Lung Cancer Diagnosis in 2007

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Learning Objectives

• Review the epidemiology of lung cancer
• Discuss the clinical presentation of lung cancer
• Review radiographic patterns of lung cancer
• Review modalities for diagnosis
• Discuss options for staging

Lung Cancer Statistics, 2007

• Greatest cause of cancer deaths worldwide
• Greatest cause of cancer deaths in U.S.
  - 210,000 new cases in 2007
  - 163,000 deaths
    - 12% of cancer cases, 29% of cancer deaths

~13% in never smokers (>22,000 cases)
5 year survival from 1995-2001 was 15.7%

More than 85% of all patients with lung cancer have a smoking history yet only 20% of smokers acquire lung cancer

Courtesy NCI
Risk Factors

- Tobacco use
- Chronic lung disease
- Genetic predisposition
- Radon
- Asbestos
- Air pollution
  - Arsenic
  - Chromates
  - Chloromethyl ethers
  - Nickel

Gender Differences In Lung Cancer

- Women with lung cancer have been shown to
  1. Have smoked less
  2. Be younger
  3. Be 2-3 times more likely to have never smoked and
  4. Get adenocarcinoma more often than males

Gender Differences In Lung Cancer

- Biological Differences: nicotine metabolism, cytochrome p-450 enzyme system, DNA adduct levels, hormonal effects
- Hormonal Differences: role of estrogen
- Genetic Differences: higher p53 mutations among women with non-small cell carcinoma, higher K-ras mutations
- Occupational: high incidence in cashiers, waitresses, orderlies, nurse’s aides
**Lung Cancer Screening**

- Based on the principle that early diagnosis allows for more definitive therapy
- Studies in the 70's and 80's did not support screening
- Low dose CT (LDCT) is most promising modality
- Two randomized trials are under way: National Lung Screening Trial (50,000 patients) and NELSON trial (16,000 patients)
- Currently screening is not recommended

**Pathology Lung Cancer: Non-Small Cell**

- **Squamous-cell carcinoma (~20%)**
  - Most commonly found in men
  - Closely correlated with smoking (dose dependent)
  - Tends to spread locally
  - More readily detected in sputum
  - Highly expressed genes encoding proteins with detoxification/anti-oxidant properties

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**Treatment “First Principles”**

- **Diagnosis**
  - Adequate biopsy sample
- **Stage**
  - Stage determines treatment
- **Treatment**
  - In NSCLC, surgery is the cornerstone of treatment
  - In SCLC, chemotherapy is the cornerstone

**Pathology Lung Cancer: Non-Small Cell**

- **Adenocarcinoma (~35%)**
  - Most common type of lung cancer in women and non-smokers
  - Lesions are usually peripheral
  - Worldwide incidence increasing
### Pathology Lung Cancer: Non-Small Cell

#### Adenocarcinoma (~35%)
- Highly expressed genes encoding small airway-associated and immunologically related proteins
- K-ras mutations frequently reported
- Bronchoalveolar carcinoma is a subtype

#### Large-cell carcinoma (5-10%)
- Very primitive, undifferentiated cells
- Lesions are usually peripheral
- High tendency to metastasize

### Bronchoalveolar Cell Carcinoma
- **Epidemiology:** 2-9% of all lung cancers, F>M
- **Clinical presentation:** solitary lesion: often asymptomatic, consolidation or bilateral disease: cough, chest pain, dyspnea, hemoptysis, weight loss, bronchorrhea (~5%, late stage)
- **Radiographic:** solitary, spiculated, peripheral nodules (43%), consolidation (30%), diffuse (27%)

### Small-cell lung cancer (SCLC)
- 13-20% of all lung cancers
- Smokers, more prevalent in women than men
- Aggressive (brain evaluation required)
Small-cell lung cancer (SCLC)

- Initially chemosensitive (Platinum based therapy better than non-platinum based) becoming resistant. Should receive concurrent chemo/rads
- Prophylactic cranial irradiation should be offered (ACCP)
- Surgery in limited disease?

Initial Workup of Suspected Lung Cancer

Thorough History and Physical constitutional symptoms localizing findings signs of metastatic disease

Serum chemistries
LFTs
CBC
Imaging
CT chest through adrenals
Brain imaging based on H + P
Bone imaging based on H + P

SVC Syndrome

- Dyspnea
- Facial swelling or head fullness, cough, arm edema, cyanosis, facial plethora
- Lung cancer is the most common malignant cause of the SVC syndrome (2-4% of lung cancers)

Up to date, 2007
**SVC Syndrome**

- 20% of small cell
- SVC obstruction is a strong predictor of poor prognosis in patients NSCLC with a median survival of only five months in one series
- Unless there is airway compromise, establish histology first

**Superior Sulcus Tumors**

- DX: Percutaneous needle bx (+) in > 90%
- Brain imaging essential since most common site of distal recurrence
- MRI may be very helpful in assessing for brachial plexus or vertebral body involvement
- TX: Preop chemoradiation/resection/chemo

**Superior Sulcus Tumors**

- < 5%
- Apex of the lung
- Adenocarcinoma is predominant cell type in some series
- SX: shoulder, arm, scapular pain, paraesthesia, weakness, 14-50% Horner syndrome

**Paraneoplastic Syndromes**

<table>
<thead>
<tr>
<th>System</th>
<th>Syndrome</th>
<th>Cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Hypercalcemia</td>
<td>Squamous cell</td>
</tr>
<tr>
<td></td>
<td>SIADH</td>
<td>Small cell</td>
</tr>
<tr>
<td></td>
<td>Cushing’s</td>
<td>Small cell/carcinoid</td>
</tr>
<tr>
<td>Neurological</td>
<td>Lambert-Eaton</td>
<td>Small cell</td>
</tr>
<tr>
<td></td>
<td>Polyneuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autonomic Neuropathy</td>
<td></td>
</tr>
<tr>
<td>Skeletal</td>
<td>Hypertrophic</td>
<td>Squamous cell and Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Osteoarthropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clubbing</td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>Metastatic</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Metabolic</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Hematological</td>
<td></td>
</tr>
</tbody>
</table>
The Diagnosis of Lung Cancer
*The Radiologist’s Perspective*

Melissa L. Rosado-de-Christenson, MD, FACR
The Ohio State University
The Uniformed Services University

Learning Objectives

1. To recognize typical imaging manifestations of lung cancer including:
   a. Mass
   b. Post-obstructive Atelectasis / Consolidation
   c. Features of advanced lung cancer
2. To understand the imaging evaluation of patients with pulmonary nodules

Acknowledgements:

AFIP radiology resident classes
Gerald F. Abbott, MD
Mark S. Parker, MD
Diane C. Strollo, MD

Imaging Features of Lung Cancer

Pulmonary mass
Atelectasis / Consolidation
Pulmonary nodule

*Mediastinal mass (metastatic lymphadenopathy)*
*Peripheral mass with extrapulmonary involvement*
*Metastatic disease*
<table>
<thead>
<tr>
<th>Advanced Lung Cancer Mediastinal Mass</th>
<th>Advanced Lung Cancer Hematogenous Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.jpg" alt="Image" /></td>
<td><img src="image2.jpg" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advanced Lung Cancer Chest Wall Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.jpg" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung Mass (&gt; 3 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High likelihood of malignancy</td>
</tr>
<tr>
<td>Well-defined borders</td>
</tr>
<tr>
<td>Lobular borders</td>
</tr>
<tr>
<td>Spiculated borders</td>
</tr>
</tbody>
</table>

DDX: Infection, benign neoplasia
<table>
<thead>
<tr>
<th>Peripheral Mass Adenocarcinoma</th>
<th>Atelectasis / Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect manifestation of malignancy</td>
<td></td>
</tr>
<tr>
<td>Post obstructive effects of a central neoplasm</td>
<td></td>
</tr>
<tr>
<td>Reverse S-sign of Golden</td>
<td></td>
</tr>
<tr>
<td>Indicative of central neoplasm with resultant atelectasis</td>
<td></td>
</tr>
</tbody>
</table>

| Peripheral Mass Adenocarcinoma | Central Mass Squamous Cell Carcinoma |
Consolidations in Adults

“Consolidations in adults must be followed to complete radiographic resolution to exclude underlying malignancy. Follow-up chest radiography is recommended six weeks after start of therapy.”
### Solitary Pulmonary Nodule Definition

**Imaging**
- Rounded opacity that is moderately well marginated and is not larger than 3 cm in diameter
- Linear opacities are not nodules
- Clustered nodular opacities are not solitary
- Irregular opacities at the apices are likely scars / fibrosis
- Ovoid or triangular fissural opacities are likely lymph nodes

### Solitary Pulmonary Nodule

<table>
<thead>
<tr>
<th>Characterization</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Do nothing</td>
<td>Definitively malignant Biopsy or Excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possibly malignant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

### Solitary Pulmonary Nodule Intrapulmonary Lymph Node

### Solitary Pulmonary Nodule Characterization

- Nodule density
- Nodule morphology
- Nodule attenuation
- Nodule size / growth
Solitary Pulmonary Nodule Density - Calcification

Solitary Pulmonary Nodule Spiculation - Emphysema

08/21/07  10/02/07

Solitary Pulmonary Nodule Morphology

Solitary Pulmonary Nodule Attenuation

Non - solid

Part - solid
Up to 2/3 malignant
Invasive adenocarcinoma
Solitary Pulmonary Nodule

### Attenuation

| Non-solid | Part-solid |

#### Fleischner Criteria


<table>
<thead>
<tr>
<th>Size</th>
<th>Low-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 mm</td>
<td>No follow up</td>
<td>12 mo follow up</td>
</tr>
<tr>
<td>4 - 6 mm</td>
<td>12 mo follow up</td>
<td>6-12, 18-24 mo follow up</td>
</tr>
<tr>
<td>6 - 8 mm</td>
<td>6-12, 18-24 mo follow up</td>
<td>3-6, 9-12, 24 mo follow up</td>
</tr>
<tr>
<td>&gt; 8 mm</td>
<td>3, 9, 24 mo f/u dynamic CT, BX</td>
<td>Same</td>
</tr>
</tbody>
</table>

#### Size

*Midthun et al. Lung Cancer 2003; 41 (Suppl 2): S40*

<table>
<thead>
<tr>
<th>Size</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 mm</td>
<td>0.2%</td>
</tr>
<tr>
<td>4 - 7 mm</td>
<td>0.9%</td>
</tr>
<tr>
<td>8 - 20 mm</td>
<td>18%</td>
</tr>
<tr>
<td>&gt; 20 mm</td>
<td>50%</td>
</tr>
</tbody>
</table>

#### Growth

09/06 5 mm 12/06 11 mm 05/07 21 mm 09/07 21 mm
Learning Objectives

1. To recognize typical imaging manifestations of lung cancer including:
   a. Mass
   b. Post-obstructive Atelectasis / Consolidation
   c. Features of advanced lung cancer
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Sputum Cytology

- Least invasive
- Depends on sampling (3 samples), tumor size and location
- More accurate with large central tumors and hemoptysis
- Recent literature review: sensitivity 0.66, specificity 0.90
- Bronchoscopy is recommended when severe dysplasia, carcinoma in situ or carcinoma are detected by sputum
Fiberoptic Bronchoscopy

- Conducted with conscious sedation
- Best sensitivity for centrally located lesions (88%) increased with TBNA
- Sensitivity for peripheral lesions <2cm=34% and >2cm=63%
- Improved sensitivity with use of fluoroscopy
- EBUS, Electromagnetic Navigation, Autofluorescence

Why is Staging so Important?

- Prognosis
- Treatment planning
- Interpretation of clinical trials
- Identifying who will benefit from surgical versus multimodality treatment

Transthoracic Needle Aspiration

- Performed under fluoroscopic or CT guidance
- Sensitivity of 90%
- Not helpful in ruling out cancer
- Pneumothorax

Traditional Staging

Primary tumor -> CXR, CT Scan, Bronchoscopy, VATS, Thoracentesis, CT guided Bx -> OR, Path
Mediastinal nodes -> CT Scan, PET, Mediastinoscopy
Distant Mets -> CT Scan (through adrenals), PET, Bone scan
### 5-year survival by TNM status in NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM classification</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>61</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td>38</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0</td>
<td>34</td>
</tr>
<tr>
<td>IIIB</td>
<td>T2N1M0 or T3N0M0</td>
<td>24</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-3N2M0 or T3N1M0</td>
<td>13</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4NanyM0 or TanyN3M0</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>T4NanyM1</td>
<td>1</td>
</tr>
</tbody>
</table>

Mountain 1997

### Limitations of Current Staging

- Are there further subgroups within stage 1 disease?
- How do we identify early stage disease with a poor prognosis? (eg. vessel invasion, molecular markers)

### SCLC Stages

- **Extensive**
  - Tumour not confined to hemithorax of origin
  - Distant metastasis

- **Limited**
  - Tumour confined to hemithorax of origin and/or the mediastinum and supraclavicular nodes

PDQ Guidelines 2000

### Limitations of Current Staging

- Are there subgroups within traditional nodal staging? Spread to the mediastinal nodes is extremely important
- Poor correlation between clinical and pathological staging
- Current staging workup may miss unexpected secondary cancers or occult metastases
Overview of Clinical Staging

<table>
<thead>
<tr>
<th>Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Disease</td>
</tr>
<tr>
<td>Invasive</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
</tr>
<tr>
<td>VATS</td>
</tr>
<tr>
<td>TBNA</td>
</tr>
<tr>
<td>EUS</td>
</tr>
<tr>
<td>EBUS</td>
</tr>
<tr>
<td>Distant Disease</td>
</tr>
<tr>
<td>Non-invasive</td>
</tr>
<tr>
<td>Molecular</td>
</tr>
<tr>
<td>Genomics</td>
</tr>
<tr>
<td>Proteomics</td>
</tr>
<tr>
<td>Invasive</td>
</tr>
<tr>
<td>Non-invasive</td>
</tr>
<tr>
<td>Molecular</td>
</tr>
</tbody>
</table>

PET Scan

• Not much better than CT scan for T staging except tumor post obstructive atelectasis

• High false positive

• Lymph node/tumor ratio

• Absolute SUV

PET Scan

• 18 F-fluoro-2-deoxy-D-glucose (FDG)

• Standardization Uptake Value (SUV): index of glucose utilization of a lesion

• Abnormal: SUV > 2.5

• Lack of spatial resolution

PET Scan: Pitfalls

• False positives: metabolically active infectious or inflammatory lesions: Rheumatoid nodules, TB, fungal granulomas, lipid pneumonia, talc, infarction

• False negatives

✓ Tumors with low activity: BAC, carcinoid, well-differentiated adenocarcinomas, renal cell and testicular carcinomas, necrotic tumors
PET Scan: Pitfalls

- Lesions <1 cm (occasionally can detect 8-10mm)
- Elevated serum glucose
- Not accurate for brain lesions
- Careful with small lesions
- Limited anatomic resolution

Surgical Nodal Staging

- Cervical Mediastinoscopy (sens 80-85%, npv 91%)  
  2R, 2L, 4R, 4L, 7, 1, 3

- Extended Mediastinoscopy (sens 69-81%, false Neg 9-11%)  
  AP window (5,6)

- Anterior Mediastinoscopy (sens 63-86%)  
  5, 6

- Video Assisted Thoracoscopy  
  5.6, 8.9


Preoperative Staging of Non-Small Cell Lung Cancer with Positron-Emission Tomography

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Mediastinoscopy</td>
<td>80-85%</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td>Extended Mediastinoscopy</td>
<td>69-81%</td>
<td>9-11%</td>
<td>79-83%</td>
</tr>
<tr>
<td>Anterior Mediastinoscopy</td>
<td>63-86%</td>
<td>91%</td>
<td>77-84%</td>
</tr>
</tbody>
</table>


EUS

- Limited to posterior and middle mediastinal nodes
- Nodes as little as 3mm
- May also detect positive nodes when CT negative
### EUS

- May detect celiac node involvement
- Can complement mediastinoscopy (Annema, JAMA, 2005)

### EBUS

- Real time guidance of TBNA
- Local anesthesia
- Extensive nodal assessment
- Cannot access subaortic and paraesophageal nodes

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**Transbronchial Needle Aspiration (Wang)**

- Early 80s
- Hilar and mediastinal nodes
- Sensitivity 36%, Specificity of 98% with blind TBNA*
- Low risk
- Underutilized

* Holty, J-E C, et al., Thorax, 2005

---

**EBUS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Mediastinoscopy</th>
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<tbody>
<tr>
<td>Krasnik et al, 2003</td>
<td>11 with 15 lymph nodes</td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Yasufuku et al, 2004</td>
<td>70</td>
<td>95.7%</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>Rintoul et al, 2005</td>
<td>18</td>
<td>85%</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>Herth FJ et al, 2006</td>
<td>502</td>
<td>94%</td>
<td>100%</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Combining EBUS/TBNA and EUS

- Should complement each other to increase yield
- Studies ongoing

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