Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small cell lung cancer

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• No financial or other relevant disclosures
Revised ESTS guidelines for preoperative mediastinal lymph node staging for NSCLC

1. ESTS guidelines 2007
2. Rationale-methodology
3. Impact of new IASLC Lymph node map
4. Primary mediastinal staging
5. Restaging
6. Conclusions
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
ESTS guideline 2007

PET or PET-CT

Negative (N0)

Positive (N2-N3)

Tissue confirmation

a

EBUS/EUS (FNA)

b

Mediastinoscopy

c

Negative

Negative

Positive

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
Rationale for revision

• The new IASLC lymph node map

• More literature available on endoscopic staging (EBUS/EUS FNA)

• Restaging
Methodology

• Approved by council ESTS Essen meeting (June 2012)
• Members of working group were selected on their experience (publications) on mediastinal staging
• Several meetings (Essen, Zürich, Brussels and Birmingham)
• Members reviewed relevant publications

Consensus
Methodology

• Presentation at yearly meeting (may 2013)
• Paper on website (june-juli 2013) for input by all ESTS members
• Paper submitted for publication (october 2013)
• Published European Journal of Cardiothoracic Surgery februari 2014
Barcelona, november 2012
The IASLC lymph node map

Shift of the oncological midline to the left paratracheal border

Rusch V et al.
J Thorac Oncol 2009; 4: 568-577
N2 for right-lung cancer

N3 for left-lung cancer
Anatomical borders are clearly defined

Lower border of 4R : lower border of azygos vein

Lower border of 4L : upper rim of the left pulmonary artery
10R node

Courtesy Dr Rami Ramon-Porta
ESTS recommendation on invasive staging (2014)

Always explore and biopsy 4R, 4L, 10 L
If present: 2R, 2L
On indication: 10R and 10L
Preoperative LN staging in NSCLC

• Imaging techniques
  CT scan
  PET-CT scan
  DW MRI

• Endoscopic techniques (Tissue diagnosis)
  Conventional TBNA
  Endoscopic (ultrasonography) : EUS-FNA and EBUS-FNA

• Surgical staging techniques (Tissue diagnosis)
  Cervical mediastinoscopy
  Anterior mediastinotomy
  Extended mediastinoscopy
  VATS
  VAMLA
  TEMLA

Vary in accuracy and morbidity
NPV (Working group aims at NPV 90%)
Cervical mediastinoscopy

EndoBronchial UltraSonography-FNA (EBUS-FNA)

Esophageal UltraSonography-FNA (EUS-FNA)
ESTS guideline 2007

PET or PET-CT

- Negative (N0)
  - a: in central tumours, tumours with large LNs and/or PET N1 disease invasive staging remains indicated
  - Negative
    - Surgical treatment
  - Positive (N2-N3)
    - Tissue confirmation
      - b: endoscopic techniques are minimally invasive and can be the first choice
    - Mediastinoscopy
      - e: due to its higher NPV mediastinoscopy remains indicated
      - Negative
      - Positive
        - Multimodality treatment
        - Positive
          - EBUS/EUS (FNA)

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

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

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

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></th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1* (Tumour ≤ 3 cm)</td>
<td>92%</td>
</tr>
<tr>
<td>T2* (Tumour &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 LNs > 1 cm) NSCLC
• PET not used
• Prevalence N2-3 : 30%

Hishida et al., Thorax 2008;63:526-531
In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered.

Depending on local expertise to adhere to minimal requirements for staging.

Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available.

Due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN's, videoassisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy.
ESTS guidelines 2007

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EUS: esophageal ultrasound
EBUS: endobronchial ultrasound
NPV: negative predictive value
Invasive mediastinal staging?
ASTER

- 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 ≥ 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

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
N=118

Endoscopic ultrasonography staging
(EBUS/EUS-FNA), if negative followed by surgical staging
N=123

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

### ASTER

<table>
<thead>
<tr>
<th></th>
<th>Surgical staging (n=118)</th>
<th>Endoscopic staging and if negative surgical staging (n=123)</th>
<th>P-value</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</td>
<td>80%</td>
<td>94%</td>
<td>0.04</td>
</tr>
<tr>
<td>(preoperative)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>85%</td>
<td>92%</td>
<td>0.23</td>
</tr>
</tbody>
</table>

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

Conclusion

Sens 80% → 94%
NPV 85% → 92%
Fut. Th. 17% → 7%

Annema et al; JAMA, 2010;304:2245-32
Published meta-analyses on bronchial and esophageal endosonography with fine needle aspiration for mediastinal nodal staging of lung cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Modality</th>
<th>Pts (N)</th>
<th>Pooled sens % (95% CI)</th>
<th>Pooled Spec % (95%CI)</th>
<th>NLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micames et al</td>
<td>2007</td>
<td>EUS</td>
<td>1201</td>
<td>83 (78-87)</td>
<td>97 (96-98)</td>
<td>-</td>
</tr>
<tr>
<td>Gu et al</td>
<td>2009</td>
<td>EBUS</td>
<td>1298</td>
<td>93 (91-94)</td>
<td>100 (99-100)</td>
<td>-</td>
</tr>
<tr>
<td>Adams et al</td>
<td>2009</td>
<td>EBUS</td>
<td>817</td>
<td>88 (79-94)</td>
<td>100 (92-100)</td>
<td>0.12</td>
</tr>
<tr>
<td>Chandra et al</td>
<td>2012</td>
<td>EBUS</td>
<td>1658*</td>
<td>92 (90-93)</td>
<td>100 (97-100)</td>
<td>0.13</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>2013</td>
<td>EUS + EBUS</td>
<td>823</td>
<td>86 (82-90)</td>
<td>100 (99-100)</td>
<td>0.15</td>
</tr>
</tbody>
</table>
(a) In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered

(b) Depending on local expertise to adhere to minimal requirements for staging

(c) Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available

(d) Due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN's, videoassisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy
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
<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</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.</td>
<td>VAM</td>
<td>240</td>
<td>0.91</td>
<td>NA</td>
<td>0.98</td>
</tr>
<tr>
<td>Lardinois et al.</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.</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.</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.</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.</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: video-assisted 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
- Bimanual dissection (LN dissection)
- International standardisation of technique
Role of super mediastinoscopies?

- Video-assisted mediastinoscopic lymphadenectomy (VAMLA)
- Transcervical extended mediastinal lymphadenectomy (TEMLA)
## 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% |
| Lescher 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% |
Role of super mediastinoscopies?

- Performed in very selected experienced centers
- High accuracy
- Morbidity may be increased
- Not recommended for routine use
Mediastinal restaging after neo-adjuvant therapy for N2 disease

- Mainly patients with mediastinal downstaging or major response will benefit from surgical multimodality treatment
- Accuracy of PET-CT is lower compared with baseline staging
- Invasive mediastinal staging (histology) is indicated
- Remediastinoscopy or EBUS-EUS/FNA
## Invasive restaging techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Author</th>
<th>N</th>
<th>Sensitivity</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remediastino</td>
<td>Call, 2012</td>
<td>83</td>
<td>0.74</td>
<td>0.79</td>
<td>0.87</td>
</tr>
<tr>
<td>Remediastino</td>
<td>Marra, 2008</td>
<td>104</td>
<td>0.61</td>
<td>0.85</td>
<td>0.88</td>
</tr>
<tr>
<td>Remediastino</td>
<td>Stamatis, 2005</td>
<td>165</td>
<td>0.74</td>
<td>0.86</td>
<td>0.92</td>
</tr>
<tr>
<td>Remediastino</td>
<td>De Leyn, 2006</td>
<td>30</td>
<td>0.29</td>
<td>0.52</td>
<td>0.84</td>
</tr>
<tr>
<td>EBUS-FNA</td>
<td>Herth, 2008</td>
<td>124</td>
<td>0.76</td>
<td>0.20</td>
<td>0.77</td>
</tr>
<tr>
<td>EBUS-FNA</td>
<td>Szulowski, 2010</td>
<td>61</td>
<td>0.67</td>
<td>0.78</td>
<td>0.80</td>
</tr>
<tr>
<td>TEMLA</td>
<td>Zielinski, 2013</td>
<td>78</td>
<td>0.97</td>
<td>0.99</td>
<td>NA</td>
</tr>
</tbody>
</table>
Restaging the mediastinum remediated

Re-mediastinoscopy: fibrosis and adhesions

Pretracheal fibrosis
# Postinduction videomediastinoscopy without previous mediastinoscopy

<table>
<thead>
<tr>
<th></th>
<th>No pretreatment (n=195)</th>
<th>Induction chemoTx (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>87%</td>
<td>81%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>95.6%</td>
<td>91%</td>
</tr>
<tr>
<td>Complication rate</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Possible new staging algorithm?

- PET-CT
- EUS-FNA
- EBUS-TBNA

Baseline staging

III A-N2

Induction tx

Restaging

Mediastinal downstaging

T response

LN response?

1st med

radical

Non-radical
Conclusions

• New IASLC map (midline)
• Minimal recommendations: routine biopsy of 4R, 4L, and 7. If present biopsy 2R and 2L. On indication 10R and 10L can be biopsied
• In peripheral T1a-b invasive staging can be omitted
• In central tumours or N1 disease (CT or PET) invasive staging is indicated
• In T > 3cm (especially adenocarcinoma with high SUV) invasive staging should be considered
Conclusions

• Surgical staging remains indicated after negative endoscopical staging in clinically suspicious LNs
• For surgical staging VAM with nodal dissection (especially station 7) is recommended
• Choice of invasive staging technique is dependent on local availability and expertise
• Each center should analyse its own results
Thank you!

University Hospital Leuven, Belgium
Department of Thoracic Surgery
Leuven Lung Cancer Group (www.LLCG.be)