Lung Cancer

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Lung Cancer Epidemiology

- 1912: Primary Malignant Growths of the Lung and Bronchi: A Pathologic and Clinical Study describes 374 cases\(^1\)
- 2010: > 210,000 new cases in the U.S. annually, with > 160,000 deaths\(^2\)

\(^1\) Adler, 1912.
\(^2\) Jemal et al, CA J Clin 2009

226,160 new cases of lung cancer
160,340 deaths each year

Cancer        Deaths
2. Colon CA    51,690
3. Breast CA   39,920
4. Pancreatic CA 37,390
5. Prostate CA 28,170
Total          157,170

Siegel et al, CA J Clin 2012
Diagnosis and Treatment Planning

- What is it?
- Where is it?
- What kind of shape are you in?

Lung Cancer Classification

- Non-small Cell Lung Cancer - 87%
- Small Cell Lung Cancer - 13%
- Squamous Cell Carcinoma - 30%
- Adenocarcinoma - 40%
- Large Cell Carcinoma - 15%

Lung Cancer Epidemiology

- Smoking
  - Shift in lung cancer histology
    - Increase in adenocarcinoma
    - Decrease in small cell and squamous cell
    - Shift associated with introduction of filtered cigarettes

Lung Cancer: Stage at Diagnosis

- 226,160 new cases of lung cancer
- 160,340 deaths each year
- Early (15%)
- Metastatic (55%)
- Locally Advanced (22%)
- Unknown (8%)

NSCLC: Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Main Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor &lt; 5 cm</td>
</tr>
<tr>
<td></td>
<td>No nodal or distant involvement</td>
</tr>
<tr>
<td>II</td>
<td>Larger tumor, or satellite site in same lobe</td>
</tr>
<tr>
<td></td>
<td>Involvement of N1 node</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of mediastinal nodes or</td>
</tr>
<tr>
<td></td>
<td>Multiple lesions within ipsilateral lung</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases</td>
</tr>
<tr>
<td></td>
<td>Malignant pleural or pericardial effusion</td>
</tr>
</tbody>
</table>

Lung CA: Metastasis

- Lung/Pleura
- Adrenals
- Bone
- Liver
- Brain

Overview of current AJCC 7 NSCLC staging system

Question: Staging Workup

A 68 year-old male smoker presents with a dyspnea and is found to have a 4 cm spiculated RUL mass with right pleural effusion on chest CT. Biopsy confirms non-small cell lung cancer. The most appropriate additional radiologic staging workup includes:

A. noncontrast head CT only
B. bone scan and brain MRI
C. PET/CT only
D. PET CT and brain MRI
E. No additional workup necessary

NSCLC: Radiologic Staging Workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT chest</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Should include liver and adrenals</td>
</tr>
<tr>
<td>Brain Imaging</td>
<td>Stage IB or greater, or</td>
</tr>
<tr>
<td></td>
<td>Anyone with neurologic symptoms</td>
</tr>
<tr>
<td></td>
<td>MRI is preferred; otherwise, CT head with</td>
</tr>
<tr>
<td></td>
<td>and without contrast</td>
</tr>
<tr>
<td>PET</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Has supplanted bone scan as modality of</td>
</tr>
<tr>
<td></td>
<td>choice for assessing bone involvement</td>
</tr>
</tbody>
</table>

SCLC: Radiologic Staging Workup

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>CT chest</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Should include liver and adrenals</td>
</tr>
<tr>
<td>Brain Imaging</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Mri is preferred; otherwise, CT head with and without contrast</td>
</tr>
<tr>
<td>PET or Bone scan</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Not enough data in SCLC to justify universal change from bone scan to PET/CT</td>
</tr>
</tbody>
</table>

NSCLC: Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year survival (Clinical)</th>
<th>5-year survival (Pathological)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IA: 50%</td>
<td>IA: 73%</td>
</tr>
<tr>
<td>II</td>
<td>IB: 47%</td>
<td>IB: 58%</td>
</tr>
<tr>
<td>III</td>
<td>IIA: 34%</td>
<td>IIA: 46%</td>
</tr>
<tr>
<td></td>
<td>IIB: 36%</td>
<td>IIB: 36%</td>
</tr>
<tr>
<td>IV</td>
<td>IV: 2%</td>
<td>IV: 2%</td>
</tr>
</tbody>
</table>

Goldstraw et al, JTO 2007

How Can We Do Better?

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year survival (Clinical)</th>
<th>5-year survival (Pathological)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<tr>
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<td>IB: 47%</td>
<td>IB: 58%</td>
</tr>
<tr>
<td>III</td>
<td>IIA: 34%</td>
<td>IIA: 46%</td>
</tr>
<tr>
<td></td>
<td>IIB: 26%</td>
<td>IIB: 26%</td>
</tr>
<tr>
<td>IV</td>
<td>IB: 7%</td>
<td>IB: 24%</td>
</tr>
<tr>
<td></td>
<td>IIIB: 7%</td>
<td>IIIB: 9%</td>
</tr>
</tbody>
</table>

Metastatic (55%)  Locally Advanced (22%)  Early (15%)  Unknown (8%)

Screening CTs for Lung Cancer?
Question: CT Screening
The National Lung Screening Trial demonstrated a decrease in lung cancer mortality with the use of CT screening in
A. All patients
B. Anyone who has ever smoked
C. Smokers and anyone with a family history of lung cancer
D. Only heavy smokers between ages 55-74
E. No one

National Lung Screening Trial

Eligibility
- Age 55-74
- Significant and recent smoking hx:
  - Smoking hx of ≥ 30 pack-years
  - If former smoker, had quit within the last 15 yrs
- No prior history of lung CA
- No recent CT chest within 18 months prior to enrollment
- No recent symptoms of hemoptysis or unexplained weight loss

Randomization and Screening
- 53,454 patients enrolled
- 26,723 Low-dose CT
- 26,733 to CXR
- Patients underwent screening at baseline and then annually for a total of 3 scans.
- Groups were well-balanced for age, sex, race, and smoking status

Lung Cancer cases per 100,000 person-years
645 572 RR 1.13, 95% CI 1.03-1.23

Lung cancer deaths per 100,000 person years
247 309 Relative reduction of 20%
(95% CI 6.8 - 26.7, p = 0.004)

Deaths from any cause, N
1877 2000 Relative reduction of 6.7%
(95% CI 1.2-13.6, p = 0.02)

False Positive Rate
- Percentage of patients with a “positive” finding on screening exam: 39.1% LD-CT, 16% CXR
- Percentage of findings that were false-positives: 96.4% LD-CT, 94.5% CXR

Is CT Screening Recommended?
Yes:
- National Comprehensive Cancer Network
- American Society of Clinical Oncology
- American College of Chest Physicians

Haven’t Provided Recommendations Yet:
- American Cancer Society
- U.S. Preventive Services Task Force
Ongoing Screening Concerns

- Other Concerns / Questions to be answered
  - Establish clear guidelines for f/u of detected nodule
  - Examine the cost-effectiveness of CT screening in this population
  - Study the impact of CT screening results on smoking habits.
  - Assess/prevent further disparities in care if/when we begin to implement CT screening into everyday practice.

NCCN Guidelines for Follow-up of Solid Nodules Found on Screening


NCCN Guidelines for Follow-up of Nonsolid Nodules Found on Screening


Stage-Specific Treatment of Lung Cancer

Small Cell Lung Cancer

- Limited stage (confined to a single radiation port):
  - Chemoradiotherapy
  - Prophylactic cranial irradiation (PCI)
- Extensive Stage
  - Chemotherapy
  - Consider PCI

Question: Early stage disease

A 68 year-old patient with a history of hypertension and hyperlipidemia is diagnosed with NSCLC in a 2 cm RUL mass, without apparent adenopathy. The most appropriate definitive therapy option is

A. Cryoablation
B. Lobectomy
C. Radioablation
D. Stereotactic radiosurgery
E. Wedge resection
Stage I and II NSCLC

- **Anatomic Resection** remains the gold standard.
- Alternatives to resection in poor operative candidates:
  - Wedge resection
  - Stereotactic radiosurgery
  - Ablation (radiofrequency, cryo)

**Adjuvant chemotherapy** is associated with benefit in:
- Stage II and III disease
- Stage I tumors larger than 4 cm
- Must weigh risks and benefits
- Overall improvement in 5 year survival is modest (5-10%)

Stage III NSCLC

- **Multimodality therapy**
- No clear standard of care at this time
- My personal preference is for chemoradiotherapy, with later consideration of resection when:
  - No obvious ongoing mediastinal nodal disease
  - Patient doesn’t require pneumonectomy

Stage IV: Chemotherapy

![Graph showing progression-free survival by EGFR mutation status](image)

Bedside

Patients More Likely to Respond:

- Adenocarcinoma
- Non-smokers
- Women
- Asian ethnicity

**Discovery of Sensitizing EGFR Mutations**


Bench

**Herceptin**

Mok et al, NEJM 2009
Tumor Responses to Crizotinib for Patients with ALK-positive NSCLC

- Progressive disease
- Stable disease
- Confirmed partial response
- Confirmed complete response

Maximum change in tumor size (%)

*Partial response patients with 100% change have non-target disease present.

Kwak et al, NEJM 2010

Historical Outcomes in EML4-alk pts

<table>
<thead>
<tr>
<th>Years</th>
<th>Median Survival, mo</th>
<th>1-yr Survival, %</th>
<th>2-yr Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

From 2nd/3rd line crizotinib

From 2nd line therapy

HR=0.36, p=0.004

Shaw et al, ASCO 2011

A Clinical Frameshift

- Adenocarcinoma
- Squamous cell Carcinoma
- Large cell Carcinoma
- Others

Lung Cancer Mutation Consortium: Adenocarcinoma

- KRAS 22%
- EGFR 17%
- EML4-alk 7%
- AKT1 3%
- NRAS 3%
- BRAF 2%
- MET amp 2%
- PIK3CA 1%

N = 516

Mutation detected in 54%

Kris et al, ASCO 2011

Making “personalized medicine” a reality for lung cancer patients

- Obtaining adequate tissue
  - Fine needle aspirates insufficient for current methods of genetic testing
  - Core needle biopsy whenever possible/feasible
- Appropriate referrals
  - Centers of excellence
  - Commercially available testing for EGFR, EML4-alk, KRAS, others

Take Home Points

- Lung cancer remains the leading cause of cancer death
- Smoking cessation!
- Appropriate staging workup
- Emerging role of CT screening
- Targeted therapies have transformed approaches, outcomes
- Pursue testing in appropriate patients: adequate tissue needed
Supplemental References


Disclosure of Financial Relationships

David Jackman, MD

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