The current practice of invasive mediastinal staging

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No financial or other relevant disclosures
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The current practice of invasive mediastinal staging

• Cases

• When?

• How?

• Take home messages
Case 1

• Male, 60 years
• 35 packyears
• Retro-obstructive pneumonia RUL with lobar atelectasis (cT2a)
• PET-CT
  – Enlarged (1.5 cm) hilar and mediastinal LN’s (10R, 4R, 4L, 7)
  – FDG uptake right paratracheal LN
• cT2aN2(single station)M0
Case 1. Invasive mediastinal staging?

A. Not indicated: induction therapy

B. EBUS/EUS–FNA, if negative resection with systematic nodal dissection

C. EBUS/EUS–FNA, if negative videomediastinoscopy

D. Videomediastinoscopy
Case 2

- Female, 64 years
- 10 packyears
- Peripheral adenocarcinoma LUL (EBUS miniprobe), 3 cm
- PET-CT
  - Positive on tumor, SUV 7
  - Positive on hilar LN (position 10)
  - Negative on mediastinal LN’s
- cT1bN1M0
Case 2. Invasive mediastinal staging?

A. Not indicated
B. EBUS/EUS-FNA
C. Videomediastinoscopy
D. VATS with exploration of station 5 and 6
Case 3

- 55 year old female
- 20 packyears
- Adenocarcinoma right lower lobe, 6 cm
- PET-CT
  - SUV primary Tumour : 10.4
  - N0, M0
- cT2bN0M0
Case 3. Invasive mediastinal staging?

A. Not indicated
B. EBUS/EUS-FNA
C. Videomediastinoscopy
D. VAMLA
Mediastinal nodal staging NSCLC.

ACCP guidelines, Detterbeck et al. Chest 2013; 143/5 7S-37S
Invasive mediastinal nodal staging NSCLC.

Cervical mediastinoscopy
EndoBronchial UltraSonography-FNA (EBUS-FNA)

Esophageal UltraSonography-FNA (EUS-FNA)
ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer

Paul De Leyn a,*, Didier Lardinois b, Paul E. Van Schil c, Ramon Rami-Porta d, Bernward Passlick e, Marcin Zielinski f, David A. Waller g, Tony Lerut a, Walter Weder b
Always explore and biopsy 4R, 4L, 7If present : 2R, 2L

‘Systematic’ instead of ‘selective’ sampling
Surgical mediastinal staging in daily practice

387 cervical mediastinoscopies in 4 hospitals

Three or more LN levels sampled: 39%

Correlation with total numbers/year performed

Smulders et al. Lung cancer 2005;47:249-52
ESTS guideline 2007

PET or PET-CT

Negative (N0)

Positive (N2-N3)

Tissue confirmation

a

Mediastinoscopy

EBUS/EUS (FNA)

b

Negative

c

Positive

Surgical treatment

Multimodality treatment

a: in central tumours, tumours with large LNs, 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

De Leyn et al.
Eur J Cardiothorac Surg
2007;32:1-8
Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer†

Paul De Leyna,*, Christophe Doomsb, Jaroslaw Kuzdzalc, Didier Lardinoisd, Bernward Passlickc,
Ramon Rami-Porta, Akif Turna, Paul Van Schilt, Frederico Venutaf, David Waller, Walter Wederk and Marcin Zielinski

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Received 3 October 2013; received in revised form 16 December 2013; accepted 20 December 2013
ESTS guideline 2007

PET or PET-CT

Negative (N0)

Positive (N2-N3)

Tissue confirmation

EBUS/EUS (FNA)

Mediastinoscopy

Negative

Positive

Surgical treatment

Multimodality treatment

---

a: in central tumours, tumours with large LNs, 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

De Leyn et al.
Eur J Cardiothorac Surg
2007;32:1-8
NPV of PET and CT for T1-2N0 NSCLC: A Meta-Analysis

- Meta-analysis (ten studies with a total of 1122 patients)

<table>
<thead>
<tr>
<th></th>
<th>NPV (mediastinal metastasis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1* (Tumour ≤ 3 cm)</td>
<td>94%</td>
</tr>
<tr>
<td>T2* (Tumour &gt; 3 cm)</td>
<td>89%</td>
</tr>
</tbody>
</table>

*Sixth edition of TNM version

Adenocarcinoma histology (Risk ratio: 2.72) and high FDG uptake in primary lesion were associated with greater risk of occult nodal metastasis

Wang et al., Clinical lung cancer 2011;13:81-9
False-negative rate after **PET-CT scan** for mediastinal staging in clinical stage I NSCLC

- Prospective study evaluating ESTS guidelines in operable NSCLC (n=153)
- All patients had dedicated thoracic CT and PET-CT (N0)
- Central tumours were excluded
- When clinical stage I, resection with systematic mediastinal dissection

<table>
<thead>
<tr>
<th>Tumour Size</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1* (≤ 3 cm)</td>
<td>92%</td>
</tr>
<tr>
<td>T2* (&gt; 3 cm)</td>
<td>85%</td>
</tr>
</tbody>
</table>

*Sixth edition of TNM version

Centrally located Tumour?
Risk factors for occult mediastinal metastasis in clinical stage I NSCLC

- Retrospective analysis (n=221)
- Prevalence of N2 disease in patients with clinical stage I NSCLC
- PET and CT negative mediastinum

<table>
<thead>
<tr>
<th>% Occult N2 metastases</th>
<th>Centrally located tumors</th>
<th>Peripherally located tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumor sizes</td>
<td>21.6%</td>
<td>2.9%</td>
</tr>
<tr>
<td>0 - 2.0 cm</td>
<td>14.3%</td>
<td>2.9%</td>
</tr>
<tr>
<td>2.1 - 3.0 cm</td>
<td>30%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

Lee et al., Ann Thorac Surg 2007;84:177-81
Problems in the current diagnostic standards of clinical **N1** NSCLC

- Retrospective analysis (n=143)
- Prevalence of N2 disease in patients with clinical N1 (CT enlarged LN < 1 cm) NSCLC
- PET not used
- Prevalence N2-3 : 30%

Hishida et al., Thorax 2008;63:526-531
Endosonography for mediastinal staging of clinical N1 NSCLC

- Prospective multicenter study
- Prevalence of N2 disease in patients with clinical N1 (CT enlarged LNs > 1 cm and/or PET positive N1 LNs) NSCLC
- **Prevalence N2 : 24%**
- Sensitivity of EBUS-EUS was only 38%, increased to 73% by adding mediastinoscopy

Dooms et al., Chest 2015;147:209-215
ESTS mediastinal nodal staging algorithm

CT and PET or PET-CT

Mediastinal LN's negative

(n0 and peripheral tumour (outer third of the lung) and tumour ≤ 3 cm)

ACCP C

Mediastinal LN's negative

tissue confirmation: EBUS/EUS or VAM

ACCP B

Mediastinal LN's positive

tissue confirmation: EBUS/EUS

ACCP D

Mediastinal LN's negative

Multimodality treatment

Mediastinal LN's positive

VAM

Mediastinal LN's negative

Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer
A Randomized Trial

- Prospective, multicenter randomised study
- Ghent, Leiden, Leuven, Papworth
- Inclusion: NSCLC with indication for invasive staging, based on ESTS guidelines 2007
  - PET positive N1-N2 nodes
  - CT N2 nodes \( \geq 1 \text{ cm} \)
  - Central tumors
- Endpoints: sensitivity to detect N2/N3; rate of futile thoracotomies

Annema et al; JAMA 2010;304:2245-32
Inclusion: NSCLC with indication for invasive staging, based on ESTS guidelines 2007

- PET positive N1-N2 nodes
- CT N2 nodes ≥ 1 cm
- Central tumors

Surgical staging (SS)  N=118
Endoscopic staging (ES) (EBUS/EUS-FNA), if negative followed by surgical staging (SS)  N=123

Annema et al; JAMA 2010;304:2245-32
# Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer

A Randomized Trial

<table>
<thead>
<tr>
<th></th>
<th>SS</th>
<th>ES</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>79 (66-88)</td>
<td>85 (74-92)</td>
<td>0.47</td>
</tr>
<tr>
<td>NPV, % (95% CI)</td>
<td>86 (76-92)</td>
<td>85 (75-92)</td>
<td>0.99</td>
</tr>
<tr>
<td>complications</td>
<td>6%</td>
<td>1%</td>
<td>0.03</td>
</tr>
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</table>

Annema et al; JAMA 2010;304:2245-32
## Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer
### A Randomized Trial

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<td>1%</td>
<td>0.03</td>
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<table>
<thead>
<tr>
<th></th>
<th>SS N=118</th>
<th>ES+SS N=123</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N2/N3 detected ; n (%)</strong></td>
<td>41 (35)</td>
<td>62 (50)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Sensitivity, % (95% CI)</strong></td>
<td>79 (66-88)</td>
<td>94 (85-98)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>NPV, % (95% CI)</strong></td>
<td>86 (76-92)</td>
<td>93 (84-97)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Annema et al; JAMA 2010;304:2245-32
A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer

(J Thorac Cardiovasc Surg 2011;142:1393-400)
Kazuhiro Yasufuku, MD, PhD, Andrew Pierre, MD, MSc, Gail Darling, MD, Marc de Perrot, MD, MSc

Endobronchial Ultrasound versus Mediastinoscopy for Mediastinal Nodal Staging of Non–Small-Cell Lung Cancer

(J Thorac Oncol. 2015;10: 331–337)
Sang-Won Um, MD, PhD, Hong Kwan Kim, MD, PhD, Sin-Ho Jung, PhD, Joungho Han, MD, PhD, Kyung Jong Lee, MD, Hye Yun Park, MD, PhD, Yong Soo Choi, MD, PhD, Young Mog Shim, MD, PhD
A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer

<table>
<thead>
<tr>
<th></th>
<th>N=153</th>
<th>EBUS</th>
<th>mediastino</th>
<th>p-value</th>
<th>ES+SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2/N3 prevalence</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>81 (68-90)</td>
<td>79 (62-87)</td>
<td>NS</td>
<td>92 (81-98)</td>
<td></td>
</tr>
<tr>
<td>NPV, % (95% CI)</td>
<td>91 (84-95)</td>
<td>90 (83-95)</td>
<td>NS</td>
<td>96 (90-99)</td>
<td></td>
</tr>
</tbody>
</table>

Number of false-negative LN stations in parentheses. LN, Lymph node; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Kazuhiro Yasufuku, MD, PhD, Andrew Pierre, MD, MSc, (J Thorac Cardiovasc Surg 2011;142:1393-400)
Endobronchial Ultrasound versus Mediastinoscopy for Mediastinal Nodal Staging of Non–Small-Cell Lung Cancer

EBUS was performed under conscious sedation
EBUS-TBNA was superior to mediastinoscopy for mediastinal staging

<table>
<thead>
<tr>
<th></th>
<th>EBUS</th>
<th>Mediastino</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2/N3 prevalence</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>88 (78-94)</td>
<td>81 (70-89)</td>
<td>0.04</td>
</tr>
<tr>
<td>NPV, % (95% CI)</td>
<td>85 (73-93)</td>
<td>79 (67-88)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Stage shift adding EUS: 7% (single level N2 EBUS → multilevel N2 by EUS, N2 by EBUS → N3 by EUS)


### Table 2  Diagnostic values of procedures in the detection of mediastinal metastasis

<table>
<thead>
<tr>
<th></th>
<th>Group A: EBUS-centred (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic accuracy, % (n/n)</td>
<td>93.2 (69/74) (87.5 to 99.0)</td>
</tr>
<tr>
<td>Accuracy of first procedure*, % (n/n)</td>
<td>91.9 (68/74) (85.7 to 98.1)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.754</td>
</tr>
<tr>
<td>Sensitivity, % (n/n)</td>
<td>85.3 (29/34) (68.9 to 95.0)</td>
</tr>
<tr>
<td>Sensitivity of first procedure, % (n/n)</td>
<td>82.4 (28/34) (65.5 to 93.2)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.742</td>
</tr>
<tr>
<td>NPV, % (n/n)</td>
<td>88.9 (40/45) (75.9 to 96.3)</td>
</tr>
<tr>
<td>NPV of first procedure, % (n/n)</td>
<td>87.0 (40/46) (73.7 to 95.1)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.777</td>
</tr>
</tbody>
</table>
Sensitivity to detect N2/N3 disease.
ESTS mediastinal nodal staging algorithm

CT and PET or PET-CT

Mediastinal LN's negative

- cN0 and peripheral tumour (outer third of the lung) and tumour ≤ 3 cm

Mediastinal LN's negative

- cN1 or central tumour
  - Tumour > 3 cm (mainly Adenoca with high FDG uptake)

  a) tissue confirmation: EBUS/EUS or VAM

  b) Mediastinal LN's negative

Mediastinal LN's positive

- tissue confirmation: EBUS/EUS

  c) Mediastinal LN's positive

  d) Mediastinal LN's negative on EBUS/EUS

  e) VAM

  f) Multimodality treatment

  g) Mediastinal LN's positive

  h) Mediastinal LN's negative

Surgery

Conventional mediastinoscopy vs video-assisted mediastinoscopy (VAM)?
VAM

- Enhanced visualisation
- Bimanual dissection
- Better teaching
- Improved accuracy?
- Less complications?

De Leyn et al,
Multimedia Manual of Cardiothoracic Surgery
10.1510/mmcts.2004.000166;2004
Martin-Ucar et al., Europ J cardiothorac Surg 2004;26:393-395
Improved accuracy of mediastinoscopy
### Table 4: Staging values of conventional mediastinoscopy and videomediastinoscopy

<table>
<thead>
<tr>
<th>Author and reference</th>
<th>Type of mediastinoscopy</th>
<th>n</th>
<th>Sensitivity</th>
<th>NPV</th>
<th>Diagnostic accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rami-Porta and Call [37]</td>
<td>CM</td>
<td>148</td>
<td>0.78</td>
<td>0.85</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>VAM</td>
<td>137</td>
<td>0.86</td>
<td>0.90</td>
<td>0.94</td>
</tr>
<tr>
<td>Venissac et al. [38]</td>
<td>VAM</td>
<td>240</td>
<td>0.91</td>
<td>NA</td>
<td>0.98</td>
</tr>
<tr>
<td>Lardinois et al. [39]</td>
<td>VAM after induction</td>
<td>24</td>
<td>0.81</td>
<td>NA</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>VAM without induction</td>
<td>195</td>
<td>0.87</td>
<td>NA</td>
<td>0.95</td>
</tr>
<tr>
<td>Leschber et al. [40]</td>
<td>CM</td>
<td>52</td>
<td>NA</td>
<td>0.81</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>VAM</td>
<td>119</td>
<td>NA</td>
<td>0.83</td>
<td>0.88</td>
</tr>
<tr>
<td>Karfis et al. [41]</td>
<td>VAM</td>
<td>87</td>
<td>0.8</td>
<td>0.59</td>
<td>0.85</td>
</tr>
<tr>
<td>Anraku et al. [42]</td>
<td>CM</td>
<td>505</td>
<td>0.92</td>
<td>0.95</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>VAM</td>
<td>140</td>
<td>0.95</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>Cho et al. [43]</td>
<td>CM</td>
<td>222</td>
<td>0.70</td>
<td>0.95</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>VAM</td>
<td>299</td>
<td>0.75</td>
<td>0.96</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Adapted from Rami-Porta and Call [37].
CM: conventional mediastinoscopy; n: number of patients; NA: not available; NPV: negative predictive value; PPV: positive predictive value; VAM: videoadsisted mediastinoscopy.
Best evidence topic
Overall comparison Videoassisted mediastinoscopy vs. Conventional mediastinoscopy (108 papers 1989-2011)

<table>
<thead>
<tr>
<th></th>
<th>VAM (n=956)</th>
<th>CM (n=5156)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td>0.83 – 2.9%</td>
<td>0 – 5.3%</td>
<td>NS</td>
</tr>
<tr>
<td>No of LN biopsied</td>
<td>6 – 8.5%</td>
<td>5 – 7.13%</td>
<td>NS</td>
</tr>
<tr>
<td>No LN stations sampled</td>
<td>1.9 – 3.6%</td>
<td>2.6 – 2.98%</td>
<td>NS</td>
</tr>
<tr>
<td>Accuracy</td>
<td>87.9 – 98.9%</td>
<td>83.8 – 97.2%</td>
<td>NS</td>
</tr>
<tr>
<td>NPV</td>
<td>83.0 – 98.6%</td>
<td>81.0 – 98.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

ESTS recommendation on invasive staging (2014)

We recommend video-assisted mediastinoscopy over conventional mediastinoscopy

- Enhanced visualisation
- Better teaching
- ‘Systematic’ instead of ‘selective’ sampling
- International standardisation of technique
Role of super mediastinoscopies?

• Video-assisted mediastinoscopic lymphadenectomy (VAMLA)
• Transcervical extended mediastinal lymphadenectomy (TEMLA)

Hürtgen et al., Eur J Cardiothorac Surg 2002;21:348-51
## Results of VAMLA and TEMLA

<table>
<thead>
<tr>
<th>Author</th>
<th>Procedure</th>
<th>N</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Side effect</th>
</tr>
</thead>
</table>
| Hürtgen et al, 2002 | VAMLA     | 46  | 100% | 100%        | Recurrent LN palsy 2.2%  
Scarring with impact on subsequent resection: 25%                            |
| Lescber et al, 2003 | VAMLA     | 23  | 100% | 100%        | Blood loss > 100ml: 12%                                                    |
| Witte et al, 2006  | VAMLA     | 144 | NA   | 100%        | Recurrent LN palsy: 3.4%  
Vascular lesions: 2.1%  
Mediastinitis: 0.7%  
Marked scarring: 19%                                                      |
| Yoo et al, 2011    | VAMLA     | 108 | NA   | NA          | Recurrent LN palsy: 3.4%                                                  |
| Zielinski et al, 2013 | TEMLA    | 256 | 97.4%| 94%         | Mortality: 0,3%  
Temporary recurrent LN palsy: 2.5%  
Permanent recurrent LN palsy : 0,7%  
Pneumothorax: 0.7%  
Pleural effusion: 1,1%                                                    |
VAM

Left recurrent nerve
Role of super mediastinoscopies?
VAMLTA, TEMLA

- Performed in very selected experienced centers
- High accuracy
- Morbidity may be increased (especially 4L)
- Not recommended for routine use
Take-home message

• In peripheral T1a-b tumours preoperative invasive mediastinal staging can be omitted
• In T > 3cm (especially adenocarcinoma with high SUV) invasive staging should be considered
• In central tumours or N1 disease (CT or PET) invasive staging is indicated
• Enlarged or PET positive mediastinal nodes need invasive staging (ACCP B)
• Invasive mediastinal staging (endoscopic or surgical) : ‘systematic’ instead of ‘sampling’
• Sensitivity to detect N2/N3 : EBUS/EUS = VAM
• Start with EBUS/EUS : less invasive, less costs, restaging issue
• Confirmatory VAM after negative EBUS/EUS
  – NPV over 95%
  – Allows nodal dissection in experienced hands
Choice of invasive staging technique is dependent on local availability and expertise

Each center should analyse its own results