Optimal Staging of the Mediastinum for Lung Cancer

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Why is accurate mediastinal staging important?
- Predicts prognosis
- Helps determine therapy
- Allows accurate comparisons across different therapeutic groups

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Why is accurate mediastinal staging important?
- Adjuvant therapy or induction therapy are now standards of care for Stage II & III
- Non-invasive ablative techniques (SBRT/SABR) are being considered as primary local control options for Stage I
Staging of NSCLC

**Non-invasive:**
- CT
- PET (PET/CT)

**Invasive:**
- Mediastinoscopy
- Chamberlain
- Transbronchial needle biopsy / EBUS
- Transthoracic needle biopsy
- EUS/FNA
- VATS
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Morbidity of Mediastinoscopy

- RLN paresis: 12 (0.55%)
- Hemorrhage: 7 (0.32%)
- Tracheal injury: 2 (0.09%)
- Pneumothorax: 2 (0.09%)
- Death: 1 (0.05%)

Lemaire, Ann Thorac Surg 2006;82:1185

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Mediastinoscopy

- Little et al. 2005
- >11,000 surgically treated patients with NSCLC
- Mediastinoscopy: 27%
- Nodal tissue obtained in 47%!!

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Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer

Kazuhiro Yasufuku, Masako Chiyo, Eitetsu Koh, Yasumitsu Moriya, Akira Iyoda, Yasuo Sekine, Kiyoshi Shibuya, Toshihiko Iizasa, Takehiko Fujisawa, Chiba University

- Cervical mediastinoscopy
  Paratracheal and subcarinal nodes
- VATS and Chamberlain
  hilar and A-P window nodes
- EUS
  periaortic, subcarinal, and periesophageal nodes.
- EBUS
  Paratracheal, hilar, and subcarinal nodes

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EBUS Accessible

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EBUS Inaccessible
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Lymphatic Collectors
3 on each side
Right side:
- R paratracheal (large)
- R tracheoesophageal
- R phrenic
Left side:
- Paraaortic (large)
- L phrenic (large)
- L paratracheal

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Patterns of Nodal Metastases
- Right upper lobe – highest rate of skip metastases (N2 in the absence of N1)
- Right upper lobe – metastasizes to 2R, 4R
- Right middle and lower lobe – subcarinal, then 2R, 4R
- Left upper lobe – metastasize to 2R, 4R
- Left lower lobe – metastasize to 2R, 4R

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Lymph Node Dissection

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Total nodes retrieved</td>
<td>15.7</td>
<td>16.2</td>
<td>0.56</td>
</tr>
<tr>
<td>N2 stations sampled</td>
<td>3.1</td>
<td>3.0</td>
<td>0.68</td>
</tr>
<tr>
<td>Involved N2 levels</td>
<td>1 station</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>66%</td>
<td>70%</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>2 station</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>&gt;2 station</td>
<td>12%</td>
<td>7%</td>
</tr>
</tbody>
</table>
**Lymph Node Dissection**

<table>
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<td>1.5</td>
<td>1.4</td>
<td>0.14</td>
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<tr>
<td>1 station</td>
<td>66%</td>
<td>70%</td>
<td>0.31</td>
</tr>
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<td>12%</td>
<td>7%</td>
<td></td>
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</tbody>
</table>

**Survival by Lymph Node Stations Involved**

Cumulative Survival Probability

- Median Survival: 25.3 months
- 1 Station: 15.5 months
- 2 Stations: 16.8 months
- >2 Stations: P<0.001

Time (months)
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**Nodal Metastases Indicating Unresectability**

- **N3** - Contralateral paratracheal nodal metastases
- **N2** - Ipsilateral paratracheal nodal metastases for left lung cancers

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**ASCO Discussion: Dr. Frank Detterbeck**

<table>
<thead>
<tr>
<th>Test Negative</th>
<th>Test Positive</th>
<th>Disease Absent</th>
<th>Disease Present</th>
<th>Formula</th>
<th>Parameters Based on Test Results</th>
<th>False Negative Rate</th>
<th>False Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N_TN</strong> (True Negative)</td>
<td><strong>N_TP</strong> (True Positive)</td>
<td><strong>N_TN</strong></td>
<td><strong>N_TP</strong></td>
<td><strong>N_FP</strong></td>
<td><strong>N_FN</strong></td>
<td><strong>N_TN + N_FP</strong></td>
<td><strong>N_TN + N_TP</strong></td>
</tr>
<tr>
<td><strong>N_FN</strong> (False Negative)</td>
<td><strong>N_FP</strong> (False Positive)</td>
<td><strong>N_FN</strong></td>
<td><strong>N_FP</strong></td>
<td><strong>N_TN</strong></td>
<td><strong>N_TP</strong></td>
<td><strong>N_FN + N_TP</strong></td>
<td><strong>N_FN + N_TN</strong></td>
</tr>
</tbody>
</table>

**Specificity** | **Sensitivity**

Parameters Based On Disease Status

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**Parameters to Assess the Value of a Test**

- You can NOT use Sensitivity or Specificity to interpret a test result in an individual patient

- For example: reliability of PET to identify distant metastases (Lancet ATS 1999;37:790-7; 97 pts with lung cancer and PET; true negative on clinical exam 30% prevalence of mets, gold standard: bx or recurrence/lack thereof in 12 mo.)

  - Sensitivity 97%
  - Specificity 53%
  - False Neg. 16%
  - False Pos. 12%

**ASCO Discussion: Dr. Frank Detterbeck**
Mediastinoscopy

- Toloza 2003 – meta-analysis of 5,687 pts
- Lemaire 2006 – single institution, 1,019 consecutive pts
- 300 pts N2/N3
- 56 false negatives (5.5%)
- 32 were at inaccessible stations (5,6,8,9)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toloza 2003</td>
<td>81</td>
<td>100</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>Lemaire 2006</td>
<td>86</td>
<td>100</td>
<td>100</td>
<td>94.5</td>
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</tbody>
</table>

Lemaire, Ann Thorac Surg 2006;82:1185
Toloza, CHEST 2003;123:157S

CT Scan Staging

- CT scan meta-analysis
- Toloza, 2003
- Meta-analysis of 4,793 patients

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>60%</td>
<td>51%</td>
<td>53%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Toloza, CHEST 2003;123:137S

Lymph node status comparing PET with final stage

By PET Final stage (No.patients)

<table>
<thead>
<tr>
<th></th>
<th>N0/N1</th>
<th>N2/N3</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>N0/N1</td>
<td>191</td>
<td>29</td>
<td>220</td>
</tr>
<tr>
<td>N2/N3</td>
<td>36</td>
<td>46</td>
<td>82</td>
</tr>
<tr>
<td>Total</td>
<td>227</td>
<td>75</td>
<td>302</td>
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</tbody>
</table>

Sensitivity 61%; specificity 84%; PPV 56%; NPV 87%.

ACOSOG Z0050 Reed et al., J Thorac Cardiovasc Surg 2003;126:1943-51
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**PET and CT (non-integrated) Compared to Mediastinoscopy/Thoracotomy**

- Negative predictive value: 0.98
- Positive predictive value: 0.51


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**Integrated PET/CT Compared to Surgical Staging**

<table>
<thead>
<tr>
<th>Assessment of Lymph Node Involvement</th>
<th>PET</th>
<th>PET/CT</th>
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<tbody>
<tr>
<td>Variables</td>
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<td></td>
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<tr>
<td>Sensitivity</td>
<td>50 (5/10; 19 to 81)</td>
<td>60 (6/10; 26 to 88)</td>
</tr>
<tr>
<td>Specificity</td>
<td>77 (26/36; 56 to 91)</td>
<td>85% (22/26; 65 to 96)</td>
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<tr>
<td>PPV</td>
<td>45 (5/11; 17 to 77)</td>
<td>60 (6/10; 26 to 88)</td>
</tr>
<tr>
<td>NPV</td>
<td>80 (20/25; 59 to 93)</td>
<td>85 (20/26; 65 to 96)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>69 (25/36; 52 to 84)</td>
<td>78 (28/36; 61 to 90)</td>
</tr>
</tbody>
</table>

Halpern, 2005;128;2289-2297 Chest

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**PET Staging**

- PET scan meta-analyses
  - Birim, 2005 - 833 pts from 17 studies
  - Toloza, 2003 - 1,111 pts from 19 studies

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toloza 2003</td>
<td>85%</td>
<td>88%</td>
<td>78%</td>
<td>93%</td>
</tr>
<tr>
<td>Birim 2005</td>
<td>93%</td>
<td>92%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consensus Statements

American College of Chest Physicians:
In patients with abnormal FDG-PET scan findings, further evaluation of the mediastinum with staging of the abnormal area should be performed prior to surgical resection of the primary tumor.

European Society of Thoracic Surgeons:
PET positive mediastinal findings should be histologically or cytologically confirmed.

PET Negative and cStage I

Incidence of mediastinal metastases

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>N2 med</th>
<th>N2 surg</th>
<th>Total</th>
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<tbody>
<tr>
<td>Cerfolio</td>
<td>136</td>
<td>9 (7%)</td>
<td>6 (4%)</td>
<td>11%</td>
</tr>
<tr>
<td>Meyers</td>
<td>178</td>
<td>5 (3%)</td>
<td>8 (5%)</td>
<td>7%</td>
</tr>
<tr>
<td>Lee</td>
<td>76</td>
<td>11 (14%)</td>
<td>5 (6%)</td>
<td>21%</td>
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PET Negative and cStage I

Incidence of mediastinal metastases

Tumor size (cm)

- Peripheral
- Central

Lee, Ann Thorac Surg 2007;84:177
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**Routine PET and selective mediastinoscopy: 2004**

Positive hilar or mediastinal uptake

- PET
- Negative
- Mediastinoscopy
- Mediastinal nodes ≥1 cm in CT

Without these criteria

- Thoracotomy
- Mediastinoscopy

*Verhagen Lung Cancer 2004

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**Comparison of RM versus PET and SM**

Thoracotomy with pN2 disease

- Routine mediastinoscopy
  - 40/655: 6.1%
- Routine PET and selective mediastinoscopy
  - 7/90: 7.8%

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**Comparison of RM versus routine PET and RM**

<table>
<thead>
<tr>
<th></th>
<th>CT*</th>
<th>PET*</th>
<th>RM</th>
<th>PET +SM</th>
<th>PET</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>0.43-0.81</td>
<td>0.67-1</td>
<td>0.85</td>
<td>0.75</td>
<td>0.85</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.26-0.61</td>
<td>0.81-1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.39-0.85</td>
<td>0.81-1</td>
<td>0.82</td>
<td>0.88</td>
<td>1</td>
</tr>
<tr>
<td>PPV</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NPV</td>
<td>0.9</td>
<td>0.89</td>
<td>0.87</td>
<td>0.87</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*Fritscher-Ravens Chest 2003

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Routine PET and SM: Results

- 33/90: Negative PET and non pN2 after direct thoracotomy

Mediastinoscopy avoided: 36.6%

M. Serra et al, ASCO Proceedings 2006, 24: 371s

ASCO Discussion: Dr. Frank Detterbeck

Discrete Nodal Enlargement (cN2,3)

- Reliability of CT:
  FP rate 40% (~ 5000 pts, 10 studies)

- Reliability of PET:
  FN rate estimated ~25% (Dietlein 00, Gould 03)
  FN rate 28% together with cN1 (Serra 06)

- Invasive biopsy is necessary
  EUS-NA Sens 85%, FN 20% (if neg then Med)
  Mediastinoscopy Sens 90%, FN 10%

ASCO Discussion: Dr. Frank Detterbeck
Central Stage I or II NSCLC

Central or cN1 (negative Mediastinum)

- Reliability of CT:
  FN rate ~25% (790 pts, 9 studies)

- Reliability of PET:
  FN rate 24% (Poco-Rodriguez 02, 30 pts)
  FN rate 85% (Verhagen 04, 12 pts)
  FN rate 28% together with cN2 (Serra 06)

Invasive biopsy is necessary
FN rate for Med ~ 10%; FN rate for EUS-NA ~30%

Cerfolio, J Thorac Cardiovasc Surg 2006;131:1229-35
A prospective controlled trial of EBUS compared to mediastinoscopy for mediastinal lymph node staging of lung cancer

- EBUS-TBNA followed by mediastinoscopy
- TBNA for all nodes >6mm short axis with dedicated needles for each node station
- Rapid on-site cytology
- Surgeon blinded to EBUS-TBNA result
- The clinical staging prior to EBUS-TBNA and MS were 47 stage IA, 26 stage IB, 3 stage IA, 10 stage II, 58 stage IIIA, 5 stage IIIB and 3 stage IV disease
- EBUS-TBNA and MS sampled an average of 3.0 and 3.8 lymph node stations/patient
- No complications from EBUS-TBNA. Complications from MS were seen in 4 patients (2.6%), including 1 RN injury

Yasufuku et al., AATS, 2011

<table>
<thead>
<tr>
<th></th>
<th>EUS-TBNA (%)</th>
<th>Mediastinoscopy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>84.3</td>
<td>86.3</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>NPV</td>
<td>92.7</td>
<td>93.6</td>
</tr>
<tr>
<td>Accuracy</td>
<td>94.8</td>
<td>95.4</td>
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Yasufuku et al., AATS, 2011
Conclusions

- The negative predictive value of PET/CT is high and additional mediastinal staging is unnecessary for cT1N0
- Equivocal negative PET/CT findings need to be investigated with invasive staging
- Positive PET/CT findings need to be confirmed with invasive staging
- EBUS-TBNA and mediastinoscopy have equivalent accuracy