A Pulmonologist’s Approach to Lung Cancer
• Epidemiology
• Risk Factors
• Biology/Pathology
• Presentation/SPN
• Staging
• Diagnosis
• Treatment
• Screening
Epidemiology

• Lung Cancer
  – Worldwide: most common cancer
    • 2,000,000 cases per year
  – US: Leading cause of cancer death
    • ACS: est 169,400 diagnoses 2002
      – 154,900 deaths per year
  – <15% 5-year survival; <2% pts in trials
  – Death rate peaked in 1990

King of all cancers…by far

- Lung Cancer deaths
  - Colon
  - Breast
  - Prostate
- Leading cause of cancer death in women since 1987
Years Life Lost to Cancer

- Lung: 2100 years
- Breast: 1000 years
- C/R: 700 years
- Panc: 400 years
- Leuk: 300 years
- NHL: 200 years
- Brain: 100 years
- Ovary: 50 years

Years: 0-2500
• Epidemiology
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20 Year Lag
Risk Factors for Lung Cancer

• Smoking and Lung Cancer
  – 1920: Lung CA comprised 1% of all cancers
  – Smoking accounts for 90% of all cases
  – Dose-dependent (#cigs smoked total)
    • Duration > cigarettes/day
  – Risk goes down after > 5 yrs cessation
    • At 15 years, 80-90% risk reduction
    • Never gets to “never smoker” risk
  – Cigars? 5-fold increase
    • Marijuana? Cocaine?
Relative Risk for Lung Cancer

![Bar chart showing relative risk for lung cancer by smoking category and gender. The x-axis represents smoking categories: Never, Former, 1 to 9, 10 to 19, 20, 21 to 39, 40, >40. The y-axis represents the relative risk ranging from 0 to 50. The chart compares women (red bars) and men (green bars).]
Smoking Cessation and Lung Cancer

[Diagram showing data on smoking cessation and lung cancer risk by smoking status and duration.]

- Quit < 5yr
- 5 - 9 yr
- 10-19 yr
- 20-29 yr
- 30-39 yr
- > 40 yr

Data categories and corresponding colors are as follows:
- 1-9 cigs/d
- 10-20 cigs/d
- 21-39
- >40
Other risk factors

- Obstructive lung disease
  - Worse spirometry = greater risk
- Passive smoke
- 1st degree relative
- Pulmonary Fibrosis ?scar carcinoma
- Air pollutants
- Radon
- Other
  - Arsenic, nickel, hydrocarbons, radiation, beta-carotene?
  - Asbestos
Asbestos and Lung Cancer

– Naturally occurring fibrous silicate
– Synergistic risk factor with smoking
– Long latency period
– Note: smoking is not a risk factor for mesothelioma
Asbestos, smoking and Lung CA

- Relative Risk of dying from Lung CA
  - NS = 1
  - NS + Asb = 5
  - S = 10
  - S + Asb = 50
  - S >1ppd + Asb = 90

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Lung Cancer Biology

• Molecular abnormalities in lung cancer
  – Deregulation of cellular replication
    • Proto-oncogenes: Ras family (GTPases)
      – K-ras mutation → constitutive Ras activation
        » Found in 50% of NSCLC
    • Retinoblastoma (Rb) protein (tumor suppressor gene)
      – Hyperphosphorylation prevents cell transcription/proliferations via TGF-β (normal)
      – Rb mutation
        » Almost all SCLC and 35% of NSCLC
Lung Cancer Biology

– Deregulation of differentiation
– Deregulation of apoptosis
  • p53: maintains normal cell growth and proliferation
    – Activation limits cell proliferation (tumor suppressor gene)
    – Mutations seen in 50% of human cancers, 50% of NSCLC, and 70% SCLC
– Genetic markers may help with diagnosis and prognosis
Genetic Mutations may predict responsiveness to chemo

- Gefitinib- Targets epidermal growth factor receptor (EGFR)
  - 10% of NSC lung CA have a dramatic response
  - Mutations in the tyrosine kinase domain of EGRF
    - Increased tyrosine kinase activity in response to epidermal growth factor
    - Increased sensitivity to inhibition of gefitinib (p <0.001)
    - Mutation found in 8% of NSC lung CA

Gefitinib responsive tumor
Lung Cancer Pathology

– Many different cancers
  • Adenocarcinoma (31%)
  • Squamous cell carcinoma (30%)
  • Small cell carcinoma (18%)
  • Large cell carcinoma (9%)
  • Mixed forms
  • Other
    – Carcinoid
Lung Cancer Pathology

- Adenocarcinoma
  - Most common pathology
  - “Non-smoker’s lung cancer”
  - Women
  - Peripheral (75%)
  - Aggressive mets
  - Bronchioloalveolar (BAC)
    - Well-differentiated, alveolar spread, bronchorrhea, “the unresolving pneumonia”
Adenocarcinoma Left Lower Lobe
Adenocarcinoma

Adenocarcinoma of the lung  Resected adenocarcinoma of the lung showing a classical peripheral location with associated invagination of the visceral pleura. Courtesy of Jeffrey Myers, MD.
Adenocarcinoma of the lung  High powered photomicrograph demonstrating the typical acinar pattern of glandular differentiation observed in adenocarcinoma. Courtesy of Jeffrey Myers, MD.
Bronchoalveolar Cell Carcinoma

- BAC
  - Aerogenous and lymphatic spread
  - Least associated with cigarette smoking
  - Usually peripheral
    - Localized, multi-nodular or diffuse
  - Slow metabolism
  - Prognosis
    - Localized vs. other
Lung Cancer Pathology

• Squamous cell carcinoma
  – Now 2\textsuperscript{nd} most common
  – Strongly linked with smoking
  – 60-80\% in the proximal airways
  – \textit{Cavitation}
  – Tendency to spread locally/regionally
  – Prognosis slightly better than adeno CA
Squamous Cell Lung Cancer
Squamous Cell Carcinoma

*Cavitary squamous cell carcinoma of the lung*
Peripherally located squamous cell carcinoma with extensive central necrosis and cavitation. Courtesy of Jeffrey Myers, MD.
Squamous Cell Carcinoma

Keratinization in lung cancer  Keratin (arrow) appears as waxy, darkly staining eosinophilic cytoplasm in this high powered photomicrograph of a well differentiated squamous cell carcinoma of the lung. Courtesy of Jeffrey Myers, MD.
Lung Cancer Pathology

• Small cell carcinoma
  – Rare in *non*-smokers
  – Large hilar mass with bulky LAN
  – 70% *present with overt metastasis*
  – Very chemoresponsive…
  – Worst prognosis
Small Cell Lung Cancer
Small cell carcinoma of the lung  High magnification photomicrograph showing the typical cytological features of small cell carcinoma of the lung. Courtesy of Jeffrey Myers, MD.
Lung Cancer Pathology

- Large cell carcinoma
  - Large peripheral mass with necrosis
    - Often with LAN
  - Malignant epithelial neoplasm
  - Poorly-differentiated
  - Aggressive mets
  - “It’s a cancer…it’s not small cell…but…”
Large Cell Lung Cancer
Large Cell pathology

Large cell undifferentiated carcinoma of the lung
High magnification photomicrograph showing large cell undifferentiated carcinoma of the lung. The tumor cells have vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. The cells are arranged in sheets without distinct architectural features. Courtesy of Jeffrey Myers, MD.
• Epidemiology
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• **Presentation/SPN**
• Staging
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Presentation

• Most patients have symptoms…
• Source of symptoms
  – Local (70%)
  – Regional (15%)
  – Systemic metastasis (10%)
  – Systemic non-metastasis (10%)
    • Paraneoplastic
    • Constitutional, clubbing
Presentation

• Local effects
  – Cough (45-75%)
    • Change; bronchorrhea
    • Hemoptysis (30-60%)
  – Dyspnea
    • Large airway obstruction
    • Pneumonia
    • Lymphangitic spread
    • Pleural or pericardial effusion
  – Localized wheeze
Presentation

• Regional effects
  – Pleural/pericardial effusions
  – Hoarseness (L recurrent laryngeal N.)
  – SVC syndrome
    • SCLC > NSCLC; Lymphoma
  – Brachial plexus involvement; Horner’s
    • Pancoast tumor (superior sulcus)
SVC Syndrome
Pancoast Tumor
Presentation

• Metastases
  – Bone- any; spine, ribs, pelvis → pain
  – Liver → weakness, weight loss
  – Brain → N/V, ICP, seizure, focal
  – Adrenals
  – Skin
Presentation

• Paraneoplastic syndromes (2%/20%)
  – Endocrine
    • Ectopic Cushing’s Syndrome-ACTH (SCLC: 2-10%)
    • SIADH (SCLC: 10%)
    • Hypercalcemia (NSCLC: 2%)
      – PTH-rP (Squamous cell LC)
  – Hematologic
    • Anemia
    • DIC
    • Migratory thrombophlebitis
Presentation

• Paraneoplastic Syndromes
  – Neurologic
    • Lambert-Eaton syndrome (SCLC: 2%)
      – Proximal muscle weakness, LE>UE; ↓ DTR’s)
      – Anti-Ca channel Ab
    • Anti-Hu antibody syndrome (SCLC: 16% + titers)
      – Encephalomyelitis, sensory neuropathy, cerebellar degeneration
    • Cancer-associated retinopathy (SCLC)
Presentation

• Other paraneoplastic syndromes
  – Nephrotic syndrome
  – Dermatomyositis
  – Hypertrophic pulmonary osteoarthropathy – HPO (adenocA)
  – Dementia
  – Lots o’ others…

• Paraneoplastic syndromes do NOT preclude potentially curative treatment
Solitary Pulmonary Nodule

- SPN by CXR: 150,000 pts/yr
  - Pulmonary nodule: < 3cm
  - Solitary: No signs of LAN, mets, atx

- Goals
  - Assess likelihood of cancer
  - Resect curable cancers ASAP
  - Avoid inappropriate thoracotomies
    - Benign
    - Metastatic disease
Solitary Pulmonary Nodule

- Neoplastic
  - Primary; metastatic
- Infectious
- Inflammatory
  - LAN, rheumatoid nodule, sarcoid
  - Hamartoma; granuloma
- Vascular
  - AV malformations
- Traumatic
- Congenital
Assessing cancer probability

• Old CXR’s!!!!!!!
  – 2 years of stability?

• Patient characteristics
  – Age, risk factors, previous malignancy

• Nodule characteristics
  – Calcification pattern
    • Benign: popcorn, laminated, diffuse, central
    • Malignant: stippled, eccentric
  – Doubling time
    • Benign: <1 month or >16 months
    • Malignant: 1 month – 1 year
Benign Calcification Patterns in an SPN

- Diffuse
- Lamellar
- Popcorn
- Central
SPN workup

- CT scan with IV contrast
  - Morphology
    - Size
    - Spiculation: 90% are malignant!
      - Smooth borders: up to 20% malignant
    - Density: calcification/fat
  - Contrast enhancement (Hounsfield units)
    - Increase in 15 HU
      - 98% sensitivity; 58% specificity
    - Feeding artery/draining vein = AVM
SPN workup

– PET: Positron Emission Tomography
  • F-18 2-fluoro-2-deoxy-D-glucose (F-18 FDG)
  • CA have increased glucose metabolism
  • Not reliably sensitive for nodules < 7-10 mm
  • Test characteristics
    – Sensitivity: 83-100%, Specificity: 63-90%
SPN workup

– PET: Positron Emission Tomography
  • False - : BAC, Carcinoid, < 1cm, hyperglycemia
  • False +: granulomas, sarcoidosis, rheumatoid nodule; other infections
  • NPV: excellent! PPV: get tissue confirmation!
PET scan
PET for SPN

• Recommendations
  – **Not** to be done for SPN < 1cm
  – **Low – Intermediate CA risk patients**
    • Negative scan has high NPV (cont’d observation by CT)
  – **High CA risk patients**
    • Little role for PET for the nodule
    • LAN/mets
  – **Marginal surgical candidates**
    • Negative scan favors continued observation by CT
SPN workup

• Biopsy options for SPN
  – Surgery
    • High CA risk patients that are operable
    • VATS vs. thoracotomy
  – Non-surgical: Beware of a negative result!
    • Bronchoscopy
    • Transthoracic needle biopsy

• Watch and wait
  – Pre-test probability
  – Patient anxiety/wishes
  – 2 years…maybe less?
• Epidemiology
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Staging Lung Cancer

- TNM classification (NSCLC)
  - Tumor
    - **T1**: < 3cm, surrounded by lung, not in main stem (MS)
    - **T2**: > 3cm or invading visceral pleura or in MS (>2cm) or associated with atelectasis to the hilum
    - **T3**: invades chest wall, diaphragm, mediastinal pleura, or parietal pericardium; or in MS (not on carina but <2cm); or total atelectasis of lung
    - **T4**: invades mediastinum, heart, great vessels, trachea, esophagus, spine or main carina; pleural or pericardial effusion; satellite tumor nodules in same lobe
Staging Lung Cancer

• TNM classification
  – Nodes
    • \textbf{N0}: None
    • \textbf{N1}: intrapulmonary, ipsilateral hilar
    • \textbf{N2}: ipsilateral mediastinal or subcarinal
    • \textbf{N3}: contralateral nodes; scalene or supraclavicular
  – Metastases
    • Distant
    • Tumor nodules outside of primary lobe
LN stations in Lung Cancer
Lung Cancer Stages (NSCLC)

- IA: T1 N0
- IB: T2 N0
- IIA: T1 N1
- IIB: T2 N1, T3 N0
- IIIA: T3 N1, and T1-3 N2
- IIIB: any T4, any N3
- IV: any metastases
Lung Cancer stages (SCLC)

- Small cell
  - Limited (30-40%)- can fit in one radiation port (hemithorax)
  - Extensive (60-70%)
- Palliation for all
  - Pain
  - Advanced directives/Hospice
Staging Methods (NSCLC)

- CT scan (MDCT) with IV contrast- chest through adrenals
  - (T) Tumor- very accurate for morphology
    - Invasion into fissure, chest wall or mediastinum
      - MRI- only for superior sulcus tumors
  - (N) Lymph Nodes (> 1cm): 60% sensitive and 80% specific...
    - PPV: 53%; NPV: 82%
  - Incidental adrenal mass....
Staging Methods (NSCLC)

- PET scan- one-stop shopping
  - T
  - (N): 66-100% sensitive; 81-100% specific
    - PPV: 78%; NPV: 93%
  - (M): more accurate than CT
    - Detects mets in 10-15% of ‘surgical candidates’
    - Changes staging more than ½ the time (worsens 2:1)
    - Blind spots: brain and kidney
  - + PET → Get tissue to confirm!
Staging Methods (NSCLC)

• PET scan- one-stop shopping
  – Recommendation
    • Little role for assessing (T) in SPN
    • Whole-body PET for surgical candidates (e.g. Stage I and II) to evaluate mediastinum and distant mets, except for peripheral stage I tumors
    • Mediastinoscopy is the gold standard for intrathoracic LN
    • Little role in patients with obvious mets
    • Role for non-obvious signs of mets (e.g. significant wt loss)
  – PET/CT hybrid- The future is now…. 
Clinical staging methods

• The basics
  – H&P guides other imaging studies (Look & listen!)
    • Performance status (Karnofsky scale): KEY!!!
    • Wt loss; hoarseness; focal skeletal pain; neuro signs
    • Bone tenderness; HM; focal neuro exam
    • Labs: Alk Phos, GGT, AST, Ca, lytes, BUN/Cr, Hct
  – Head CT
    • small cell (10% with brain mets); ?adeno; focal sxms
  – Bone scan
    • One study: PET + bones in 13% → 75% asymptomatic
  – MRI
• Epidemiology
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• Staging
• **Diagnosis**
• Treatment
• Screening
Diagnosis

• Diagnosis of primary tumor
  – Sputum cytology
    • Dependent on adequacy and number of samples and location of tumor
    • Sensitivity – high variation when studied
      – Central: 71%
      – Peripheral: 49%
    • Specificity: 99%
    • Underutilized for central tumors
      – Collect ≥ 3 specimens is a reasonable 1st step
Diagnosis

• Diagnosis of primary tumor
  – Bronchoscopy- endobronchial disease

• Sensitivity
  – Endobronchial biopsy: 74%
  – Brushing (cyto): 59%
  – Washing: 48%
  – All: 88%
Diagnosis

• Diagnosis of primary tumor
  – Bronchoscopy - peripheral disease
    • Sensitivity
      – Transbronchial biopsy: 46%
      – Brushing (cyto): 52%
      – Washing: 43%
      – All: 69%
    • < 2 cm versus > 2 cm
      – Sensitivity: 33% vs. 62%
Diagnosis

• Diagnosis of primary tumor
  – Transthoracic Needle Aspiration (TTNA)
    • Sensitivity 90%
    • Negative result for highly suspicious lesion…hmmmm
    • No role for solitary highly suspicious nodule (no signs of LAN/mets)
      – Straight to surgery
Before sending your patient to the wolves…

• Pre-tx evaluation (How will they tolerate treatment/surgery?)
  – Age alone is not a contraindication
  – Cardiac evaluation
  – Pulmonary
    • PFT’s: spirometry, DLCO, ABG
      – FEV$_1$ predicted post-op: Split lung perfusion scan
        » Pre-op >2L OK; <1L bad; 1-2L → perfusion scan
      – CO$_2$ > 45 mm Hg?; DLCO < 50%; smoking?
      – O$_2$ sat < 90%
  – Exercise performance
    • CPET = Cardiopulmonary exercise testing (VO$_2$ max)
Pre-op Lung functions

• Pre-op spriometry
  – $\text{FEV}_1$
    • > 80% predicted or 2L – OK for pneumonectomy
    • > 1.5L – OK for lobectomy
• Predicted Post-Operative (ppo) lung function
  – $\text{FEV}_1 < 40\%$ pred = high risk for complications/death
    » Consider CPET
  – $\text{FEV}_1 < 30\%$ pred ⇒ consider non-operative tx
Pre-op Lung functions

• Pre-op spriometry
  – If significant DOE or ILD is present – DLCO
    • DLCO > 80%
    • DLCO < 80% = 2-3x increased complications
    • DLCO < 60% = increased mortality
    • DLCO < 40% = high risk
      – CPET
Exercise Testing

• CPET
  – VO$_2$ max
    • > 20 mL/kg/min – No increased risk for complications/death
    • < 15 mL/kg/min – increased risk
    • < 10 mL/kg/min – very high risk

• Stair climbing
  – 5 flights = > 20 mL/kg/min
  – < 1 flight = < 10 mL/kg/min

• Desaturation with exercise = increased risk
  – > 4% desaturation
Pathologic staging methods

- Surgery
  - VATS, Thoracotomy
  - Mediastinoscopy – MUST do!
- Bronchoscopy
  - Wang needle
- Transthoracic Needle Aspiration
- Thoracentesis
  - If negative x2, consider VATS
- Endoscopic Ultrasound
• Epidemiology
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• **Treatment**
• Screening
Lung Cancer treatment

- **NSCLC**
  - Stages I and II
    - Surgery- VATS
    - Neoadjuvant chemo?
  - Stage IIIA
    - Neoadjuvant chemo & ?surgery
  - IIIB and IV
    - Chemo
    - Surgery for isolated mets if o/w stage I or II
- **Small Cell**
  - Limited stage
    - XRT + chemo
  - Extensive
    - Chemo
    - ?PCI
- **Palliation**
  - XRT
- **Clinical Trials!**
Lung Cancer + LVRS

- **LVRS indications**
  - Heterogenous emphysema
    - Predominantly upper lobe
      - Cancer must present in area resected
  - Low baseline exercise capacity ($\leq 25 \text{ W}$)

- **Exclusions**
  - $\text{FEV}_1 < 20\%$ predicted AND either
    - Homogenous emphysema OR
    - DLCO $< 20\%$ predicted

- **Recommend pre-op exercise testing**
## 5-year survival (NSCLC)

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<th>Stage</th>
<th>Clinical (CT)</th>
<th>Pathologic</th>
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<td>61%</td>
<td>67%</td>
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<tr>
<td>IB</td>
<td>38%</td>
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<tr>
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<td>24%</td>
<td>39%</td>
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<tr>
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<tr>
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<tr>
<td>IV</td>
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</table>
Small Cell Lung Cancer

• 5-year survival
  – Limited disease: 3-17%
  – Extensive disease: 1-3%
  – Prophylactic Cranial Irradiation improves survival slightly
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Catch ‘em early…

• Lung Cancer screening
  – CXR +/- sputum cytology
    • Diagnosed at earlier stage
    • Improved survival
    • No change in mortality!
  • Lessons:
    – Undetected mets
    – Biases of screening
Problems of screening

• Biases
  – Lead-time bias
  – Length-bias sampling
  – Overdiagnosis bias

• All can affect survival rates

• Mortality not affected…
CT screening for Lung Cancer

• Screening Helical Low-Dose CT
  – Not known yet if mortality is affected
  – Has picked up lung cancers at earlier stages
  – False positives and false negatives have been reported
  – Costs: screening, follow-up visits, f/u CT’s, biopsies, PET scans, surgery
  – Ongoing studies….Stay tuned…
Screening for Lung Cancer

• What effects prognosis?
  – Stage?
  – Size of tumor?
    • 0.5 cm vs. 1cm vs. 2cm?
  – Tumor biology
    • Microarray analysis of tumor may help prognosis

• Future screening
  – Genetic markers
Quiz Time!
True/False

• Lung cancer deaths outnumber the next three most common cancers combined
• Squamous cell lung cancer is the most common
• Adenocarcinoma of the lung is strongly associated with smoking
• Mediastinoscopy is the gold standard for identifying spread to intrathoracic LN
True/False

• Climbing 5 flights of stairs is a good marker for tolerating thoracic surgery
• Spirometry pre- and post BD, DLCO and ABG are adequate PFT’s to assess patient for surgical resection
• Blind spots for PET imaging are the brain and liver
• Positive PET generally requires tissue conformation
• PET has outstanding utility in both NSC and SCLC
Matching

1. Bronchorrhea
2. SIADH
3. PTH-rP
4. Anti-Hu Ab
5. Large peripheral mass with necrosis
6. HPO

A. Adeno
B. Bronchioloalveolar
C. Large cell
D. Small cell
E. Squamous cell
PET scan for SPN

1. BAC
2. Infectious granuloma
3. Adeno CA
4. Scar
5. Hyperglycemia
6. Carcinoid
7. Lesion < 1cm

A. False positive
B. False negative
C. Not affected
• Which mutation is associated with increased responsiveness to gefitinib?

  A. Ras
  B. p53
  C. Rb
  D. EGFR
We’ll be back!