**Cancer in the United States, 2009**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Estimated New Cases</th>
<th>% Male</th>
<th>% Female</th>
<th>Total New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>210,660</td>
<td>29%</td>
<td>71%</td>
<td>281,820</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>114,170</td>
<td>11%</td>
<td>89%</td>
<td>137,340</td>
</tr>
<tr>
<td>Colorectum</td>
<td>72,180</td>
<td>70%</td>
<td>30%</td>
<td>92,360</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>60,040</td>
<td>1%</td>
<td>99%</td>
<td>60,040</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>34,230</td>
<td>4%</td>
<td>96%</td>
<td>35,370</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>22,770</td>
<td>4%</td>
<td>96%</td>
<td>23,320</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>17,600</td>
<td>4%</td>
<td>96%</td>
<td>18,040</td>
</tr>
<tr>
<td>Leukemia</td>
<td>24,680</td>
<td>5%</td>
<td>95%</td>
<td>25,420</td>
</tr>
<tr>
<td>Chol. &amp; biliary</td>
<td>24,180</td>
<td>3%</td>
<td>97%</td>
<td>25,260</td>
</tr>
<tr>
<td>Pancreas</td>
<td>39,500</td>
<td>3%</td>
<td>97%</td>
<td>40,280</td>
</tr>
<tr>
<td>All Sites</td>
<td>575,500</td>
<td>18%</td>
<td>82%</td>
<td>775,800</td>
</tr>
</tbody>
</table>

**Lung Cancer in the United States**

**Cancer Death Rates, US 1973-1997**

**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”)

**The Scheme: From Nicotine Addiction to Lung Cancer**

**Smoking Prevalence Rates, US**

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

Youth Behavior Survey, MMWR 2000; 49

Presentation of Lung Cancer
- Local Symptoms
  - Cough
  - Dyspnea
  - Hemoptyis
  - Chest Pain
  - SVC Syndrome
  - Wheezing

- Systemic Symptoms
  - Constitutional
  - Skeletal
    - Clubbing
    - Hypermetabolic Pulmonary Osteoarthropathy
  - Endocrine
    - SIADH (sclc)
    - Hypercalciemia (squamous)
    - Cushings Syndrome (sclc)
  - Neurologic
    - Horner's Syndrome
    - Eaton-Lambert syndrome (sclc)
  - Vascular
    - Thrombophlebitis, DIC

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)

Differential Diagnosis
- Benign
  - Granuloma
  - Hamartoma
- Malignant
  - Metastasis
  - Primary Lung Ca
    - Small Cell
    - Carcinoid
    - Non-small Cell
      - Adenocarcinoma
      - Squamous
      - Large Cell

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

Lung Tumor Classification

- Malignant epithelial tumors
  - Small cell carcinoma
  - Non small cell carcinoma
  - Carcinoids
    - Atypical carcinoids
  - Adenocarcinoma
  - Squamous Ca
  - Large cell CA
  - Bronchioloalveolar
    - 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.
- Critical divide between small cell and non-small cell carcinoma
  - Small cell carcinoma staged differently, treated with chemoradiation not surgery.

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)
**Atypical adenomatous hyperplasia—adenocarcinoma precursor**

- 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)

**Adenocarcinoma**

- 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.

**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

Adenocarcinoma/"BAC features"

Combined non-invasive and invasive carcinoma

Is there a meaning to the histologic diversity of adenocarcinoma?

- Studies examining response to gefitinib (EGFR targeting tyrosine kinase inhibitor) found activating EGFR mutations in patients with favorable response.
- Gene profiling studies found distinct subclasses of adenocarcinoma.
**Malignant tumors - classification**

Lung Tumor Classification

- Malignant epithelial tumors
  - Small cell carcinoma
  - Non small cell carcinoma
  - Carcinoids
    - Atypical carcinoids
  - Adenocarcinoma
  - Squamous Ca
  - Large cell CA

- Bronchioloalveolar
- Various subtypes

**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)

**Gene expression profiling in lung adenocarcinoma**

**Are these observations relevant?**

- EGFR mutation and amplification correlates with response to EGFR targeted agents (tyrosine kinase inhibitors gefitinib and erlotinib).
  - This subgroup of patients are also more likely to be women, non-smokers, and of Asian descent but not exclusively so.
- Activating K-ras mutations indicate resistance to these agents (about 30% of lung adenocarcinomas)
- Few, if any, lung adenocarcinomas have both activating K-ras and EGFR mutations in the same tumor.
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

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
**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)

**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

**Lung Cancer Staging**

- Small Cell Carcinoma
  - Limited- confined to hemithorax
  - Extensive

- Non-small Cell Carcinoma
  - T, N, M- Clinical Stage 1-4
**Therapy- small cell**

- Limited
  - Chemotherapy + Radiation
- Extensive
  - Chemotherapy

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**International Staging System, Revised 1997**

- Stage IA T1, N0, M0
- Stage IB T2, N0, M0
- Stage IIA T1, N1, M0
- Stage IIB T2, N1, M0
- Stage III A T1-3, N2, M0
- Stage III B T3, N1, M0
- Stage IV Any T, N3, M0

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**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

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**Tumor Biology**

- Morphology
  - Small cell Non-small cell
    - Squamous Adeno (BAC, Invasive) Large cell
- Progression
  - Clinical Stage: Size Local invasion Metastasis
- Response to therapy- ERCCI
- Recurrence propensity

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**Kaplan-Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone**

-Death despite chemotherapy
-Survive without chemotherapy


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**ERCC1 Negative Tumors benefit from Cisplatin Adjuvant Therapy**

NEJM 355:983
**Genomic Signatures of Resected Tumors Predict Outcome**

A Genomic Strategy to Refine Diagnosis in Early-Stage Non-Small-Cell Lung Cancer

Columbia Pilot

- Pathology Assessment
  - Invasion
  - Immunostaining
    - IRS1, CCNB1, LOX
  - Kras, EGFR
- Gene Expression Profiling
  - Comparison with Prognosis GeneSets.

Adjuvant Lung
https://www.adjuvantonline.com/insights/

CUMC Approach

- Screen High Risk Individuals
- Algorithm for Nodule Management
- Stage Diagnosed Tumors with PET/CT
- Resect with Minimally Invasive Techniques
- Individualize Decisions regarding Adjuvant Chemotherapy
  - Pathology Panel
    - Research assays
    - Gene Profiling