Approach to Lung Cancer Screening and Staging in 2011

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The Ohio State University Medical Center

Lung Cancer Statistics

• Greatest cause of cancer deaths worldwide
• Greatest cause of cancer deaths in U.S.
  ✓ 200,00 new cases in 2010
  ✓ 165,000 deaths 12% of cancer cases, 29% of cancer deaths
  ✓ ~13% in never smokers (>22,000 cases)
• More than 85% of all patients with lung cancer have a smoking history yet only 20% of smokers acquire lung cancer

Learning Objectives

• Review the epidemiology of lung cancer
• Discuss controversies in lung cancer screening
• New lung cancer staging guidelines
• Discuss options for staging
Challenges in Lung Cancer Diagnosis and Treatment

- How do we screen for lung cancer?
- How do we identify “early disease”? 
- Are we staging patients correctly?
- Identifying new therapeutic targets
- Further characterizing the molecular heterogeneity in lung cancer
- Clinically relevant biomarkers (sputum, blood, CT, tumor?)
- Is lung cancer in non-smokers a different disease?

Keys to Successful Lung Cancer Screening

- Sensitive

Case

- 60 year old male present to your clinic to enquire about being “screened” for lung cancer
- 60 pack year smoker
- HTN, DM
- Fam hx: CAD
- Exam: nonfocal
- How would you advise this patient?
Keys to Successful Lung Cancer Screening

- Sensitive
- High incidence and prevalence
- Diagnose early treatable disease
- Decrease number of patients with late disease
- Cost effective
Keys to Successful Lung Cancer Screening

- Sensitive
- High incidence and prevalence
- Diagnose early treatable disease
- Decrease number of patients with late disease
- Cost effective
- Decrease mortality

Historical Perspective on Lung Cancer Screening

- Philadelphia Pulmonary Neoplasm Research Project
- Mayo Lung Project
- Czech Study
- Johns Hopkins MSK
- ELCAP
- Swenson
- Single arm low dose CT

Lung Screening Feasibility Study
3518 patients CT vs. CXR

CXR vs. usual care
International Early Lung Cancer Action Project

- Based on ELCAP
- Prospective, international, multi-institutional study
- 31,567 patients at high risk for lung cancer screened
  - Azumi Health Care Program, Japan
    - 3,087 (10%) current or former smokers
    - 3,299 (10%) non-smokers
- Criteria for enrollment varied by institution
- 27,456 annual screens (second or later?)


Sounds Good Right?

- No comparison group
<table>
<thead>
<tr>
<th>Sounds Good Right?</th>
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<td>• Lead time bias</td>
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<td>• Survival versus mortality</td>
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<td>• No comment as to how many biopsies done outside protocol</td>
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<td>• What was the course of those with positive screening but no biopsy?</td>
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</tbody>
</table>
Sounds Good Right?

- No comparison group
- Lead time bias
- Survival versus mortality
- No comment as to how many biopsies done outside protocol
- What was the course of those with positive screening but no biopsy?
- 10 year survival estimated to be 88% but median follow-up was 40 months

November 2010: Lung cancer trial results show mortality benefit with low-dose CT:

- Twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray
  - Important caveats (positives)
    - Prospective randomized nature of study
    - 6.9% reduction in all cause mortality
    - No universal protocol for follow-up of positive CT scan so likely to be reproducible in community
  - Important caveats (negatives)
    - Actual study has NOT been published
    - Reduction in deaths in a target group (ages 55-74) so extrapolation not possible
    - Small number of lung cancer deaths (LDCT 354 vs. 442 CXR)
    - Cost analysis

NLST

- Randomized CXR versus low-dose helical CT scan
- Initially screening followed by annual for two years
- 53,564 participants
- Ages 55-74
- Heavy smoker or former smoker
- Asymptomatic
- No prior cancer
- Powered to detect 20% reduction in mortality

NELSON

- Launched in 2003
- 16,000 patients
- Screening by MDCT versus no screening
- Years 1, 2 and 4
- Volumetric nodule assessment
- Powered to detect mortality reduction of 20%
Should we be screening?

- Currently not recommended by any organization
- Awaiting final publications
- Further long term analysis of risk/benefit
- Cost analysis
- Individualized discussion with patient

Learning Objectives

- Review the epidemiology of lung cancer
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- New lung cancer staging guidelines
- Discuss options for staging

Treatment “First Principles”

- Diagnosis
  - Adequate biopsy sample (bronchoscopy versus CT guided biopsy)
- Stage
  - Stage determines treatment
- Treatment
  - In NSCLC, surgery is the cornerstone of treatment
  - In SCLC, chemotherapy is the cornerstone

Lung Cancer Diagnostic Strategies: Principles

- Peripheral lesions
  - Bronchoscopy
  - TTN
  - VATS
- Pleural effusions
  - Thoracentesis
  - Pleural biopsy
  - VATS
- Large central lesions
  - Sputum cytology
  - Bronchoscopy
- Pleural effusions
  - Thoracentesis
  - Pleural biopsy
  - VATS
- Metastatic node or lesion
  - Node, bone, skin biopsy

Diagnosis by easiest method
Avoid unnecessary invasive tests
History and physical may guide approach
Traditional Staging

Primary tumor 
- CXR, CT Scan
- Bronchoscopy
- VATS
- Thoracentesis
- CT guided Bx
  → OR
  → Path

Mediastinal nodes 
- CT Scan, PET
  → Mediastinoscopy

Distant Mets 
- CT Scan (through adrenals), PET
- Bone scan
### 5-year survival by TNM status in NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM classification</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>61</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td>38</td>
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<tr>
<td>IIA</td>
<td>T1N1M0</td>
<td>34</td>
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<tr>
<td>IIB</td>
<td>T2N1M0 or T3N0M0</td>
<td>24</td>
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<tr>
<td>IIIA</td>
<td>T1-3N2M0 or T3N1M0</td>
<td>13</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4NanyM0 or T3N3M0</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>TanyNanyM1</td>
<td>1</td>
</tr>
</tbody>
</table>

Mountain 1997

### New Staging System

- Based on 81,105 cases from around the world
- Between 1990-2000
- Cases: 41% surgery only, chemotherapy only in 23%, radiation only in 11%
- Staging in T,N,M status was based on overall SURVIVAL. This is based on pathological stage if possible.

### SCLC stages

- **Extensive**
  - Tumour not confined to hemithorax of origin
  - Distant metastasis

- **Limited**
  - Tumour confined to hemithorax of origin and/or the mediastinum and supraclavicular nodes

*PDQ Guidelines 2000*

### New Staging According to T Status

- A primary lesion of 7cm or greater is essentially like a T3 tumor that invades mediastinal pleura, diaphragm
- All lesions between 0-3 cm are not the same
New Staging According to Additional Nodules, Invasion

- Separate nodules in the same lobe are like a T3 primary lesion. That could be IIIB instead of IIIB
- Additional nodule in different ipsilateral lobe is like T4 so IIIA


What about small cell?

- 12,000 cases in new cohort
- 349 surgically resected
- Evaluated according to TNM and correlated with survival

New Staging According to N Status

- No changes have been made

Current Controversies in Nodal Staging

- What test should be performed following negative CT of mediastinum?
- Does a negative PET obviate the need for mediastinoscopy?
- What is the best modality for comprehensive sampling of mediastinal nodes?
- Should we factor in nodal characteristics when staging?
- How many nodes should be sampled at the time of mediastinoscopy?
- How should re-staging be done following induction chemotherapy?
Learning Objectives

- Review the epidemiology of lung cancer
- Discuss controversies in lung cancer screening
- New lung cancer staging guidelines
- Discuss options for staging

Real time EBUS

- Diagnostic yield 93% (470/502)
- PPV 100%, NPV 11%
- Duration 12.5min
- Accessible stations 2, 3, 4, 7, 10, 11
- Subaortic and paraesophageal nodes not accessible
- Surgical diagnosis recommended in negative biopsies

Transbronchial Needle Aspiration (Wang)

- Early 80s
- Hilar and mediastinal nodes
- Sensitivity 36%, Specificity 98% with blind TBNA*
- Low risk
- Underutilized

* Holty, J-E C, et al., Thorax. 2005

Endobronchial Ultrasound

- Visualize tracheobronchial wall and surrounding structures
- Color doppler for vessel identification
- Can identify multilayer structure of tracheobronchial wall, determine extent of tracheobronchial wall involvement for surgical excision
- Mediastinal lymph node biopsy, staging of cancer specially non-surgical N2 N3 staging
- Decrease surgical interventions

Falcone et al. Respiration. 2003; 70:179-94
**EBUS**

- N=242
- Successful lymphoid access 86% (n=207)
- Diagnostic yield 71% (n=170)
- Surgical procedure in Non-diagnostic: n=70
  - Non-diagnostic (lymphocyte neg) 14% (n=35)  
    - Malignancy (27/35)
  - Non-diagnostic lymphocyte positive:  
    - No additional diagnosis
- Average duration 5.7m


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**EUS**

- Limited to posterior and middle mediastinal nodes
- Nodes as little as 3mm
- May also detect positive nodes when CT negative
- May detect celiac node involvement
- Can complement mediastinoscopy (Annema, JAMA, 2005)

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**EBUS vs. Mediastinoscopy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Mediastinoscopy</th>
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<tbody>
<tr>
<td>Krasnik et al, 2003</td>
<td>11 with 15 lymph nodes</td>
<td></td>
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<tr>
<td>Yasufuku et al, 2004</td>
<td>70</td>
<td>95.7%</td>
<td>100%</td>
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<tr>
<td>Rintoul et al, 2005</td>
<td>18</td>
<td>85%</td>
<td>100%</td>
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<tr>
<td>Herth FJ et al, 2006</td>
<td>502</td>
<td>94%</td>
<td>100%</td>
<td>Yes</td>
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</table>

For patients allocated to EUS-FNA, surgical staging was needed in 32% (P<0.001).
The sensitivity to detect malignant lymph node invasion was 93% (95% CI 66-99) for EUS-FNA and 73% (95% CI 39-93) for surgical staging (P=0.26).

Tournery, et al 2007
Combining EBUS/TBNA and EUS

- Should complement each other to increase yield
- Studies ongoing

Yasufuku, K. et al., 2006

PET Scan: Distant Mets

- ~10% of patients have enlarged adrenal at time of presentation: 2/3 benign adrenal adenomas
- 35-45% will have detectable extra-thoracic spread at the time of diagnosis
- Most common brain, bones, liver and adrenal glands in that order
- PET scan may be useful in detecting adrenal, bone, liver mets

PET Scan

- Based on differences in metabolism of tissues
- 18 F-fluoro-2-deoxy-D-glucose (FDG)
- Standardization Uptake Value (SUV): index of glucose utilization of a lesion
- Abnormal: SUV>2.5 or uptake greater than background activity of the mediastinum

PET is a double edged sword

PET Scan: Pitfalls

- False positives: metabolically active infectious or inflammatory lesions: Rheumatoid nodules, TB, fungal granulomas, lipoid pneumonia, talc, infarction
- False negatives
  - Tumors with low activity: BAC, carcinoid, well-differentiated adenocarcinomas, renal cell and testicular carcinomas, necrotic tumors
  - Lesions <1 cm (occasionally can detect 8-10mm)
  - Elevated serum glucose
  - Not accurate for brain lesions
  - Careful with small lesions
  - Limited anatomic resolution

PET Scan: Current Recommendations

- Chest 2007
  - Patients who are candidates for surgery should have a whole body FDG-PET to evaluate the mediastinum
  - Abnormal FDG-Pet scan findings should be followed by mediastinal sampling
  - Early studies suggest that PET scan may identify 10-20% of non-CNS metastatic disease not detected by standard methods

Mediastinal Node Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Techniques</th>
<th>Sens</th>
<th>Spec</th>
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<tr>
<td>Antoch</td>
<td>27</td>
<td>PET/CT</td>
<td>89</td>
<td>94</td>
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<td></td>
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<td>PET</td>
<td>89</td>
<td>89</td>
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<td>CT</td>
<td>70</td>
<td>59</td>
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<td>Shim</td>
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<td>PET/CT</td>
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<tr>
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<td>CT</td>
<td>70</td>
<td>69</td>
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<tr>
<td>Halpern</td>
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<td>PET/CT</td>
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<tr>
<td></td>
<td></td>
<td>PET</td>
<td>50</td>
<td>77</td>
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PET caveats

- Keep in mind causes of false negatives and false positives
- A suspicious nodule with an SUV of 0-2.5 still has a 24% chance of being malignant
- Negative PET in the mediastinum does not obviate the need for mediastinal sampling
- PET increasingly being used to assess response/survival
Overall Survival in New Staging System

Future for Staging

- Increased use of EBUS/TBNA and EUS as first line in suspected mediastinal involvement
- Including molecular markers in initial pathological evaluation
- Mediastinal Ultrasonography
- Transcervical Extended Mediastinal Lymphadenectomy

Stage groups according to TNM descriptor and subgroups

<table>
<thead>
<tr>
<th>T/M</th>
<th>Subgroup</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tbody>
<tr>
<td>T1</td>
<td>T1a</td>
<td>Ia</td>
<td>IIa</td>
<td>IIIa</td>
<td>IIb</td>
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<tr>
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<td>T2b</td>
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<td>IIIb</td>
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<tr>
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<td>IIb</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
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<td>IIIa</td>
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<td>IIIa</td>
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<td>IIIb</td>
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<td>T4a</td>
<td>IIIa</td>
<td>IIIa</td>
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<td>IIIb</td>
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<td></td>
<td>T4b</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIa</td>
<td>IIIb</td>
</tr>
</tbody>
</table>

New Staging According to M Status

- Two distinct M groups M1a and 1b
- Remember ipsilateral nodule is no longer considered M1
- M1a is pleural involvement or contralateral nodule
Lung Cancer 2011
Towards an individualized approach

Gregory A. Otterson, MD
The Ohio State University
Comprehensive Cancer Center

The Promise of Genotype-Directed Therapy

Drug will work (EGFR mutation)
Drug will work briefly, but resistance will emerge (T790M, met?)
Same diagnosis, same prescription
Drug unlikely to work (EGFR wild type)
Another drug better (ALK)

Chemotherapy plateau

The New England Journal of Medicine

Phase III Trial of Bevacizumab in NSCLC—ECOG 4599

Eligibility:
- Nonsquamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

Stratification variables:
- RT vs no RT
- Stage IIIB or IV vs recurrent
- Wt loss <5% vs ≥5%
- Measurable vs nonmeasurable

Bevacizumab: recombinant humanized MAbs to VEGF-A
Hx = history, RT = radiation therapy, AUC = area under the curve

No crossover to bevacizumab permitted

PC Paclitaxel 200 mg/m^2 Carboplatin AUC = 6 (q3w) × 6 cycles
PCB PC × 6 cycles + Bevacizumab (15 mg/kg q3w) to PD
E4599: Bevacizumab in NSCLC—Overall Survival

- PC = paclitaxel/carboplatin; PCB = PC + bevacizumab; HR = hazard ratio.
- NEJM December 14, 2006; 355;2542-50

Histology Matters - Study Design

- Stage IIIb/IV NSCLC
- PS 0 - 1
- No prior chemo
- Randomization: gender, PS, stage, histo vs cyto dx, brain mets

- B12, folate, and dexamethasone given in both arms
- Preplanned secondary analysis

Overall Survival

- Median (95% CI)
  - CP: 10.3 (9.8, 11.2)
  - CG: 10.3 (9.6, 10.9)
  - CP vs CG: Adjusted HR (95% CI) 0.94 (0.84-1.05)

Overall Survival in Patients With Adenocarcinoma or Large Cell Ca

- Median (95% CI)
  - CP: 11.8 (10.4, 13.2)
  - CG: 10.4 (9.6, 11.2)
  - CP vs CG: Adjusted HR (95% CI) 0.81 (0.70-0.94)
Subgroup Analyses Forest Plot

Primary Endpoint Results - All Histologies

Phase III nab-P/C vs P/C Study Design

Objective Responses by Histology

<table>
<thead>
<tr>
<th>Squamous</th>
<th>Nonsquamous</th>
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<tbody>
<tr>
<td>P-value</td>
<td>P-value</td>
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<tr>
<td>&lt; 0.001</td>
<td>0.060</td>
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<tr>
<td>0.808</td>
<td>0.069</td>
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</tbody>
</table>

Percent Responses

nab-Paclitaxel 100 mg/m² d1, 6 15
Carboplatin AUC 6 d1
No Premedication
n = 525

Paclitaxel 200 mg/m² d1
Carboplatin AUC 6 d1
With Premedication of Dexamethasone + Antihistamines
n = 525

Stratification factors:
- Stage (IIb vs IV)
- Age (<70 vs >70)
- Sex
- Histology (squamous vs nonsquamous)
- Geographic region

Socinski, et al, ASCO 2010
**Histology Matters**

- **Adenocarcinoma**
  - Bevacizumab added to carboplatin and paclitaxel adds to response, PFR, OS
  - Pemetrexed is superior to gemcitabine when combined with cisplatin

- **Squamous carcinomas**
  - Bevacizumab has intolerable toxicity in this population (hemoptysis)
  - Pemetrexed is inferior to gemcitabine when combined with cisplatin
  - Nab-paclitaxel seems to offer a superior response rate (PFS and OS still pending) to solvent paclitaxel

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**IPASS: Study Design**

- **Patients**
  - Chemonaive
  - Age ≥ 18 years
  - Adenocarcinoma histology
  - Never or light ex-smokers
  - Life expectancy ≥ 12 weeks
  - PS 0-2
  - Measurable stage IIIB/IV disease

- **Endpoints**
  - Gefitinib (250 mg / day)
  - 1:1 randomization
  - Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m2) 3 weekly

- **Treatment**
  - Gefitinib
  - Carboplatin / paclitaxel

---

**Progression-Free Survival in ITT Population**

- **Probability of PFS**
- **N**
- **Events**
- **HR (95% CI)**
- **P**
- **Median PFS (months)**
- **4 months progression-free**
- **6 months progression-free**
- **12 months progression-free**
- Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

---

**Progression-Free Survival in EGFR Mutation Positive and Negative Patients**

- **EGFR mutation positive**
  - Gefitinib
  - Carboplatin / paclitaxel
  - HR (95% CI)
  - No. events Gefitinib
  - No. events C/P
  - Median PFS (months)

- **EGFR mutation negative**
  - Gefitinib
  - Carboplatin / paclitaxel
  - HR (95% CI)
  - No. events Gefitinib
  - No. events C/P

---

* Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥ 15 years ago and smoked ≤ 10 pack years; # limited to a maximum of 6 cycles

Carboplatin / paclitaxel was offered to gefitinib patients upon progression

PS, performance status; EGFR, epidermal growth factor receptor

**NEJM 361:947, Sept 3 2009**
Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M-group.

- **Mutation Positive Patients**
  - TKI 1st line better than chemotherapy wrt OR% and PFS
  - Confirmatory randomized trial from Europe is pending
  - Until then, non-smokers or light smokers with adenocarcinoma should be tested for EGFR mutation status in order to make 1st line treatment decisions
  - If mutation status is not known, chemotherapy is appropriate 1st line therapy
Rapid Translation to Clinic

The NEW ENGLAND JOURNAL OF MEDICINE

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Tumor, Rapid 300 kb C 2p23 250 kb

NEJM 2010;363:1693-703

NEJM 2010;363:1693-703
**Who are these patients?**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Patients (#)</th>
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<tbody>
<tr>
<td>Median Age in years</td>
<td>59 years</td>
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<td>(Range 29 – 85 years old)</td>
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</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>8</td>
</tr>
<tr>
<td>Men</td>
<td>11</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>7</td>
</tr>
<tr>
<td>Light smokers (less than 10 pack years)</td>
<td>5</td>
</tr>
<tr>
<td>Smokers (&gt; 10 pk yrs) or Unknown</td>
<td>7</td>
</tr>
</tbody>
</table>

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**OSU Experience with ALK (+) NSCLC**

- 283 NSCLC patients
- Screened for KRAS/EGFR mutation over 12 month period
- 202 patients negative for EGFR or KRAS mutation
- 30 patients positive for ALK translocation

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**Who are these patients?**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Histology</td>
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<tr>
<td>Adenocarcinoma</td>
<td>14</td>
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<tr>
<td>Adenosquamous</td>
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</tr>
<tr>
<td>Squamous cell</td>
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<tr>
<td>Small cell</td>
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<tr>
<td>Treatment</td>
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<td>Platinum-based chemotherapy</td>
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<td>Other single-agent chemotherapy</td>
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<td>Erbitux</td>
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<td>ALK inhibitor clinical trial</td>
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</tbody>
</table>

Average Survival: 31.5 months
Outliers: 5 patients with survival > 5 years with metastatic disease (63-64 months)
Interesting Findings

- Percentage of screened patients positive for ALK translocation: 16%
- Histology:
  - Squamous/adenosquamous
  - Small cell lung cancer
- Survival Trends
  - Several patients with prolonged survival (> 5 years)
  - 3 patients with prolonged response to single agent pemetrexed (13-36 cycles)
  - 1 patient with prolonged response to single agent paclitaxel (37 cycles)

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Ongoing ALK related projects

- FISH versus IHC analysis of ALK positivity
- ALK tyrosine kinase inhibitor clinical trials:
  - OSU 09090: Phase 2, Open-label Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients with Advanced Non-small Cell Lung Cancer Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus
  - OSU 09081: Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell cancer (NSCLC) harboring a translocation or inversion event involving the Anaplastic lymphoma kinase (ALK) gene locus

Conclusions

- One size fits all is inappropriate
- Biomarker directed therapy is here
- NSCLC ~170,000 pts per year
  - Non-Squamous (~70% or ~120,000)
  - Mutant EGFR (~10% or ~17,000)
  - Mutant KRAS (~25% of Adenos or ~ 34,000)
  - ALK Translocated (~4% or ~ 8,000)
- CML ~5,000 pts per year
- GIST ~3,500-5,000 pts per year