Les techniques invasives et minimalement invasives dans le staging du cancer bronchopulmonaire

V. Ninane, Hôpital Saint-Pierre, Bruxelles, Belgique
Invasive Mediastinal Staging

- **Purpose:** to exclude
  - Involvement of mediastinal **contralateral side**
  - Extensive involvement of the **ipsilateral side**
  - **Medical management**

- **Before PET introduction**
  - Nearly all cases (low performance of CT scan)
  - Or enlarged lymph nodes on CT scan

- **After PET introduction**
  - Positive hot spots (inflammatory processes)
  - Additional situations (PET + N1 tumors, mediastinal lymph nodes > 16 mm on CT scan, low SUV tumors, central tumors)

Survival prognostic factors for N2 disease

- **Favourable**
  - Complete resection
  - One-level metastasis
  - cN0-N1
  - T1-T2N2
  - Intranodal microscopic metastasis
  - Without subcarinal nodal involvement
  - T < 20 mm

- **Unfavourable**
  - Incomplete resection
  - Multi-level metastasis
  - Radiological N2 disease
  - T3-T4N2
  - Extranodal expansion
  - Number
  - Subcarinal node involvement
  - T > 50 mm

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  - **Medical management**

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  - Or enlarged lymph nodes on CT scan

- **After PET introduction**
  - Positive hot spots in N2/N3 zones (inflammatory processes)
  - Additional situations (PET + N1 tumors, mediastinal lymph nodes > 16 mm on CT scan, low SUV tumors, central tumors)

Surgical mediastinal staging procedures

- **Cervical mediastinoscopy** (+/- extended mediastinoscopy)
- **Anterior mediastinotomy** (Chamberlain)
- **Video-mediastinoscopy**
- **Thoracoscopic staging**
Cervical mediastinoscopy

- Usually under general anesthesia
- Morbidity (2%) and mortality (0.08%)
- Stations 2R, 2L, 4R, 4L, anterior 7, pretracheal 1 and 3
- Videomediastinoscopy
  - Better visualization
  - More extensive sampling (including posterior 7), even complete dissection
  - Improvement in sensitivity and false negative rates
Accuracy of standard cervical mediastinoscopic biopsies in LC

<table>
<thead>
<tr>
<th>Source</th>
<th>Years</th>
<th>No of patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>FP</th>
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### Cervical Mediastinoscopy in LC patients

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Comparison of characteristics of invasive tests

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</table>

Mediastinoscopy is the gold standard!

*Detterbeck et al. Chest 2003;123:167S-175S*
## Guidelines: invasive intrathoracic staging

|-----------------------------------|-----------|-----------|-----------|-----------|
| Mediastinal sampling if enlarged LN (> 1 cm) | ● Extensive infiltration: TTNA or EUS-NA or TBNA  
● CT enlarged discrete LN: mediastinoscopy  
● PET + LN: mediastinoscopy  
● CT normal LN: mediastinoscopy  
● PET – LN: mediastinoscopy | Biopsy if enlarged LN (>1cm) on CT  
(even PET -)  
Or PET + LN | Histo/cytological sampling if enlarged LN (>1cm) on CT  
Or PET + LN (PET - enlarged LN should not be controlled) | ● Extensive infiltration: radiographic assessment  
● CT enlarged discrete LN (PET + or -): invasive or minimally invasive  
● Central tumor or N1: mediastinoscopy (needles 2nd choice)  
● Peripheral stage I tumor and PET + mediastinum: mediastinoscopy (needles 2nd choice) |
Ultrasound puncture bronchoscope

- Convex probe with a frequency of 7.5 MHz
  - Linear transducer that scans parallel to the insertion direction of bronchoscope
  - Contact with/without balloon inflated with saline

- Ultrasound scanner

- Doppler mode

- Bronchoscope: outer diameter of 6.7 mm, direction of view is 30° toward oblique, channel diameter of 2.0 mm

- Dedicated 22-gauge needle
EBUS-EUS

- Outpatient basis; 20-30 min
  - Conscious sedation (iv midazolam)
  - EBUS : anaesthesia of the airways
  - O₂ (2 L/min; nasal prongs)
  - Transcutaneous hemoglobin saturation and cardiac rhythm monitoring
- NB : EBUS under general anaesthesia in some centers
EBUS-EUS complementarity
Technical aspects EUS/EBUS

- Standardized order of examination and sampling
  - **Examination**: from distally to proximally
    - EUS: left adrenal gland and liver lobe
    - All accessible mediastinal lymph nodes
      - EBUS: also N1 stations in a diagnostic+staging strategy
      - Detection of lymph nodes down to a size of 2-3 mm
    - Shape, size, demarcation and echo pattern not accurate enough for distinction benign-malignant
  - **Sampling**: because of the risk of contamination
    - from N3 to N2 stations
    - Also
      - EUS: left adrenal gland
      - EBUS: N1 or the tumor at the end of the procedure, for diagnostic purpose only
Technical aspects : sampling

- Accessible lymph node for puncture: short diameter ≥ 5 mm
- Optimal number of aspirations per lymph node station, if ROSE not used
  - EBUS-TBNA: 3
  - EUS-FNA: 4

Technical aspects

- **Cytopathological specimens**
  - in some cases, tissue cores

- **Results**: positive (tumor cells), negative (lymphocytes or lymphoid tissue), inadequate (blood only, bronchial epithelial cells, cartilage)

- **ROSE** (rapid on-site sample evaluation)
  - Shortening the procedure
EBUS-TBNA: Tolerance and Complications

- **Tolerance under local anaesthesia**
  - Cough is frequent (active smokers, open tracheostomy)

- **Complications**
  - Only mild bleeding
  - Pneumothorax (1/∼500 examinations)
EBUS-TBNA needles

Contamination score and Number of passes

P = 0.035

V Gounant et al. Provisionally accepted
EBUS-TBNA rinses

Rinsing solutions after successive introduction and withdrawal of the stylet

Mineral analysis by energy dispersive X ray

V Gounant et al. Provisionally accepted
# EBUS-TBNA for mediastinal staging

<table>
<thead>
<tr>
<th>Authors</th>
<th>Nb patients</th>
<th>Enrolment</th>
<th>Selection</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Prevalence (%)</th>
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<tr>
<td>Yasufuku 2005</td>
<td>108</td>
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<td>94.1</td>
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<td>Herth 2006</td>
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Sensitivity and 1-specificity of EUS-FNA in the evaluation of lymph node metastasis (N2/N3). Error bars = 95% CI.
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## Guidelines: invasive intrathoracic staging

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CT scan

- Negative (N0)
  - T1N0 Sq CC
    - Surgical treatment
  - All others
    - EBUS/EUS (FNA)
      - -
      - +
    - Medscopy
      - -
      - +

- Positive (N2-N3)
  - Tissue confirmation
    - a
    - b
  - Multimodality treatment

**EBUS/EUS**: minimally invasive procedure (a) but lower negative predictive value than mediastinoscopy (b)

PET/PET-CT

Negative (N0)

Tissue confirmation

Medscopy

EBUS/EUS (FNA)

Surgical treatment

Multimodal treatment

Positive (N2-N3)

a : PET N1 +; central tumors; low tumoral FDG uptake; LN size $\geq$ 1.6 cm

EBUS/EUS : minimally invasive procedure (b) but lower negative predictive value than Medscopy (c)

Staging: Particular situations

- **Extensive infiltration of the mediastinum**
  - Radiographic assessment only (grade 2C ACCP 2007)
  - Invasive procedure sometimes required for diagnosis (blinded TBNA during the first bronchoscopy)

- **PET N1, Central tumor, Tumor with low SUV and with normal PET mediastinum**
  - Invasive staging required
  - EBUS-EUS not the first choice
    - Low prevalence of N2 and low NPV
<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Definition</th>
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<tr>
<td>A</td>
<td>Mediastinal infiltration</td>
<td>Tumor mass within the mediastinum; LN cannot be distinguished or measured</td>
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<tr>
<td>B</td>
<td>Enlarged discrete mediastinal LN</td>
<td>LN ≥ 1 cm (short axis on transversal CT)</td>
</tr>
<tr>
<td>C</td>
<td>Clinical stage II or central stage I</td>
<td>Normal mediastinal LN (&lt;1 cm) but enlarged N1 nodes or central tumor</td>
</tr>
<tr>
<td>D</td>
<td>Peripheral clinical stage I tumor</td>
<td>Normal mediastinal and N1 nodes and peripheral tumor</td>
</tr>
</tbody>
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## EBUS-TBNA for mediastinal staging

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</table>
Impact on therapeutical strategy

- Prevent ~ 60-70 % of scheduled mediastinoscopies
- N upstaging, in comparison with mediastinoscopy alone
  - EUS + mediastinoscopy improves staging and reduces the number of futile thoracotomies
  - Combined EBUS + EUS equal to or superior to mediastinoscopy?

Waiting for the results of the ASTER STUDY: randomized clinical trial comparing complete endoscopic ultrasound staging with surgical staging (current standard of care)
EBUS-EUS complementarity
Three belgian centers 2007-2009

94 SCLC diagnosed using EBUS

- Preceding non-diagnostic standard bronchoscopy
- 37 (39%) peripheral tumors and 20 (21%) cases without primary tumours (cTX)
- TX-4 N0-3 M1 : 35 (37%)
- TX-4 N0-1 M0 : 8 (9%)
- FDG-PET before diagnosis : 58 (62%)

Manuscript in preparation
Only downstaged patients seem to benefit from multimodality treatment including surgery

- Role of linear EBUS/EUS for restaging?
### Surgical restaging

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<td>0.91</td>
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<td>70</td>
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# EUS-FNA in mediastinal restaging (initial N2)

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<th>Nb of patients</th>
<th>EUS-FNA diagnostic value</th>
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<th>NPV</th>
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<td>67%</td>
<td>75%</td>
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<td>86%</td>
<td>86%</td>
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EBUS-TBNA in mediastinal restaging (tissue-proven IIIA-N2)

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<th>Number</th>
<th>Sensitivity</th>
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<th>Negative predictive value</th>
<th>Accuracy</th>
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<td>124</td>
<td>76%</td>
<td>100%</td>
<td>20%</td>
<td>77%</td>
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<td>(89/117)</td>
<td></td>
<td></td>
<td>(7/35)</td>
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CT restaging: 66 PR; 58 SD

Initial and post-induction invasive mediastinal staging

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<th>Post-induction</th>
<th>Limitations</th>
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<td>Mediastinoscopy</td>
<td>Mediastinoscopy</td>
<td>Remediatedoscopy technically difficult;</td>
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<td></td>
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<td>Accuracy decreased</td>
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<td>EBUS/EUS</td>
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<tr>
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<td>EBUS/EUS</td>
<td>incomplete EBUS/EUS</td>
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<tr>
<td>EBUS/EUS</td>
<td>Mediastinoscopy</td>
<td>incomplete staging by EBUS/EUS</td>
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False negative EBUS/EUS incomplete staging by EBUS/EUS
General conclusions: invasive mediastinal staging of NSCLC

- **Mediastinoscopy** is the gold standard
- **Initial staging**
  - EBUS and EUS are safe and accurate and will reduce the need for mediastinoscopy as well as cost
    - Indications: enlarged LN and/or FDG-PET positive LN
  - Combined EBUS and EUS may be a superior approach
- **Restaging**: the best combination (staging-restaging) needs to be assessed