Optimal Staging of the Mediastinum for Lung Cancer

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Houston, Texas
Why is accurate mediastinal staging important?

- Predicts prognosis
- Helps determine therapy
- Allows accurate comparisons across different therapeutic groups
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
Mediastinoscopy
Surgical Staging
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
Mediastinoscopy

Little et al, 2005

>11,000 surgically treated patients with NSCLC

Mediastinoscopy

27%

Nodal tissue obtained in 47%!!
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*
Lung Cancer (2005) 50, 347—354
- Cervical mediastinoscopy
  Paratracheal and subcarinal nodes

- VATS and Chamberlain
  hilar and A-P window nodes

- EUS
  periaortie, subcarinal, and
  periesophageal nodes.

- EBUS
  Paratracheal, hilar, and subcarinal nodes
EBUS Accessible
EBUS Inaccessible
Lymphatic Collectors
3 on each side

Right side:
- R paratracheal (large)
- R tracheoesophageal
- R phrenic

Left side:
- Paraaortic (large)
- L phrenic (large)
- L paratracheal
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 – AP window and periaortie (5, 6), then subcarinal and paratracheal (2L, 4L)
- Left lower lobe – metastasize to 2R, 4R
## Lymph Node Dissection

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Total nodes retrieved</strong></td>
<td>15.7</td>
<td>16.2</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>N2 stations sampled</strong></td>
<td>3.1</td>
<td>3.0</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Involved N2 levels:</strong></td>
<td>1.5</td>
<td>1.4</td>
<td>0.14</td>
</tr>
<tr>
<td>1 station</td>
<td>66%</td>
<td>70%</td>
<td>0.31</td>
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<tr>
<td>2 station</td>
<td>22%</td>
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Survival by Lymph Node Stations Involved

Cumulative Survival Probability

Time (months)

Median Survival

1 Station

2 Stations

>2 Stations

P<0.001

15.5

16.8

25.3

0.0

0.2

0.4

0.6

0.8

1.0

0 10 20 30 40 50 60
Nodal Metastases Indicating Unresectability

- N3 - Contralateral paratracheal nodal metastases
- N2 - Ipsilateral paratracheal nodal metastases for left lung cancers
<table>
<thead>
<tr>
<th>Test</th>
<th>Disease Absent</th>
<th>Disease Present</th>
<th>Formula</th>
<th>Parameters Based on Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>$N_{TN}$ (True Negative)</td>
<td>$N_{FN}$ (False Negative)</td>
<td>$\frac{N_{FN}}{N_{TN} + N_{FN}}$</td>
<td>False Negative Rate</td>
</tr>
<tr>
<td>Positive</td>
<td>$N_{FP}$ (False Positive)</td>
<td>$N_{TP}$ (True Positive)</td>
<td>$\frac{N_{FP}}{N_{FP} + N_{TP}}$</td>
<td>False Positive Rate</td>
</tr>
</tbody>
</table>

**Specificity**  
Parameters Based On Disease Status  

**Sensitivity**  

ASCO Discussion: Dr. Frank Detterbeck
**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 (Saunders ATS 1999;67:790-7; 97 pts with lung cancer that had PET, no data on clinical eval, 29% 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>93</td>
</tr>
<tr>
<td>Lemaire 2006</td>
<td>86</td>
<td>100</td>
<td>100</td>
<td>94.5</td>
</tr>
</tbody>
</table>

CT Scan Staging

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

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<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>
</tr>
</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><strong>Total</strong></td>
<td><strong>227</strong></td>
<td><strong>75</strong></td>
<td><strong>302</strong></td>
</tr>
</tbody>
</table>

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

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

Negative predictive value 0.98

Positive predictive value 0.51
# Integrated PET/CT Compared to Surgical Staging

## Assessment of Lymph Node Involvement

<table>
<thead>
<tr>
<th>Variables</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<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 (20/26; 56 to 91)</td>
<td>85% (22/26; 65 to 96)</td>
</tr>
<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 (22/26; 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
## PET Staging

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

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</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>83%</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 sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor.’

2003

European Society of Thoracic Surgeons:

‘PET positive mediastinal findings should be histologically or cytologically confirmed.’

2007
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>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>
PET Negative and cStage I

N2 metastases %

Tumor size (cm)

- 0-2.0
- 2.1-3.0
- >3.0

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

**PET**

- Positive hilar or mediastinal uptake: Mediastinoscopy
- Negative
  - Tumour contacting mediastinum
  - Mediastinal nodes ≥1 cm in CT
  - Without these criteria: Thoracotomy

*Verhagen Lung Cancer 2004*

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

M. Serra et al, ASCO Proceedings 2006, 24: 371s
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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.43-0.81</td>
<td>0.67-1</td>
<td>0.85</td>
<td>0.75</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>0.56-0.94</td>
<td>0.81-1</td>
<td>1.0</td>
<td>1.0</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>0.59-0.85</td>
<td>0.8-1</td>
<td>0.94</td>
<td>0.92</td>
<td>0.82</td>
</tr>
<tr>
<td>PPV</td>
<td></td>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td>0.74</td>
</tr>
<tr>
<td>NPV</td>
<td></td>
<td></td>
<td>0.9</td>
<td>0.89</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*Fritscher-Ravens Chest 2003

M. Serra et al, ASCO Proceedings 2006, 24: 371s
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
Discrete Lymph Node Enlargement

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

ASCO Discussion: Dr. Frank Detterbeck
Central or cN1 (negative Mediastinum)

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

- Reliability of PET:
  FN rate 24% (Poco-Rodriguez 05, 21 pts)
  FN rate 83% (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%

ASCO Discussion: Dr. Frank Detterbeck
Suspected N2 disease on imaging (CT and/or PET/CT)

Pathological confirmation of N2 disease -
- Mediastinoscopy (all patients)
  - if LN #5, 7, 8, 9 suspected - EUS-FNA (or Left VATS)

N2 Negative → Evaluate for resection
N2 Positive → Chemoradiotherapy

4-8 weeks later

RESTAGING
CT, PET/CT
EUS-FNA

N2 Negative → Evaluate for resection
N2 positive → (Residual disease) Refer to oncologist

128 patients with N2 disease

4 - died during neoadjuvant therapy
3 - lost to follow-up
15 - clinical evidence of progression
13 - too weak or ill, did not return for restaging
93 clinically restaged and had pathologic confirmation of their disease

28 restaged by PET/CT as N2 POSITIVE

21 N2 positive on path TRUE POSITIVE
7 N2 negative on path FALSE POSITIVE

65 restaged by PET/CT as N2 NEGATIVE

13 N2 positive on path FALSE
52 N2 negative on path TRUE NEGATIVE

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 >5mm short axis with dedicated needle 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 IIA, 10 stage IIB, 59 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
A prospective controlled trial of EBUS compared to mediastinoscopy for mediastinal lymph node staging of lung cancer

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<th>Mediastinoscopy (%)</th>
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<tr>
<td>Sensitivity</td>
<td>84.3</td>
<td>86.3</td>
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<td>Accuracy</td>
<td>94.8</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.