Mediastinal staging: EBUS, EUS, mediastinoscopy or What?

P. De Leyn, MD, PhD

Head Department of Thoracic Surgery
University Hospitals Leuven
Belgium
LEUVEN LUNG CANCER GROUP

Department of Thoracic Surgery
P. De Leyn, W. Coosemans, H. Decaluwé, G. Decker
Ph. Nafteux, D. Van Raemdonck, H. van Veer

Department of Pneumology
J. Vansteenkiste, K. Nackaerts, C. Dooms

Department of Radiotherapy
S. Peeters

Department of Nuclear Medicine
C. Deroose

Department of Radiology
W. Dewever
Mediastinal staging 2011

- Introduction-rationale
- Primary staging
  - PET
  - Mediastinoscopy
  - EBUS/EUS-FNA
- Restaging
- Conclusions
Introduction

• Mediastinal nodal involvement: 1/3 of NSCLC (M0)

• Primary surgery or RT for mediastinal nodal involvement is unrewarding (5-yr: 9%)

• Treatment strategy
  - N0-N1: Surgery (+ adjuvant chemotherapy)
  - N2: Surgical multimodality - chemoradiotherapy?
  - N3: Chemoradiotherapy
PRIMARY STAGING OF THE MEDIASTINUM

• Imaging
  - CT scan
  - PET scan

• Invasive surgical staging (Tissue diagnosis)
  - Cervical mediastinoscopy
  - Anterior mediastinotomy
  - Extended mediastinoscopy
  - VATS

• Invasive non-surgical staging (Tissue diagnosis)
  - EBUS-FNA
  - EUS-FNA
ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer

Paul De Leyn\textsuperscript{a,*}, Didier Lardinois\textsuperscript{b}, Paul E. Van Schil\textsuperscript{c}, Ramon Rami-Porta\textsuperscript{d}, Bernward Passlick\textsuperscript{e}, Marcin Zielinski\textsuperscript{f}, David A. Waller\textsuperscript{g}, Tony Lerut\textsuperscript{a}, Walter Weder\textsuperscript{b}
PET scan

High NPV (> 90%)
Negative PET scan can omit invasive mediastinal staging

1. Sufficient FDG-uptake in the primary tumour
2. Absence of hilar LN disease
3. Absence of central tumour

Unforeseen N2 disease: 5-7%

Low PPV (80%)
Histopathological proof of positive PET findings is required
NPV of FDG-PET

- Overall NPV: 71%
- NPV in case of N1 or centrally located tumor: 17%
- NPV in PET negative N1 and non-centrally located tumor: 96%
Cervical mediastinoscopy

- Low morbidity
- Almost no contraindications
- Outpatient procedure
- Ipsilateral and contralateral nodes
- Full mapping of mediastinal LN’s
- NPV > 90% (10% unforeseen N2 disease)
Cervical mediastinoscopy
Cervical mediastinoscopy
Vide Mediastinoscopy

- Enhanced visualisation
- Improved accuracy
- Better teaching
- International standardisation of technique

De Leyn et al,
Multimedia Manual of Cardiothoracic Surgery
10.1510/mmcts.2004.000166;2004
De Leyn et al,
Minimal Access Cardiothoracic Surgery
Saunders Compnay, 2000
Videomediastinoscopy
Videomediastinoscopy
Level 5 and 6 nodes
Level 5 and 6 nodes

- Anterior mediastinotomy
- Extended mediastinoscopy
- VATS
Moderstinoscopy: risks

Minimal morbidity – very low mortality.

Outpatient procedure

Major complications of mediastinoscopy

- Bleeding
- Oesophageal perforation
- Injury of trachea or bronchi
- Infection
- Recurrent nerve injury

0.1-0.5% (Kirschner, review of > 20,000 mediastinoscopies)
Mediastinoscopy: limitations

- Operation with morbidity and mortality
- Not all mediastinal zones are reachable (5,6,8,9)
  - 42 to 57% of FN
- Limitations when restaging the mediastinum
Invasive non-surgical staging

TBNA ± EBUS

EUS-FNA
EBUS-TBNA
=Endobronchial UltraSound guided-TransBronchial Needle Aspiration
EBUS-TBNA
EUS-FNA = Endoscopic UltraSound-Fine Needle Aspiration
EUS-FNA

station 4L

station 5

station 4L

station 5
EUS-FNA

- Trachea
- Lung
- Aorta
- Esophagus
- Diaphragm
- Right upper lobe tumor
- Lower paratracheal lymph nodes
- Aorto-pulmonary window lymph nodes
- Subcarinal lymph nodes
- Lower para-esophageal lymph nodes
- Pulmonary ligament lymph nodes
- Left adrenal metastasis
- Liver metastasis
- Left kidney
Cervical mediastinoscopy
EBUS-TBNA

EUS-FNA
Invasive mediastinal staging of lung cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Patients No</th>
<th>Sensitivity %</th>
<th>FP %</th>
<th>FN %</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinoscopy</td>
<td>6505</td>
<td>78%</td>
<td>0%</td>
<td>11%</td>
<td>39%</td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>918</td>
<td>90%</td>
<td>0%</td>
<td>20%</td>
<td>68%</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>1003</td>
<td>84%</td>
<td>0.7%</td>
<td>19%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Detterbeck et al., Chest 2007;132:202S-220S
ESTS recommendations on primary staging (PET)

De Leyn et al,
JTO, 2007; 2:357-61

De Leyn et al.
Eur J Cardiothorac Surg
2007;32:1-8

a: in central tumours, tumours with large LNs (= 1.6 cm) and/or PET N1 disease invasive staging remains indicated
b: endoscopic techniques are minimally invasive and can be the first choice
c: due to its higher NPV mediastinoscopy remains indicated

EUS: esophageal ultrasound
EBUS: endobronchial ultrasound
NPV: negative predictive value
Improved accuracy of mediastinoscopy
Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer

Potentially operable NSCLC scheduled for invasive mediastinal staging

Prospectively randomized to EUS-FNA or invasive surgical staging. If EUS-FNA was negative, patients underwent surgical staging

Reduction of 68% (±2/3) of surgical invasive staging procedures
Impact of EBUS/EUS on number of mediastinoscopies for NSCLC

UZ Leuven, unpublished data
Invasive mediastinal staging?
ASTER 1

Annema et al; JAMA 2010;304:2245-32
Invasive mediastinal staging?
ASTER 1

- Prospective, multicenter randomised study
- Ghent, Leiden, Leuven, Papworth
- Inclusion: NSCLC with indication for invasive staging, based on ESTS guidelines
  - PET positive N1-N2 nodes
  - CT N2 nodes ≥ 1 cm
  - Central tumors
- Endpoints: sensitivity to detect N2/N3; rate of futile thoracotomies

Annema et al; JAMA 2010;304:2245-32
# Invasive mediastinal staging? 
## ASTER 1

<table>
<thead>
<tr>
<th></th>
<th>Surgical staging (n=118)</th>
<th>Endoscopic staging. If negative surgical staging (n=123)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop detection N2/N3</td>
<td>35% (n=41)</td>
<td>50% (n=62)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sensitivity for N2-N3 (preoperative)</td>
<td>80%</td>
<td>94%</td>
<td>0.04</td>
</tr>
<tr>
<td>NPV</td>
<td>85%</td>
<td>92%</td>
<td>0.23</td>
</tr>
<tr>
<td>Unnecessary thoracotomy</td>
<td>18% (n=21)</td>
<td>7% (n=9)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Annema et al; JAMA 2010;304:2245-32
Invasive mediastinal staging?
ASTER 1

Conclusion

Sens 79% → 94%
NPV 86% → 93%
Fut. Th. 17% → 7%

Annema et al; JAMA, 2010;304:2245-32
EBUS versus mediastinoscopy for mediastinal staging

- Prospective single center study (July 2006-august 2010)
- N=153
- EBUS followed by mediastinoscopy (same general anesthesia)
- Mediastinoscopy in all patients (irrespective of result EBUS)
- Thoracotomy with SND if no N2/N3
- Prevalence N2 : 35%
<table>
<thead>
<tr>
<th></th>
<th>Number of MLN sampled</th>
<th>Sensitivity</th>
<th>NPV</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS</td>
<td>3</td>
<td>81%</td>
<td>91%</td>
<td>None</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>4</td>
<td>79%</td>
<td>90%</td>
<td>Minor : 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hematoma : 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transient recurrent nerve palsy :1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wound infection : 1</td>
</tr>
<tr>
<td>Combined</td>
<td>NA</td>
<td>NA</td>
<td>96%</td>
<td></td>
</tr>
</tbody>
</table>
EBUS versus mediastinoscopy for mediastinal staging

- Role for adding mediastinoscopy if EBUS is negative?

- BUT: Single center study
  Experienced thoracic surgeons performing EBUS/mediastinoscopy
  Intubated patient (may increase NPV in EBUS)
  Use of different needles

Yasufuku, J Thoracic Cardiovasc Surg; 2011;142:1393-400
4. Restaging

Role of surgical multimodality is still investigational
Role in potentially resectable N2 NSCLC
Important prognostic factors

- Tumour clearance of mediastinal LNs (mediastinal downstaging)
- Pathologic response of the primary tumour

Multidisciplinary baseline assessment and re-assessment is essential!
N2 NSCLC
UZ Leuven experience

N = 92 (2000-2006)

R0 resection: 68%
Operative mortality: 2.3%

Surgical survival rate
64% at 2 years
37% at 5 years

Decaluwé et al., Europ J Cardiothorac Surg, 2009;36:433-9
N2 NSCLC
UZ Leuven experience

N Status downstaged

pN downstaged
n=38

pN not downstaged
n=47

P=0.095

Decaluwé et al., Europ J Cardiothorac Surg, 2009;36:433-9
Multimodality (re-)assessment

CT
PET-CT

EUS-FNA
EBUS-TBNA

Mediastinoscopy

IIIA-N2
Induction tx

Mediastinal downstaging (N)?
T response?

? - radical
- Non-radical

Baseline staging

Restaging
Reassessment with invasive techniques

Re-mediastinoscopy and EBUS-NA have a low accuracy after induction treatment

<table>
<thead>
<tr>
<th></th>
<th>sensitivity</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-mediastinoscopy</td>
<td>29.4%</td>
<td>52%</td>
</tr>
<tr>
<td>EBUS-NA</td>
<td>76%</td>
<td>20%</td>
</tr>
<tr>
<td>(first) Mediastinoscopy after induction</td>
<td>81%</td>
<td>86%</td>
</tr>
</tbody>
</table>
Survival in persistent N2 disease

- Survival is worse compared with nodal downstaging
- BUT, subgroup of patients with persistent N2 after induction chemotherapy with good prognosis

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>5-year in pN2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albain (2009)</td>
<td>88</td>
<td>24% (pN1, pN2)</td>
</tr>
<tr>
<td>Dooms (2008)</td>
<td>16</td>
<td>19%</td>
</tr>
<tr>
<td>Van Schil (2008)</td>
<td>17</td>
<td>30% (negative remed)</td>
</tr>
<tr>
<td>Cerfolio (2008)</td>
<td>14</td>
<td>42%</td>
</tr>
<tr>
<td>Decaluwé (2008)</td>
<td>47</td>
<td>27%</td>
</tr>
<tr>
<td>Meacci (2011)</td>
<td>40</td>
<td>19%</td>
</tr>
</tbody>
</table>

Dooms, J Clin Oncol 2008;26:1128-34
Decaluwé, Eur J Cardiothorac Surg, 2009;433-439
Re-assessment with PET-CT and mediastinoscopy

- Re-assessment N factor (LN downstaging)
  - Quantitative morphology of mediastinal Ln’s in 3 categories of histopathological grading
    - pathological complete response
    - <10% viable cells
    - all others
- Re-assessment T factor (tumour response)
  - Serial PET-CT pre- and post-induction

Prognostic Stratification of Stage IIIA-N2 Non-Small-Cell Lung Cancer After Induction Chemotherapy: A Model Based on the Combination of Morphometric-Pathologic Response in Mediastinal Nodes and Primary Tumor Response on Serial 18-Fluoro-2-Deoxy-Glucose Positron Emission Tomography: A Leuven Lung Cancer Group Study

Christophe Dooms, Eric Verbeke, Sigrid Stroobants, Kris Nackaerts, Paul De Leyn, and Johan Vansteenkiste

**Graph 1:**
- **Cumulative survival (%)**
- **Months**
- **5YS 43 vs 19% - log-rank P=0.11**
- **HR 0.50 (95% CI 0.21-1.18)**

**Graph 2:**
- **Cumulative survival (%)**
- **Months**
- **5YS: 62 vs 6% - log-rank P<0.0001**
- **HR 0.18 (95% CI 0.06-0.38)**
New staging algorithm

PET-CT
EUS-FNA EBUS-TBNA

Baseline staging

IIIA-N2 Induction tx

Restaging

Mediastinal downstaging T response

T response LN response?

1st med

LN response?

radical
Non-radical
Case

Female, 54 y

Adenocarcinoma RUL, cT2N2M0 (11-2007)

CT : enlarged LN 4R (PET +);
EBUS-TBNA : 4R pos
EUS-FNA : 7 neg
Case

Induction chemotherapy (3 courses cis-gem)
Major response on CT and PET (>60%)
Case

02-2008 : Vide Mediastinoscopy : + 4R, + 7 : < 10% viable tumor

Upper bilobectomy + lymph node dissection
ypT2N2M0, complete resection

03-2008 : adjuvant RT (56 Gy)

04-2012 : alive and no evidence of disease (44 mo)
5. Conclusions

- When invasive staging is indicated, endoscopic staging is recommended.
- In case of negative endoscopic findings, surgical staging is indicated.
- This strategy of invasive staging increases sensitivity for N2/N3, it reduces invasive surgical staging to one third and further reduces futile thoracotomies.
- Endoscopic staging and surgical staging are complimentary. Local expertise and analysis is required.
- For restaging after induction therapy for N2 disease, integration of different methods is indicated.
Thank you!

K.U. Leuven, Belgium
University Hospital Gasthuisberg
Leuven Lung Cancer Group (www.LLCG.be)