Lung Cancer: Part I

Gerard A. Silvestri MD, MS, FCCP
Hillenbrand Professor of Thoracic Oncology
Medical University of South Carolina
Charleston, SC
Disclosure

Research Funding

- Patient Centered Outcomes Research Institute
- NIH/NCI
- Olympus America
- Integrated Diagnostics
- Exact Sciences
- Veran
- Veracyte
- Boston scientific Corporation
- Auris Medical
Objectives

• Epidemiology
• Classification
• Diagnosis
• Screening
• SPN
• Staging
Executive Summary

Diagnosis and Management of Lung Cancer,
3rd ed: American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines

Frank C. Detterbeck, MD, FCCP; Sandra Zelman Lewis, PhD; Rebecca Diekemper, MPH;
Doreen J. Addrizzo-Harris, MD, FCCP; and W. Michael Alberts, MD, MBA, FCCP

CHEST 2013; 143(5)(Suppl):S7–S7S and it is now a vibrant field with a rapid pace of
Lung Cancer: Global Impact

- Most common cause of cancer death
- 1.8 million new lung cancer cases per year
- 1.6 million deaths per year (more than TB, malaria, HIV)

Percentage of tobacco use among adults, 2005
4th Highest lung cancer rates in the world
## Trends in Five-year Relative Survival Rates (%), 1975-2013

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>49</td>
<td>55</td>
<td>69</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>84</td>
<td>91</td>
</tr>
<tr>
<td>Colorectum</td>
<td>50</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>12</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>82</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>47</td>
<td>51</td>
<td>73</td>
</tr>
<tr>
<td>Ovary</td>
<td>36</td>
<td>38</td>
<td>47</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Prostate</td>
<td>68</td>
<td>83</td>
<td>99</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>72</td>
<td>79</td>
<td>78</td>
</tr>
</tbody>
</table>


Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2017.

*Age-adjusted to the 2000 US standard population. †Includes intrahepatic bile duct, gallbladder, and other biliary.

NOTE: Due to International Classification of Diseases coding changes, numerator information for colorectal, liver, and lung cancers has changed over time.


*Age-adjusted to the 2000 US standard population. †Uterus includes uterine corpus and uterine cervix combined. ‡Includes intrahepatic bile duct, gallbladder, and other biliary.

NOTE: Due to International Classification of Diseases coding changes, numerator information for colorectal, liver, lung, and uterine cancers has changed over time.

Etiology of Lung Cancer

• Tobacco causes 80 – 90%
  – Clear dose response relationship
  – Passive smoking may cause up to 25% of lung cancer in non-smokers (2.5 – 5% of all)

• Individual (genetic) susceptibility
  – 10 – 15% of active smokers will develop lung cancer
Etiology of Lung Cancer

• Other causes include asbestos, radon, polycyclic hydrocarbons, cadmium, chloromethyl ether, chromium, nickel, arsenic may cause lung cancer

• Age is a risk factor
  – Average age at dx is 70

• COPD is a risk factor
  – More so than just shared etiology (3-6x more likely than smoking alone)
Lung Cancer in Never Smokers

• Some individuals develop lung cancer without a significant smoking history
  – Defined as < 100 cigarettes in lifetime
  – In the US, 10-15% occur in never smokers

• Worldwide, 15% of men and 53% of women with lung cancer are never smokers
  – Accounts for ¼ of all cases

• If considered separately, LCINS would rank as the 7th most common cause of cancer death worldwide

• More than the number who develop ovarian cancer or Hodgkin’s disease
## Classification of Lung Cancer

### WHO Histologic Class

<table>
<thead>
<tr>
<th>Major types</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>32</td>
</tr>
<tr>
<td>– 3% of total are pure BAC</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>29</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>18</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>Unclassified/undifferentiated</td>
<td>12</td>
</tr>
</tbody>
</table>
Histology and Presentation

Squamous cell:
- 95% are smokers, Usually centrally located, can cavitate, Associated with HPO and hypercalcemia

Adenocarcinoma:
- Most common histologic subtype, Increased incidence in never smokers, peripheral, metastatic
- Small cell:
  - Almost all smokers, central, metastatic at presentation,
  - If you have to choose paraneoplastic syndromes related to lung cancer pick small cell.
Formerly known as Bronchoalveolar Cell

- Subtype of adenocarcinoma (5%)
- New classification which does away with the word BAC
- Often non-smokers, more female
- May present as Solitary Nodule, Lobar consolidation, or Multiple nodules
  - Different presentations may be different diseases with different prognoses
Formerly known as Bronchoalveolar Cell

- Staged and treated as an adeno
  - If pure BAC, may consider lesser resection
  - 50% are responsive to EGFR inhibitors

- Slow growing with late metastases
  - Potential for aerogenous and lymphatic spread
    - Lower likelihood of a (+) PET

- Bronchorrhea may be a problem

- Can complain of salty tasting sputum
**Categories of New Adenocarcinoma Classification**

**Where Former BAC Concept was Used**

<table>
<thead>
<tr>
<th>TABLE 3. Categories of New Adenocarcinoma Classification Where Former BAC Concept was Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adenocarcinoma in situ (AIS), which can be nonmucinous and rarely mucinous</td>
</tr>
<tr>
<td>2. Minimally invasive adenocarcinoma (MIA), which can be nonmucinous and rarely mucinous</td>
</tr>
<tr>
<td>3. Lepidic predominant adenocarcinoma (nonmucinous)</td>
</tr>
<tr>
<td>4. Adenocarcinoma, predominantly invasive with some nonmucinous lepider component (includes some resected tumors, formerly classified as mixed subtype, and some clinically advanced adenocarcinomas formerly classified as nonmucinous BAC)</td>
</tr>
<tr>
<td>5. Invasive mucinous adenocarcinoma (formerly mucinous BAC)</td>
</tr>
</tbody>
</table>

BAC, bronchioloalveolar carcinoma.
DIAGNOSIS
Patient Identification – Paraneoplastic Syndromes

• Many paraneoplastic syndromes
  - HPO (clubbing)
  - Hypercalcemia
    ▪ Often due to production of PTH-like hormone
    ▪ More common with NSCLC (Squamous)
  - SIADH
    ▪ Most common syndrome in SCLC
  - Cushing’s Syndrome
• Does not preclude curative tx
Question 1

Which of the following statements regarding the results of the National Lung Screening Trial for lung cancer is not true?

A. It randomized >50,000 persons to either low dose chest CT or chest x-ray
B. There was a lung cancer specific mortality reduction of 20% in the CT arm
C. There was no reduction in overall mortality
D. Approximately 25% of the CT screens discovered an abnormality
Screening: National Lung Screening Trial

- 53,454 participants
- Age 55-74
- Current or former smokers – 30 pack years
- Randomized to Low Dose CT (LDCT) vs CXR
- Scanned for 3 years followed for 3.5 years

Screening: National Lung Screening Trial

- 20% reduction in lung cancer mortality
- 7% reduction in overall mortality
- 26,309 LDCT screens
- 7,191 (27%) 96.4% false positives
- Most false positives needed only radiographic f/u
- 1% mortality with surgery
- Multi-society guideline recommends screening for same population tested in trial
Solitary Pulmonary Nodule
Differential Diagnosis: Benign SPN

- Non-specific or healed granulomas (25%)
- Infectious granulomas (15%)
- Benign neoplasms (15%)
  - Hamartoma
  - Lipoma, fibroma, countless others (rare)
- Others: lung abscess, pseudotumor, round atelectasis, AVM, infarct, mucoid impaction, hematoma, rheumatoid nodule, Wegener’s
Differential Diagnosis: Malignancy in a pulmonary nodule

- Adenocarcinoma (~50%)
  - Bronchoalveolar cell carcinoma (~5%)
- Squamous cell carcinoma (~20%)
- Solitary metastasis (~10%)
- Undifferentiated NSCLC (~10%)
- Small cell carcinoma (<2%)
SPN

• Pre-test Probability: Facilitates selection and interpretation of subsequent tests
• Validated model from Mayo Clinic
  – Six independent predictors of malignant SPN

  - Patient characteristics: *Age, smoking status, history of extrathoracic malignancy*

  - Nodule characteristics: *diameter, spiculation, upper lobe location*

  Swensen et al. Arch Intern Med 1997;157:849
CT: Size Matters

<table>
<thead>
<tr>
<th>Size</th>
<th>% malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 mm</td>
<td>1%</td>
</tr>
<tr>
<td>6-10 mm</td>
<td>24%</td>
</tr>
<tr>
<td>11-20 mm</td>
<td>33%</td>
</tr>
<tr>
<td>21-45 mm</td>
<td>80%</td>
</tr>
</tbody>
</table>

CT: Edge Characteristics

<table>
<thead>
<tr>
<th>Border type</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Smooth</td>
<td>0.2</td>
</tr>
<tr>
<td>2. Lobulated</td>
<td>0.5</td>
</tr>
<tr>
<td>3. Spiculated</td>
<td>5.0</td>
</tr>
<tr>
<td>4. Corona radiata</td>
<td>14</td>
</tr>
</tbody>
</table>

Siegelman et al. Radiology 1986;160:307
CXR: Patterns of Calcification

Patterns A-D are benign; patterns E and F are non-specific.
SPN Management

- Pre-test probability of cancer and management recommendations
  - Low < 5% risk of cancer
    - Serial CT’s
  - Intermediate is 5 – 60%
    - Consider PET, TTNA, Bronch
  - High is > 60%
    - Excisional biopsy with frozen section
CT-Guided FNA

11 studies with data about accuracy in SPN:

- Median sensitivity 90% (range 65% to 94%)
- Median specificity 100% (range 96% to 100%)
- Specificity assumed to be 100% in some studies
- Non-diagnostic results 5x more common in benign than malignant nodules, but non-diagnostic biopsy does not rule out malignancy
- Median probability of PTX 15% (range 15% to 43%)
- ~6% required chest tube (range 4% to 18%)

ACCP recs: In patients with an indeterminate SPN (10 mm) it is appropriate to perform a TTNA or bronchoscopy in the following circumstances:

- when clinical pre-test probability and findings on imaging tests are discordant, for example, when the pre-test probability of cancer is high and the lesion is not hypermetabolic by PET
- when a benign diagnosis requiring specific medical treatment is suspected
- when a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.
- Patient non operative and need tissue to rx
FDG-PET Imaging

- Non-invasive, functional imaging test
- FDG accumulates in metabolically active tumor cells
- Sensitivity ~72-95%, specificity ~83%
- False negative results:
  - Small nodules <8 mm to 10 mm
  - Well-differentiated adenocarcinoma, BAC, carcinoid
- False positive results:
  - Granulomatous infection/inflammation

Gould et al, Chest 2013
Cronin. Radiology, 2008
Bronchoscopy

Central lesions
- 30 studies, total of 3,754 patients
- Overall sensitivity 88%

Procedure Sensitivity %

Direct endobronchial Bx 74%
Endobronchial brush 59%
Bronchial wash 48%

Rivera, Chest 2013
Role of Bronchoscopy

- Peripheral lesions
  - 30 studies, 4,136 patients
  - Overall sensitivity 30-60%

- Factors affecting yield:
  - Size of the lesion
    - >2cm sensitivity 62%
    - <2cm only 33%
  - Bronchus extending to the lesion (60%)
  - Use of fluoroscopy, number of biopsies (>5)
Diagnosis of Lung Cancer

• Pleural Fluid Cytology
  – If fluid is present, tap it
    ▪ For tissue diagnosis and assists in staging
  – Only 50% are cytologically positive
    ▪ Direct invasion is not the only mechanism
  – If cytology is negative in 2 taps
    ▪ Proceed to VATS or pleuroscopy
  – Blind biopsy improves recovery by only 8%
Diagnosis of Lung Cancer

- Biopsy of possible metastatic sites
  - Supraclavicular nodes
  - Liver Lesions
  - Adrenal Enlargement
- Not only makes the diagnosis but also stages as IV
Staging

- TNM system
  - Estimate prognosis
  - Select treatment options
  - Report outcomes
**T Descriptor Definition Changes**

- **Size: divided by 1 cm cut-points**
  - $T_1 \rightarrow T_{1a} \leq 1 \text{ cm}, T_{1b} > 1-2 \text{ cm}, T_{1c} > 2-3 \text{ cm}$
  - $T_2 \rightarrow T_{2a} > 3-4 \text{ cm}, T_{2b} > 4-5 \text{ cm}$

- **Tumors greater than 5 cm reclassified**
  - $T_3 > 5-7 \text{ cm}, T_4 > 7 \text{ cm}$

- **Central tumors (mainstem bronchus) are $T_2$,**
  - regardless of distance from carina or total or partial atelectasis

- **Invasion of Mediastinal pleura no longer counts as a T descriptor**
  - (previously $T_4$)
N Category (8th edition)
N (Node) Descriptor

Nx  Not assessed
N0  No regional lymph nodes involved
N1  Ipsilateral hilar, peribronchial or intrapulmonary nodes involved, including direct extension
N2  Ipsilateral mediastinal nodes involved
N3  Contralateral mediastinal nodes involved

...or...

Supraclavicular nodes involved
M Category (8th edition)
M (Metastasis) Descriptor

M0  No distant metastases

M1a  Pleural/pericardial implants
     Malignant pleural/pericardial effusion
     2nd cancer nodule in contralateral lung

M1b  Single distant metastasis

M1c  Multiple distant metastases (multiple lesions in single organ or in multiple organs)
Stage Groups (8th edition)
Stage Groups (8th edition)
Clinical Stage (8th edition)

Ref: Goldstraw J Thor Oncol 2016;11:39-51
Pathologic Stage (8th edition)

Ref: Goldstraw J Thor Oncol 2016;11:39-51
Small Cell Lung Cancer - Staging

- SCLC may be staged using the revised TNM system
- May be staged using an older VA Lung Cancer Study group system
  - Extensive Stage
  - Limited Stage
Small Cell Lung Cancer

- **Limited Stage (30%)**
  - Tumor is confined to one hemithorax, the mediastinum, or the supraclavicular nodes
  - “All tumor is encompassed in a single XRT port”
  - Not contralateral hilar or supraclavicular

- **Extensive Stage (70%)**
  - Clinically detectable distant metastases
  - Including (+) pleural and pericardial effusions
  - Most commonly = Bone, Liver, CNS, Adrenal
Diagnosis - Now what?

• Two Main Questions:
  – Is the tumor resectable (staging)?
    ▪ No benefit from debulking
    ▪ Answerable from work-up
  – Is the patient operable (gen’l health)?
    ▪ Can the pt withstand the stress of surgery?
    ▪ Do the potential benefits outweigh the risks?
Pre-Treatment Evaluation - History

- Weight loss
- Skeletal pain, Chest pain
- Headache
- Syncope
- Seizure
- Extremity Weakness
- Mental Status Change
Staging for Lung Cancer

- Non-invasive Staging:
  - CT
  - PET

- Invasive Staging:
  - Non-surgical:
    - EUS
    - EBUS
  - Surgical:
    - Mediastinoscopy
    - Anterior Mediastinotomy (Chamberlain procedure)
    - VATS
Why Do Invasive Staging?  
Accuracy of CT and PET Staging  
Mediastinal Lymph Nodes

Summary of 43 (CT) and 45 (PET) trials

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>55%</td>
<td>81%</td>
</tr>
<tr>
<td>N=7,368</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>80%</td>
<td>88%</td>
</tr>
<tr>
<td>N=4,105</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methods of Obtaining Tissue

- Mediastinoscopy
- Mediastinotomy
- Thoracoscopy
- Trans bronchial needle aspirate
- EUS with FNA
- EBUS with FNA
Confirmation of Intrathoracic Stage

**Extensive Infiltration**

CT neg. but central, adeno, N1

**Discrete N2, 3 enlargement**

Peripheral clinical stage I
## Accuracy of Staging Tests in Lung Cancer Patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Studies</th>
<th>N</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinoscopy</td>
<td>35</td>
<td>10,648</td>
<td>81</td>
<td>100</td>
</tr>
<tr>
<td>EUS</td>
<td>26</td>
<td>2,443</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>EBUS</td>
<td>26</td>
<td>2,756</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>EBUS/EUS</td>
<td>7</td>
<td>811</td>
<td>91</td>
<td>100</td>
</tr>
</tbody>
</table>

Silvestri et al. *CHEST 2013; 143(5)(Suppl):e211S–e250S*
Recommendations

- ACCP guidelines 2013: In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test.