Cancer in the United States, 2004

Estimated New Cases

- Prostate (30%)
- Lung and Bronchus (12%)
- Colon and Rectum (11%)
- Uterine Corpus (9%)
- Breast (9%)
- Melanomas of the Skin (8%)
- Non-Hodgkin Lymphoma (6%)
- Kidney (5%)
- Endometrium (3%)
- Leukemia (3%)
- Pancreas (2%)
- Uterine Cervix (2%)
- All Other Sites (1%)

Estimated Deaths

- Lung and Bronchus (23%)
- Prostate (19%)
- Colon and Rectum (16%)
- Pancreas (8%)
- Non-Hodgkin Lymphoma (6%)
- Leukemia (6%)
- Breast (4%)
- Uterine Corpus and Uterine Cervix (1%)
- Liver (1%)
- Uterine Cervix (1%)
- All Other Sites (1%)

Five-year Cancer Survival Rates (%)
US 1974-1998

- Prostate
- Lung
- Colon
- Breast

Source: CA Cancer J Clin 2000;50:7-33
The Scheme: From Nicotine Addiction to Lung Cancer

Cigarette smoking → Metabolic Activation (eg. Cytochrome P450) → Field Carcinogenesis

NICOTINE ADDICTION → CARCINOGENS (Ba-P, NNK) → DNA ADDUCTS → MUTATIONS, etc (p53, k-ras, LOH) → LUNG CANCER

Metabolic Detoxification (eg. Glutathione S-Transferase (alpha, mu, pi, theta)) → Excretion → Repair → Normal DNA → Apoptosis

Modified from Hecht JNCI; 1999

Lung Cancer Risks

• Cigarette Smoking
  – Environmental Tobacco Smoke
• Other Carcinogens
  – Asbestos, Arsenic, Radon,
  – Bis(chloromethyl) ether, Chromium, Foundry fumes, nickel, mustard gas, coke oven emissions
• Air Pollution (foundries, diesel exhaust)
• Family History
• Diet (Vitamins A, C, E and selenium “protective”)

Rates per 100,000, age-adjusted

Source: SEER

Smoking Prevalence Rates, US

*Surgeon General's Report
Garfinkel, Prev Med 26:447
Percentage of High School Students Who Reported Current Cigarette Smoking

Risk of lung cancer, men vs. women

<table>
<thead>
<tr>
<th>Pack-years</th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1-19</td>
<td>2.4 (1.4-4.1)</td>
<td>6.8 (4.1-11.4)</td>
</tr>
<tr>
<td>20-39</td>
<td>5.6 (3.6-8.7)</td>
<td>11.2 (7.5-16.8)</td>
</tr>
<tr>
<td>40-49</td>
<td>11.6 (7.7-17.6)</td>
<td>21.4 (14.3-32.3)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>13.8 (9.2-20.9)</td>
<td>32.7 (19.0-56.2)</td>
</tr>
</tbody>
</table>

Relative risk for developing lung cancer is 1.25 for women for any “dose” of tobacco

Zang, JNCI 88:183, 1996
Presentation of Lung Cancer

• Local Symptoms
  – Cough
  – Dyspnea
  – Hemoptysis
  – Chest Pain
  – SVC Syndrome
  – Wheezing

• Systemic Symptoms
  – Constitutional
  – Skeletal
    • Clubbing
    • Hypertrophic Pulmonary Osteoarthropathy
  – Endocrine
    • SIADH (sclc)
    • Hypercalcemia (squamous)
    • Cushings Syndrome (sclc)
  – Neurologic
    • Horners Syndrome
    • Eaton-Lambert syndrome (sclc)
  Vascular
    Thrombophlebitis, DIC

Differential Diagnosis

• Benign
  • Granuloma
  • Hamartoma

• Malignant
  • Metastasis
  • Primary Lung Ca
    – Small Cell
    – Carcinoid
    – Non-small Cell
      • Adenocarcinoma
      • Squamous
      • Large Cell
Pathologic diagnosis: specimen types

- Transbronchial biopsy
- Transthoracic needle biopsy
- Cytology
  - Bronchial brushing
  - Lavage
  - Aspiration (transthoracic or transbronchial)
- Thoracotomy/VATS

Lung tumors - Benign

- The majority of pulmonary neoplasms are malignant
- Benign tumors/lesions
  - Hamartoma (most common)
  - Mesenchymal- leiomyoma, lipoma, chondroma (all unusual)
  - Alveolar adenoma (rare)
Hamartoma

Likely a misnomer as these are probably true benign neoplasms, with common chromosomal abnormality (6p21 or 12q14-15).

Squamous precursors

- Squamous metaplasia, dysplasia and carcinoma in situ in lung progresses in a sequence similar to the changes described in the head and neck and cervix.
- Koilocytosis is not common; this HPV viral cytopathic change is seen in papillomatosis of larynx and trachea (HPV 6/11)
Metaplasia, dysplasia and invasive carcinoma sequence
**Diffuse Idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)**

- Bronchiolar proliferation of neuroendocrine cells
- RARE as a disease that can cause severe obstruction, simulating obstructive bronchiolitis
- More common as an incidental finding
- When these cells go through airway wall, called carcinoid tumorlets (up to 0.5cm)
Atypical adenomatous hyperplasia

- Focal, 5.0 mm or less, with defined borders
- Alveoli lined by cuboidal to low columnar cells with variable atypia
- Alveolar walls may be slightly thickened
- Non-mucinous
- Clinical significance unclear (time to progression to carcinoma)
Lung Tumor Classification

Malignant epithelial tumors

- Small cell carcinoma
- Non small cell carcinoma
- Carcinoids
  - Atypical carcinoids

- Adenocarcinoma
  - Bronchioloalveolar
  - Various subtypes

- Squamous Ca
  - Various subtypes

- Large cell CA
  - Various subtypes

Small cell carcinoma

- Usually hilar/ central tumor
- The majority have extrapulmonary spread at time of presentation.
- Only 5% present as early stage disease.
Small cell carcinoma

- High grade tumor
- Small cells with high nuclear to cytoplasmic ratio
- Nuclear molding with stippled, salt and pepper chromatin
- Frequent mitosis and apoptosis
- “Crush” artifact - very fragile cells
- Neuroendocrine differentiation can be demonstrated by electron microscopy and immunohistochemistry (few neurosecretory granules due to poor differentiation)
Small Cell

Malignant tumors - classification

Lung Tumor Classification

Malignant epithelial tumors

- Small cell carcinoma
- Non small cell carcinoma
- Carcinoids
  - Atypical carcinoids

- Adenocarcinoma
  - Bronchioloalveolar
  - Various subtypes
- Squamous Ca
  - Various subtypes
- Large cell CA
  - Various subtypes
• Most often a peripheral tumor
• Many are near pleura and cause pleural puckering.
• Cut surface can be mucoid or firm, depending on degree of fibrosis and mucin production
• Small tumors can be associated with lymph node and distant metastasis.
Adenocarcinoma

- Histologic varieties are multiple, including solid, acinar, papillary, mucinous types even within the same tumor
- Rarer types include signet ring morphology
- Differentiation can recapitulate goblet cell, Clara cell or type II pneumocyte differentiation
- Bronchial glands can produce a distinct subtype mimicking salivary gland type tumors
  - These unusual tumors are central and in younger patients
Adenocarcinoma - Bronchioloalveolar

- Distinct morphologic and clinical variant
- Grows along pre-existing alveoli and terminal bronchioles without stromal invasion
- Grossly can form a nodule, but can also produce diffuse disease mimicking pneumonia
- Can be mucinous or non-mucinous.
- Often multifocal
Malignant tumors - classification

Malignant epithelial tumors

- Small cell carcinoma
- Non small cell carcinoma
- Carcinoids
  - Atypical carcinoids

Malignant tumors

- Adenocarcinoma
  - Bronchioloalveolar
  - Various subtypes
- Squamous Ca
  - Various subtypes
- Large cell CA
  - Various subtypes
Squamous carcinoma

• Usually of bronchogenic origin; however can also arise from peripheral areas of squamous metaplasia
• Frequently have central necrosis
• Faster doubling time than adenocarcinoma; often larger at presentation
• Metastasis in relation to tumor size may occur later than adenocarcinoma
Large cell carcinoma

- This subtype shows no differentiation towards either squamous or adenocarcinoma
- Aggressive tumors with poor prognosis
- If subjected to ultrastructural examination, many of these tumors show either glandular or squamous differentiation.
- Nevertheless, these tumors are separated out because of their high grade and poor prognosis
Large cell/ Giant cell carcinoma

Carcinoids

- Malignant neoplasm of neuroendocrine cell origin
- Can be central or peripheral; central lesions can cause bronchial obstruction
- Project into bronchial lumen but often have intact mucosa above them (grow under the mucosa)
- Typical carcinoids are low grade malignancies; atypical carcinoids (mitoses and necrosis) are intermediate grade when compared to non-small cell carcinomas
Endobronchial carcinoid

Carcinoids

- Histologic features
  - Nests and cords surrounded by delicate stroma
  - Uniform cells with salt and pepper chromatin
  - Neurosecretory granules are abundant and easily demonstrated by electron microscopy or immunohistochemistry (well differentiated tumors)
CARCINOID

Metastatic Carcinoma

- The lung is a frequent site of metastatic tumor, both from extrapulmonary and intrapulmonary primaries.
- In autopsy series, between 20 and 50% of patients that expire from extra-pulmonary primaries have lung metastasis.
- Melanoma, sarcomas, renal cell carcinoma, germ cell tumors, breast carcinoma as well as carcinomas of bladder, larynx, thyroid and prostate
Metastasis

Melanoma
Lung Cancer Staging

• Small Cell Carcinoma
  Limited- confined to hemithorax
  Extensive

• Non-small Cell Carcinoma
  – T, N, M– Clinical Stage 1-4

TNM Staging - T2
**TNM Staging - Node Definitions**

**N\(_2\) NODES**
- Superior Mediastinal Nodes:
  - 1. Highest Mediastinal
  - 2. Upper Paratracheal
  - 3. Pre-vascular and Retrotracheal
  - 4. Lower Paratracheal (including Azygos Nodes)

**Aortic Nodes**:
- 5. Subaortic (A-P window)
- 6. Para-aortic (ascending aorta or phrenic)

**Inferior Mediastinal Nodes**:
- 7. Subcarinal
- 8. Paraesophageal (below carina)
- 9. Pulmonary Ligament

**N\(_3\) NODES**:
- 10. Hilary
- 11. Interlobar
- 12. Lobar
- 13. Segmental
- 14. Subsegmental

---

**International Staging System, Revised 1997**

- **Stage IIA**: T1, N1, M0
- **Stage IIB**: T2, N1, M0
- **Stage IIIA**: T1-3, N2, M0
- **Stage IIIB**: T4, any N, M0
- **Stage IV**: Any T, any N, M1

---

*Graph showing stage distribution over time.*

*Ches. 111:1710-17*
Therapy- Non-small Cell Lung Cancer

- Stage I, II
  - Lobectomy + adjuvant chemotherapy
- Stage IIIa
  - Neoadjuvant chemotherapy, radiation, surgery
- Stage IIIb
  - Chemotherapy +/− radiation
- Stage IV
  - Chemotherapy

Therapy- small cell

- Limited
  - Chemotherapy + Radiation
- Extensive
  - Chemotherapy
CT Screening
Assessment of Interval Growth

Benign or Malignant?