Lung Cancer Treatment: What should we expect from the specialists?

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Cancer Treatment Centers of America

Oklahoma Osteopathic Association
2015 Summer CME Seminar

Financial Disclosures: None
Objectives

1. Introduction
2. Case Presentation
3. Staging
4. Methods of Staging
5. Importance of Accurate Staging
6. Treatment Guidelines
7. Management of Side Effects
8. Summary

Introduction

2004-2010 Overall 5-year lung cancer survival rate: 16.8%

Colon cancer 64.7%  Stomach cancer 28.3%
Breast cancer 89.2%  Pancreatic cancer 6.7%
Prostate cancer 98.9%  Liver/Biliary cancer 16.6%
Endometrial cancer 81.5%  Esophageal cancer 17.5%
Renal cancer 72.4%  Brain cancer 33.4%
Leukemia 57.2%
Melanoma cancer 91.3% (Seer.cancer.gov)
Thyroid cancer 97.8%
Introduction

Death due to lung cancer > colon + breast + prostate

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2014</th>
<th>Estimated Deaths 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate Cancer</td>
<td>235,000</td>
<td>29,480</td>
</tr>
<tr>
<td>2. Breast Cancer (Female)</td>
<td>232,670</td>
<td>40,000</td>
</tr>
<tr>
<td>3. Lung and Bronchus Cancer</td>
<td>224,210</td>
<td>159,260</td>
</tr>
<tr>
<td>4. Colon and Rectum Cancer</td>
<td>136,830</td>
<td>50,310</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>76,100</td>
<td>9,710</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>74,690</td>
<td>15,580</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>70,800</td>
<td>18,990</td>
</tr>
<tr>
<td>8. Kidney and Renal Pelvis Cancer</td>
<td>63,920</td>
<td>13,860</td>
</tr>
<tr>
<td>9. Thyroid Cancer</td>
<td>62,080</td>
<td>1,890</td>
</tr>
<tr>
<td>10. Endometrial Cancer</td>
<td>52,630</td>
<td>8,590</td>
</tr>
</tbody>
</table>

(Seer.cancer.gov)

Introduction

New Cases, Deaths and 5-Year Relative Survival

Colon: 48.6% -> 65.9%
Breast: 75.2% -> 90.6%
Liver: 3% -> 16.8%

(Seer.cancer.gov)
Case Presentation

- 45-year-old female from Arkansas
- Chief complaint: hemoptysis
- PMHx: HTN, GERD
- PSHx: c-section, tubal ligation
- Social Hx: 60 pack per year history of smoking, no drugs, moderate alcohol use
- Occupation: Nurse at a prison
- ECOG (Eastern Cooperative Oncology Group) performance status: 0
Case Presentation

• Transthoracic biopsy of left upper lobe nodule:
  – Moderately differentiated adenocarcinoma
    (TTF-1 positive, CK 5/6 negative)
• Brain MRI: negative
• Clinical stage IIIB (T1bN3M0) – by PET/CT
  - N3 due to FDG-avid right paratracheal node
• Treatment: Cisplatin and Etoposide concurrently with radiation therapy
**Staging**

**NCCN Guidelines Version 4.2015 Staging**
**Non-Small Cell Lung Cancer**

**Table 1. Definitions for T, N, M**

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion or extension to the visceral pleura or pleural effusion</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 2 cm in greatest dimension, with extension to the visceral pleura or pleural effusion</td>
</tr>
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</table>

**N Stage**

<table>
<thead>
<tr>
<th>N Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Regional lymph nodes negative</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to ipsilateral lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to ipsilateral mediastinal, contralateral hilar, or contralateral mediastinal lymph nodes</td>
</tr>
</tbody>
</table>

**M Stage**

<table>
<thead>
<tr>
<th>M Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

**Stage Groups**

**Stage IA**

<table>
<thead>
<tr>
<th>Staging Group</th>
<th>T0</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

**Stage IB**

<table>
<thead>
<tr>
<th>Staging Group</th>
<th>T0</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
</tbody>
</table>

**Stage IIIA**

<table>
<thead>
<tr>
<th>Staging Group</th>
<th>T1a</th>
<th>N2</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIA</td>
<td>T1b</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

**Stage IIIB**

<table>
<thead>
<tr>
<th>Staging Group</th>
<th>T1a</th>
<th>N3</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIB</td>
<td>T1b</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T2a</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T2b</td>
<td>N3</td>
<td>M0</td>
</tr>
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</table>

**Stage IV**

<table>
<thead>
<tr>
<th>Staging Group</th>
<th>T1a</th>
<th>N1</th>
<th>M1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

Methods of Staging

• Positron Emission Tomography (PET)
  – Should be performed before biopsy
  – FDG (fluorodeoxyglucose) with radiolabeled fluorine18(18F)
  – FDG phosphorylated into FDG-6-PO4
  – FDG-6-PO4 accumulates in malignant cells
  – False positive due to inflammatory/infectious lesions
    (granuloma, sarcoidosis, active infections)
  – FDG-6-PO4 accumulates in malignant cells
  – False negative due to small or low-metabolism lesions
    • Sensitivity 56-93%
    • Specificity 77-98%

Post-obstructive pneumonia
Methods of Staging

- **Endobronchial Ultrasound**
  - Useful for stations 1, 2, 4, 7 and 10 nodes
  - Sensitivity 79-95%
  - Specificity 100%

- **Endoscopic Ultrasound**
  - Useful for stations:
    - 5 (AP window)
    - 7 (Subcarinal)
    - 8 (esophageal)
    - 9 (Inferior pulmonary ligament)
  - Biopsy of left adrenal gland
  - Sensitivity 61-100%
  - Specificity 98-100%
Methods of Staging

- **Video Cervical Mediastinoscopy**
  - “Gold standard”
  - Stations 1, 2, 4, 7, 10R
  - Sensitivity >90%
  - Specificity 100%
Methods of Staging

- Complications of cervical mediastinoscopy
  - Mortality: 0.05%
  - Morbidity: 1-5%
    - Left recurrent nerve injury: 1-5%
    - Pneumothorax: <1%
    - Tracheal injury: <1%
    - Esophageal injury: <1%
    - Major vascular injury: <0.1%
      - Will need median sternotomy
Methods of Staging

• Anterior Mediastinotomy
  - Reliability not extensively documented
  - Sensitivity 33-52%
  - Specificity 100%
• For station 5 (aortopulmonary) nodes

Thoracoscopy
  - VATS – Video Assisted Thoracic Surgery
  - Robotic
Importance of **Accurate Staging**

- 83,913 patients with clinical IIIA with N2 disease, prior to therapy
- 1998-2011
- Rate of mediastinal lymph node biopsy
  - **Non-surgically treated:** 23%
  - **Surgically treated:** 56%
Importance of **Accurate Staging**

  - Review of 45 studies
  - If activity > background: sensitivity 77.4%, specificity 90.1%
  - If max SUV ≥ 2.5: sensitivity 81.3%, specificity 79.4%
- Conclusion: Management cannot be based on PET/CT alone

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Importance of **Accurate Staging**

- Accuracy of FDG-PET within the clinical practice of the ACOSOG Z4301 trial to diagnose clinical stage I NSCLC *(Ann Thorac Surg. 2014; 97:1142-1148).*
  - 682 patients in sub-analysis, 83% prevalence
  - Sensitivity/specificity: 82% / 31%
  - Positive predictive value: 85%
  - negative predictive value: 26%
  - 69% of false positive: granuloma
Importance of **Accurate Staging**

- Accuracy of FDG-PET to diagnose lung cancer in areas with infectious lung disease: A meta-analysis. *(JAMA 2014;312: 1227-1236)*
  - Reviewed 1,979 articles that can be used to calculate sensitivity/specificity
  - Included 70 studies, 10 studies documented endemic infectious lung disease
  - Pooled sensitivity/specificity among 70 studies: 89% / 75%
  - Pooled specificity among 10 studies: 54%
  - Significant heterogeneity among studies
Importance of **Accurate Staging**

  - Retrospective review
  - PET/CT results compared to mediastinoscopy or formal resection
  - 200 patients

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<th>Over Staged</th>
<th>Under Staged</th>
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<td>PET/CT</td>
<td>49.5%</td>
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Importance of **Accurate Staging**

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  - 1998-2011
  - Rate of mediastinal lymph node biopsy
  - Non-surgically treated: 23%
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PET may underestimate the extent of thoracic disease in lung cancer patients. *(Eur J Cardiothoracic Surg 2009:35: 781-785)*
  - Retrospective review
  - PET/CT results compared to mediastinoscopy or formal resection
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Transthoracic biopsy of left upper lobe nodule:
- moderately differentiated adenocarcinoma
  (TTF-1 positive, CK 5/6 negative)

Brain MRI: negative

Clinical stage 3B? (T1bN3M0)

Treatment: Cisplatin and Etoposide concurrently with radiation therapy

Importance of **Accurate Staging**

![Survival curve graph](image)
Treatment Guidelines

- Per NCCN guidelines (simplified)

| Stage I & II | Operable → resection  
<table>
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<tr>
<td></td>
<td>Inoperable → if N0, Radiation if N1, chemoradiation</td>
</tr>
</tbody>
</table>
| Stage IIIa    | Surgery → +/- chemoradiation or chemotherapy  
|               | Neoadjuvant chemoradiation → Restage → +/-  
|               | Surgery → +/- chemotherapy |
| Stage IIIb    | Chemoradiation |
| Stage IV      | Chemotherapy |

Treatment Guidelines

- Multidisciplinary Approach
  - Medical oncologist
  - Radiation oncologist
  - Pulmonologist
  - Radiologist
  - Pathologist
  - Thoracic surgeon
Treatment Guidelines

Surgical Therapy

Anatomic Resection
- Lobectomy, sleeve lobectomy, pneumonectomy

Sublobar Resection
- Segmentectomy
- Wedge resection

Lobectomy > segmentectomy >> wedge resection

Needs complete lymphadenectomy

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Treatment Guidelines

Surgical Therapy
- Thoracotomy
- Minimally invasive
  - VATS (video-assisted thoracic surgery)
  - Robotic
- Adherence to standard oncologic and dissection principles
Treatment Guidelines

Chemotherapeutic Agents
- Cisplatin
- Carboplatin
- Paclitaxel (Taxol)
- Docetaxel (Taxotere)
- Vinorelbine (Navelbine)
- Gemcitabine (Gemzar)
- Etoposide
- Irinotecan
- Vinblastine
- Mitomycin
- Ifosfamide
- Pemetrexed (Alimta)
- Bevacizumab (Avastin)

Targeted Agents for Patients with Genetic Alterations
- **EGFR** (epidermal growth factor receptor)
  - Tyrosine kinase inhibitor (TKI): erlotinib (Tarceva), gefitinib, afatinib
  - **KRAS** (Kirsten rat sarcoma virus oncogene): resistant to erlotinib, gefitinib
- **ALK** (anaplastic lymphoma kinase)
  - ALK inhibitors: Crizotinib, ceritinib
- ROS-1 rearrangements: crizotinib
- BRAF V600E mutation: vemurafenib, dabrafenib
- HER2 mutations: trastuzumab, afatinib
- RET rearrangements: cabozantinib
- MET amplification: crizotinib
Treatment Guidelines

Immunotherapy
- Checkpoint inhibitors
  - IgG4 monoclonal antibody against PD-1 (programmed death receptor 1) on T-cells
  - IgG4 monoclonal antibody against PD-L1 (programmed death receptor ligand 1) on tumor cells
  - IgG1 monoclonal antibody against CTLA-4 on tumor cells
  - Monoclonal antibody against killer-cell IgG-like receptor on NK cells
  - Monoclonal antibody against lymphocyte-activation gene 3 on tumor infiltrating lymphocytes
- Vaccines
  - Exposed core peptide of MUC-1
  - Patient idiotype-specific vaccine against NGg GM3
- Nonspecific immune stimulators
  - Recombinant human lactoferrin

Treatment Guidelines

Radiation Therapy
- SABR (stereotactic ablative radiotherapy)
  - Also known as SBRT (stereotactic body radiotherapy)
- IMRT (intensity modulated radiotherapy)
- 3D External Beam radiation
- IGRT (Image-guided radiotherapy)
- Brachytherapy
Treatment Guidelines

Stage IV Treatment
- stage IV ≠ hospice
- platinum based doublet
  - cisplatin + pemetrexed for non-squamous
  - cisplatin + gemcitabine for squamous
- Erlotinib if sensitizing EGFR mutation
- crizotinib if ALK rearrangements
- bevacizumab for maintenance therapy
- docetaxel, pemetrexed or erlotinib for second-line agents

Management of Side Effects
- Osteopathic Manipulative Medicine (OMM)
  - i.e. rib raising
- Naturopathic medicine
  - Specialty in oncology
- Acupuncture
  - Treatment of nausea
- Mind/Body Medicine
  - Support groups
- Rehabilitation therapy
So, what should we expect from the specialists?

- **Correct staging** is crucial in evaluating prognosis and optimizing care
- **Multidisciplinary approach**
  - If first line therapy fails, **other treatment options** should be explored
  - Utilization of osteopathic manipulation, naturopathic medicine, acupuncture, mind/body medicine and rehabilitation therapy to combat side effects

Recommendations and Summary

- iPhone App: Lung Cancer Stage
Questions?