the scope.

14. The needle is retracted into the sheath.

15. The needle housing is unlocked and the needle and the sheath are removed together.
"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."
EBUS Specimens

Kazuhiro Yasufuku MD
21G or 22G?

Comparison of 21-gauge and 22-gauge aspiration needle during endobronchial ultrasound-guided transbronchial needle aspiration

TAKAHIRO NAKAJIMA,1,2 KAZUHIRO YASUFUKU,2 RYO TAKAHASHI,1 MASATO SHINGYOJI,1 TETSUSHI HIRATA,3 MAKIKO ITAMI,3 YUKIKO MATSUI,1 MEIJI ITAKURA,1 TOSHIKIKO IIZASA1 AND HIDEKI KIMURA1

- Comparison of 21G and 22G during EBUS-TBNA
  - No differences in the diagnostic yield
  - Histological structure more preserved in some samples
  - More blood contamination in 21G samples

Nakajima et al, Respirology. 2011; 16(1): 90-4
21G or 22G?

- American College of Chest Physicians Quality Improvement Registry, Education, and Evaluation Registry (AcQuIRe) – data analysis (n=1299)

- Sample adequacy
  - 22G 94.9% vs 21G 94.6% (P = 0.81)

- Diagnosis made in
  - 22G 51.4% vs 21G 51.3% (P = 0.98)

- ROSE associated with significantly fewer needle passes per procedure when using the 21G needle

How many aspirations

• How many aspiration per LN?
  • 102 NSCLC, 163 med LN (Sensitivity 93.8%)
  • Maximum diagnostic values achieved in three aspirations
  • When at least one tissue-core specimen is obtained by the first or second aspiration, two aspirations per LN station can be acceptable

• How many LN stations per patient?
  • 92 NSCLC, 271 med LN (2.9 per patient)
  • In 15 patients (60%), mediastinal disease was detected in the first station sampled; three samples were required to detect 90% of disease
  • Routinely sampling more than two mediastinal stations may improve staging

Lee et al. Chest. 2008;134: 368-74
Suction or no suction

- EBUS-TBNA vs EBUS-TBNCS (EBUS-guided transbronchial needle capillary sampling)
- N=115,192 LNs
- Regardless of LN size, no differences in adequacy, diagnosis, and quality of samples
- No evidence of benefit applying suction to EBUS-guided biopsies

Experts Recommend

- Start with suction
- If aspirate is bloody, repeat procedure without suction
- For subcarinal LN with higher vascularity, start without suction

Casal et al, Chest. 2012; 142(3):568-73
Beyond Tissue Dx: Personalized Medicine for NSCLC

- The “tissue is the issue” remains an important principle for further progress in personalized medicine.
- EBUS-TBNA samples can be used for biomarker assessments
  - EGFR mutation
  - cell-cycle proteins
  - Aberrant methylation
  - EML4-ALK Fusion Gene

Mohamed et al. Thorax. 2008; 63: 642-7
Nakajima et al. JOB 2009; 16: 10-14
Indications for EBUS-TBNA

- Lung cancer staging
- Lung cancer staging after neoadjuvant chemotherapy
- Diagnosis of mediastinal or hilar lymphadenopathy
- Diagnosis of anterosuperior mediastinal mass
- Diagnosis of a lung mass, usually more centrally located lung masses.
- Diagnosis of abnormal imaging findings (e.g., FDG-avid lesions discovered on PET scan).
Regional Lymph Node Mapping by EBUS
**Lung – 7th edition**

includes non-small cell and small cell carcinoma & carcinoid

<table>
<thead>
<tr>
<th>T1</th>
<th>≤3 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>≤2 cm</td>
</tr>
<tr>
<td>T1b</td>
<td>&gt;2 – 3 cm</td>
</tr>
</tbody>
</table>

**T2** Main bronchus ≥2 cm from carina, invades visceral pleura, partial atelectasis

<table>
<thead>
<tr>
<th>T2a</th>
<th>&gt;3- 5 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2b</td>
<td>&gt;5 cm -7 cm</td>
</tr>
</tbody>
</table>

**T3** >7 cm; chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus <2 cm from carina, total atelectasis, separate nodule(s) in same lobe (was T4)

<table>
<thead>
<tr>
<th>T4</th>
<th>Mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebra; separate tumour nodule(s) in a different ipsilateral lobe (was M1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Ipsilateral peribronchial, ipsilateral hilar</td>
</tr>
<tr>
<td>N2</td>
<td>Ipsilateral mediastinal, subcarinal</td>
</tr>
<tr>
<td>N3</td>
<td>Contralateral mediastinal or hilar, scalene or supraclavicular</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumour nodule(s) in a contralateral lobe; pleural nodules or malignant pleural or pericardial effusion (was T4)</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

*Changes from 6th edition*
## TNM staging system for lung cancer (seventh edition)

### Primary tumor (T)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor ≤2 cm in diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus*</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤2 cm in diameter</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;2 cm but ≤3 cm in diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;3 cm but ≤5 cm, or tumor with any of the following features:</td>
</tr>
<tr>
<td>T2a</td>
<td>Involves main bronchus, &gt;2 cm distal to carina</td>
</tr>
<tr>
<td>T2b</td>
<td>Involves visceral pleura</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;5 cm or any of the following:</td>
</tr>
<tr>
<td>T3a</td>
<td>Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus &lt;2 cm from carina (without involvement of carina)</td>
</tr>
<tr>
<td>T3b</td>
<td>Associated with atelectasis or obstructive pneumonia of the entire lung</td>
</tr>
</tbody>
</table>

### Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral prebronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supracoaviculat lymph node(s)</td>
</tr>
</tbody>
</table>

### Distant metastasis (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis (in extrathoracic organs)</td>
</tr>
</tbody>
</table>

### Stage groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a-T1b</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T1a,T1b,T2a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T2b</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T1a,T1b,T2a,T2b</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T2</td>
<td>N1,N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T4</td>
<td>N0,N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>T4</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a or M1b</td>
</tr>
</tbody>
</table>

* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

# EBUS and Staging

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Diagnostic Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>76.9%</td>
<td>55.3%</td>
<td>60.8%</td>
</tr>
<tr>
<td>PET</td>
<td>80%</td>
<td>70.1%</td>
<td>72.5%</td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>92.3%</td>
<td>100%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Yasufuku et al. Comparison of Endobronchial Ultrasound, PET, and CT for Lymph Node Staging of Lung Cancer. Chest 2006; 130:710-718
Nodal staging

N0: No regional node metastases

N1: Metastases in ipsilateral intrapulmonary/peribronchial/hilar node(s), including nodal involvement by direct extension
Nodal staging

N2

Metastases in ipsilateral mediastinal and/or subcarinal lymph nodes(s), including "skip" metastases without N1 involvement

Metastases in ipsilateral mediastinal and/or subcarinal lymph node(s) by extension from N1 disease
Nodal staging

Metastases to contralateral hilar/mediastinal/scalene/supraclavicular node(s)

Metastases to ipsilateral scalene/supraclavicular node(s)
EBUS and EUS

<table>
<thead>
<tr>
<th>Lymph Node Station</th>
<th>Endobronchial Approach (n = 160)</th>
<th>Endoesophageal Approach (n = 160)</th>
<th>Combined Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lymphocytes (n)</td>
<td>Diagnosis (n)</td>
<td>Lymphocytes (n)</td>
</tr>
<tr>
<td>2R</td>
<td>19</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>2L</td>
<td>16</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>4R</td>
<td>19</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>4L</td>
<td>17</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>10R</td>
<td>18</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>10L</td>
<td>17</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>142 (88%)</td>
<td>137 (85%)</td>
<td>126 (78%)</td>
</tr>
</tbody>
</table>
Algorithm for Invasive Staging of Lung Ca

- Diagnosis or Suspicion of NSCLC
  - Chest CT and PET Scan
    - Bulky Mediastinal Disease
    - Suspicious N2 Lymph Nodes
    - Central Tumour or N1 nodes
    - Small Peripheral Tumour
      - Biopsy of target nodes by endoscopic technique
        - EBUS, EUS or CUS
          - + ve - ve
          - + ve - ve*
          - + ve - ve
      - Chemoradiation
        - Mediastinoscopy
          - + ve - ve
  - Surgery

*If sonographic staging was done by expert surgeon in high volume centre, may proceed directly to surgery

Hanna W, Yasufuku K. Curr Respir Care Rep 2013
Causes of mediastinal lymphadenopathy

- **Malignant**
  - Lymphoma and other lymphoid neoplasms
  - Leukemia (e.g., acute lymphoblastic leukemia)
  - Metastatic cancer (e.g., lung, esophagus, gastrointestinal, breast)
  - Lymphangitis carcinomatosis
  - Kaposi sarcoma
  - Lymphosarcoma
  - Non-malignant lymphoid disorders (e.g., lymphoid histiocytosis)

- **Non-malignant**
  - **Infectious**
    - Mycobacterial disease – M. tuberculosis, atypical mycobacterium
    - Fungal infection – histoplasmosis, coccidioidomycosis
    - Infectious mononucleosis (Epstein Barr virus)
    - Human immune deficiency virus
    - Pulmonary anthrax (Bacillus anthracis)
    - Bacterial abscess (e.g., actinomycosis)
    - Tularemia (Francisella tularensis)
  - **Inflammatory**
    - Sarcoidosis
    - Rheumatoid arthritis
    - Systemic sclerosis
    - Systemic lupus erythematosus
    - Whipple’s disease
    - Cystic fibrosis
    - Hypersensitivity pneumonitis
    - Pneumoconiosis (coal, beryllium, silica, asbestos)
    - Lymphomatoid granulomatosis
    - Rosai-Dorfman disease
    - Amyloidosis
  - **Reactive**
    - Local infection (e.g., pneumonia, pharyngitis)
    - Pulmonary edema
    - Mediastinal hematoma
Sarcoidosis

- Overall yield of 90-96% in pts with med/hilar adenopathy suspicious for sarcoidosis
- Randomized controlled trial of EBUS-TBNA vs TBNA
  
  - Overall yield 95.8% vs 73.1%
- Comparison with other bronchoscopic modalities
  
  - EBUS-TBNA (90.3%) vs TBBx (61.3%) vs BAL (32.3%)

Nakajima et al. Respir Med. 2010; 103: 1796-1800
Lymphoma

- Data for the role of EBUS-TBNA in lymphoma still limited
- Four retrospective case series studies (n=11, n=21, n=10, n=8)
- Sensitivity 57-91%
- Limitations in the samples that can be obtained by EBUS-TBNA
- Hematologists/oncologists may feel dx based on results of EBUS-TBNA may not be sufficient to fully describe lymphoma type
- Study from Toronto Group*:
  - EBUS-TBNA provides sufficient sample for definitive primary diagnosis and classification of malignant lymphoma
  - Rapid on-site specimen assessment is invaluable for appropriate assignment of sample to ancillary studies

*Ko et al. Diagn Cytopahol. 2011; May 31, Epub ahead of print
Limitations of EBUS

- **Small sample size** – Compared to surgical biopsy, the amount of tissue obtained by a single needle pass on EBUS-TBNA is small and may be insufficient for architectural and molecular assessment unless additional steps are taken.

- **Lymph node access** – EBUS cannot access all stations in the mediastinum. For example, prevascular, periaortic, paraesophageal, or pulmonary ligament lymph node stations (3a, 5, 8, 9) cannot be sampled.

- **Availability** – Not every facility has the equipment and fully trained team of operators to perform EBUS-TBNA.

- **Time consumption** – The time required to obtain samples with EBUS has been estimated in one study to be 22 minutes per three needle passes per site sampled.

- **Complications** – Complications of EBUS-TBNA (eg, pneumothorax, hemorrhage) are uncommon (<1.5 percent).
CP-EBUS TBNA has revolutionised mediastinal staging of lung cancer with sensitivity approaching mediastinoscopy associated with few complications.

Radial probe EBUS improves the yield of TBBx

Molecular analysis of cytological specimens obtained by EBUS-TBNA from metastatic lymph node is possible

It is one of the few diagnostic techniques that has truly revolutionized lung cancer diagnostics.
"Your x-ray showed a broken rib, but we fixed it with Photoshop."