Early Diagnosis and Treatment of Lung Cancer

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Objectives:

- Epidemiology of Lung cancer
- Diagnostic strategies for suspected Lung CA
  - Case presentation
  - Risk factors
  - Imaging
- Diagnostic and surgical treatment options
  - Cases Presentations
  - VATS Lobectomies (video)
  - Minimally invasive staging
    - EBUS / EUS
  - Marginal operative candidate
    - RFA & SRT
- Advances in biomarker based diagnostic strategies
Cancer Statistics 2007 - United States

Number of patients

<table>
<thead>
<tr>
<th>Histology</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>200,000</td>
<td>150,000</td>
</tr>
<tr>
<td>Breast</td>
<td>150,000</td>
<td>100,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>100,000</td>
<td>50,000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>50,000</td>
<td>25,000</td>
</tr>
<tr>
<td>Esoph</td>
<td>25,000</td>
<td>10,000</td>
</tr>
</tbody>
</table>

http://www.cancer.org/statistics
U.S. Age Adjusted Death Rates for Lung Cancer

Age-Adjusted Death Rates for United States, 2001 - 2005
Lung & Bronchus
All Races (includes Hispanic), Both Sexes, All Ages

Age-Adjusted Annual Death Rate
(Deaths per 100,000)

Quantile Interval

- 63.7 to 79.0
- 58.9 to 63.6
- 54.3 to 58.8
- 50.4 to 54.8
- 46.0 to 50.3
- 24.4 to 45.9

United States Rate (95% C.I.)
54.1 (53.9 - 54.2)

Healthy People 2010 Goal 03-02
44.9
FIGURE 5. Annual Age-adjusted Cancer Death Rates among Females for Selected Cancers, United States, 1930-2005.
Objectives:

- Epidemiology of Lung cancer
- Diagnostic strategies for suspected Lung CA (workup)
  - Case presentation
  - Risk factors
  - Imaging
- Diagnostic and surgical treatment options
  - Cases Presentations
  - VATS Lobectomies (video)
  - Minimally invasive staging
    - EBUS / EUS
  - Marginal operative candidate
    - RFA & SRT
- Advances in biomarker based diagnostic strategies
Case Presentation
Case Presentation

- Options?
- Probability lesion is malignant
Case Presentation

- Options?
- Probability lesion is malignant
- OR
  - Axillary thoracotomy – NSCLC
  - Lobectomy, MLND
  - T1NoMo - Stage 1a disease
Diagnosis of NSCLC Solitary Pulmonary Nodule (SPN)

- > 150,000 cases / yr by CT and CXR
- Chance of malignancy is multifactorial
  - Patient risk factors
  - Characteristics of the lesion
- Biopsy is the only way to make a definitive diagnosis

### SPN Management: Estimating Risk - Clinician

#### Probability of Cancer

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>40-60</td>
<td>&gt; 60</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking history</th>
<th>Never smoked</th>
<th>&lt; 20 pack-yrs</th>
<th>≥ 20 pack-yrs</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lesion size</th>
<th>&lt; 1.0</th>
<th>1.1-2.0</th>
<th>&gt; 2.0</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lesion margins</th>
<th>Smooth</th>
<th>Scalloped</th>
<th>Spiculated</th>
</tr>
</thead>
</table>

Henschke. Radiology 2000;215:s607
SPN Management: 'Mayo Model'

- Multivariate logistic regression analysis
- 629 patients
  - 65% benign, 23% malignant, 12% indeterminate

\[
\text{Probability of Malignancy} = e^x (1 + e^x)
\]

where \( x = -6.8272 + (0.0391 \times \text{Age}) + (0.7917 \times \text{Cigarettes}) + (1.3388 \times \text{Cancer}) + (0.1274 \times \text{Diameter}) + (1.0407 \times \text{Spiculation}) + (0.7838 \times \text{Upper}). \)

Swensen. Arch Intern Med 1997;157:849
SPN Management:

Estimating Risk with Bayesian Analysis

Statistical procedure which estimates parameters of an underlying distribution based on the observed distribution.

SPN: Management Goals

- Cure all curable lung cancers
  - Resect appropriate metastatic lesions
  - ACCP guidelines
    - SPN Growth = Tissue

- Avoid unnecessary surgery

- Optimize quality of life
SPN: Evaluation & Workup

- Clinical risk assessment
- Imaging
  - CXR
  - CT Scan
  - FDG-PET
- Bronchoscopy
- Fine needle aspiration
- Excisional biopsy
  - VATS
  - Thoracotomy
SPN: Clinical Risk Factors for NSCLC

- Smoking history
- Age
  - Rare below age 40
  - Incidence increases until age 80
- Occupational / environmental risk
  - Asbestos, radon, heavy metals, radioactivity
- Extrathoracic malignancy
  - Type and stage dependent
  - \( \approx 40\% \) of SPN are metastatic
- Geography
# 1 Risk Factor
SPN Imaging - CXR:

- The “2 year rule” – search for old films
  - 9/26 nodules with no growth on CXR in 2 years were malignant
  - > 95% accurate if stable by CT
- Limits of detectable changes
  - 3.0 to 5.0 mm by CXR
  - 0.3 mm by high-resolution CT
  - BE CAREFUL USING CXR FOR DOUBLING TIME!
- All suspicious nodules should be evaluated and followed with high resolution CT scan

Yankelevitz. AJR 1997;168:325
SPN Imaging - CT scan

- High Resolution
  - Standard of care
  - Accurate to < 1mm
- Sensitivity 95-99%
- Specificity 50%
- Spiculation is most predictive of cancer

Zhang. Radiology 1997;205:471
SPN Imaging – FDG-PET

- High degree of accuracy – published literature
  - False positives:
    - Infection - Histoplasmosis
    - Inflammatory processes
  - False negatives:
    - small size < 1 cm
    - bronchoalveolar carcinoma (BAC) (ground glass)
    - carcinoid
- Upstages 10-15% of time
  - False positive lymph nodes

SPN Imaging – FDG-PET:

- Meta-analysis
  - 40 studies, 1,474 patients with nodules
- Sensitivity 96.8%
- Specificity 77.8%
- Conclusions
  - FDG-PET is very accurate
  - The utility of FDG-PET depends on the pretest probability for malignancy
  - “For low-risk patients, FDG-PET has a high negative predictive value and observation is probably safe”

Gould. JAMA 2001;285:914
Objectives:

- Epidemiology of Lung cancer
- Diagnostic strategies for suspected Lung CA
  - Case presentation
  - Risk factors
  - Imaging
- Diagnostic and surgical treatment options
  - Cases Presentations
  - VATS Lobectomies (video)
  - Minimally invasive staging
    - EBUS / EUS
  - Marginal operative candidate
    - Wedge / Brachytherapy, SRT & RFA
- Advances in biomarker based diagnostic strategies
Diagnostic and Therapeutic options

“Let’s just start cutting and see what happens.”
Excisional Biopsy: VATS & Thoracotomony

- Definitive diagnostic technique
- Risk/Benefit ratio
  - Malignancy vs M&M
- Radiotracer guided surgery for small nodules
  - <1cm nodules
  - Select centers
- VATS (Thoracoscopy)
  - Peripheral lesions
  - > 1cm
  - Tolerate single lung ventilation
- Thoracotomy
  - Central lesions
  - Increased morbidity and mortality
Radiotracer-guided VATS Resection

CT - fluoroscopy
- 22 gauge needle
Tc99m MAA
- 0.3 millicuries
- (0.3 ml volume)
- 0.3 ml saline flush

Radiotracer-guided VATS Resection

- CT localization procedure
- Nuclear scintigraphy – to ensure “hot spot”
- Gamma probe guided excision

![Image of surgical procedure with 30-degree probe and port for stapler and probe]
Case Presentation

- 69 y/o nonsmoker
- URI – CXR - RUL SPN
- CT scan – Spiculated lesion RUL
- FDG PET positive lesion, mediastinum negative
- FNA - nondiagnostic – pneumothorax
- Options?
Surgical options

- **VATS wedge**
  - Peripheral nodules > 1cm
  - Marginal Pulmonary function

- **VATS Lobectomy**
  - Small access incision
  - No rib spreading

- **Axillary thoracotomy**
  - Muscle sparing – rib spreading
  - No division of ribs

- **Posterior-lateral thoracotomy**
  - Sacrifice or spare latissimus muscle
  - Divide rib
Case Presentation

- 69 y/o nonsmoker
- URI – CXR - RUL SPN
- CT scan – Spiculated lesion RUL
- FDG PET positive lesion, mediastinum negative
- FNA - nondiagnostic – pneumothorax
- OR VATS wedge
  - NSCLC
  - VATS lobe
- Home POD 4
- T1NoMo – Stage 1
VATS Lobectomy
VATS Lobectomy: Advantages

- Less Pain – all incisions same at 3-6 mo
- Shorter Length of Stay / Reduced Cost
- Faster return to full activity
- Fewer complications (less pneumonia)
- Improved compliance with adjuvant Chemotherapy
- Equivalent oncologic results for Stage I Lung Ca

Case presentation

- 58 y/o smoker presented with hemoptysis
  - Self employed brick layer
- CT scan 2.5 cm spiculated nodule
- Risk calculator?
Case presentation

- 58 y/o smoker presented with hemoptysis
  - Self employed as a brick layer
- CT scan 2.5 cm spiculated nodule
- Risk calculator – 100% chance of malignancy
- OR – VATS wedge
  - Mass in fissure along Pulmonary Artery
  - Open thoracotomy – lobectomy
  - Benign granulomatous disease
  - Home 5 days doing well
    - Out of work 6 weeks
Surgical Staging
Mediastinoscopy
EBUS
EUS
Invasive diagnosis and staging

- Cervical mediastinoscopy
- Chamberlain’s procedure
- Thoracoscopy or thoracotomy
Less invasive Diagnostic & Staging Techniques

- FDG-PET (requires tissue)
- Endobronchial ultrasonography (EBUS)
- Esophageal Ultrasound
Endobronchial Ultrasonography (EBUS)
Esophageal ultrasound (EUS)

Enlarged lymph node by EUS

- Esophagus
- Lymph node
- Vascular structure
EBUS vs Mediastinoscopy

- CT and PET directed EBUS & EUS
  - Excellent - minimally invasive tools
- Mediastinoscopy
  - Standard of care for mediastinal staging
  - Necessary if EBUS negative with suspicious nodes
Therapeutic options for **high risk** surgical candidates

- Chemo / XRT
- Limited Resections
  - Segmental
  - Wedge
  - Wedge with local brachytherapy
- Stereotactic radiation therapy (SRT)
- Radiofrequency ablation (RFA)
## Limited Resection vs. Lobectomy (T1N0)

### Event Rate Tables

<table>
<thead>
<tr>
<th>Event</th>
<th>Limited N</th>
<th>Recurrence Rate</th>
<th>Lobectomy N</th>
<th>Recurrence Rate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence NOT 2nd primary</td>
<td>38</td>
<td>.101</td>
<td>23</td>
<td>.057</td>
<td>.02</td>
</tr>
<tr>
<td>Recurrence 2nd primary</td>
<td>42</td>
<td>.112</td>
<td>32</td>
<td>.079</td>
<td>.079</td>
</tr>
<tr>
<td>Recurrence local-regional</td>
<td>21</td>
<td>.06</td>
<td>8</td>
<td>.02</td>
<td>.008</td>
</tr>
<tr>
<td>Recurrence Distant</td>
<td>17</td>
<td>.048</td>
<td>15</td>
<td>.037</td>
<td>.672</td>
</tr>
<tr>
<td>Death w/ Ca</td>
<td>30</td>
<td>.073</td>
<td>21</td>
<td>.049</td>
<td>.094</td>
</tr>
<tr>
<td>Death (all causes)</td>
<td>48</td>
<td>.117</td>
<td>38</td>
<td>.089</td>
<td>.088</td>
</tr>
</tbody>
</table>

# Sublobar Resection and Brachytherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>#pts</th>
<th>LR</th>
<th>5 yr. Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santos, <em>Surgery, 2003</em></td>
<td>101</td>
<td>2% vs 18.6% *</td>
<td></td>
</tr>
<tr>
<td>Lee, <em>Ann Thor Surg, 2003</em></td>
<td>33</td>
<td>6%</td>
<td>T1No 77% (5 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2No 53% (5 yr)</td>
</tr>
<tr>
<td>Birdas, <em>Ann Thor Surg, 2006</em></td>
<td>41 (lb)</td>
<td>4.8%</td>
<td>43% (4 yr)</td>
</tr>
</tbody>
</table>

* Without Brachytherapy
Solitary pulmonary nodule in a patient at high risk of morbidity/mortality from lobectomy

Lambright - VUMC PI
Brachytherapy - ACOSOG Z4032

- Creation of brachytherapy mesh
Brachytherapy - ACOSOG Z4032

- Placement of brachytherapy mesh
Stereotactic radiation therapy (SRT)
Stereotactic radiation therapy (SRT)

- 3D Radiotherapy
- Use in U.S. increasing
- Sustained local control rates as high as 90% in early lesions
- < 3cm lesions
- RTOG 0236: prospective study ongoing using modified dosing schedule
Local Ablative Therapies

Microwave Tx

RFA

ACOSOG Z4033

A Pilot Study of Radiofrequency Ablation in High-Risk Patients Stage 1A NSCLC
# Local Ablative Therapies - RFA

<table>
<thead>
<tr>
<th>Author</th>
<th># lesions</th>
<th>Local Recurrence</th>
<th>Survival (Overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanuti et al, <em>J Thor Card Surg</em>, 2009</td>
<td>31 pts St I NSCLC</td>
<td>11%</td>
<td>47% (4 yr)</td>
</tr>
<tr>
<td>Pennathur et al, <em>J Thor Card Surg</em>, 2007</td>
<td>19 pts St I NSCLC</td>
<td>42%</td>
<td>95% (1 yr)</td>
</tr>
<tr>
<td>Ambrogi et al, <em>Eur J Cardiothor Surg</em>, 2006</td>
<td>64 lesions</td>
<td>39%</td>
<td>n/a</td>
</tr>
<tr>
<td>Simon et al, <em>Radiology</em>, 2007</td>
<td>116 pts lesions</td>
<td>43% T1 (3 yr) 75% T2 (3 yr)</td>
<td>27% (5 yr)</td>
</tr>
</tbody>
</table>
RFA - pre and post

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HU</td>
<td>(35.9)</td>
<td>(0.0)</td>
<td>(4.0)</td>
<td>(26.0)</td>
<td>(15.0)</td>
</tr>
</tbody>
</table>
Limitations of non-surgical local control therapy

- Cannot obtain a pathological stage
- Cannot assess completeness of treatment
  - No pathological margins
  - Follow-up is essential
- Long-term follow-up unavailable
  - Clinical trials ongoing
  - Local recurrence and survival as objectives
Objectives:

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- Advances in biomarker based diagnostic strategies
MOLECULAR BIOMARKERS FOR DIAGNOSIS OF NSCLC

Eric L. Grogan, MD, MPH
Stephen Deppen, MA, MS (PhD Epi student)
Pierre Massion, MD (Mentor)

Dept of Thoracic Surgery
Institute for Medicine and Public Health
VPSD program
Problem

- Many new lung nodules
- Accurate diagnosis essential (95%)
  - Low threshold for resection
  - 20-30% benign diagnosis rate
  - “Appendectomy”
- Need noninvasive tests to exclude benign nodules
  - Biomarkers
  - New imaging techniques
### Surgically Evaluated Pulmonary Nodules


<table>
<thead>
<tr>
<th>Compared to All Cases</th>
<th>Number of Pts</th>
<th>Malignancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases</td>
<td>191</td>
<td>72%</td>
</tr>
<tr>
<td>Age &gt; 50 Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET Positive</td>
<td>87</td>
<td>90%</td>
</tr>
<tr>
<td>PET Negative</td>
<td>36</td>
<td>69%</td>
</tr>
<tr>
<td>Age &lt; 50 OR Nonsmoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET Positive</td>
<td>31</td>
<td>65%</td>
</tr>
<tr>
<td>PET Negative</td>
<td>37</td>
<td>38%</td>
</tr>
<tr>
<td>High Likelihood for Benign Disease</td>
<td>104</td>
<td>57%</td>
</tr>
<tr>
<td>No Preop Diagnosis and size &lt;=3cm</td>
<td>88</td>
<td>54%</td>
</tr>
</tbody>
</table>

Isbell et al – Accepted STS Jan 2010
Predicting cancer with current models (Mayo)

- ROC curves
- Different malignancy rates
- Similar curves

Isbell et al – Accepted STS Jan 2010
How good is FDG PET to diagnose NSCLC?

<table>
<thead>
<tr>
<th>Category</th>
<th>All Cases</th>
<th>Size ≤ 3cm &amp; No Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>217</td>
<td>87</td>
</tr>
<tr>
<td>Malignant Cases</td>
<td>171 (79%)</td>
<td>56 (63%)</td>
</tr>
<tr>
<td>Accuracy (PET)</td>
<td>78%</td>
<td>72%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td>Specificity</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>84%</td>
<td>72%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>49%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Grogan et al – Submitted AATS
# Diagnostic testing 2X2

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Positive</td>
<td>a</td>
</tr>
<tr>
<td>Negative</td>
<td>c</td>
</tr>
</tbody>
</table>

- **Prevalence** = \( \frac{a+c}{N} \)
- **Accuracy** = \( (\text{prevalence})(\text{Sensitivity}) + (1-\text{prevalence})(\text{Specificity}) \)
- **Positive Predictive value** = \( \frac{a}{a+b} \)
- **Negative Predictive Value** = \( \frac{d}{c+d} \)
- **Sensitivity** = \( \frac{a}{a+c} \)
- **Specificity** = \( \frac{d}{b+d} \)
What do we need?

- Test to exclude lung cancer
  - Highly specific
  - High negative predictive value
- Better predictive models
  - Biomarker based
- Improved imaging techniques
Ayers Institute Biomarker Pipeline

Integrate with other information:
- gene expression
- mutations, SNPs
- cancer biology

Stage:
- Discovery shotgun proteomics

Tasks:
- identify and acquire samples
- inventory proteins
- compare cancers, normals
- identify marker candidates (~100s)
- confirm candidates in tissue/plasma
- eliminate candidates with inconsistent detection
- identify top priority candidates (~10-15)
- generate antibodies
- establish detection in blood, tissue
- establish assay performance characteristics
- evaluate candidates in appropriate clinical context
- co-development with commercial partners
- FDA submissions

Samples:
- ~20
- ~25-200
- ~200-5,000+

Timeline:
- ~6 mos.
- ~6 mos.
- ~1-2 yrs
- ~3-5+ yrs


Figure 1
3 phases of our work

- Identify who will benefit from additional testing
- Serum MALDI-MS biomarker profile
  - Establish performance characteristics
  - Clinically relevant patient population (nodules <3cm)
- Validate biomarker profile
  - ACOSOG Z4031 trial (completed)
### Biomarker Test Population

<table>
<thead>
<tr>
<th></th>
<th>Older smokers</th>
<th>Younger non-smokers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PET Positive</strong></td>
<td>42</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td><strong>PET Negative</strong></td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50</td>
<td>21</td>
<td>71</td>
</tr>
</tbody>
</table>

VUMC SPORE DATABASE – Massion Nodule Cohort
### Diagnostic Characteristics of Biomarker

<table>
<thead>
<tr>
<th>Cancer</th>
<th>MALDI</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

- Prevalence = 64%
- Sensitivity = 26%
- Specificity = 100%
- Pos Pred Value = 100%
- Neg Pred Value = 47%

Small numbers: Pilot study

VUMC SPORE DATABASE – Massion Nodule Cohort
Conclusions

• More accurate diagnosis of NSCLC in patients with SPN is needed
• Sub-populations of patients exist with “intermediate probability for disease” who will benefit from an additional tests
• New diagnostic strategies with high specificity and high negative predictive value will reduce unnecessary operations for benign pulmonary nodules
Acknowledgements

- Mentors
  - Pierre Massion, MD
  - Bill Putnam, MD
  - Bob Dittus, MD, MPH, Ted Speroff, PhD

- Research Team
  - Stephen Deppen (PhD Epidemiology student)
  - Emphasis Students – Jodi Weinstein, Aaron Dawes, Gabriella Andrade

- Dept of Thoracic Surgery
  - Bill Putnam, Eric Lambright, Jon Nesbitt
PATZ model

- Classification and regression tree analysis
  - Complex algorithm
  - CEA, RBP, SCC, AAT

- Results
  - Sensitivity 77.8%
  - Specificity 75.4%

- In one of 3 “bins” 90% chance of cancer
- Complex – not practical for use
Metagene models for prognosis in NSCLC

ACOSOG Validation Cohort

Survival (%)

P<0.001

CALGB Validation Cohort

Survival (%)

P<0.001

CALGB 30506 (Stage 1)– Harpole
If Metagene is high risk
RTC for Chemotherapy vs none