LUNG CANCER
2009

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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 (even pediatric!)
- Advances in understanding of molecular origin are beginning to guide treatments (molecular profiling)
- Multidisciplinary approach to treatment

Multidisciplinary approach

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

Multidisciplinary approach

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

Multidisciplinary approach

- Nephrology
- Urology
- Endocrinology
- ENT
- Dermatology
- Psychiatry
- Rehabilitation Medicine

Lung Cancer

1. Epidemiology
2. Etiology
3. Pathology
4. Clinical Manifestations/Staging
5. Management
2008 Incidence
Total U.S. (all types): 1,437,180

Lung cancer 215,000 (15%)
Breast cancer 184,000
Leukemia 44,000
Esophagus cancer 16,000
Lung Cancer

Cigarette smoking causes 90% of cases

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 cases</th>
<th>No. of control subjects</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>117</td>
<td>190</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Cigar, pipe smokers</td>
<td>35</td>
<td>51</td>
<td>5.6</td>
<td>2.9-10.6</td>
</tr>
<tr>
<td>Cigarettes, pipe smokers</td>
<td>25</td>
<td>31</td>
<td>13.3</td>
<td>6.9-23.3</td>
</tr>
<tr>
<td>Cigar and cigarettes, pipe smokers</td>
<td>43</td>
<td>77</td>
<td>9.0</td>
<td>5.8-14.1</td>
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<tr>
<td>Pipe, pipe smokers</td>
<td>46</td>
<td>52</td>
<td>7.9</td>
<td>5.7-10.8</td>
</tr>
<tr>
<td>Cigarettes, pipe smokers</td>
<td>408</td>
<td>900</td>
<td>14.9</td>
<td>12.3-18.1</td>
</tr>
<tr>
<td>Mixed smokers</td>
<td>1,182</td>
<td>1,300</td>
<td>12.7</td>
<td>10.3-15.6</td>
</tr>
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</table>

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

Excludes 408 case patients and 60 control subjects who smoked cigars, cigarettes, and pipe tobacco but not cigarettes.

Journal of the National Cancer Institute, Vol. 91, No. 8, April 21, 1999

LUNG CANCER

ETIOLOGY

Passive cigarette smoke

Associated with a small increased risk

Risk Factors

- Radon
- Asbestos
- Radon daughters
- Nickel compounds
- Thorium compounds
- Polycyclic aromatic hydrocarbons
- Tobacco smoke
- Mineral oils
- Vinyl resins
- Wood dust

(Adapted from International Agency for Research on Cancer, occupational classification and modification: https://www.iarc.fr/professional-risk/2001/).
LUNG CANCER

ETIOLOGY

Asbestos

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

Radiation

1. Uranium miners
   – synergistic interaction with cigarette smoking
2. Radon in homes
   – controversial, degree of risk (if any) debated

LUNG CANCER

CLINICAL FEATURES

1. Growth at primary site/direct extension
2. Metastatic spread
3. Paraneoplastic (remote) effects

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 Ca-Genetic Abnormalities

| NEJM 2008; 359:1389 |

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**Table 1. Genetic abnormalities in the lung.**

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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

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)

Horner's Syndrome
Sympathetic chain, spinal cord C8,T1
- Ptosis
- Miosis
- Anhidrosis

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(malignant effusions)
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

Staging Systems
- Separate patients into groups that are meaningful for prognosis and treatment
- “TNM” is most commonly used:
  - T = Tumor
  - N = Nodes
  - M = Metastases
- Other staging systems........
Small Cell Carcinoma-Staging

Limited Disease (1/3)

Vs.

Extensive Disease (2/3)

Small cell carcinoma Limited Disease

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

- PCI (prophylactic cranial irradiation)
  - Meta analysis: 5% survival benefit at 3 years
  - Limit dose
  - Avoid chemo agents with CNS toxicity

Small Cell Carcinoma Limited Disease

Median survival by stage (months)

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

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)

Small cell carcinoma Limited Disease

- Chemotherapy
  - Etoposide and Cisplatin
  - Etoposide and Carboplatin

  Four cycles
  - No maintenance chemotherapy

Non-Small Cell Carcinoma
Non-small cell lung cancer is staged as follows:

### Primary Tumor (T)
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor 2 cm or less in greatest dimension, accompanied by non-metastatic extrathoracic disease
- T2: Tumor greater than 2 cm, accompanied by non-metastatic extrathoracic disease
- T3: Tumor 2 cm or less, accompanied by metastatic extrathoracic disease
- T4: Tumor greater than 2 cm, accompanied by metastatic extrathoracic disease

### Regional Lymph Nodes (N)
- N0: No regional lymph node involvement
- N1: Metastasis to ipsilateral hilar or paratracheal lymph nodes
- N2: Metastasis to ipsilateral mediastinal lymph nodes
- N3: Metastasis to contralateral mediastinal lymph nodes

### Distant Metastasis (M)
- M0: No distant metastasis
- M1: Distant metastasis

### Stage groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>1A</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>1B</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>2A</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>2B</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>3A</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>3B</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>4</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
</tbody>
</table>

### Five-year Relative Survival

Survival rates for different stages, including subcategories for race and gender (White and African American). The graph shows survival percentage over time for each stage.

### Nodal Staging

The staging system includes:
- N0: No regional lymph node involvement
- N1: Metastasis to ipsilateral hilar or paratracheal lymph nodes
- N2: Metastasis to ipsilateral mediastinal lymph nodes
- N3: Metastasis to contralateral mediastinal lymph nodes

### Stage 1 – Lung Cancer Staging

[Diagram showing stages 1A and 1B with corresponding lung structures]
NSCLC – Staging/ w/u
- Physical exam!
- Chest x-ray
- Chest CT scan
- PET/CT scan
- Bone scan?
- Brain MRI with gadolinium
- Bronchoscopy/EBUS/TBNA
- Mediastinoscopy
- Tumor markers?(CEA)

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>Chemotherapy</th>
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</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>1697</td>
<td>Cis/Vin or VP16</td>
</tr>
<tr>
<td>BLT</td>
<td>RCT</td>
<td>I-IIIA</td>
<td>488</td>
<td>Cis/Vin</td>
</tr>
<tr>
<td>JBR.16</td>
<td>RCT</td>
<td>I-B-II</td>
<td>344</td>
<td>Cis/Vin</td>
</tr>
<tr>
<td>CALGB</td>
<td>RCT</td>
<td>III</td>
<td>344</td>
<td>Carbo/Pac</td>
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<tr>
<td>ANITA</td>
<td>RCT</td>
<td>I-IIIA</td>
<td>848</td>
<td>Cis/Vin</td>
</tr>
<tr>
<td>LACE</td>
<td>Meta</td>
<td>I-IIIA</td>
<td>4585</td>
<td>Cisplatin doublet</td>
</tr>
</tbody>
</table>

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 – 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

Adjuvant chemotherapy

Stage II
Yes

NSCLC – Stages I & II
No role for adjuvant radiotherapy

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 IV
Initial treatment
Chemotherapy vs. Targeted therapy?

Targeted therapies in NSCLC
- erlotinib (Tarceva) – EGFR tyrosine kinase inhibitor
- cetuximab (Erbitux) – EGFR antibody
- bevacizumab (Avastin) – VEGF antibody

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

Toxicities of bevacizumab
- Hemorrhage
- Thrombosis
- Hypertension
- Proteinuria
- GI tract perforation

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

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 + → no response
- IHC for EGFR expression
  - EGFR amplification by FISH
  - EGFR mutation

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

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

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
- Palliative radiotherapy

Non-small cell lung cancer
Stage IV
- Paclitaxel/carboplatin +/- bevacizumab
- Vinorelbine/cisplatin +/- cetuximab
- Pemetrexed/cisplatin/bevacizumab