Lung Cancer and Mesothelioma

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Malignant mesothelioma

- A tumor arising from the pleural or peritoneal surfaces approximately 30 to 40 years after asbestos exposure
- Exposure can be brief and intense, or chronic
- Over 80% are in the pleural cavity rather than peritoneal cavity
- About 2500 to 3500 cases per year in USA, mostly in men
- Estimated to peak in years 2000 to 2010, later in Europe
Malignant mesothelioma

- Asbestos fibers and silicate fibers cause murine mesothelioma in laboratory experiments
- Mesothelioma associated with 100% loss of p16 tumor suppressor gene expression
- Some evidence for presence of SV40 DNA sequences in human mesothelioma tumors
- SV40 is a tumorigenic virus that contaminated polio vaccines given in 1950’s
- 20% of mesothelioma patients have no strong history of asbestos exposure
Treatment of malignant mesothelioma

1. Median survival 9 to 12 months
2. Pemetrexed and cisplatinum chemotherapy extends survival but is not curative
3. Patients with localized mesothelioma in good physical condition are candidates for extra-pleural pneumonectomy (EPP)
4. Removal of lung, pleura, and diaphragm
5. 20 months median survival in single institution trials

Fig 1. Kaplan-Meier estimates of overall survival time for all patients (Pts) (A) and for fully supplemented patients (B)

Pemetrexed With Folic Acid and Vitamin B₁₂ Supplementation

Asbestos exposure and mesothelioma

- Amphibole fibers (long and sharp) are thought to be dangerous component ("Amphibole hypothesis")
- No good epidemiological evidence for safety of chrysotile (serpentine) fibers
- Both fibers can cause mesothelioma following injection into the pleural cavity of rodents
- Only amphibole fibers can be detected as foreign bodies in lung and pleural cavity (ferruginous bodies)
- Latency period of 10 to 40 years after exposure until onset of disease has argued for amphibole hypothesis
Asbestos exposure and mesothelioma

No safe level of asbestos exposure established
Approximately 14 million US citizens heavily exposed (largely prior to 1960’s)
Normal lungs average about 1 million fibers per dry gram weight of lung
70 million fibers per gram in patients with asbestos related diseases
Well documented cases of mesothelioma have occurred in family members of asbestos miners, particularly spouses who did laundry

Chrysotile asbestos
Summary of mesothelioma treatment

• Early stage patients may be candidates for extra-pleural pneumonectomy
  – Upcoming CALGB trial of resection followed by adjuvant chemotherapy and radiation
• Standard chemotherapy will consist of pemetrexed and cis-platinum
• First line therapy with experimental agents still acceptable
  – CALGB 30307 currently open as first and second line therapy
Lung Cancer

1) 175,000 new cases per year in US
2) Approximately 14% of all new cancers
3) 125,000 deaths per year
4) Approximately 32% of all cancer deaths

Lung Cancer

1) 80% are non-small cell lung cancer
   (NSCLC)
   a) Adenocarcinomas (40%)
   b) Squamous cell carcinomas (40%)
   c) Large cell, bronchioloalveolar, undifferentiated

2) 20% are small cell lung cancer (oat cell)
   (SCLC)
Lung cancer

1) Lung cancer is strongly tied to tobacco abuse
   a) Established in 1950’s
   b) 1964 first surgeon general’s warning

2) Risk of lung cancer is dose dependent

Lung cancer incidence by dose

<table>
<thead>
<tr>
<th>No. of Cigarettes Smoked per Day</th>
<th>American Cancer Society Volunteers</th>
<th>US Veterans</th>
<th>British Physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Current cigarette smokers*</td>
<td>9.2</td>
<td>12.1</td>
<td>14.0</td>
</tr>
<tr>
<td>1–9</td>
<td>4.6</td>
<td>5.5</td>
<td>7.8</td>
</tr>
<tr>
<td>10–19</td>
<td>8.6</td>
<td>9.9</td>
<td>17.4</td>
</tr>
<tr>
<td>20–39</td>
<td>14.7</td>
<td>17.4</td>
<td>25.1</td>
</tr>
<tr>
<td>40+</td>
<td>18.8</td>
<td>23.9</td>
<td></td>
</tr>
</tbody>
</table>

* Classification of current smokers refers to American Cancer Society study. The categories for US veterans were 1–9, 10–20, 21–39, and 40+, and for the British physicians were 1–14, 15–24, and 25+ cigarettes per day.
NNK induced lung cancer in rodents

![Graph showing lung tumor incidence vs total dose.](image)

Lung cancer incidence after quitting

**TABLE 16-4. Relative Risks of Lung Cancer Among Men According to Years after Quitting Smoking**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>0</th>
<th>1-4</th>
<th>5-9</th>
<th>10-14</th>
<th>15-19</th>
<th>20+</th>
</tr>
</thead>
<tbody>
<tr>
<td>British physicians</td>
<td>15.8</td>
<td>16.0</td>
<td>5.9</td>
<td>5.3</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>US Veterans</td>
<td>11.3</td>
<td>19.8</td>
<td>7.5</td>
<td>5.0</td>
<td>5.0</td>
<td>2.1</td>
</tr>
<tr>
<td>American Cancer Society†</td>
<td>13.7</td>
<td>12.0</td>
<td>7.2</td>
<td></td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

* All risks relative to lifelong nonsmokers.
† Excludes those who smoked less than one pack of cigarettes per day.
Second hand smoke

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. of Lung Cancers</th>
<th>Husband’s Smoking Status</th>
<th>Light</th>
<th>Heavy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higginson, 1983</td>
<td>291</td>
<td>1.4</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Temeljnik et al., 1983</td>
<td>71</td>
<td>1.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Guttner, 1983</td>
<td>153</td>
<td>1.3</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Caruso et al., 1993</td>
<td>72</td>
<td>1.2</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Klotz et al., 1994</td>
<td>86</td>
<td>1.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Yan et al., 1995</td>
<td>21</td>
<td>1.2</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Gagner et al., 1980</td>
<td>144</td>
<td>1.1</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Ak et al., 1980</td>
<td>84</td>
<td>1.4</td>
<td>2.1</td>
<td></td>
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<tr>
<td>Poon et al., 1987</td>
<td>6</td>
<td>1.6</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Lee et al., 1987</td>
<td>199</td>
<td>1.5</td>
<td>3.1</td>
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<tr>
<td>Gao et al., 1987</td>
<td>406</td>
<td>1.7</td>
<td>3.1</td>
<td></td>
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<tr>
<td>Johansson et al., 1993</td>
<td>118</td>
<td>0.8</td>
<td>5.1</td>
<td></td>
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<tr>
<td>Ramakrishnan et al., 1994</td>
<td>430</td>
<td>1.1</td>
<td>1.3</td>
<td></td>
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<tr>
<td>Brennich et al., 1992</td>
<td>422</td>
<td>0.9</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Gouine et al., 1992</td>
<td>210</td>
<td>1.5</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

* Definitions of heavy smokers varied by study and typically included those who smoked 20 or more cigarettes per day.

Lung cancer incidence by age

Figure 18.5: Age-specific lung cancer incidence ratios per 100,000 males and females, United States, 2000.
Lung cancer incidence

<table>
<thead>
<tr>
<th>Year of Diagnosis</th>
<th>White</th>
<th>Black</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>1975</td>
<td>75.7</td>
<td>21.9</td>
</tr>
<tr>
<td>1980</td>
<td>82.0</td>
<td>28.3</td>
</tr>
<tr>
<td>1985</td>
<td>81.9</td>
<td>35.9</td>
</tr>
<tr>
<td>1990</td>
<td>78.8</td>
<td>41.5</td>
</tr>
</tbody>
</table>

Lung cancer screening

- No effective screening strategy
- Routine CXR has no effect on survival in prospective studies of heavy smokers
- Spiral CT effective at detecting early lesions and is under investigation as a potential screening strategy
  - Cost?
  - Speed?
Diagnostic workup of suspected lung cancer

1) CXR: PA and lateral
2) CT of chest through adrenals
3) Laboratory evaluation
   - CBC, lytes, bun, creatinine, lfts, ca, mg, alb
4) Physical examination
5) Bronchoscopy or open biopsy

Diagnostic workup of suspected lung cancer

6) SCLC
   a) Bone scan
   b) Head CT
   c) Possible bone marrow biopsy
7) NSCLC
   a) Bone scan if indicated by symptoms
   b) Head CT if indicated by symptoms
   c) PET if patient to undergo thoracotomy
TNM* Staging of NSCLC³

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Ib</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

*T = primary tumor; N, nodal involvement; M, distant metastasis.

Stage IIIa

| T1-3 | N2 | M0 |
| T3   | N1 | M0 |

Stage IIIb

| T4   | Any N | M0 |
| Any T| N3    | M0 |

Stage IV

| Any T | Any N | M1 |

*T = primary tumor; N, nodal involvement; M, distant metastasis.
Lung cancer survival by stage

Survival of NSCLC without therapy

Survival without therapy

Survival with therapy

Chest 1994; 106, 1797-1800

Chest, 1986. 189:225s
Survival in colon cancer and breast cancer

Staging and SCLC

- Staging in SCLC commonly uses two stages only
- Disease either “limited” or “extensive”
- Limited disease represents disease that is confined to one radiation field or one hemithorax
- SCLC not commonly staged by TMN system
Survival in treated SCLC

Treatment of Limited Stage SCLC

- Randomized studies have shown a survival advantage to combined modality therapy with radiation and chemotherapy in limited stage SCLC
- Typically patient will receive 4 cycles of platinum based chemotherapy with radiation to tumor volume concurrent with two cycles of chemotherapy
Treatment of Limited Stage SCLC

- Treatment associated with a high response rate (90%) and small cure rate (10%)
- Treatment associated with median survival greater than one year
- Untreated SCLC associated with historic survival of 6 to 9 weeks

Surgery and adjuvant chemotherapy for limited SCLC

- Only one prospective trial to examine surgical resection and adjuvant therapy in SCLC
- Appears highly effective and at least as effective as standard radiation and chemotherapy treatment
Treatment of Extensive SCLC

- Treatment uses chemotherapy only
- Associated with approximately 9 months median survival
- Treatment usually consists of 4 to 6 cycles of platinum based chemotherapy
- Extremely rare long term survivors

NSCLC Treatment by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ia/b</td>
<td>Tumor of any size is found only in the lung</td>
<td>Surgery followed by chemotherapy (stage Ib)</td>
</tr>
<tr>
<td>Stage IIa/b</td>
<td>Tumor has spread to lymph nodes associated with the lung</td>
<td>Surgery followed by chemotherapy</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>Tumor has spread to the lymph nodes in the tracheal area, including chest wall and diaphragm</td>
<td>Combination of surgery, radiation, and chemotherapy</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>Tumor has spread to the lymph nodes on the opposite lung or in the neck</td>
<td>Combination of chemotherapy and radiation</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Tumor has spread beyond the chest</td>
<td>Chemotherapy and/or palliative (maintenance) care</td>
</tr>
</tbody>
</table>
Treatment of Stage I NSCLC

- Exploration by mediastinoscopy
- If mediastinal nodes are negative for tumor, patient undergoes resection
- Resection by lobectomy or pneumonectomy
- Sometimes resection by VATS (video assisted thoracoscopy) in patients with limited lung function
- Adjuvant chemotherapy may be indicated in T2N0 patients
- Approximately 60% cure rate
Adjuvant therapy for NSCLC: CALGB 9633

CALGB 9633
OVERALL SURVIVAL

- Chemotherapy
- Observation

p=0.028

Survival Time (Months)

Adjuvant therapy for NSCLC:
CALGB 9633
Adjuvant therapy for NSCLC: NCIC BR.10

JBR.10 - Study Design

Stratified by Nodal
*M 0/ N0
* N1
* 0/ Neg
* 1/ Pos
* UNR

JBR.10 - Overall Survival

Vindesine, Observation
*HR 0.7, p<0.012
Treatment of Stage II NSCLC

- Similar to treatment of Stage I
- Patients often get adjuvant radiation, but of no proven value with potential for harm
Treatment of Stage IIIA NSCLC

- Surgery alone results in cure rate of less than 10%
- Patients usually treated with pre-operative chemotherapy or combined modality therapy, followed by surgery, or by chemotherapy and radiation alone
- Intergroup trial data indicates non-operative approach may be equivalent in outcome
Pre-operative or neoadjuvant therapy for stage 3A NSCLC

### Lung Intergroup Trial 0139 Study Design

**STRATIFY**

- KPS 70-80 vs 90-100
- T1 vs T2 vs T3
- Contralateral N3 node bx: yes or no

**RANDOMIZE**

- Induction CT/RT
  - Cisplatin, 50 mg/m² IVPB d1, 8, 29, 36
  - Etoposide, 50 mg/m² IVPB d1-5, 29-33
  - Thoracic RT, 45 Gy (1.8 Gy/d), begin d1

**RE-EVALUATE**

- 2-4 weeks after completion of RT
- 7 days before completion of RT

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**TABLE 3. Neoadjuvant Approaches for Non-Small Cell Lung Cancer**

<table>
<thead>
<tr>
<th></th>
<th>Roth</th>
<th>Rosell</th>
<th>Elias</th>
<th>Wagner</th>
<th>Depierre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIA/8</td>
<td>IIb/IIIA</td>
</tr>
<tr>
<td>TTP (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chemo</td>
<td>9</td>
<td>8</td>
<td>12</td>
<td>–</td>
<td>*</td>
</tr>
<tr>
<td>Chemo</td>
<td>&gt;37</td>
<td>20</td>
<td>9</td>
<td>–</td>
<td>*</td>
</tr>
<tr>
<td>Survival (mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Chemo</td>
<td>11</td>
<td>8</td>
<td>23</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>26</td>
<td>19</td>
<td>12</td>
<td>36</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of patients; TTP, time to progression; mo, months.
* P<.05.
Lung Intergroup Trial 0139 Study Design

- No progression at re-evaluation
- Surgical Resection
- Continue RT to 61 Gy without interruption
- CONSOLIDATION: cisplatin plus etoposide X 2 cycles

Intergroup 0139/RTOG 9309
Progression-Free Survival by Treatment Arms

- CT+RT+Surgery (n=201)
- CT+RT (n=191)

Logrank p = 0.03
Intergroup 0139/RTOG 9309
Survival by Treatment Arms

Treatment of Stage IIIB NSCLC
Treatment of Stage IIIB NSCLC

- Surgery usually not a good option
- Patients are treated with chemotherapy and radiation therapy
- Associated with 15% to 20% long term survival in most randomized trials
- Radiation therapy alone associated with less than 5% survival in randomized series
- Stage IIIB with pleural effusion equivalent in prognosis to stage IV


<table>
<thead>
<tr>
<th>Treatment schema for the three study arms in CALGB 9431</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I:</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>80</td>
</tr>
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<td>80</td>
</tr>
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<td>80</td>
</tr>
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<td>80</td>
</tr>
<tr>
<td>80</td>
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<tr>
<td>80</td>
</tr>
</tbody>
</table>

Overall survival by study arm for all patients treated on 
CALGB 9431


Treatment of Stage IV NSCLC

- At least five randomized studies have documented survival advantage to treatment with chemotherapy over no treatment (usually only about 3 months)
- Two randomized trials have shown improved quality of life in patients with chemotherapy
- Two randomized studies (1 Canadian and 1 American) demonstrated equivalent costs
Treatment of Stage IV NSCLC

- If appropriate, patients offered chemotherapy, preferably on study
- Supportive care only an acceptable option
- Therapy based on patient’s goals and desires

ELVIS trial of single navelbine in stage 4 NSCLC

[Graph showing survival rates with different arms, JNCI 1999; 91:66.]
EGFR as a molecular target in NSCLC therapy

- EGFR is a 170 kD transmembrane tyrosine kinase.
- Over-expressed (>50% of NSCLC) in many squamous cell cancers, but also in adeoncarcinomas
- EGFR inhibitors Gefitinib (Iressa; AstraZeneca) and Erlotinib (Tarceva; Genentech) have been approved by the FDA for second and third line treatment of NSCLC

Bronchoalveolar cancer and EGFR inhibitors

- Bronchoalveolar carcinoma (BAC) is a multifocal variant of adenocarcinoma
- SEER data indicates slight increase in incidence but still less than 4% of total NSCLC diagnoses
- Associated with younger age, women, non-smokers
- Prognosis may be better than other NSCLC
- Etiology may be associated with carcinogens other than tobacco
Bronchoalveolar cancer

BAC and EGFR inhibitors

• Molecular studies have identified activating mutations in EGFR associated with good response to gefitinib and erlotinib
• Mutations of EGFR more common in non-smokers, BAC, women, East Asians
• Clinical test for mutations is currently available
BAC and gefitinib

- Mutations are in catalytic kinase domain
- Gefitinib targets ATP cleft of the kinase domain
- Mutations result in gain of function in kinase activity
- In small series of patients about 90% of patients with clinical responses had mutations
  - NEJM 350:21(2129)
  - Science. 2004 304(5676):1497

Bronchoalveolar lung cancer and response to EGFR inhibitor therapy
Non-surgical treatment of early stage NSCLC

• Open question
• Radiation therapy not necessarily less toxic or less expensive than surgery
• Optimal therapy for medically unresectable tumor (or patient refusing surgery) not established
  – Observation
  – Radiation
  – Chemotherapy plus radiation

Summary of lung cancer treatment

• Limited stage SCLC should receive chemotherapy and radiation with some possibility of long term remission
• Extensive stage SCLC should be offered chemotherapy with the intent to ameliorate symptoms and prolong survival
Summary of lung cancer treatment

- Stage I and II NSCLC should be offered surgery with a curative intent possibly followed by adjuvant chemotherapy in selected patients
- Stage IIIA NSCLC patients should be offered either chemotherapy and radiation or chemotherapy and surgery
- Stage IIIB NSCLC patients should be offered chemotherapy and radiation
- Stage IV NSCLC should be offered chemotherapy or experimental therapy, or best supportive care

“Just don’t smoke”

Yul Brynner 1920-1985 (dead of lung cancer)