Mediastinal Staging of NSCLC

EUS-FNA and EBUS-TBNA

Mediastinoscopy

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University Hospitals Leuven
ACCP clinical practice guidelines.

- Patient groups are defined (group A – D) on chest CT.
- Endoscopic **needle techniques** are increasingly acceptable staging methods.


ESTS clinical practice guidelines.

- Incorporated **FDG-PET** to guide invasive staging.
- Endoscopic **needle techniques** are increasingly acceptable staging methods.

Conclusion.

Mediastinoscopy: An Endangered Species?

Valerie W. Rusch, Memorial Sloan-Kettering Cancer Center, New York, NY
Mediastinal staging techniques.

Non-invasive staging:
- Computed Tomography
- FDG-PET scan

Invasive staging:
- Surgical (Mediastinoscopy, VATS, Chamberlain)
- Endoscopic ultrasound controlled:
  - EndoBronchial UltraSound - TBNA
  - Esophageal UltraSound - FNA
Test selection based on LN location.

6th edition of TNM staging

- anatomic borders of each LN station poorly defined!

Mountain and Dresler.
Chest 1997;111:1718.
Test selection based on LN location.

7th edition of TNM staging

→ anatomic borders of each LN station well defined!

Test selection based on LN location.

- LN 4L: Med/EBUS/EUS
- LN 11R: EBUS
- LN 4R: Med/EBUS
- LN 7: Med/EBUS/EUS
Test selection based on LN location.

<table>
<thead>
<tr>
<th></th>
<th>EUS-FNA</th>
<th>EBUS-TBNA</th>
<th>cervical mediastinoscopy</th>
<th>parasternotomy</th>
<th>VATS left</th>
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<td>2R</td>
<td>+/-</td>
<td>+</td>
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<td>3P</td>
<td>+</td>
<td>+</td>
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## Performance characteristics.

<table>
<thead>
<tr>
<th>c I-III</th>
<th>select</th>
<th>N pats</th>
<th>Sens</th>
<th>FP</th>
<th>FN</th>
<th>Prev Ca</th>
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</thead>
<tbody>
<tr>
<td>Mediastino&lt;sup&gt;1&lt;/sup&gt;</td>
<td>all</td>
<td>6505</td>
<td>78</td>
<td>0</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>EUS-FNA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CT +</td>
<td>560</td>
<td>90</td>
<td>0.7</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>EBUS-TBNA&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CT/PET+</td>
<td>1036</td>
<td>94</td>
<td>0</td>
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### Performance characteristics.

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<td>Tradit Med.</td>
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\(^1\) Detterbeck et al. Chest 2007;132:202s.

Mediastinoscopy = gold standard in mediastinal lymph node staging

= performed in unselected patients
### Performance characteristics.

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**Annema et al. JCO 2005;23:8357.**
- EUS-FNA in LNs >10mm
- Single center study: 242 patients
- LN size: mean 24mm (13-77)
- Prevalence of N2/3 Ca: 65%
- Sensitivity of EUS-FNA: 91%
- NPV of EUS-FNA: 74%

**Rintoul et al. J Thorac Oncol 2009;4:44.**
- EBUS-TBNA in PET pos. MLNs
- Multicenter study: 109 patients
- LN size: median 15mm (6-30)
- Prevalence of N2/3 Ca: 80%
- Sensitivity of EBUS-TBNA: 91%
- NPV of EBUS-TBNA: 60%
Case: false negative EBUS-TBNA
Performance characteristics.

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Complementary techniques !

1. EBUS/EUS : for “selected” patients =
   * all PET positive MLNs >5mm
   * all enlarged MLNs on CT (>10-15mm)

2. Mediastinoscopy : for “selected” patients =
   * normal mediastinum but mediastinal staging required (central tumor, enlarged hilar LN, weak FDG in primary tumor)
   * after a negative EBUS/EUS needle aspiration (NPV).
Staging algorithm for operable disease

PET-CT

- PET justified to detect unsuspected extrathoracic disease
- PET has the ability to direct invasive technique (echoendoscopy)

MLNs ≥10mm
- any PET+ MLN

EUS-FNA, EBUS-TBNA or both

Proven N2/3

No N2/3

Multimodal therapy

Surgical staging

if normal mediastinum but
- hilar LN ≥10mm
- central T
- low FDG in T
Comparison (dis)advantages.

1. Mediastinoscopy
   **PRO:**
   - full mediastinal mapping
   - intra vs extracapsular disease
   
   **CON:**
   - operating room, general anaesthesia
   - overnight admission
   - incision → neck scar
   - morbidity 2% (arrhythmia, haemorrhage, recurrent laryngeal nerve injury, bronchial laceration) and mortality 0.08%

2. Echoendoscopic technique
   **PRO:**
   - endoscopy room, local anaesthesia
   - ambulatory
   - no incision
   - morbidity <0.5% (pneumoTx, hemomediast) and no mortality
   
   **CON:**
   - overstaging of patient (N2 instead of N0 or N1)
   - full mapping feasible ?, extracapsular disease not detectable
   - damage to the endoscope
Important issues.

1. Pathology issues for needle aspirations
   • Laboratory technique: cytologic preparation techniques
   • Cytopathologist: reproducibility of diagnosis

2. Mediastinal staging of operable NSCLC
   • False positive/negative samples
   • Staging = disease status of mediastinal lymph nodes
     → requires lymph node ‘mapping’
     → lack of standardization
     → ESTS guidelines: ≥ 3 levels: (2R), 4R, 4L, (2L), 7


3. Implementation issues for E(B)US
   • Expert centers → test centers
1. Pathology issues: Laboratory technique

Liquid-based preparations *versus* Conventional smears

Addition of cell block preparation

= essential for immunohistochemical and molecular analysis
1. Pathology issues: ROSE (smears) needed?

**Controversial**: extra cost for trend (NS) in better accuracy

<table>
<thead>
<tr>
<th></th>
<th>N studies</th>
<th>N pats.</th>
<th>Pooled Sens</th>
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<tbody>
<tr>
<td><strong>EUS-FNA</strong>¹</td>
<td>ROSE</td>
<td>8</td>
<td>459</td>
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<tr>
<td></td>
<td>No ROSE</td>
<td>10</td>
<td>742</td>
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<tr>
<td><strong>EBUS-TBNA</strong>²</td>
<td>ROSE</td>
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<td>254</td>
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<tr>
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<td>No ROSE</td>
<td>8</td>
<td>1045</td>
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<table>
<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NPV</td>
<td>87%</td>
<td>92%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>90%</td>
<td>94%</td>
</tr>
</tbody>
</table>
1. Pathology issues: Reproducibility.

4 observers with at least 15 years of pathology experience

<table>
<thead>
<tr>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Kappa value round 1</th>
<th>95% CI round 1</th>
<th>Kappa value round 2</th>
<th>95% CI round 2</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>0.54</td>
<td>0.42-0.65</td>
<td>0.71</td>
<td>0.60-0.82</td>
</tr>
<tr>
<td>A</td>
<td>C</td>
<td>0.89</td>
<td>0.80-0.97</td>
<td>0.87</td>
<td>0.78-0.96</td>
</tr>
<tr>
<td>A</td>
<td>D</td>
<td>0.72</td>
<td>0.61-0.83</td>
<td>0.87</td>
<td>0.78-0.96</td>
</tr>
<tr>
<td>B</td>
<td>C</td>
<td>0.55</td>
<td>0.44-0.67</td>
<td>0.71</td>
<td>0.60-0.83</td>
</tr>
<tr>
<td>B</td>
<td>D</td>
<td>0.52</td>
<td>0.40-0.65</td>
<td>0.65</td>
<td>0.53-0.80</td>
</tr>
<tr>
<td>C</td>
<td>D</td>
<td>0.69</td>
<td>0.57-0.81</td>
<td>0.78</td>
<td>0.67-0.89</td>
</tr>
</tbody>
</table>

Reproducibility of diagnosis: very good → excellent

2. Mediastinal staging issues in operable LC.

Studies comparing EUS-FNA to mediastinoscopy


* prevalence malignant N2/3 disease 52%
* EUS-FNA understaged in 7%: N2 (EUS) → N3 (Mediast)

*Tournoy et al. AJRCCM 2008;177:531.*

* prim EP: reduction of 68% of surg. mediastinal proc.
* sec EP: mediastinal LN mapping

<table>
<thead>
<tr>
<th>prosp. RCCT</th>
<th>Surgical</th>
<th>EUS-FNA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N pats.</td>
<td>21</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>cN2/3 (preval Ca 66%)</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>N MLNs sampled</td>
<td>4</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
2. Mediastinal staging issues in operable LC.

Randomized controlled trials ongoing/awaited:

1. **ASTER**: Assessment of **Surgical sTaging** vs **Endoscopic ultrasound** in lung cancer: a **Randomized clinical trial**.
   - EUS+EBUS *versus* surgical staging (n=240; expected 2010)
   - Multicenter European study (Ghent - Leiden - Cambridge - Leuven)

2. **Yasufuku**
   - EBUS *versus* mediastinoscopy (n=150; expected 2010)
   - Single center Asian study (Japan)

3. **Mayo Clinic**
   - EBUS+EUS *versus* mediastinoscopy/thoracoscopy (n=300)
   - Multicenter US study (Mayo Rochester/Jacksonville – S Carolina)

A. False positive needle aspiration: potential reasons:

1. Contamination of material
   Needle passes through foci of neoplastic mucosa

2. Misclassification by pathologist
   a. activated/enlarged lymphocytes $\rightarrow$ suspicious ep cells
   $\rightarrow$ Criteria malignancy: $\geq$3 groups malignant cells in background of Ly’s


2. Misclassification by pathologist

b. Bronchial contamination:
   * Reactive/metaplastic/dysplastic bronchial epithelial cells
     \[\sim\] seen in 80% of samples
   * Morphologic changes \(<\) air drying or poor fixation ROSE
     \[\sim\] “atypical” diagnosis or even FP interpretation


3. Sampling error by endoscopist

In all EUS series: specificity and PPV of 100% but only 1 study confirmed all EUS-FNA with CM

→ FP rate of 4% < sampling of central left lower lobe tumor and not LN7.

=> LN adjacent to tumor: be careful


→ can result in overstaging of patient

cT3cN2cM0

↓

pT3pN0cM0

B. False negative needle aspiration: reasons:

1. Not representative sample

2. Anatomic miss: wrong lesion has been sampled

3. Sampling error in the target lesion
   e.g. presence of small metastatic deposit (<2mm)

4. Representative sample but **not conclusive diagnosis**
   e.g. EBUS-TBNA case
3. Implementation of E(B)US-FNA.

A. EUS-FNA: Implementation for lung cancer staging.
   • Expert center (1) vs test centers (5).
   • Prevalence N2/3 Ca: +/- 50%

<table>
<thead>
<tr>
<th>Center</th>
<th>N pts</th>
<th>Sensitivity</th>
<th>NPV</th>
<th>Accuracy</th>
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</thead>
<tbody>
<tr>
<td>Test (5)</td>
<td>263</td>
<td>83</td>
<td>76</td>
<td>89</td>
</tr>
<tr>
<td>Expert (1)</td>
<td>150</td>
<td>81</td>
<td>73</td>
<td>87</td>
</tr>
<tr>
<td>Total</td>
<td>413</td>
<td>82</td>
<td>75</td>
<td>88</td>
</tr>
</tbody>
</table>

Courtesy of Annema.

B. EBUS-TBNA: real-world setting, non-experienced center
   → first 38 pats. (ACCP group B; prevalence 75%): Se 83% and NPV 67%

Mediastinal restaging after IT.

<table>
<thead>
<tr>
<th>Stage IIIA-N2</th>
<th>N stud</th>
<th>Sens</th>
<th>FP</th>
<th>NPV</th>
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<tbody>
<tr>
<td>PET</td>
<td>9</td>
<td>70</td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>Re-CM</td>
<td>6</td>
<td>60</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>3</td>
<td>70</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>1</td>
<td>76</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>1st CM</td>
<td>1</td>
<td>85</td>
<td>0</td>
<td>90</td>
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</table>

→ Multimodal therapy for resectable stage IIIA-N2 NSCLC:

staging = endoscopic needle techniques
restaging = cervical mediastinoscopy
Potentially resectable stage IIIA-N2 NSCLC.

3 cycles induction CT

PET-CT
E(B)US-NA

Mediastinoscopy

CT
Mediastinoscopy

PRE-HOC
Surgery
Conclusion.

1. E(B)US replace surgical staging for operable NSCLC?
   Results of RCCT awaited: EUS+EBUS versus surgical
   EBUS versus mediastinoscopy
   → complete endoscopic MLN mapping?
   → improvement of FN rate?

2. Invasive staging tests are complementary, not competitive.
Case 1

Male, 69yr

H : 12 yrs ago Hodgkin’s disease R/ CRT
A : persistent cough
→ Imaging and staging → bronchoscopy : SqCC LLL

→ EUS-FNA para-oesophageal LN : squamous cell Ca
Case 1

How would you stage this patient in 2010?

- cT2b cN0 cM0
- cT2b cN1 cM0
- cT2b cN2 cM0
- cT2b cN3 cM0
- ....
Case 1: answer.

cT2b cN2 based on EUS-FNA of LN8L

pN1(LN10L) instead of cN2

Case 2

Female, 72yr

→ Imaging and staging:

→ How would you stage this patient in 2010
Case 2

How would you stage this patient in 2010?

- cT1a cN2 cM0
- cT1a cN3 cM0
- cT1b cN2 cM0
- cT1b cN3 cM0
- I don’t like staging any more
Case 2: answer

Case 3

Female, never smoker

→ Imaging and staging:

→ CT-guided TTP and EUS-FNA
Case 3

→ CT-guided TTP right lower lobe: lung adenoCa
→ EUS-FNA para-oesophageal node: Ly’s and adenoCa

→ How would you stage this patient in 2010?
Case 3

→ CT-guided TTP right lower lobe : lung adenoCa
→ EUS-FNA para-oesophageal node

→ How would you stage this patient in 2010?
Case 3

How would you stage this patient in 2010?

- cT2a cN0 cM0
- cT3 cN0 cM0
- cT2a cN1 cM0
- cT3 cN1 cM0
- cT2a cN2 cM0
- cT3 cN2 cM0
- I don’t like staging any more
Case 3: answer
High-tech staging/restaging model
→ potentially resectable stage IIIA-N2 NSCLC

Prospective multicenter study
* UZ Antwerpen (S Stroobants, P Van Schil, P Germonprez)
* UZ Leuven (C Deroose, P De Leyn, C Dooms / J Vansteenkiste)
High-tech staging/restaging model → potentially resectable stage IIIA-N2 NSCLC

1. Baseline staging: echoendoscopy (EBUS+/-EUS)
2. Early response prediction during chemo: PET-CT
3. Restaging after induction chemotherapy:
   PET-CT for primary tumor response combined with mediastinal response on mediastinoscopy
Potentially resectable stage IIIA-N2 NSCLC.

**STAGING**
- SUV\(_{\text{max}}\) 19
- PET-CT n°1
- E(B)US-NA

**3 cycles induction CT**
- PET-CT n°2

**PRE-HOC**
- PET-CT n°3
- Mediastinoscopy

**Surgery**
“Potentieel resecabel” stadium IIIA-N2.

Inclusie criteria:
- primaire tumor potentieel resecabel bij diagnose, zn pneumectomie
- cN2 mediastinale klier(en) potentieel resecabel bij diagnose
  - cN2 bewezen bij diagnose met E(B)US naald aspiratie
  - cN2 grootste korte as <25mm op spiraal CT
- fitte patient (PS 0-1)
- informed consent

Exclusie criteria:
- marginaal / niet resecabele primaire tumor bij diagnose
- cN2 cytologisch bewezen klier met grootste korte as ≥25mm