LUNG CANCER
2010
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Division of Medical Oncology
Lung Cancer

- Very common
- Very lethal
- Median age of diagnosis approximately 70 years, but affects all ages
- In the United States, the highest incidence is in African-Americans
- Multidisciplinary approach to treatment
Multidisciplinary approach

- Medical Oncology
- Pulmonary
- Thoracic Surgery
- Radiotherapy
- Radiology
- Pathology
Multidisciplinary approach

- Neurology
- Neurosurgery
- Orthopedic surgery
- General surgery
- Vascular surgery
- Gastroenterology
- Cardiology
Multidisciplinary approach

- Nephrology
- Urology
- Endocrinology
- ENT
- Dermatology
- Psychiatry
- Rehabilitation Medicine
- Pediatrics (rarely)
Lung Cancer

1. Epidemiology
2. Etiology
3. Pathology
4. Clinical Manifestations/Staging
5. Management
# Lung Cancer Incidence 2008

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated New Cases</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>114,590</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>77,250</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>51,230</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,450</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>34,950</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>33,130</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,310</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,180</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>745,180</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>182,460</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>100,330</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>71,560</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>40,100</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>30,670</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>28,410</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>27,530</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,650</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>21,260</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>19,090</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>692,000</strong></td>
<td></td>
<td><strong>100%</strong></td>
</tr>
<tr>
<td>Cancer Type</td>
<td>Incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>219,440</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>194,280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>44,790</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus cancer</td>
<td>16,470</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Lung Cancer Deaths 2008

## Estimated Deaths

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th>%</th>
<th>Females</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>90,810</td>
<td>31%</td>
<td>Lung &amp; bronchus</td>
<td>71,030</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,660</td>
<td>10%</td>
<td>Breast</td>
<td>40,480</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>24,260</td>
<td>8%</td>
<td>Colon &amp; rectum</td>
<td>25,700</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17,500</td>
<td>6%</td>
<td>Pancreas</td>
<td>16,790</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,570</td>
<td>4%</td>
<td>Ovary</td>
<td>15,520</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,460</td>
<td>4%</td>
<td>Non-Hodgkin lymphoma</td>
<td>9,370</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,250</td>
<td>4%</td>
<td>Leukemia</td>
<td>9,250</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>9,950</td>
<td>3%</td>
<td>Uterine corpus</td>
<td>7,470</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,790</td>
<td>3%</td>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5,840</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,100</td>
<td>3%</td>
<td>Brain &amp; other nervous system</td>
<td>5,650</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>294,120</strong></td>
<td><strong>100%</strong></td>
<td><strong>All Sites</strong></td>
<td><strong>271,530</strong></td>
</tr>
</tbody>
</table>
FIGURE 4 Annual Age-adjusted Cancer Death Rates* Among Males for Selected Cancers, United States, 1930 to 2004.
*Rates are age-adjusted to the 2000 US standard population.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes.
Lung Cancer Deaths-Females

*Figure 5. Annual Age-adjusted Cancer Death Rates* Among Females for Selected Cancers, United States, 1930 to 2004

*Notes:*
- Rates are age-adjusted to the 2000 US standard population.
- Uterus includes uterine cervix and uterine corpus.
- Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the uterus, ovary, lung and bronchus, and colon and rectum are affected by these changes.
Lung Cancer

Cigarette smoking causes 90% of cases
Fig. 4. Relative risk of lung cancer (Kreyberg Group I) by number of cigarettes: 408 male lung cancer patients and 2,272 controls, New York, Los Angeles, and Houston, 1966–71.
Fig. 5. Relative risk of lung cancer (Kreyberg Group I) by duration of ex-smoking. (Males, Memorial Hospital, N.Y.C., 210 cases; 420 controls, 1966–69: hospitals in Los Angeles, Houston, and New York City [incl. Memorial], 188 cases; 376 controls, 1970–71. Controls matched by age and hospital.)
Table 1. Odds ratios of lung cancer for various categories of tobacco use among ever smokers, adjusted for age and study center

<table>
<thead>
<tr>
<th>Category of tobacco use*</th>
<th>No. of case patients</th>
<th>No. of control subjects</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>117</td>
<td>1750</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Cigars, pure smokers</td>
<td>16</td>
<td>42</td>
<td>5.6</td>
<td>2.9–10.6</td>
</tr>
<tr>
<td>Cigarillos, pure smokers</td>
<td>21</td>
<td>31</td>
<td>12.7</td>
<td>6.9–23.7</td>
</tr>
<tr>
<td>Cigars and cigarillos, pure smokers†</td>
<td>43</td>
<td>77</td>
<td>9.0</td>
<td>5.8–14.1</td>
</tr>
<tr>
<td>Pipe, pure smokers</td>
<td>61</td>
<td>129</td>
<td>7.9</td>
<td>5.3–11.8</td>
</tr>
<tr>
<td>Cigarettes, pure smokers</td>
<td>4204</td>
<td>3930</td>
<td>14.9</td>
<td>12.3–18.1</td>
</tr>
<tr>
<td>Mixed smokers‡</td>
<td>1182</td>
<td>1309</td>
<td>12.7</td>
<td>10.3–15.6</td>
</tr>
</tbody>
</table>

*Pure smokers are those considered to smoke only one type or category of tobacco product; mixed smokers are those who used cigarettes and cigars, cigarillos, or pipe tobacco.

†Combines pure smokers of cigars, pure smokers of cigarillos, and smokers of both cigars and cigarillos but not cigarettes or pipe tobacco.

‡Excludes 14 case patients and 60 control subjects who smoked cigars, cigarillos, and pipe tobacco but not cigarettes.
LUNG CANCER

ETIOLOGY

Passive cigarette smoke

Associated with a small increased risk
Risk Factors

<table>
<thead>
<tr>
<th>Established Lung Carcinogens</th>
<th>Suspected Lung Carcinogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic (inorganic)</td>
<td>Acrylonitrile</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Beryllium</td>
</tr>
<tr>
<td>Bis(chloromethyl)ether</td>
<td>Cadmium</td>
</tr>
<tr>
<td>Chloromethyl methyl ether</td>
<td>Ceramic fibres</td>
</tr>
<tr>
<td>Chromium compounds</td>
<td>Diesel engine exhaust</td>
</tr>
<tr>
<td>Gamma radiation</td>
<td>Ferric oxide dust</td>
</tr>
<tr>
<td>Ionizing radiation (x-rays)</td>
<td>Insecticides</td>
</tr>
<tr>
<td>Mustard gas</td>
<td>Lead</td>
</tr>
<tr>
<td>Nickel compounds</td>
<td></td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td></td>
</tr>
<tr>
<td>Radon decay products</td>
<td></td>
</tr>
<tr>
<td>Soots</td>
<td></td>
</tr>
<tr>
<td>Tars</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoke</td>
<td></td>
</tr>
<tr>
<td>Mineral oils</td>
<td></td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td></td>
</tr>
<tr>
<td>Wood dust</td>
<td></td>
</tr>
</tbody>
</table>

LUNG CANCER

ETIOLOGY

Asbestos

1. Long latent period
2. Brief exposures
3. Indirect (low level) exposures
4. Multiplied risk in cigarette smokers (synergistic effect)
LUNG CANCER

ETIOLOGY

Radiation

1. Uranium miners
   – synergistic interaction with cigarette smoking

2. Radon in homes
   – controversial, degree of risk (if any) debated
# Lung Ca-Genetic Abnormalities

*NEJM 2008; 359:1369*

## Table 1. Genetic Abnormalities Specific in the Lung to Non–Small-Cell Lung Cancer and Small-Cell Lung Cancer.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Squamous-Cell Carcinoma</th>
<th>Non–Small-Cell Lung Cancer</th>
<th>Small-Cell Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precursor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion</td>
<td>Known (dysplasia)</td>
<td>Probable (atypical adenomatous hyperplasia)</td>
<td>Possible (neuroendocrine field)†</td>
</tr>
<tr>
<td>Genetic change</td>
<td>$\beta$53 mutation</td>
<td>$KRAS$ mutation (atypical adenomatous hyperplasia in smokers), $EGFR$ kinase domain mutation (in nonsmokers)</td>
<td>Overexpression of c-MET</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$KRAS$ mutation</td>
<td>Very rare</td>
<td>10 to 30%;‡</td>
<td>Very rare</td>
</tr>
<tr>
<td>$BRAF$ mutation</td>
<td>3%</td>
<td>2%</td>
<td>Very rare</td>
</tr>
<tr>
<td>$EGFR$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinase domain mutation</td>
<td>Very rare</td>
<td>10 to 40%;‡</td>
<td>Very rare</td>
</tr>
<tr>
<td>Amplification</td>
<td>30%</td>
<td>15%</td>
<td>Very rare</td>
</tr>
<tr>
<td>Variant III mutation</td>
<td>5%†</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>$HER2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinase domain mutation</td>
<td>Very rare</td>
<td>4%</td>
<td>Very rare</td>
</tr>
<tr>
<td>Amplification</td>
<td>2%</td>
<td>6%</td>
<td>Not known</td>
</tr>
<tr>
<td>$ALK$ fusion</td>
<td>Very rare</td>
<td>7%</td>
<td>Not known</td>
</tr>
<tr>
<td>$MET$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>12%</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Amplification</td>
<td>21%</td>
<td>20%</td>
<td>Not known</td>
</tr>
<tr>
<td>$TITF-1$ amplification</td>
<td>15%</td>
<td>15%</td>
<td>Very rare</td>
</tr>
<tr>
<td>$\beta$53 mutation</td>
<td>60 to 70%</td>
<td>50 to 70%;‡</td>
<td>75%</td>
</tr>
<tr>
<td>$LKB1$ mutation</td>
<td>19%</td>
<td>34%</td>
<td>Very rare</td>
</tr>
<tr>
<td>$PIK3CA$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>2%</td>
<td>2%</td>
<td>Very rare</td>
</tr>
<tr>
<td>Amplification</td>
<td>33%</td>
<td>6%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*‡ Non–small cell lung cancer includes squamous cell carcinoma and adenocarcinoma.*
### 1999 WHO classification of invasive malignant epithelial lung tumors

#### Squamous cell carcinoma
- Variants: papillary, clear cell, small cell, basaloïd

#### Small cell carcinoma
- Variant: combined small cell carcinoma

#### Adenocarcinoma
- Acinar
- Papillary
- Bronchioloalveolar carcinoma
- Non-mucinous (Clara cell/type II pneumocyte type)
- Mucinous (Goblet cell type)
- Mixed mucinous and non-mucinous (Clara cell/type II pneumocyte/goblet cell type) or indeterminate
- Solid adenocarcinoma with mucin formation
- Mixed
- Variants: well-differentiated fetal adenocarcinoma, mucinous ("colloid"), mucinous cystadenocarcinoma, signet ring, clear cell

#### Large cell carcinoma
- Variants: large cell neuroendocrine carcinoma, combined large cell neuroendocrine carcinoma, basaloïd carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, large cell carcinoma with rhabdoid phenotype

#### Adenosquamous carcinoma

#### Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
- Carcinomas with spindle and/or giant cells
- Pleomorphic carcinoma
- Spindle cell carcinoma
- Giant cell carcinoma
- Carcinosarcoma
- Blastoma (Pulmonary blastoma)

#### Carcinoid tumor
- Typical carcinoid
- Atypical carcinoid

#### Carcinomas of salivary gland type
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Others

#### Unclassified carcinoma
Pathology

- Small cell carcinoma 14%
- Non-small cell carcinoma 86%
  - Adenocarcinoma
    - Bronchioloalveolar carcinoma
  - Squamous carcinoma
  - Large cell carcinoma
    - Large cell neuroendocrine carcinoma
  - Adenosquamous carcinoma
LUNG CANCER

CLINICAL FEATURES

1. Growth at primary site/direct extension

2. Metastatic spread

3. Paraneoplastic (remote) effects
LUNG CANCER

MANIFESTATIONS OF LOCAL TUMOR GROWTH

1. Hemoptysis – ulceration of tumor
2. Cough – stimulation of nerve endings
3. Wheezing – partial airway obstruction
4. Pneumonia – airway obstruction
5. Atelectasis – airway obstruction
LUNG CANCER

DIRECT EXTENSION

1. Neurological structures
2. Pericardium
3. Pleura
4. Esophagus
5. Chest wall
6. Vertebral column
SUPERIOR VENA CAVA COMPRESSION

SYMPTOMS

1. Swelling of the face
2. Swelling of the arms
3. Shortness of breath
4. Cough
SUPERIOR VENA CAVA COMPRESSION

SIGNS

1. Distention of jugular veins
2. Distention of veins over shoulders, chest wall, upper abdomen
3. Edema of the face
4. Plethora of the face
5. Congestion of retina
6. Edema of arms, hands
Superior Vena Cava Syndrome

The photograph shows massive engorgement of collateral subcutaneous veins of the chest and abdomen in a 36-year-old man with partial obstruction of the superior vena cava caused by small-cell lung cancer. The patient also had distended neck veins but minimal facial edema. The venous distalation improved transiently with radiation therapy. The patient died several weeks after the photograph was taken.

Ronald G. Kovac, R.B.P.
Samuel M. Agbaye, M.D.
Atlanta Veterans Affairs Medical Center
Decatur, GA 30033
Horner’s Syndrome
Sympathetic chain, spinal cord C8,T1

- Ptosis
- Miosis
- Anhidrosis
LUNG CANCER

METASTATIC SPREAD

1. Lymphatic channels
2. Hematogenously
Lymph Node Metastases

- Peribronchial (N1)
- Hilar (N1)
- Ipsilateral Mediastinal (N2)
- Contralateral Mediastinal N3)
- Supraclavicular (N3)
- Distant (M1)
Lymph Node Metastases

- Superior vena cava syndrome
- Hoarseness (vocal cord paralysis due to recurrent laryngeal nerve involvement)
- Paralyzed hemidiaphragm (phrenic nerve involvement)
- Lymphedema
- Effusions
LUNG CANCER

SYSTEMIC METASTASES

1. Lungs/pleura
2. Liver
3. Bones
4. Adrenal glands
5. Brain
LUNG CANCER

PARANEOPLASTIC (REMOTE) EFFECTS

1. Cushing’s syndrome (Ectopic ACTH)
   - small cell lung cancer
2. Syndrome of inappropriate ADH secretion
   - small cell lung cancer
3. Eaton-Lambert syndrome
   - small cell lung cancer
4. Hypercalcemia – PTHrP (small cell & squamous)
5. Pulmonary osteoarthropathy
   - non-small cell lung cancer
6. Subacute cerebellar degeneration (small cell)
7. Peripheral neuropathies (small cell)
LUNG CANCER

Finger Clubbing
LUNG CANCER

THERAPY

Small Cell Lung Cancer

1. Rapidly proliferating cells

2. Systemic metastases have developed by time the primary lesion presents
Small cell carcinoma
Clinical Presentation

- Decreasing frequency
- Smokers!
- Central presentation-cough, hemoptysis, hoarseness, pneumonia, SVC syndrome, dysphagia
- Rapid growth
- Markers: LDH, CEA
- Paraneoplastic syndromes
Small Cell Carcinoma-Staging

Limited Disease (1/3) Vs. Extensive Disease (2/3)
# Small Cell Carcinoma

## Limited Disease

Median survival by stage (months)

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited disease</td>
<td>3</td>
<td>18-24</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>1.5</td>
<td>9</td>
</tr>
</tbody>
</table>

(continued)
Small cell carcinoma
Limited Disease

Chemotherapy

- Etoposide and Cisplatin
- Etoposide and Carboplatin

Four cycles
No maintenance chemotherapy
Small cell carcinoma
Limited Disease

- Thoracic radiotherapy
  - Early/concurrent
  - Twice-daily fractionation, 45 Gy
  - >esophagitis

- PCI
  - Meta analysis: 5% survival benefit at 3 years
  - Limit dose
  - Avoid chemo agents with CNS toxicity
Small Cell Carcinoma
Extensive Disease

- Chemotherapy
  - etoposide/cisplatin
  - etoposide/carboplatin
  - irinotecan/cisplatin
  - topotecan/cisplatin (ASCO, 2008)

- Thoracic radiotherapy – selected cases

- PCI – sometimes (if chemo response)
Non-Small Cell Carcinoma
Non-small cell
Staging - T

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TX:</strong> Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but visualized by imaging or bronchoscopy</td>
</tr>
<tr>
<td><strong>T0:</strong> No evidence of primary tumor</td>
</tr>
<tr>
<td><strong>Tis:</strong> Carcinoma in situ</td>
</tr>
<tr>
<td><strong>T1:</strong> Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus</td>
</tr>
<tr>
<td><strong>T2:</strong> Tumor with any of the following features of size or extent:</td>
</tr>
<tr>
<td>- More than 3 cm in greatest dimension</td>
</tr>
<tr>
<td>- Involves main bronchus, 2 cm or more distal to the main carina</td>
</tr>
<tr>
<td>- Invades the visceral pleura</td>
</tr>
<tr>
<td>- Associated with aplectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
</tr>
<tr>
<td><strong>T3:</strong> Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus within 2 cm, but not involving the main carina; or associated aplectasis or obstructive pneumonitis of the entire lung</td>
</tr>
<tr>
<td><strong>T4:</strong> Tumor of any size that invades any of the following: heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion</td>
</tr>
</tbody>
</table>
## Non-small cell Staging – N,M

<table>
<thead>
<tr>
<th>Nodal Involvement (N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX: Regional lymph nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>N0: No regional lymph node involvement</td>
<td></td>
</tr>
<tr>
<td>N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor</td>
<td></td>
</tr>
<tr>
<td>N2: Metastasis to ipsilateral mediastinal and/or sub-carinal lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N3: Metastases to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastases (M)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX: Distant metastases cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>M0: No distant metastases</td>
<td></td>
</tr>
<tr>
<td>M1: Distant metastases present (may include tumor nodules in separate lobes of lung)</td>
<td></td>
</tr>
</tbody>
</table>
Nodal Staging

Brachiocephalic (innominate) a
Azygos v
2R
4R
10R
11R
12, 13, 14R
7
8
10L
11L
12, 13, 14L

Phrenic n
Ligamentum arteriosum

Ao
PA
## Stage groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult carcinoma</td>
<td>TX</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 1A</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 1B</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 3A</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 3B</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Stage I – Lung Cancer Staging

Stage IB
T2 N0 M0
Involving mainstem bronchus > 2 cm distal to carina

Stage IA
T1 N0 M0
Peripheral "coin" lesion

T2 N0 M0
Involving visceral pleura

No Lymph Node Involvement

Sources: Mountain CF. Chest. 1986;89:225s–233s.
Stage II – Lung Cancer Staging

Stage IIB
T3 N0 M0
Superior sulcus tumor

Stage IIB
T2 N1 M0
Involving visceral pleura and peribronchial and hilar lymph nodes

Stage IIA
T1 N1 M0
≤ 3 cm involving peribronchial lymph nodes (by direct extension)

Intrapulmonary and/or hilar Nodes Involved

Stage IIB
T2 N1 M0
Involving main bronchus and hilar lymph nodes

Stage IIIA – Lung Cancer Staging

T3 N1 M0
Peripheral tumor involving chest wall and intrapulmonary lymph nodes

T2 N2 M0
> 3 cm tumor involving ipsilateral hilar and mediastinal lymph nodes

Mediastinal parietal pleura

Stage IIIA

Sources: Mountain CF. Chest. 1986;89:225s–233s.
Stage IIIIB – Lung Cancer Staging

T4 N3 M0
Involvement of mediastinum, (ipsilateral and) contralateral mediastinal lymph nodes, contralateral hilar nodes, supravacular lymph nodes

Mediastinal parietal pleura

Sources: Mountain CF. Chest. 1986;89:225s–233s.
NSCLC – Staging w/u

- Physical exam!
- Chest x-ray
- Chest CT scan – with or without contrast?
- PET/CT scan
- Bone scan?
- Brain MRI with gadolinium
- Bronchoscopy
- Mediastinoscopy/ TBNA / EBUS
- Tumor markers?
Non-small cell lung cancer

Management by stage
Stage 1

- Surgery
- Adjuvant chemotherapy?
**Adjuvant Chemotherapy Trials**

### Adjuvant Chemotherapy for NSCLC

**Trials post 1995 Meta Analysis**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Stage</th>
<th>n</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>RCT</td>
<td>I-III</td>
<td>1209</td>
<td>Cis/multi</td>
</tr>
<tr>
<td>IALT</td>
<td>RCT</td>
<td>I-III</td>
<td>1867</td>
<td>Cis/Vin or VP16</td>
</tr>
<tr>
<td>BLT</td>
<td>RCT</td>
<td>I-III A</td>
<td>488</td>
<td>Cis/VP16</td>
</tr>
<tr>
<td>JBR.10</td>
<td>RCT</td>
<td>IB-II</td>
<td>344</td>
<td>Cis/Vin</td>
</tr>
<tr>
<td>CALGB</td>
<td>RCT</td>
<td>IB</td>
<td>344</td>
<td>Carbo/Pac</td>
</tr>
<tr>
<td>ANITA</td>
<td>RCT</td>
<td>I-III A</td>
<td>840</td>
<td>Cis/Vin</td>
</tr>
<tr>
<td>LACE</td>
<td>Meta Analysis</td>
<td>I-III A</td>
<td>4585</td>
<td>Cisplatin doublet</td>
</tr>
</tbody>
</table>

**Total n**: 5,112
Adjuvant chemotherapy

Stage II
Yes
NSCLC – Stages I & II

No role for adjuvant radiotherapy
NSCLC – Stage IIIA
Combined modality therapy

- Surgery → Chemotherapy +/- RT
- Chemotherapy → Surgery → RT
- Chemotherapy → Surgery → Chemo + RT
- Chemo/RT → Surgery
- Chemo/RT → Surgery → Chemo
- Chemotherapy/Radiotherapy
- Chemotherapy → Surgery
NSCLC – IIIA
Advantages of neoadjuvant chemo

- Decrease tumor bulk
- Improve operability, sometimes allow a more limited resection
- Control micrometastatic disease
- Allows assessment of tumor sensitivity to drugs
NSCLC – Stage IIIb

- IIIb with malignant effusion (“wet IIIb”)
  - local management of effusion
  - treat similar to stage IV

- IIIb without effusion (“dry IIIb”)
  inoperable → chemo/RT > RT alone
  “operable” → chemo/RT → Surgery
NSCLC – Stage IV
Initial treatment
Chemotherapy vs. Targeted therapy?
Toxicities of chemotherapy

- Myelosuppression (infections, anemia, bleeding)
- Emesis
- Alopecia
- Nephrotoxicity
- Neurotoxicity
- CNS effects
Toxicities of EGFR inhibitors

- Rash
- Diarrhea
- Many other side effects are much less common
Toxicities of bevacizumab

- Hemorrhage
- Thrombosis
- Hypertension
- Proteinuria
- GI tract perforation
Targeted therapies in NSCLC

- erlotinib (Tarceva) – EGFR tyrosine kinase inhibitor

- cetuximab (Erbitux) – EGFR antibody

- bevacizumab (Avastin) – VEGF antibody
NSCLC – Stage IV Response to EGFR TK inhibitor

- Clinical profile
  - Never smoker or limited smoker
  - Asian background
  - Adenocarcinoma
  - Female
NSCLC – Stage IV
Response to EGFR TK inhibitor

Laboratory profile

KRAS mutation
EGFR mutation
Immunohistochemistry
EGFR amplification by FISH
Non-small cell lung cancer
Stage IV

Chemotherapy:
Platinum-based doublet +/- antibody therapy
Non-small cell lung cancer
Stage IV

- Paclitaxel/carboplatin +/- bevacizumab
- Vinorelbine/cisplatin +/- cetuximab
- Pemetrexed/cisplatin/bevacizumab
Response assessment
“RECIST”

- Complete Response (CR): disappearance of all target lesions
- Partial Response (PR): 30% or greater decrease in the sum of the LD of target lesions
- Stable Disease (SD)
- Progressive Disease (PD): 20% or greater increase in sum of the LD of target lesions, or new lesions
NSCLC – Stage IV

- Histology
- Metastatic sites and extent
- Better prognosis subgroups:
  - solitary/few brain mets
  - solitary adrenal mets
- Coagulopathy
- Comorbid medical problems
- Elderly
Supportive/Adjunct Care

- Growth factors
- Bisphosphonates
- Pain management
- Coagulopathies
- Brain mets- surgery, radiosurgery, WBRT
- Anti-emetics: aprepitant/palonosetron/dexamethasone
- Radiotherapy