Endobronchial Ultrasound in the Diagnosis & Staging of Lung Cancer

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ESMO-Christie Lung Cancer Course
Manchester 2017
Overview

• What is Endobronchial Ultrasound?
• Why & When Do We Use It?
• Comparison of Non-Invasive/ Minimally Invasive Staging
• Performance Characteristics
• How to Handle Negative or Inadequate Results
• Quality Assurance
• Case Based
DB
85yr old male
Ex-smoker 22 years
(40 pack years)
Retired Roofer
MRC3  WHO PS1
FEV1 1.8L(90%)
FVC 3.15L (114%)
DLCO 49%
Kco 59%

October 2012
Cough – few months
Minor haemoptysis
CXR 29/10/2012: Normal

January 2013
Wt loss 9lbs, anorexia, SOBOE
CXR 18/01/2013:
Increased density inferior right hilum
Considerations

✓ What Next?
1. Choose investigations that give the most information about diagnosis and staging with the least risk to the patient (NICE 2011)
2. All cases to be proved microscopically
3. TNM clinical and pathological classification
4. Attribute group staging
5. Where there is doubt, the patient should receive the benefit of doubt

• Stage determines treatment/ prognosis
• Which Investigation(s), which order?
• Impact of comorbidity/ age
  - safety of investigations
  - potential treatments/ radical vs palliative
  - physiological fitness
• EDD: Estimated Date of Discussion at MDT
• Sample type/ size/ quality

(Thorax 2003;58:711–720)
NICE Guidance 2011

High suspicion of lung cancer

CT scan and spirometry

Factors to consider when choosing tests for diagnosis and staging

Peripheral lesion with low probability of mediastinal malignancy (nodes < 10 mm)

Peripheral or central lesion with intermediate probability of mediastinal malignancy (nodes 10–20 mm)

Peripheral or central lesion with high probability of mediastinal malignancy (nodes > 20 mm)

Advanced and metastatic disease is obvious clinically

Further tests before treatment with curative intent
Endobronchial Ultrasound

- Linear
- Radial (and adjunct to navigational bronchoscopy)
- Tissue Diagnosis
- Staging & Depth of Invasion
Indications for (Linear) EBUS-TBNA

Staging
• Nodes >1cm in size (CT), >5mm US
• Central tumour, normal mediastinum (CT)
• FDG Positive Nodes (PET)

Tissue Diagnosis
Serial Biopsy
Confirmation of Recurrent Disease
Lymphadenopathy in Extra Thoracic Malignancy
Isolated Hilar/ Mediastinal Lymphadenopathy
Parenchymal Disease adjacent to Major Airways
- Linear EBUS

Patient and procedure characteristics

451 patients underwent EBUS-TBNA and mean age was 66.9 ± 11.9 years (range 20-93 years). 253 patients were <70yrs (56.1%) and 198 (43.9%) ≥70yrs. 56 patients were aged over 80. Performance status was significantly lower in patients ≥70yrs (p=0.0001) (Table 1).

Table 1:
Comparison of sex, performance status, sedation dose, duration of procedure and complications stratified by age group.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Age category (years)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>&lt;70</td>
<td>≥70</td>
</tr>
<tr>
<td></td>
<td>253</td>
<td>198</td>
</tr>
<tr>
<td>Sex : M/F (%M)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>130/123 (51.4)</td>
<td>112/86 (56.6)</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>95 (37.5)</td>
<td>16 (8.1)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>115 (45.5)</td>
</tr>
<tr>
<td></td>
<td>93 (47.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>32 (12.6)</td>
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<tr>
<td></td>
<td>77 (38.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td></td>
<td>12 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Lung function mean ±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.9 ± 0.8</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>FEV1 predicted (%)</td>
<td>70.7 ± 27.3</td>
<td>80.8 ± 34.2</td>
</tr>
<tr>
<td>DLCO predicted (%)</td>
<td>66.0 ± 15.8</td>
<td>63.3 ± 18.9</td>
</tr>
<tr>
<td>Nodal Staging^</td>
<td>142 (56.1)</td>
<td>131 (66.2)</td>
</tr>
<tr>
<td>Indication for EBUS-TBNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced Stage</td>
<td>26 (10.3)</td>
<td>25 (12.6)</td>
</tr>
<tr>
<td>Isolated LNs</td>
<td>51 (20.2)</td>
<td>19 (9.6)</td>
</tr>
<tr>
<td>Extra-pulmonary Ca^</td>
<td>14 (5.5)</td>
<td>8 (4.0)</td>
</tr>
<tr>
<td>Intra-pulmonary mass^</td>
<td>20 (7.9)</td>
<td>15 (7.6)</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam [mg]</td>
<td>3.4 ± 1.2</td>
<td>2.6 ± 1.0</td>
</tr>
<tr>
<td>Alfentanil [mcg]</td>
<td>531 ± 214</td>
<td>394 ± 187</td>
</tr>
<tr>
<td>Procedure duration [min]^</td>
<td>39.4 ± 10.0</td>
<td>37.0 ± 11.5</td>
</tr>
<tr>
<td>Complications n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>22 (8.7)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td>Major : all</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Minor : all</td>
<td>22 (8.7)</td>
<td>8 (4.0)</td>
</tr>
<tr>
<td>Classification of minor complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor tolerance/early termination</td>
<td>16 (6.3)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>4 (1.6)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Transient hypotension</td>
<td>2 (0.8)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

^ Nodal Staging = suspected or pathologically confirmed primary lung cancer requiring nodal staging to define management
^ Advanced Stage = suspected advanced stage lung cancer where only pathological confirmation required without formal nodal staging
^ Isolated LNs = isolated mediastinal hilar lymphadenopathy without an intra-pulmonary or extra-pulmonary mass
^ Extra-pulmonary Ca = mediastinal hilar lymphadenopathy in a known extra-pulmonary malignancy, suspected nodal metastases
^ Intra-pulmonary mass = isolated central intra-pulmonary mass accessible with EBUS-TBNA
^ Time taken from start of sedation to end of EBUS procedure (includes standard bronchoscopy examination).
EBUS is not required!
Non-Invasive Staging of the Mediastinum

- Provides clarity of the pulmonary abnormality
- Categories defined by anatomic characteristics (size, location, extent)
- CT is inexpensive, widely available
- In combination with clinical history and examination, can decide which other tests indicated
- Subsequent invasive tests driven by anatomic characteristics
CT Scanning

- Delineates anatomy
- Uses 1 cm short-axis diameter cut-off for malignancy
- IV Contrast
- ACCP Guidelines
  - (peer review, n>50, pathological confirmation of nodes, raw data. 35 studies 1991-2006, 5111 patients)
  - Sensitivity 51% (95%CI: 47-54)
  - Specificity 86% (95%CI: 84-88)
  - Prevalence of nodal metastases 28% (range, 18-56%)
- 40% of enlarged nodes are benign
- 20% of normal-sized nodes contain malignancy


McLeod et al. Radiology 1992
Based on biological activity of neoplastic cells ie function not anatomy
- No standardised quantitative criteria
- Qualitative assessment of lesion vs background
- Low limit of spatial resolution (7-10mm)
- ACCP Guideline
  (peer review, n>20, pathological nodal confirmation, raw data. 44 studies, 1994-2006, 2865 patients)
- Sensitivity 74% (95%CI: 69-79)
- Specificity 85% (95%CI: 82-88)
- Prevalence mediastinal metastases 29% (range, 5-64%)
- Inaccurate in upto 25% of nodes >1cm
- Whole body study
  Unexpected M1 in Stage 1: 7.5%, Stage II: 18%, Stage III: 24%
- PET positive mediastinal nodes ($\text{SUV}_{\text{max}}>2.5$) requires invasive sampling (NICE, ACCP, ESTS) before surgery is ruled out

CT Scanning

Positive Likelihood Ratio 3.4
Negative Likelihood Ratio 0.6

PET Scanning

Positive Likelihood Ratio 4.9
Negative Likelihood Ratio 0.3

There is no node size that can reliably determine tumor stage and operability. Where CT scan criteria for metastatic node are met, the clinician must still prove beyond a reasonable doubt that the node is indeed malignant.

PET is more accurate than CT scanning, but far from perfect.

Utility of Linear EBUS
EBUS-TBNA:
Systematic Review & Meta-analysis

Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Paper</th>
<th>Eligible patients (n)</th>
<th>Patient population</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okamoto (2002)</td>
<td>37</td>
<td>Suspected lung cancer</td>
<td>ND</td>
</tr>
<tr>
<td>Yasufuku (2005)</td>
<td>108</td>
<td>Known/suspected lung cancer</td>
<td>CT mediastinal lymph nodes &gt; 1 cm on short axis</td>
</tr>
<tr>
<td>Rintoul (2005)</td>
<td>20</td>
<td>Known/suspected lung cancer</td>
<td>CT mediastinal lymph nodes &gt; 1 cm on short axis</td>
</tr>
<tr>
<td>Yasufuku (2006)</td>
<td>102</td>
<td>Known/suspected lung cancer</td>
<td>Stage I–IIa</td>
</tr>
<tr>
<td>Plat (2006)</td>
<td>33</td>
<td>Suspected lung cancer</td>
<td>PET positive mediastinal lymph nodes</td>
</tr>
<tr>
<td>Pierard (2006)</td>
<td>51</td>
<td>Suspected lung cancer</td>
<td>PET positive mediastinal lymph nodes</td>
</tr>
<tr>
<td>Herth (2006)</td>
<td>100</td>
<td>Known NSCLC</td>
<td>CT mediastinal lymph nodes &lt; 1 cm on short axis</td>
</tr>
<tr>
<td>Yasufuku (2007)</td>
<td>45</td>
<td>Known/suspected lung cancer</td>
<td>Operable disease</td>
</tr>
<tr>
<td>Skwarski (2007)</td>
<td>300</td>
<td>Known/suspected lung cancer</td>
<td>ND</td>
</tr>
<tr>
<td>Annema (2007)</td>
<td>21</td>
<td>Known NSCLC</td>
<td>ND</td>
</tr>
</tbody>
</table>

Quality Assurance

ACCP Simulation Based Accreditation

ERS – no statement

BTS Quality Standards

Endobronchial ultrasound (EBUS)

- EBUS services should be properly regulated, available in large centres with significant experience and good outcomes in terms of sensitivity and specificity of diagnosis accuracy.
- These centres should be nationally accredited by the British Thoracic Society.
CT-WLB-EBUS correlations for regional lymph nodes by IASLC system

Upper and Lower borders of Stations 2, 4, 7, 10 and 11

© Bronchoscopy International 2010
Septimiu Murgu, MD & Henri Colt, MD
Radial Endobronchial Ultrasound

Radial EBUS (miniprobe - 1.7mm)  Radial EBUS (staging – 2.6mm)
Transbronchial Biopsy?

n=293, randomised study

<table>
<thead>
<tr>
<th>Variables</th>
<th>EBUS-TBB (n = 87)</th>
<th>TBB (n = 119)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>78.7 (68.4–89)</td>
<td>55.4 (44.7–66.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>NPV</td>
<td>66.7 (53.3–80)</td>
<td>49.3 (34.9–63.8)</td>
<td>NS</td>
</tr>
<tr>
<td>PPV</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Accuracy</td>
<td>85 (77.9–92.5)</td>
<td>69 (60.6–77.2)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

- Useful
  - with limited lung function
  - CT biopsy risky
- Add guidesheath
  - <2cm
Radial EBUS - miniprobe

For diagnostic guided sampling of primary tumour or distal nodes

‘Cheap’ Navigational Bronchoscopy

Useful where Pulmonary Function poor/ intolerant of pneumothorax
Radial EBUS - miniprobe

• Lesion amenable to Biopsy in 96/117 (82%)
• 68% malignant
• 50% false negative rate
Navigational Bronchoscopy

**VERSATILE PLANNING & SOPHISTICATED GUIDANCE**
Easy Set-Up, Simple to Use

- Import CT from PACS server, disc or flash drive
- System reconstructs 3D airways / major vessels from CT scan; Calculates centerline for each airway
- User IDs target on CT image and up to 3 pathways are calculated based on target location
- Virtual bronchoscopic simulation of airway view for each pathway shows all generations greater than 3mm
- Target is superimposed on virtual bronchoscopic view
- Distance & airway diameter measurements provided, enabling localization of target

**VIRTUAL BRONCHOSCOPIC NAVIGATION (VBN) SYSTEM**

*Image Guidance for Bronchoscopy*
- Provides real-time path navigation within the lungs for lung biopsy and other Dx/Tx procedures
- Side-by-side navigation pairs real time and virtual images throughout procedure
- Navigation guides user to target with 3mm accuracy
- System operation does not require specialized, disposable instruments

Real-time guidance with LungPoint® Virtual Bronchoscopic Navigation simultaneously shows the live and virtual views and the path to follow—with navigation accuracy of 3mm
Radial EBUS - Staging

66 year old female
Smoker
Multiple Sclerosis
RMZ mass, biopsy apical segment RUL
T3N1M0 Squamous carcinoma 2009
RULobectomy and intolerant adjuvant chemotherapy
CIS at resection margin
Sample Size & Quality

Small sample size is a problem

Cytology vs Histology = Inaccuracy
Led to NSCLC-NOS term 20 yrs ago

Cell block aids accuracy, better still with IHC

Handling & Reporting probably as important as the sample provided

Anecdotally, very few samples from EBUS where cancer can be diagnosed are insufficient for clinical practice
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

Patients with suspected or known NSCLC underwent EBUS-TBNA (n=774)

Squamous Cell Carcinoma (n=145)
- IHC performed (n=52)
  - CK5/6 positive (n=42)
- IHC not possible (n=2)

Large cell carcinoma (n=26)
- IHC performed (n=136)
  - TTF-1 positive (n=65)
- IHC not possible (n=3)

Adenocarcinoma (n=158)
- EGFR mutation testing performed (n=64)
  - EGFR mutation testing not possible (n=4)
- EGFR mutation (n=7)

Mixed (n=4)
- IHC performed (n=53)
  - IHC not possible (n=6)

NSCLC NOS (n=101)
- IHC performed (n=32)
  - Lymphoid Cells only (n=225), inadequate (n=16)

Granulomas (n=32)

Other (n=67)
- 69 NSCLC subsequently diagnosed by mediastinoscopy (n=12), at surgery (n=8), by EUS (n=1) or by clinical follow-up (n=48)

Navani et al. Am J Respir Crit Care Med 2012, 185: 12 (1316–1322)
EBUS samples can successfully be used in the majority (>95%) mutation profiling and gene rearrangement studies
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Ex-smoker 22 years
(40 pack years)
Retired Roofer
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FEV1 1.8L(90%)
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85 year old male
Ex-smoker 22 years

Pre-clinic:
CT scan of thorax (21 January 2013)
1. Attenuation RBI and RML
2. 3.1x2.2cm Subpleural Mass medial RML
3. Associated consolidation and GGO RML
4. Centrilobular Emphysema
5. 11R 1.4cm
   7 1.0cm
   4R Suspicious by number (<1cm)
   R SCF 5mm
6. Bilateral Pleural Plaques
   Probable basal subpleural fibrosis
   (Stable)
   Small HH
   Liver cyst segment 2
   Normal R adrenal
   Thickening of body of L adrenal 11mm

Conclusion:
Subpleural mass with hilar/mediastinal nodes
and bulky L adrenal
(T2aN3Mx).
Emphysema, pleural plaques and asbestosis.
DB
85 year old male
Ex-smoker 22 years

31 January 2013

US Neck
Cluster of prominent nodes identified in the right supraclavicular region (level 4), largest 17x11mm. A smaller adjacent node measures 14x8mm and has loss of fatty hilum with distorted architecture.
No evidence of cervical lymphadenopathy (levels 1-6)

FNAC performed.
DB
85 year old male
Ex-smoker 22 years

FNAC R Neck Level 4 nodes
Numerous small lymphocytes and occasional large lymphocytes, confirming aspiration from a lymph node. No malignant cells are seen.
DB
85 year old male
Ex-smoker 22 years

FDG PET-CT: 6 February 2013
1. Occlusive lesion RML Bronchus 10mm
(SUV max 8.5)
2. Distal collapse/ consolidation RML
(SUVmax upto 12)
3. Several non-enlarged ipsilateral and
contralateral nodes
(SUVmax 2.5-4.4)
Station 7 & RSCF SUVmax 3.5

Staging: T2aN2M0
DB
85 year old male
Ex-smoker 22 years

Bronchoscopy + EBUS-TBNA
7 February 2013

1. Endobronchial tumour distal RBI, probably originating from RML.
2. 4L, 2R, 4R and 7 assessed
   Features of benign disease including central hilar structure, <1cm short axis.

RBI Biopsy: Pieces of bronchial mucosa infiltrated by tumour of variable appearance. There is insitu dysplastic squamous epithelium and an isolated fragment of keratinising malignant squamous epithelium. There are infiltrating components with trabecular, insular and small cell appearances, positive for Cam5.2, 34bE12, p63 and CK5/6 and negative for TTF1, napsin and CD56.

Pure squamous cell carcinoma with poorly differentiated component

CXR 18/01/13
CT Scan 21/01/13
OPC 22/01/13
Neck US 31/01/13
PET-CT 06/02/13
EBUS 07/02/13
DB
85 year old male
Ex-smoker 22 years

Lymph node FNAC: 2R, 4R/L and 7
Lymph node aspirate. No malignant cells identified
Thoracic MDT

Summary: 85 yr old male, 40 pack year smoker, with cough, SOBOE, haemoptysis over 3 months

Comorbidity: Emphysema, Asbestosis, Pleural Plaques
BMI 23  WHO PS: 1  MRC Dyspnoea score 3
PFTs: FEV1 90%  FVC 114%  DLCO/Kco: 49% / 59%

Shuttle walk: Not performed
ECG: Normal

Operative Risk:  Thoracoscore: 8.24%

Cardiac Risk:  Revised Cardiac Index: 1%

Postop Breathlessness  (assuming 6 of 7 RML/RLL segments already occluded)
ppoFEV1: 1.66L
ppoDLCO: 45%

MDT Review
- T2aN0M0 – Stage Ib
- Surgical/ ClinOncolReview

CXR 18/01/13  CT Scan 21/01/13  OPC 22/01/13  Neck US 31/01/13  PET-CT 06/02/13  EBUS 07/02/13  MDT 14/02/13
In Summary.....

- Endobronchial Ultrasound comes in several forms, with differing indications
- EBUS has extended our diagnostic and staging reach, with better patient tolerability
- EBUS-TBNA is the preferred staging modality compared with image based technologies or mediastinoscopy, but...
- Combination of PET findings & US nodal characteristics may be useful in ‘inadequate’ sampling
- Quality Assurance is key/ mandatory; individual professional societies need to consider key performance outcomes
- Tissue profiling & needs of molecular precision medicine is supported by minimally invasive cytological techniques