Overview

• Review:
  – epidemiology
  – staging system

• Conventional staging of the mediastinum
  – PET-CT
  – TBNA
  – Medisatinoscopy

• Image guidance
  – EBUS-TBNA
  – EUS-FNA
NSCLC: Survival by Clinical Stage

Heffner et al, Chest 1997; 111: 170
<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Surgery</th>
<th>Chemo +/- XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>TIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage Ia</td>
<td>T1, N0, M0</td>
<td>Surgery possible</td>
<td></td>
</tr>
<tr>
<td>Stage Ib</td>
<td>T2, N0, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1, N1, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2, N1, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3, N1, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1-3, N2, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3, N1, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4, any N, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>any T, N3, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>any T, any N, M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heffner et al, Chest 1997; 111: 170
• **N1**: peribronchial / intrapulmonary / ipsilateral hilar
  – double digit

• **N2**: ipsilateral mediastinal / subcarinal
  – single digit

• **N3**: contralateral hilar / mediastinal, scalene / supraclavicular
  – single digit (contralateral)
Non-Invasive Staging: Radiology

• **Standard CT:** using > 10 mm as abnormal
  – sensitivity: ~ 60%
  – specificity: ~ 80%

• **Integrated PET-CT:**
  – improved staging and anatomic accuracy
  – sensitivity: ~ 84 – 90%
  – specificity: ~ 85 – 94%

• Perhaps even less accurate for:
  – early stage disease
  – re-staging

Dwamena et al, Radiology 1999; 213: 530
Antoch et al, Radiology 2003; 329:526
Chest 2003; 123: 137s
Staging cont.

- Clinical staging can markedly differ from pathologic staging
  - 24% clinically overstaged
  - 20% clinically understaged
  - 190 cN2 patients: 38% pN0 / pN1, 6% pN3
  - 199 cN2 negative patients: 28% with pN2
    - posterior 7
- ATS/ERS/ESTS: obtain pathologic evaluation in all patients thought to be a surgical candidate before thoracotomy

Bülzebruck et al, Cancer 1992; 70: 1102
Am J Respir Crit Care Med 1997; 156: 320
• “If you don’t look at the lymph nodes, everyone has stage 1 disease”
## Invasive Staging

### Table 4—Comparison of Characteristics of Invasive Tests

<table>
<thead>
<tr>
<th>Tests</th>
<th>Sensitivity, %</th>
<th>Specificity, %*</th>
<th>FP Rate, %*</th>
<th>FN Rate, %</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinoscopy</td>
<td>81</td>
<td>100</td>
<td>0</td>
<td>9</td>
<td>Clinical N0–2</td>
</tr>
<tr>
<td>Chamberlain procedure†</td>
<td>87</td>
<td>100</td>
<td>0</td>
<td>15</td>
<td>Clinical N0–2</td>
</tr>
<tr>
<td>TTNA</td>
<td>91</td>
<td>100</td>
<td>0</td>
<td>22</td>
<td>Clinical N2</td>
</tr>
<tr>
<td>EUS-NA</td>
<td>88</td>
<td>91</td>
<td>2</td>
<td>23</td>
<td>Clinical N2</td>
</tr>
<tr>
<td>TBNA</td>
<td>76</td>
<td>96</td>
<td>0</td>
<td>29</td>
<td>Clinical N2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tests</th>
<th>Sens.</th>
<th>Spec.</th>
<th>FP%</th>
<th>FN%</th>
<th>Prevalence%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med</td>
<td>78</td>
<td>100</td>
<td>0</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>90</td>
<td>100</td>
<td>0</td>
<td>20</td>
<td>68</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>84</td>
<td>99.5</td>
<td>0.7</td>
<td>19</td>
<td>61</td>
</tr>
</tbody>
</table>

Detterbeck et al, Chest 2003; 123: 167s
Detterbeck et al, Chest 2007; 132: 202
Mediastinoscopy

• Considered “gold standard”
  – sensitivity ~ 78 – 90%, specificity 100%
  – FN rate ~ 9-11%

• The downsides:
  – unable to reach all nodal stations
    • 5, 6, posterior 7, 8, 9
  – invasive (mortality 0.2%, morbidity up to 2.5%)
  – more expensive
  – non-operable candidates undergoing surgical procedure

Mediastinoscopy

• Mediastinum is + is up to 10% of patients with clinical stage 1 disease

• Only performed in 27% of patients undergoing lung CA surgery
  – nodal tissue obtained in 47%

Benefits of TBNA

- Most stations are accessible
- Couple staging with diagnostic bronchoscopy
- Safe
- Less invasive
- Less expensive
- Precludes surgery in up to 29%

Am J Respir Crit Care Med 2000; 161: 601
Problems with TBNA

• Underused
  – 12 % of pulmonologists routinely use TBNA in evaluation of malignant disease
    • training / fear / support
• Operator dependent
  – sensitivity ranges from 37 – 89%
• Failure to place the needle directly into the lesion
  – depends on LN size / station and experience
  – benefit of ROSE

Chest 1991; 100: 1668
Am Rev Respir Dis 1993; 147: 1251
Chest 1998; 114: 4
Endobronchial Ultrasound: EBUS
Radial Probe EBUS

- water filled balloon surrounds the crystal
  - ensures “coupling”
- 2.6mm probe
  - through 2.8 channel
- 1.7mm probe
  - through 2.0 channel
EBUS Anatomy cont.
EBUS TBNA

• Randomized 80 patients EBUS vs standard TBNA
  – high sensitivity in both groups
    • 82.6% vs. 90.5% (NS)
  – negative correlation of LN size to # of aspirates with standard TBNA, not with EBUS
  – EBUS most beneficial in:
    • paratracheal nodes < 2cm
    • post. sub-carinal, “AP window”

Shannon et al, Am J Respir Crit Care Med 1996; 153: 1424
EBUS TBNA

- 242 patients with mediastinal and hilar adenopathy
- Mean nodal size 1.7 cm
- Specific Dx or lymphocytes seen in 86%
  - lymphocyte only group → no further info with mediastinoscopy
- Yield independent of LN station
- In the 14% with lymph neg TBNA, 77% had CA

Herth et al, Chest 2003;123:604-7
EBUS of PET + Nodes

• 33 patients
  – 139 samples: mean 4.2 / patient
  – diagnosis made in 27 pts (82%)
    • 6 pts (18%) without Dx: LN in 3
      – 3 true neg on med, 1 clinical f/u to 20m, 2 presumed +
    – mediastinoscopy avoided in 25 cases (76%)

Plat et al, Eur Respir J 2006; 27: 276
Real-Time EBUS Guided TBNA

• Options were:
  – rigid bronchoscope
  – 2-channel scope
Real Time EBUS with the Radial Probe

- 55 patients randomized to EBUS-TBNA with single or double lumen bronchoscope
- 19ga needle
- Accuracy:
  - EBUS-D: 97%
  - EBUS-S: 76% (p=0.025)

Kanoh et al, Chest 2005; 128: 388
Convex-probe EBUS (CP-EBUS)

Scanning Range: 50 degrees

2.0mm Instrument Channel

Outer Diameter: 6.9mm

Direction of View: 30 degrees forward oblique

Ridges for balloon
Convex-probe EBUS (CP-EBUS)
EBUS-TBNA cont.

- 102 potentially resectable patients with known (96) / suspected (6) lung CA
  - 147 mediastinal nodes, 53 hilar nodes

Table 4—Characteristics of CT, PET, and EBUS-TBNA in the Correct Prediction of Mediastinal Lymph Node Staging*

<table>
<thead>
<tr>
<th>Tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>76.9</td>
<td>55.3</td>
<td>37.0</td>
<td>87.5</td>
<td>60.8</td>
</tr>
<tr>
<td>PET</td>
<td>80.0</td>
<td>70.1</td>
<td>46.5</td>
<td>91.5</td>
<td>72.5</td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>92.3</td>
<td>100</td>
<td>100</td>
<td>97.4</td>
<td>98.0</td>
</tr>
</tbody>
</table>

*Yasufuku et al, Chest 2006; 130: 710
EBUS-TBNA cont.

- 572 nodes in 502 patients
  - patients confirmed by thoracotomy, VATS or clinical f/u
- Diagnosis in 535 of punctures (94%)
- No ROSE
- 37 non-diagnostic
  - sarcoid in 2, CA in 35 on surgical Bx
- Sens. 94%, Spec. 100%, PPV 100%
- No complications

Herth et al, Thorax 2006; 61: 795
EBUS in the Radiologically Normal Mediastinum

- 100 patients with NSCLC and CT with no mediastinal LN > 10mm → EBUS-TBNA of all identifiable nodes → surgical staging with med (15) or thoracotomy (85)
  - mean LN diameter: 8.1mm
  - 2 aspirates / node
  - CA seen in 19, missed in 2
    - N0 → N1 3, N2 13, N3 3
  - Sens 92.3%, Spec 100%, NPV 96.3%
  - could avoid surgery in 17%

Herth et al, Eur Respir J 2006; 28: 910
EBUS in the PET neg. Mediastinum

• 97 patients with known / suspected NSCLC and neg PET-CT in the mediastinum
• EBUS-TBNA f/b surgical staging
  – mean diameter 7.9mm
  – + in 8 patients: N3 in 1, N2 in 5, N1 in 2
  – 1 additional patient found with N1 disease on surgical staging

Herth et al, Chest 2008; 133:887
EUS and EBUS Curvilinear Probes
EUS - FNA

- Only modality for level 8 LN
- Can stage adrenal
  - L seen in 97%
  - R seen in 20%
- Decreases need for more invasive staging
- Many patients still need bronchoscopy

Ringbaek et al, Lung Cancer 2005; 48: 247
Larsen et al, Lung Cancer 2005; 49: 377
Additional Value of EUS to Med

- 107 consecutive pts with potentially resectable NSCLC
- 16% of patients with neg Med found with N2, T4 or N2&T4 disease on EUS
- 2% FP (due to bx of the tumor, not the node)

Table 3. Diagnostic Values in the Analysis of N2/N3 Lymph Node Stations in Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>(n = 100)</td>
</tr>
<tr>
<td></td>
<td>69 (69)</td>
</tr>
<tr>
<td>Specificity</td>
<td>49 (49)</td>
</tr>
<tr>
<td>Predictive value</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>43 (43)</td>
</tr>
<tr>
<td>Negative</td>
<td>73 (73)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>56 (56)</td>
</tr>
</tbody>
</table>

Annema et al, JAMA 2005; 294:931
**Combined EBUS-EUS**

- 138 patients with known / suspected lung CA
- TBNA, EBUS-TBNA, EUS-FNA in a single procedure, all under moderate sedation, no ROSE
- Surgical / clinical (6-12m) confirmation

**Table 3. Estimated Sensitivities and Negative Predictive Values (NPVs) for Separate and Paired Procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBNA</td>
<td>15/42 (36) [22-52]</td>
<td>96/123 (78) [70-85]</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>29/42 (69) [53-82]</td>
<td>96/109 (88) [80-93]</td>
</tr>
<tr>
<td>EBUS-FNA</td>
<td>29/42 (69) [53-82]</td>
<td>96/109 (88) [80-93]</td>
</tr>
<tr>
<td>EUS-FNA + TBNA</td>
<td>33/42 (79) [63-90]</td>
<td>96/105 (91) [84-96]</td>
</tr>
<tr>
<td>EBUS-FNA + TBNA</td>
<td>32/42 (76) [61-88]</td>
<td>96/106 (91) [83-95]</td>
</tr>
<tr>
<td>EUS-FNA + EBUS-FNA</td>
<td>39/42 (93) [81-99]</td>
<td>96/99 (97) [91-99]</td>
</tr>
</tbody>
</table>

Wallace et al, JAMA 2008; 299: 540
EBUS for Re-staging

- 124 patients with IIIa-N2 disease
  - induction chemo
  - CT → 58 stable disease, 66 partial response
- EBUS-TBNA and thoracotomy with LN dissection
  - persistent nodal mets in 89 (72%)
  - 35 without nodal mets
    - 28 + on thoracotomy
    - sens 76%, spec 100%, PPV 100%, NPV 20%, accuracy 77%

Herth et al, J Clin Oncol 2008; 26:3346
EBUS & Sarcoid

Suspected sarcoidosis (n=65)

EBUS-TBNA (n=65)

Noncaseating epithelioid cell granuloma-positive (n=56)

Noncaseating epithelioid cell granuloma-negative (n=9)

Mediastinoscopy (n=5)

Sarcoidosis (n=61)

Observed (n=1)

VATS (n=1)

Indefinite (n=3)

Wegener's granulomatosis (n=1)

Wong et al, Eur Respir J 2007; 29:1182
EBUS & Lymphoma

**Suspected lymphoma**
- EBUS-TBNA
  - Lymphoma: n = 10
  - No lymphoma: n = 14
  - Inadequate sample: n = 1

**Non-caseating granuloma**
- n = 7

**Other benign histology**
- Reactive hyperplasia
  - n = 4
    - Normal: n = 3
  - Lymphoma diagnosed by other test (false negative): n = 1

<table>
<thead>
<tr>
<th>Lymphoma present</th>
<th>Lymphoma absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBNA positive</td>
<td>10</td>
</tr>
<tr>
<td>EBUS-TBNA negative</td>
<td>1</td>
</tr>
</tbody>
</table>

Adequate lymphoid tissue: 24/25 (96%)*
Sensitivity: 90.9% (95% CI 0.74 to 1.00)
Specificity: 100% (95% CI 0.75 to 1.00)
Positive predictive value: 100% (95% CI 0.69 to 1.00)
Negative predictive value: 92.9% (95% CI 0.79 to 1.00)

*Kennedy et al, Thorax 2007; 63: 360*
Practical EBUS: The US Processor

- US / ext / freeze / release
- Contrast
- Gain
- CPD
- Measure / select
- Optimize
- Menu
- Depth
The Balloon
NA-201SX-4022

- Connecting slider
- Needle adjuster
- Needle slider
- Aspiration port
- Sheath adjuster knob
- Needle adjuster knob
- Stylet knob
- Stopper
- Scale
- Dimpled needle improves US visualization
EBUS Caveats cont.

- Injury to the bronchoscope
- Vocal cord injury
EBUS Caveats: Understand the Orientation
Position Your Target
The Future

• 3D technology

• Molecular characterization to predict aggressiveness and response

Andreassen et al, Ultrasound Med Biol 2005; 41: 473
Zudaire et al, Histol Histopathol 2008; 23:33
Limitations of EBUS TBNA

• Learning curve
  – 30° view
  – extra-bronchial anatomy
• 22ga needle
• Can’t reach levels 5, 6, 8, 9 (or L adrenal)
• Non-Dx does not mean negative
• Hybrid imaging → lesser quality image
• Medicare removed the technical fee in 1/08
Summary

• Endoscopic staging can reach almost all stations
• Associated with minimal complications
• EBUS-TBNA can obviate the need for surgery in up to 56% of patients
  – EUS-FNA: up to 68%
• Real time guidance no substitute for good technique
• Will likely be positioned as procedure of choice for initial (and possibly re-) staging

Bauwens et al, Lung Cancer 2008
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